ISSVA World Congress 2024 Program Book

Table of Contents

Presidential Welcome Letter

On behalf of ISSVA, it is my great pleasure to extend a warm welcome to all participants of the 24th Scientific Congress in Madrid.

The ISSVA Scientific Congress serves as a vital platform for fostering collaboration, sharing knowledge, and exploring innovative solutions to the myriad challenges facing healthcare providers, researchers, and patient advocacy groups focused on vascular anomalies. As we convene for this meeting, we acknowledge the remarkable advancements and breakthroughs in the field of Vascular Anomalies that have revolutionized our understanding of these disorders and has led to improved therapeutic, patient quality of life and outcomes worldwide. I encourage all attendees to take full advantage of the myriad opportunities for networking, learning, and professional development available throughout the conference. By leveraging the collective expertise and passion of our diverse community of researchers, clinicians, educators, advocacy groups, and industry partners, we can catalyze positive change and drive meaningful impact in the lives of our patients. Together, let us seize this moment to forge new connections, exchange ideas and foster collaborations.

This year's conference underscores the critical importance of interdisciplinary cooperation and cutting-edge research in addressing the complex issues we face. Through engaging panel discussions, thought-provoking presentations, and interactive poster presentations, we aim to inspire, educate, and empower attendees to push their boundaries of medical knowledge, curiosity, and practice.

I extend my deepest gratitude to the organizing committee, sponsors, speakers, and volunteers whose dedication and hard work have made this event possible. Your unwavering support and commitment to this meeting is truly commendable.

I want to thank the local hosts – Dr. Lopez Gutierrez and his team, the Meetings Committee, the Scientific Committee, and the EDI Team for the many hours of ZOOM meetings, phone calls, emails and thoughtful contributions to organizing what we hope will be the most successful meeting. This would not be possible without the support of our corporate sponsors: Novartis (Platinum Sponsor), Pierre Fabre (Gold Sponsor), and IGEA Medical and our exhibitors: Children's Hospital of Philadelphia, PolyNovo, CMTC & Other Vascular Malformations, Bundesverband Angiodysplase, and LGD Alliance.

I wish you all a productive, enriching, and memorable experience at the ISSVA Scientific Congress in Madrid. May your time here be filled with meaningful insights, fruitful collaborations, and lasting friendships.

Warmly,
Francine Blei

Introduction to ISSVA

The International Society for the Study of Vascular Anomalies (ISSVA) is a multidisciplinary international society of physicians, scientists, and health care providers united by an interest in vascular anomalies. The Society aims to promote the highest standards of care for patients with vascular anomalies by advancing clinical and scientific knowledge concerning causes, diagnosis and treatment, and by education of physicians, health care providers, patients and the community. The Society encourages the free flow of information between its members and interested groups, through meetings and teaching programs, and by the dissemination of a classification scheme and pertinent scientific data.

About the World Congress
(formerly the Workshop)

The International Society for the Study of Vascular Anomalies (ISSVA) is the formalization of prior biennial international workshops, which were started in 1976. Over time, the ISSVA workshops grew to the point of gathering hundreds of international specialists of various medical disciplines involved in the treatment of patients afflicted with vascular anomalies. These biennial workshops, which eventually evolved into the World Congress, have fostered time proven personal contacts, collaboration, and informal exchange of scientific knowledge concerning vascular anomalies.

2022-2024 Board of Directors

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Local Organizing Committee

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Paloma Triana
Hospital Universitario La Paz - Vascular Anomalies Team

General Information and Hybrid Format

General Information & Travel

The ISSVA World Congress: The Latest in Vascular Anomalies is ISSVA's biannual Congress, which is attended by a wide array of specialists including intervention radiologists, dermatologists, plastic surgeons, ENT surgeons, pediatricians, pediatric surgeons, oncologists and pathologists, presents the latest developments in this fast-moving area.

For in-person attendees, detailed information about travel to Madrid, Spain, and other important information is available on the ISSVA Travel Web Page.

Entry into Spain

The Spanish Government requires that all international visitors carry a valid passport to enter Spain. In addition to your passport, you may also require a visa. Advance travel planning and early visa application are important and up to you.

Madrid, Spain

Madrid, Spain's capital city and has much to see and explore! It is famous for its vibrant art culture (visual and music), unique architecture, amazing food, history, its famous football club, and so much more! Find out everything you'll need to know about Madrid from its official tourism website.

Time Zone

Madrid's time zone during the World Congress is CEST (Central European Summer Time).

Venue

The ISSVA World Congress is being held at the IFEMA, which is located at Av. del Partenón, 5, Barajas, 28042 Madrid, Spain. The closest metro stop is Feria de Madrid, and is a short walk across from the venue.

The ISSVA World Congress 2024 will be held in the North Convention Center (West Hall). There will be escalators to take up to the first floor at the main North Entrance.

Virtual Meeting Website

The virtual meeting will be hosted by our onsite AV company, which will be accessible to anyone who registered for the virtual programming. This platform will offer live talks during the Scientific Program. You will receive an email with your login instructions prior to the start of the ISSVA World Congress.

Recorded Content

All sessions will be recorded and available to all attendees (in-person and virtual) after the World Congress. Once posted, you'll receive an email with instructions and recordings will be available for 30 days (once available).

Continuing Medical Education Credits

Accreditation Statement

In support of improving patient care, this activity has been planned and implemented by Amedco LLC and International Society for the Study of Vascular Anomalies. Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Physicians (ACCME) Credit Designation

Amedco LLC designates this live activity for a maximum of 25.25 *AMA PRA Category 1 Credits™* for physicians. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Claim CME Credits

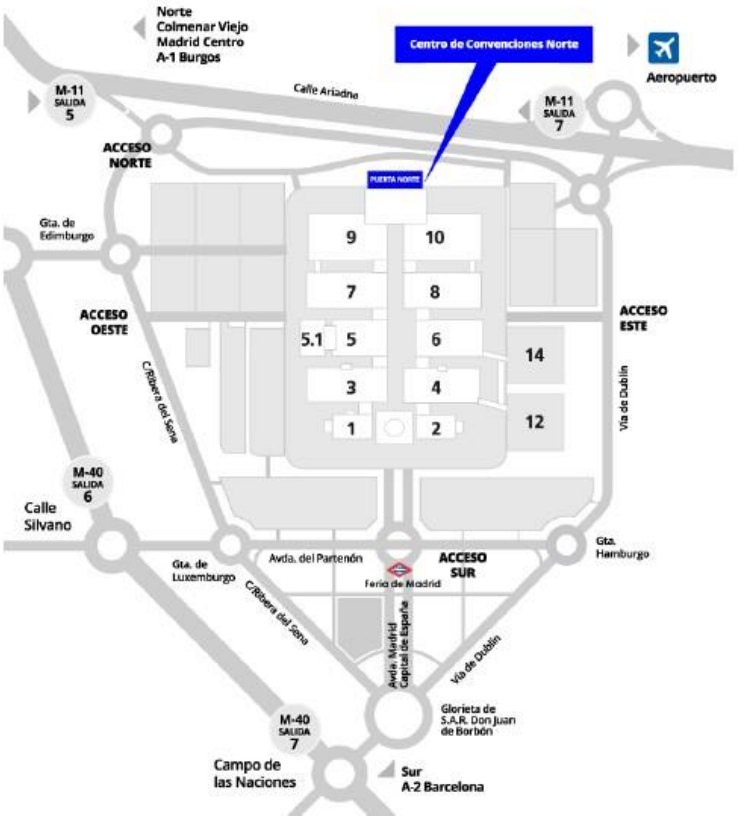
1. Go to http://issva.cmecertificateonline.com/
2. Click on the "World Congress 2024" link.
3. Evaluate the meeting.
4. Save/Download/Print all pages of your certificate for your records.

Questions? Email Certificate@AmedcoEmail.com

Click here to read the full Learner Notification regarding disclosures of faculty and planners, and additional information regarding CME.

Venue Maps

Getting there from Metro Stops



The ISSVA World Congress is in the **North Convention Center, West Hall**.

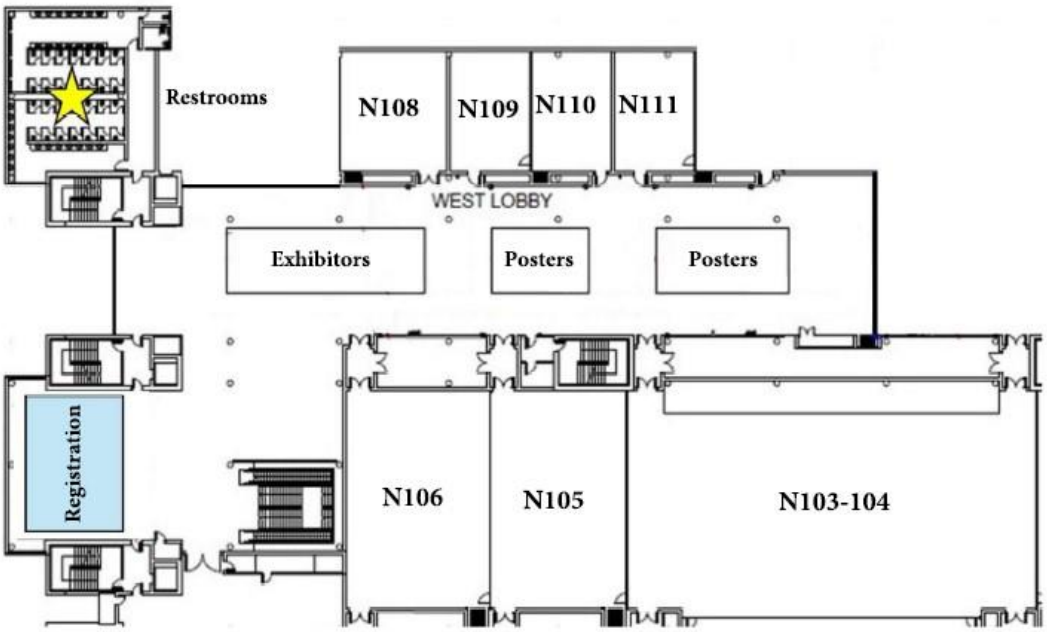
To get there from the Metro/Bus stops, please use the map. If you are taking a taxi, ask for North Convention Center drop-off.

The yellow star is where the Metro/Bus stops are for IFEMA. Please follow the red arrow through the avenue all the way to the end, which is where the North Convention Center (blue banner).

The doors **will not open** until 8:30am each day of the World Congress, so you will need to wait outside until the doors open.

When you get inside, please follow the signs for the West Hall. You will need to go upstairs. Once there you will see the registration desk.

North Convention Center, West Hall Map



Program at a Glance

Tuesday, 7 May (Primer Day)		
Time	**Session Title**	**Room**
Primer Sessions		
09:30 - 11:19	Primer, Part I: Vascular Tumors	N103-104
11:20 - 11:45	Coffee Break	Main Hallway
10:30 - 12:30	Primer, Part II: Vascular Malformations	N103-104
14:05 – 15:05	Lunch Break	Main Hallway
15:05 – 16:35	State of the Art Pathology, IR and Surgical Management of VA	N103-104
16:35 - 17:00	Coffee Break	Main Hallway
17:00 - 18:30	Difficult Case Panel Discussion	N103-104
Welcome Reception & Opening Remarks		
18:30 - 20:00	Welcome Reception & Opening Remarks	N103-104 & Main Hallway

Wednesday, 08 May		
Time	**Session Title**	**Room**
Oral Abstract Presentations		
09:30 - 11:25	Session 1: Vascular Tumors I	N103-104
11:25 - 12:00	Coffee Break	Main Hallway
12:00 - 13:00	Session 2: Vascular Tumors II	N103-104
13:00 - 13:35	Keynote Address: Ilona Frieden	N103-104
13:35 - 15:00	Lunch Break Poster Session IGEA Non-CME Lunch Symposium – see full program for details	Main Hallway Main Hallway N106
15:00 - 16:40	Session 3: Venous Malformations	N103-104
16:40 - 17:00	Coffee Break	Main Hallway
General Assembly (ISSVA Members Only)		
17:00 - 18:00	General Assembly	N103-104

Thursday, 09 May

Time	Session Title	Room
Oral Abstract Presentations		
09:00 - 11:00	Session 4: Arteriovenous Malformations	N103-104
11:00 - 11:30	Coffee Break	Main Hallway
11:30 - 13:00	Session 5: Lymphatic Malformations	N103-104
13:00 - 14:30	Lunch Break Poster Session	Main Hallway Main Hallway
13:30 – 14:30	Pierre Fabre Non-CME Lunch Symposium - see program for details	N105
14:30 - 16:30	Session 6: Combined Malformations	N103-104
16:30 - 17:00	Coffee Break	Main Hallway
17:00 - 18:40	Session 7: Capillary Malformations	N103-104
Congress Social Event (ticket required)		
20:00 - 23:00	Congress Social Event – Casino de Madrid	Off-site

Friday, 10 May

Time	Session Title	Room
Running Club (pre-registration required)		
06:30 - 07:30	ISSVA Running Club	Off-site
Oral Abstract Presentations		
09:00 - 11:00	Session 8: Other Studies in Vascular Anomalies I	N103-104
11:00 - 11:30	Coffee Break	Main Hallway
11:30 - 12:50	Session 9: Difficult Cases	N103-104
12:50 - 13:50	Lunch Break Poster Sessions Novartis Non-CME Lunch Symposium – see program for details	Main Hallway Main Hallway N106
13:50 - 15:40	Session 10: Other Studies in Vascular Anomalies II	N103-104
Closing Ceremony & Farewell Reception		
15:40 - 16:00	Closing Ceremony	N103-104
16:00 - 17:00	Farewell Reception	Main Hallway

Primer Day Sessions

All session and presentation times are in **local time**. Presenters are subject to change.

Tuesday, 7 May (Pre-Congress Day)

Primer Part I: Introduction to Vascular Anomalies - Classification; Vascular Tumors

9:30 **Welcome** | *Francine Blei (United States)*
9:40 **The ISSVA Classification** | *Emir Haxhija (Austria)*
10:00 **Infantile Hemangioma: Diagnosis and Associations** | *Eulalia Baselga (Spain)*
10:20 **Infantile Hemangioma: Management** | *Carine van der Vleuten (Netherlands)*
10:40 **Liver Hemangioma & Other Tumors** | *Steven Fishman (United States)*
11:00 **KHE** | Alexandria Borst (United States)

Primer Part II: Introduction to Vascular Anomalies - Vascular Malformations
Moderators: Gresham Richter (Unites States), Anita Gupta (United States)

11:45 **Vascular Malformations -Multidisciplinary Approach/Networks** | Miikka Vikkula (Belgium)
12:05 **Genetics of Vascular Malformations** | Sarah Sheppard (United States)
12:25 **Pathology of Vascular Malformations** | Isabel Colmenero (Spain)
12:45 **Imaging in Vascular Malformations** | Annouk Bisdorff-Bresson (France)
13:05 **Vascular Malformations - IR Options** | Gilles Soulez (Canada)
13:25 **Vascular Malformations - Surgical Options** | Dov Goldenberg (Brazil)
13:45 **Vascular Malformations - Medication Options** | Adrienne Hammil (United States)

Primer Part III: State of the Art in Pathology, IR and Surgical Management of Vascular Anomalies
Moderators: Juan Carlos Lopez-Gutierrez (Spain), Eulalia Baselga (Spain)

15:05 – **Arteriovenous Malformations - Molecular Mechanisms, two hit drivers and beyond I**| Henar Cuervo Grajal (Spain)
15:20 – **Arteriovenous Malformations - Molecular Mechanisms, two hit drivers and beyond II** | Lara Rodriguez Laguna (Spain)
15:35 – **Percutaneous management of Head and Neck Arteriovenous Malformations** | Alfredo Casasco (Spain)
15:50 – **Current Multidisciplinary Surgical Management of Complex Arteriovenous Malformations of the Head and Neck** | Teresa González-Otero (Spain)
16:05 – **Congenital Hemangiomas. Are they tumors?** | Isabel Colmenero (Spain)
16:20 – **Congenital Hemangiomas. Are they Fetal Vascular Disorders?** | Paloma Triana-Junco (Spain)

Primer Part IV: Difficult Case Panel Discussion
Moderators: Leo Schultze-Kool (Netherlands), Denise Adams (United States)

17:00 – 18:30 **Difficult Case Panel Discussion**
Panel 1 – Francine Blei (United States), Josee Dubois (Canada), James Bennett (United States), Beth Drolet (United States), Adrienne Hammill (United States)

- It's the tip of an iceberg - a unique presentation of arteriovenous malformations in a young girl | Luke Toh (Singapore)

- Venous Insufficiency and Stasis as a presenting symptom for a patient with inherited and somatic variant EPHB4 Mutations | Frederic Bertino (United States)

Panel 2 – Miikka Vikkula (Belgium), Michel Wassef (France), Par Gerwins (Sweden), Annouk Bisdorff-Bresson (France), Friedrich Kapp (Germany), Willemijn Klein (Netherlands)

- Isolated Kaposiform Lymphangioma: Fact or Fiction? | Sonja Chen (United States)
- Difficult Case of a Vascular Anomaly with Progressive Arteriopathy | Kelly Blache (United States)

Congress Program

All session and presentation times are in the **local time**. Presenting author is underlined; presenters are subject to change. See below for full abstracts.

Wednesday, 8 May

Session 1: Vascular Tumors

Moderators: Alyaa Al-Ibraheemi (United States), Thuy Phung (United States)

9:30 **Welcome** | *Francine Blei (United States)*

9:45 **Differences in the clinical characteristics of Infantile Hemangiomas in preterm and term infants: Prematurity confers greater risk of permanent cutaneous sequelae.** | *Flora Bradley (United States), Esteban Fernandez Faith, Sonal D. Shah, Mitchell Braun, Elena Pope, Irene Lara-Corrales, Patricia M. Witman, Katya Harfmann, Amy Buros Stein and Ilona Frieden*

9:55 **Multifocal congenital hemangiomas: expanding our understanding of "neonatal hemangiomatosis"-case series** | *Daniela Peeva (United Kingdom), Gabriela Petrof and Lea Solman*

10:05 **Clinical features of rapid involuting congenital hemangioma: a prospective study** | *Yi Ji (China)*

10:15 **DeepIH: A Near-patient Diagnostic System for Infantile Hemangiomas** | *Yajing Qiu (China), Mengjie Xu, Zihao Zhao, Lanzhuju Mei, Sheng Wang, Qian Wang, Dinggang Shen and Lin Xiaoxi*

10:25 **Remote treatment of infantile hemangiomas of high and highest risk with topical beta-blockers** | *Olga Bogomolets (Ukraine)*

10:35 **Subglottic Hemangioma Practice Patterns** | *Megan Gaffey (United States), Sukaina Hasnie and Francine Blei*

10:45 **A study of the complex genetic mechanisms associated with PHACE syndrome. |** *Dawn Siegel (United States), Elizabeth S. Partan, Nirmal Vadgama, Francine Blei, Sarah Chamlin, Beth Drolet, Gifford Casey, Hanmin Guo, Ilona Frieden, Ioannis Karakikes, Anthony Mancini, Denise Metry, Anthony Oro, Alexander E. Urban, Kevin C. Wang and Nara Sobreira*

10:55 **Disparities in management of Infantile Hemangioma: Impact of social determinants of health in a large population over a 10-year period** | *Nicole Reynoso (United States), Ana Marija Sola, Ilona Frieden, Nicole Kittler, Erin Mathes, Kristina Rosbe and Josephine Czechowicz*

11:05 **Pediatric hepatic hemangiomas: lessons learnt** | *Sarah Cherian (Canada), Josee Dubois, Niina Kleiber, Julie Powell and Martha Dirks*

11:15 **Prospective study to assess the utility and validity of a chromameter in the assessment of infantile hemangiomas.** | *Luis Sánchez Espino (Canada), Alexandra Pennal and Elena Pope*

Session 2: Vascular Tumors

Moderators: Denise Adams (United States), Maria Garzon (United States)

12:00 **Single-cell transcriptional profiling identifies a LAMA4 as a potential target gene in Kaposiform hemangioendothelioma** | *Zuopeng Wang (China) and Kai Li*

12:10 **PQ interval prolongation and first-degree AV block in children with infantile hemangiomas treated with propranolol** | *Lidia Babiak-Choroszczak, Joanna Strzemecka, Wieslawa Wieczorek and Kaja Krystyna Gizewska-Kacprzak (Poland)*

12:20 **Treatment Experience for Different Risk Groups of Kaposiform Haemangioendothelioma** | *Miao Miao Li (China)*

12:30 **Different doses of sirolimus for kaposiform hemangioendothelioma: a randomized clinical trial** | *Jiangyuan Zhou (China) and Yi Ji*

12:40 **Neurointerventional treatment of life-threatening vascular tumors in newborns** | *Huy Do (United States), Mai-Thy Truong, Karthik Balakrishnan, Ann Marqueling, Arjun Pendharkar, Andrew Gauden and Joyce Teng*

12:50 **Novel Genomic Structural Variations in Angiosarcoma** | *Thuy Phung (United States)*

Keynote Address

13:00 "A 30+ year Journey thru the Landscape of Vascular Anomalies: Reflections on our Origins and Lessons Learned" | *Ilona Frieden (United States)*

Session 3: Venous Malformations

Moderators: Sheena Pimpalwar (United States), Annouk Bisdorff-Bresson (France)

15:00 **Endothelial cell-derived extracellular vesicles contribute to abnormal perivascular cell coverage by transferring miR-4432 in venous malformations** | *Gao-Hong Chen (China), Jian-Gang Ren and Gang Chen*

15:10 **Aggressive phenotype of blue rubber bleb naevus syndrome caused by mosaic TEK fusion** | *Roli Adollo (United Kingdom), Alicia Lopez Bruzos, Aimie Sauvadet, Davide Zecchin, Ignacio Del Valle Torres, Amir Sadri, Claire O'Neill, Lea Solman, Mary Glover, Veronica A. Kinsler and Satyamaanasa Polubothu*

15:20 **The four clinical manifestations of verrucous venous malformation** | *Shih-Jen Chang (China), Yajing Qiu, Rui Chang, Lizhen Wang and Lin Xiaoxi*

15:30 **FIXED DOSING OF ALPELISIB IN CHILDREN: WHEN WILL THE MAGIC FADE?** | *Albert Etingin (Canada), Amandine Remy, Thomas Sonea, Francis Fortin, Josee Dubois, Sandrine Essouri, sandra ondrejchak, Chantal Lapointe, Yves Théôret, Audrey Denoncourt, Facundo Garcia-Bournissen, Jérôme Coulombe, Julie Powell, Thai Tran and Niina Kleiber*

15:40 **First In-human Clinical Experience with Direct Stick Embolization of Low-flow Vascular Malformations with an mTOR Inhibitor** | *Valentina Restrepo (United States), Wilma Flores, Stephanie Prozora, Alfred I. Lee, Prashant Patel and Naiem Nassiri*

15:50 **Outcome of Bleomycin Electrosclerotherapy of Slow-Flow Malformations in Adults and Children** | *Moritz Wildgruber (Germany), Vanessa F. Schmidt, Özlem Cangir, Lutz Meyer, Constantin Goldann and Walter A. Wohlgemuth*

16:00 **Ablation of Venous Malformations by Photothermal Therapy with Intravenous Gold Nanoshells** | *Kathleen Cullion (United States), Claire Ostertag-Hill, Michelle Pan, Brian Timko, Elisa Boscolo and Daniel S. Kohane*

16:10 **Total Hip Arthroplasty in Extensive Venous Malformations with Intravascular coagulation disorder (= IVCD): An Experience of Four Cases** | *Claude Laurian (France), Emma Vuilletet, Pomme Jouffroy and Annouk Bisdorff Bresson*

16:20 **TOTAL KNEE ARTHROPLASTY IN EXTENSIVE VENOUS MALFORMATIONS: A Single CENTER EXPERIENCE OF 10 CASES** | *Claude Laurian (France), Emma Vuilletet, Pomme Jouffroy and Annouk Bisdorff Bresson*

16:30 **Two Cases of Sarcomas Misdiagnosed as Venous Malformations** | *Christopher Ingraham (United States), Eric J. Monroe, Sandeep Vaidya, Mark Meissner and Rush Chewning*

Thursday, 9 May

Session 4: Arteriovenous Malformations
Moderators: Gulraiz Chaudry (United States), Miikka Vikkula (Belgium)

9:00 **Oncogene targeted next-generation-sequencing in extracranial arteriovenous malformations** | *Sarah Bernhard (Switzerland), Aleksandra Tuleja, Yvonne Döring, Erik Vassella, Ursula Amstutz, Christiane Zweier, Jochen Rössler, Laurence M. Boon, Miikka Vikkula, Fabian Haupt, Györgyi Hamvas, Rafael Kammer and Iris Baumgartner*

9:10 **Trametinib prevents formation of vascular lesions in a MAP2K1 p.K57N arteriovenous malformation mouse model** | *Patrick Smits (United States), Yu Sheng Cheng, Michal Ad, Matthew Vivero and Arin Greene*

9:20 **Somatic RIT1 indels identified in arteriovenous malformations hyperactivate RAS-MAPK signaling and are amenable to MEK inhibition** | *Friedrich G Kapp (Germany), Farhad Bazgir, Nagi Mahammadzade, Erik Vasella, Yvonne Döring, Annegret Holm, Caroline Seebauer, Axel Karow, Natascha Platz Batista da Silva, Walter A. Wohlgemuth, Pia Kröning, Charlotte M. Niemeyer, Denny Schanze, Martin Zenker, Whitney Eng, Mohammad R. Ahmadian, Iris Baumgartner and Jochen Rössler*

9:30 **Clinical Response to MEK Inhibitors in Arteriovenous Malformations** | *Whitney Eng (United States), Meghan O'Hare, Caroline Johnston and Melisa Ruiz-Gutierrez*

9:40 **Monocentric Pilot Trial on the use of Trametinib in refractory to standard care Arterio-Venous Malformations: follow-up after cessation of therapy.** | *Julien Coulie, Emmanuel Seront (Belgium), Valérie Dekeuleneer, Frank Hammer, Annouk Bisdorff Bresson, Miikka Vikkula and Laurence M. Boon*

9:50 **Extracranial Vascular Anomalies Driven by RAS/MAPK Variants - Spectrum and Genotype-Phenotype Correlations** | *Vanessa Schmidt (Germany), Friedrich G Kapp, Veronika Vielsmeier, Caroline Seebauer, Armin-Johannes Michel, Max Seidensticker, Wibke Uller, Beate Häberle, Denny Schanze, Jens Ricke, Melanie A. Kimm, Walter A. Wohlgemuth, Martin Zenker and Moritz Wildgruber*

10:00 **The VASCERN-VASCA Working Group Diagnostic and Management Pathways for Arteriovenous Malformations** | *Julien Coulie (Belgium), Rune Andersen, Maria Barea, Eulalia Baselga, Miguel Bajarano, Sigurd Berger, Annouk Bisdorff Bresson, olivia boccara, Petra Borgards, Maria Bon Sucesso, Laurence M. Boon, Andrea Diociaiuti, Veronika Dvorakova, May El Hachem, Sofia Frisk, Nader Ghaffarpour, Paolo Gasparella, Emir Haxhija, Annegret Holm, Thomas Hjuler, Alan D. Irvine, Mikkel Kaltoft, Friedrich G. Kapp, Kristiina Kyrklund, Antonio Miguel Madureira, Darius Palionis, Päivi Salminen, Birute Vaisnyte, Carine van der Vleuten, Leo Schultze Kool and Miikka Vikkula*

10:10 **Thalidomide as (neo-)adjuvant treatment to reduce postoperative recurrence of extracranial arteriovenous malformations.** | *Julien Coulie (Belgium), Valérie Dekeuleneer, Emmanuel Seront, An-Katrien De Roo, Dana Dumitriu, Frank Hammer, Liliane Marot, Nicole Revencu, Pascal Brouillard, Miikka Vikkula, and Laurence M. Boon*

10:20 **Differential diagnosis of arteriovenous malformation and capillary malformation-arteriovenous malformation syndrome using two-dimensional and three-dimensional ultrasound** | *Xia Gong (China), Ping Xiong and Jia Li*

10:30 **The Sandwich Neoadjuvant+Adjuvant use of Bleomycin and Surgery for Limited S3 AVMs of the head and neck** | *Giacomo Colletti (Italy), Linda Rozell-Shannon, Sara Negrello, Giangiacomo Sanna, Gregory Levitin and Luigi Chiarini*

10:40 **Research and Development of Novel Image-guided Ethanol Injection: Pre-clinical Investigations, and Clinical Application in Vascular Malformation.** | *Yuchen Shen (China), Lixin Su, Deming Wang and Xindong Fan*

10:50 **Ethanol Embolotherapy Management of Pelvic Arteriovenous Malformations (AVM)** | *Wayne Yakes (Unites States)*

Session 5: Lymphatic Malformations

Moderators: Eulalia Baselga (Spain), Renata Maricevich (United States)

11:30 **Assessing pharmacological inhibition and defining pathogenesis in KRAS-driven zebrafish lymphatic malformation models** | *Scott Paulissen (United States), Dhyanam Shukla, Benjamin Sempowski, Gennady Margolis, Ryan Dale and Sarah Sheppard*

11:40 **A high throughput zebrafish chemical screen identifies Pan-AKT and tyrosine kinase as novel candidate treatment for Kaposiform Lymphangiomatosis (KLA)** | *Ivan Bassi (Israel), Amani Jabali, Shany Egozi, Naama Farag, Noga Moshe, Gil S. Leichner, Jonathan Long, Lotan Levin, Karina Yaniv and Shoshana Greenberger*

11:50 **Hyperactive KRAS/MAPK signaling disrupts normal lymphatic vessel architecture and function** | *Michael Dellinger (United States)*

12:00 **Precision Engineering of Patient-Specific Lymphatic Malformation Models Reveals Alpelisib Responsiveness and Unveils Non-Hot Mutations in the PI3K/Akt/mTOR Pathway** | *Yarelis Gonzalez-Vargas (United States), Greta Hiehle, Katie Skinner, Jennifer Spangle, Andrew Hong, Matt Hawkins and J. Brandon Dixon*

12:10 **The Antenatal and Perinatal Management of Fetuses with Extensive Lymphatic Malformations**| *Paolo Campisi (Canada), Yada Kunpalin, Tim Van Mieghem, Joao Amaral, Dilkash Kajal, Greg Ryan and Manuel Carcao*

12:20 **Predicting postnatal outcomes and therapeutic needs by combining pre- and post-natal imaging characteristics and clinical data in patients with neck lymphatic malformations versus cystic tumors** | *Monica Matsumoto (United States), Anne Marie Cahill, Deborah M. Zarnow, Seth Vatsky, Abhay Srinivasan, Denise Adams and Tamara Feygin*

12:30 **An audit of the treatment costs of pediatric lymphatic malformations – a tertiary center experience** | *Hanna Hyvönen (Finland), Hannele Salonen, Johanna Aronniemi, Päivi Salminen and Kristiina Kyrklund*

12:40 **Comparisons of Clinical Features Between Pediatric and Adult Patients with Surgically-resected Abdominal Lymphatic Malformations** | *Min Yang (China), Cong-xia Yang and Yi Ji*

12:50 **Kaposiform Lymphangiomatosis (KLA): Update on clinical features, treatment approach, and use of targeted medical therapy** | *Whitney Eng (United States), Alexindra Wheeler, Melisa Ruiz-Gutierrez, Harry Kozakewich, Kiersten Ricci, Adrienne Hammill and Denise Adams*

Session 6: Combined Malformations

Moderators: Ionela Iacobas (United States), Shoshana Greenberger (Israel)

14:30 **Genomic Characterization of Patients with Vascular Anomalies and Neurocutaneous Disorders Using Paired Exome Analysis and RNA Sequencing** |*Ying-Chen Claire Hou (United States), Bhuvana Setty, Anna Lillis, Ibrahim Khansa, Gregory D. Pearson, Esteban Fernandez Faith, Archana Shenoy, Sonja Chen, Brandon Stone, Erica Macke, Mari Mori, Gregory Wheeler, Heather Costello, Benjamin Kelly, Mariam Mathew, Kathleen M. Schieffer, Elizabeth Varga, Elaine R. Mardis and Catherine E. Cottrell*

14:40 **Utility of cfDNA in comprehensive genomic profiling of complex vascular anomalies** | *Dong Li (United States), Sarah Sheppard, Michael March, Mark Battig, Lea Surrey, Abhay Srinivasan, Alexandra Borst, Fengxiang Wang, Tamjeed Sikder, Nora O'Connor, Alexandria Thomas, Erin Pinto, Allison Britt, Joseph Napoli, David Low, Seth Vatsky, James Treat, Janet R. Reid, Christopher Smith, Kristen Snyder, Anne Marie Cahill, Yoav Dori, Denise Adams and Hakon Hakonarson*

14:50 **MEK inhibition restores dysregulated genes in human endothelial cells expressing the NRAS Q61R mutation identified in kaposiform lymphangiomatosis** | *Sara Alharbi (United States), Patricia Pastura, C. Griffin McDaniel, Dermot Fox, Andrew Wagner, Yan Xu, Punam Malik, Denise Adams and Timothy D. Le Cras*

15:00 **Clinical phenotype of the PIK3R1-related vascular overgrowth syndrome** | *Paul Kuentz (France), Camille Engel, Fanny Morice-Picard, Didier Bessis, Hélène Aubert, Bertrand Isidor, Alice Phan, Olivia Boccara, Annabel Maruani, Juliette Mazereeuw, Hagen Ott, Anne-Marie Guerrot, Eve Puzenat, Jehanne Martel, Laurence Faivre and Pierre Vabres*

15:10 **New promising ways for sirolimus treatment: from continuous to intermittent administration of sirolimus in slow-flow vascular malformations** | *Emmanuel Seront (Belgium), An Van Damme, Julien Coulie, Miikka Vikkula and Laurence M. Boon*

15:20 **Sirolimus for Vascular Anomalies Associated with PTEN Hamartoma Tumor Syndrome** | *Alexandra Zabeida (Canada), Kelley Zwicker, Michelle Fantauzzi, Laura Willis, Jack Brzezinski, Cheryl Cytrynbaum, Jonathan Wasserman, Rosanna Weksberg, Kevin Zbuk and Manuel Carcao*

15:30 **Adverse events during alpelisib and sirolimus treatment in PROS patients. A comparative study** | *Paloma Triana Junco (Spain) and Juan Carlos Lopez Gutierrez*

15:40 **Accelerated Repurposing of Sotorasib for Vascular Malformations Associated with KRAS G12C Mutation**| *Guillaume Canaud (France)*

15:50 **Percutaneous Sclerotherapy of Lymphatic and Venous Malformations with Osseous Involvement** | *Alan Kim (United States), Mohammad Mirza-Aghazadeh-Attari, Arun Kamireddy and Clifford R. Weiss*

16:00 **Clinical features and advances in treatment of Gorham-Stout disease: a systematic review** | *Zilong Zhou(China) and Yi Ji*

16:10 **Oncologic outcomes for patients with Ollier disease and Maffucci syndrome** | *Whitney Eng (United States)*

16:20 **Analysis of related factors of functional impairment caused by fibro-adipose vascular anomaly (FAVA)** | *Bin Sun (China), Changxian Dong and Hongzhao Lei*

Session 7: Capillary Malformations

Moderators: Ane Dompmartin (France), Marta Ivars (Spain)

17:00 **Generation of a mouse model for Capillary Malformation** | *Patrick Smits (United States), Yu Sheng Cheng, Matthew Vivero, Leanna Marrs, Michal Ad, Christopher Sudduth, Joyce Bischoff and Arin Greene*

17:10 **Endothelial permeability in mosaic GNAQ p.R183Q driven capillary malformations** | *Sana Nasim, Colette Bichsel, Mariam Baig, Jill Wylie-Sears, Matthew Vivero, Patrick J. Smits, Sanda Alexandrescu, Anna Pinto, Arin K. Greene and Joyce Bischoff (United States)*

17:20 **Development of an AlphaLISA high-throughput technique to screen for targeted pharmacotherapy for capillary malformation** | *Matthew Vivero (United States), Leanna Marrs, Sana Nasim, Michal Ad, Patrick Smits, Joyce Bischoff, Matthew Warman and Arin Greene*

17:30 **Somatic mutations GNAQ183 do not only cause Port Wine Stain/Capillary malformation: Troncular venous abnormalities in a series of patients.** | *Eulalia Baselga (Spain), Luisa Fernanda Montenegro, Elena Marin-Manzano, Marta Ivars, Carine Van der Vleuten, Olivia Boccara, Laurence Boon, Valerie Dekeuleneer, Ana Martin _Santiago, Marie-Antoinette Sevestre, MArtin Theiler, Lisa Weibel, Sonia Paco, Cinzia Lavarino, Daniel Antonio Brualla, Carolina Prat, Aasuncion Vicente-Villa, M Angeles Muñoz-Miguelsanz, Miikka Vikkula and Juan Carlos Lopez-Gutierrez*

17:40 **Application of Artificial Intelligence in Quantitative Evaluation of Facial Port-Wine Stains** | *Lan Luo (China), Wenjun Fu, Shanfeng Zhu and Lin Xiaoxi*

17:50 **Comparison of pulsed dye Laser Medicine and photodynamic therapy in the treatment of port-wine stain: a retrospective paired control study** | *Gang Ma (China), Yuyan Zhang, Lan Luo, Yue Han, Hanru Ying, Wenxin Yu, Jiafang Zhu, Lixin Zhang and Lin Xiaoxi*

18:00 **Staged Surgical Correction for Patients with Facial Port-Wine Stains** | *Hanru Ying (China), Lei Chang, Yun Zou, Zhixu Liu, Yajing Qiu, Gang Ma, Hui Chen and Lin Xiaoxi*

18:10 **Macrocephaly Associated with Sturge-Weber Syndrome: Presentation of Two Cases** | *Marta Ivars (Ivars), Ana Martin-Santiago, Aniza Giacaman, Carmen Fons, Jordi Muchart, Cinzia Lavarino, Sonia Paco, Sandra D. Castillo, Mariona Graupera, Carlota Rovira and Eulalia Baselga*

Friday, 10 May

Session 8: Other Studies in Vascular Anomalies I

Moderators: Dov Goldenberg (Brazil), June Wu (United States)

9:00 **Double non allelic somatic activating oncogene variants in a series of vascular anomalies.** | *Pierre Vabres (France), Thomas Hubiche, Stéphanie Mallet, Annabel Maruani, Bertille Bonniaud, Jehanne Martel, Laurence Faivre and Paul Kuentz*

9:10 **Assessment of gene–disease associations and recommendations for genetic testing for somatic variants in vascular anomalies by VASCERN-VASCA** | *Nicole Revencu (Belgium), Astrid Eijkelenboom, Claire Bracquemart, Pia Alhopuro, Judith Armstrong, Eulalia Baselga, Claudia Cesario, Marialisa Dentici, Melanie Eyries, Sofia Frisk, Helena Gásdal Karstensen, Nagore Gene-Olaciregui, Sirpa Kivirikko, Cinzia Lavarino, Inger-Lise Mero, Rodolphe Michiels, Elisa Pisaneschi, Bitten Schönewolf-Greulich, Ilse Wieland, Martin Zenker and Miikka Vikkula*

9:20 **The Mini-Multidisciplinary Vascular Anomalies Team Clinic: Steps to Improve Patient Access and Volumes** | *Gresham Richter (United States), Amber Smith and Joana Mack*

9:30 **A Precision Medicine Approach for Vascular Anomalies: Clinical Impact of Molecular Testing in 315 Patients Treated at a Single Center** | *Whitney Eng (United States), Melisa Ruiz-Gutierrez, Samantha Spencer, Harry Kozakewich, Alyaa Al-Ibraheemi, Marilyn Liang, Amir Taghinia, Arin Greene, Ahmad Alomari, Raja Shaikh, Steven J. Fishman, John Mulliken, Denise Adams and Alanna Church*

9:40 **Improvement of histopathological diagnostics of vascular anomalies through spatial deep-phenotyping using non-destructive 3D histopathology** | *Rene Haegerling (United States)*

9:50 **Bridging Cells and Cures: From Mechanisms to Dual Approach to Target Endothelial and Intervascular Stromal Cells for Vascular Anomaly Treatment** | *Johanna Laakkonen (Finland)*

10:00 **Evaluation of content and readability of ChatGPT-generated Educational Materials for Vascular Anomalies** | *Christine Wong (United States), Ilona Frieden, Erin Mathes and Josephine Czechowicz*

10:10 **Case Series of Prenatal Administration of Sirolimus (Tolerance and Efficacy)** | *Ionela Iacobas (United States), Tara Rosenberg, Roopali Donepudi, Sharada H. Gowda, Ahmed Nassr, Alireza Shamshirsaz and Magdalena Sanz Cortes*

10:20 **How to increase the safety of surgical excision of facial vascular malformations. The role of adjuvant intraoperative technologies in avoiding complications.** | *Rebecca Rossener (Brazil), Dov Goldenberg, Marilia Ito and Rolf Gemperli*

10:30 **Why do adults present with new-onset Vascular Malformations? Retrospective cohort study from a Multidisciplinary Vascular Anomalies Center** | *Ayushi Gautam (United States), Josephine Czechowicz, Erin Mathes, Mark Mamlouk, Arman Shoyatev and Ilona Frieden*

10:40 **A Decade of Bleomycin** | *Joseph Miller (United States), Shimwoo Lee, Erin Delfosse, Mary Timbang, Gabriel Gomez, Minnelly Luu, Meagan Hughes, Jessica Lee, Sara Kreimer and Dean Anselmo*

10:50 **Scientific Committee Talk** | *Dov Goldenberg (Brazil)*

Session 9: Difficult Cases

Moderators: Tony Penington (Australia), Paulo Gasparella (Austria)

11:30 **Lightening striking twice: patients with two distinct vascular malformations** | *Maya Muldowney (United States), Beth Drolet, Catharine Garland, Jason Pinchot, Sarah Mc Dermott, Todd Le, Donglin Zhang, and Lisa Arkin*

11:40 **GNA11+ Frontal Segmental Vascular Anomaly Associated With Intracerebral Vascular Malformation: A Challenging Case** | *Daniela Kramer (Chile), Antonella Muñoz, Maria Cossio, Camila Downey, Paulo Zuñiga, Lizbet Perez, Laura Moneguini and Giacomo Colletti*

11:50 **Unusual Presentation of Coronary Artery Fistula in Capillary Malformation-Arteriovenous Malformation 2 Syndrome** | *Tyson Echols (United States), Seth E. Vatsky, Jonathan J. Rome, Bryan A. Pukenas, Allison Britt, Jennifer Colt and Alexandra J. Borst*

12:00 **Difficult Case Presentation: Dual therapy with beta blockers and sirolimus in an infant with diffuse hemangiomatosis** | *Elizabeth Cappello (United States), Neeraja Swaminathan, Meghan Beatson, Jami Miller, Alan Boyd and Elizabeth Snyder*

12:10 **GPR161 Unmasked: Expanding the Gene-Phenotype Relationship of an Emerging Tumor Suppressor** | *Catherine Cottrell (United States), Ying Chen Claire Hou, Vinay Prasad, Anna Lillis, Ibrahim Khansa, Thomas Scharschmidt, Kim Bjorklund and Elizabeth Varga*

12:20 **Initial experience with bleomycin electro-embolotherapy (BEET) for the treatment of extracranial arterio-venous malformations** | *Oleksandr Bidakov (Germany)*

12:30 **Lymphangiographic Features of Lymphedema -Distichiasis Syndrome (FOXC2 Mutation) in a Stillborn Fetus** | *Ahmad Alomari (United States) and Harry P.W Kozakewich*

12:40 **Large Pediatric NTRK-rearranged Neoplasm Mimicking a Vascular Malformation** | *Mohammad Sadic (United States), Alexander Hien Vu, Erol Bayraktar, Naomi Strubel, Sheel Sharma, Francine Blei, George Jour and Sandra Tomita*

Session 10: Other Studies in Vascular Anomalies II

Moderators: Victor Martinez-Gonzalez (Spain), Israel Fernandez-Pineda (Ireland)

13:50 **The clinical implications of readily available genetic testing in a vascular anomalies service |** *Maria Shilova, Sinead O'Sullivan, Chris Richmond, Roy Kimble and Romi Das Gupta (Australia)*

14:00 **A Highly Sensitive Genetic Panel to Evaluate Patients with Mosaic Vascular Anomalies** | *Sara Kreimer (United States), Erin Delfosse, Juyon Yi, Dean Anselmo, Jessica Lee, Minelly Luu, Meagan Hughes, Joseph Miller, Vandana Mehta, Jenny Ji, Ryan Schmidt, Miao Sun, Cindy Fong, Dejerianne Ostrow, Jaclyn Biegel, Avinash Dharmadhikari and Matthew Deardorff*

14:10 **Somatic PIK3CA variants are associated with eccrine angiomatous hamartomas** | *Roy M. Kimble, Romi Das Gupta (Australia), Chris M. Richmond, Diane Payton and Yun Phua*

14:20 **Patient Reported Outcome Measurement Information System (PROMIS) Measures in Action: Development of a visualization tool in Epic** | *Lauren Hill (United States), Taizo Nakano, Aparna Annam, Michelle Klos and Ann Kulungowski*

14:30 **Clinical Use and Adverse Effects of Bortezomib in Pediatric Patients: A Systematic Review and Meta-Analysis** | *Averill Clapp, Zachary LeBlanc, Samantha Kaplan, Carrie J. Shawber and June Wu (United States)*

14:40 **Evaluating the Impact of Sirolimus Treatment on Quality of Life in Individuals with Vascular Anomalies: A Comparative Analysis Before and After Intervention** | *Nicolas Affranchino (Argentina), Silvia Caino, Nicolas Sticco, Torres Natalia, Mariana Roizen, Sergio Sierre and Dario Teplisky*

14:50 **Sirolimus: friend or enemy of surgeons dealing with vascular anomalies?** | *Noureddine Hassayoune (Belgium), Julien Coulie, Christina Flucher, Paolo Gasparella, Birute Vaisnyte, Darius Palionis, Isabelle Quere, Pierre-Louis Docquier, Audrey Lentini, Maite Van Cauter, Sandra Schmitz, Emir Haxhija, An Van Damme, Emmanuel Seront and Laurence M. Boon*

15:00 **Fetal Magnetic Resonance Imaging of Vascular Anomalies** | *Riikka Schultz (Finland)*

15:10 **Vascular malformations in the abdominal cavity of children** | *Uwe Huebner (Germany)*

15:20 **Complete unilateral pulmonary embolisation and antiangiogenic treatment in a child with diffuse pulmonary vascular malformations and severe hypoxaemia** | *Marcelo Serra (Argentina), Magali Squitin Tasende, Juan Pedro Alvarez and Oscar Peralta*

15:30 **Facial Asymmetry Related to Vascular Malformations: Insights from Characteristics, Surgical Management, and Outcomes (2012-2022)** | *Bin Sun (China), Hongrui Chen, Wei Gao, Chen Hua and Lin Xiaoxi*

Oral Abstracts

Session 1: Vascular Tumors

Differences in the clinical characteristics of Infantile Hemangiomas in preterm and term infants: Prematurity confers greater risk of permanent cutaneous sequelae.

Flora E. Bradley (Department of Dermatology, University of California, San Francisco School of Medicine, San Francisco, California); Esteban Fernandez Faith (Nationwide Children's Hospital and Ohio State University); Sonal D. Shah (Department of Dermatology, University Hospitals Cleveland Medical Center, Case Western Reserve University School of Medicine, Cleveland, Ohio); Mitchell Braun (University of California San Francisco); Elena Pope (The Hospital for Sick Children and University of Toronto, Toronto, Canada); Irene Lara-Corrales (Division of Pediatric Dermatology, The Hospital for Sick Children and University of Toronto, Toronto, Canada); Patricia M. Witman (Division of Dermatology, Department of Pediatrics, Nationwide Children's Hospital and The Ohio State University College of Medicine, Columbus, Ohio); Katya Harfmann (Division of Dermatology, Department of Pediatrics, Nationwide Children's Hospital and The Ohio State University College of Medicine, Columbus, Ohio); Amy Buros Stein (Pediatric Dermatology Research Alliance); Ilona Frieden (UC San Francisco)

Purpose: Preterm infants have a higher incidence of infantile hemangiomas (IH) as well as a risk of multiple IH. However, specific morphologic characteristics of IH in premature infants have not been well-characterized. We observed many preterm infants with unexpectedly thick IH, a subtype known to be associated with increased risk of scarring. Because of the potential clinical significance for management, we undertook a study to compare the clinical features of localized IH in preterm versus term infants, to confirm this observation with the goal of improving the care of this patient population.

Methods: A retrospective study at tertiary referral centers was conducted on 830 consecutive patients with a clinical diagnosis of localized IH and available clinical photographs. We compared the clinical features of hemangiomas in preterm (<33 weeks and 33-<37 weeks) versus term (37 weeks) infants.

Results: Preterm infants had a significantly higher incidence of superficial IH (75% in <33weeks, 57% in 33-<37 weeks, and 50% in term infants, p=0.007). Prematurity and degree of prematurity were also associated with a thicker superficial component (p<0.001). A stepped border was more frequent in premature infants: (79% in <33weeks, 54% in 33-<37 weeks, and 35% in term infants, p<0.001). These features correlated with the degree of prematurity. The average chronological age at presentation to the specialist was 5.6 (SD=6.2) months, with no difference between gestational age.

Conclusion: IH in premature infants are significantly thicker with stepped borders, specific morphologic characteristics that have previously been shown to have a greater risk of permanent skin textural changes. This has obvious implication for systemic therapies. Most of these infants were seen by pediatric dermatologists for evaluation and initiation of treatment beyond the typical proliferative phase when irreversible skin changes may have already occurred. Early specialty referral and evaluation are critical to determine if and when intervention is needed.

Multifocal congenital hemangiomas: expanding our understanding of "neonatal hemangiomatosis"- case series

Daniela Peeva (GOSH); Gabriela Petrof (GOSH); Lea Solman (GOSH)

Purpose: Congenital haemangiomas are rare, benign, vascular tumors, that are present and fully grown at birth. They are typically solitary, categorised by their postnatal behavior as rapidly involuting(RICH),

non-involuting(NICH), or partially involuting (PICH).They differ from infantile haemangiomas by the lack of immunostaining for GLUT-1. We present three infants with congenital, small, multifocal, non-progressive haemangiomas on the skin.

Methods: We present three cases with multiple congenital haemangiomas, which would previously be named neonatal haemangiomatosis.

Results: Our first patient was a male, born with 18 small vascular lesions. Abdominal ultrasound showed three vascular lesions in his liver and one in his left kidney, which were not visible on the repeated ultrasound in 3 months. MRI of the thorax showed a vascular lesion in the right hemithorax. He was completely asymptomatic, and the lung lesion was monitored annually with ultrasound. The second patient was a male, born with eight vascular lesions. He had an abdominal ultrasound, which was clear. He was also asymptomatic, and the lesions disappeared in the first year. The third patient was a female, born with 24 vascular lesions. Cranial ultrasound was clear; however, MRI head revealed nine punctate white matter lesions suggestive of vascular lesions. She had three small foci in the liver, consistent with haemangiomas, which were not detected after 6 weeks. All three patients had skin biopsy, which showed thin-walled dilated vessels in the dermis, negative for GLUT1 and D240. None of the patients had coagulopathy.

Conclusion: These three cases expand the diagnosis of congenital haemangioma to include a multifocal phenotype and demonstrate their possible association with visceral and intracranial lesions/abnormalities.

Clinical features of rapid involuting congenital hemangioma: a prospective study
Yi Ji (West China Hospital of Sichuan University)

Purpose: Rapid involuting congenital hemangiomas (RICHs) are rare benign tumors that occur in infancy. We conducted a prospective study to evaluate the clinical characteristics, complications, requirements for therapeutic intervention, and sequelae of patients with RICHs.

Methods: Eligible patients were ≤7 days old and had RICH. The primary endpoint was the time of complete involution of RICH.

Results: Eighty-six patients were included. The involution of RICH was nonlinear. All RICH patients had signs of involution within 4 weeks of age. The time of greatest involution was between 1.3 months and 2.3 months, with a mean complete involution occurring at 10.1 months. In total, 5.8% of patients experienced complications caused by or possibly related to RICH, and only 1.2% received some form of early treatment during the study period. Severe/significant sequelae were observed in 18.6% of subjects. The location of head-face-neck was the only risk factor that predicted severe/significant sequelae (odds ratio: 4.673; 95% confidence interval: 1.326-16.667; P=0.016).

Conclusion: RICH exhibits rapid regression within the first few months of life. Although clinical observation is recommended in patients with RICH, some lesions may leave severe/significant sequelae, especially those involving the head-face-neck area.

DeepIH: A Near-patient Diagnostic System for Infantile Hemangiomas
Yajing Qiu (Department of Plastic and Reconstructive Surgery, Shanghai Ninth People's Hospital, School of Medicine, Shanghai Jiaotong University); Mengjie Xu (ShanghaiTech University); Zihao Zhao (ShanghaiTech University); Lanzhuju Mei (ShanghaiTech University); Sheng Wang (ShanghaiTech

University); Qian Wang (ShanghaiTech University); Dinggang Shen (ShanghaiTech University); Lin Xiaoxi (Department of Plastic and Reconstructive Surgery, Shanghai Ninth People's Hospital, School of Medicine, Shanghai Jiaotong University)

Purpose: Infantile hemangiomas (IH) can pose potential complications, leading to functional impairment or permanent disfigurement if not properly diagnosed and treated. However, the traditional diagnostic methods for IH heavily rely on clinical expertise and expensive medical imaging equipment, presenting challenges for resource-limited hospitals. To address this issue, we propose DeepIH, a deep learning-based near-patient diagnostic system that enables patients to receive clinical advice using images captured on their smartphones.

Methods: The DeepIH system consists of two stages. In the first stage, a convolutional neural network (CNN)-based detector is trained to localize potential lesion regions within the images. Subsequently, in the second stage, the detected region, along with its surrounding pixels to ensure a comprehensive field of view, is fed into a ResNet50 model for feature extraction. These features are then utilized by a multi-layer perceptron (MLP) to provide treatment advice based on the features of the lesion areas. To enhance the reliability of the treatment advice, we incorporate the modeling of visual and clinical uncertainty via Gaussian distance mask and distribution estimation.

Results: Experiments were conducted on 5081 samples collected from Shanghai Ninth People's Hospital. The results demonstrated a detection performance of 94.2% Top-1 localization accuracy, with over 95% F1-score. For treatment advice prediction in the second stage, DeepIH achieved an 84.9% top-3 accuracy performance, surpassing all compared baseline methods. Ablation studies confirmed the effectiveness of uncertainty modeling, and qualitative results exhibited consistency with human experts.

Conclusion: DeepIH is a near-patient diagnostic system for infantile hemangiomas that utilizes smartphone-captured images and deep learning techniques. The system achieves high accuracy in lesion detection and provides reliable treatment advice based on features of the detected lesion areas. It has the potential to improve IH diagnosis in resource-limited settings and facilitate timely interventions for better patient outcomes.

Remote treatment of infantile hemangiomas of high and highest risk with topical beta-blockers

Olga V. Bogomolets (Ukrainian Medical Military Academy)

Purpose: Treatment of infantile hemangiomas (IH), which belong to the high and highest risk group according to the protocols is carried out with the help of systemic beta-blockers. Treatment requires - examination of the child, exclusion of contraindications, and hospitalization to monitor the child's heart/health condition. Implementation of these protocols became impossible after the beginning of the war in Ukraine. Due to shelling, hospitals stopped accepting children, parents did not have the possibility to evacuate children.

Methods: We were forced to start remote store-and-forward treatment and expand the indications for the treatment of IH of the high and highest risk group using topical beta-blockers. In 2022-23 we distantly diagnosed 434 children with IH: 156 - belonged to a low risk group, 98- medium, 89-high, 91-the highest. 37-were complicated with ulceration,1 with secondary infection. 415 - were prescribed topical beta-blockers. 19- were referred for urgent hospitalization. 38 - did not start or interrupt the treatment. A sterile solution of timolol maleate gel 0.25%, 0,5%, 1% was used. The concentration, method and frequency of application were chosen according to the child's age, size, location, growth rate of IH.

Results: Significant or complete regression was achieved in 99% patients, if therapy was started before the age of 3 month, in 92% - if started at 3-5 month, in 82% - if started at 6-10 month. The average duration of the treatment was 10.5 month. In 1 patient a systemic skin allergic reaction was noted, in 1 - mild bronchospasm, manifested in the form of coughing, in 12 - local skin irritation. In all other cases parents did not complain about systemic side effects.

Conclusion: Topical beta-blockers are an effective and safe method of remote treatment of IH of all risk groups, including high and highest risk. The timing of treatment initiation is critical to achieve complete tumor regression.

Subglottic Hemangioma Practice Patterns

Megan Gaffey (University of Arkansas for Medical Sciences, Department of Otolaryngology, Division of Pediatric Otolaryngology, Arkansas Children's Hospital); Sukaina Hasnie (NYU Langone); Francine Blei (NYU Langone/NYU Grossman School of Medicine)

Purpose: Subglottic hemangioma (SGH) is a common benign vascular anomaly of infancy, which left untreated can have devastating consequences from airway obstruction. Early diagnosis and proper intervention are necessary for prevention of growth of these vascular tumors. Diagnostic advancements such as awake flexible fiberoptic laryngoscopy, as well as collective experience in the post-Propranolol era, have broadened the approaches to the diagnosis and treatment of SGH. At our institution, there has been a paradigm shift in the conventional practice of this disease entity. While management was once strictly inpatient, it has become variably outpatient and inpatient, depending on patient presentation. Our internal shift impelled us to research the experience of vascular anomaly airway surgeons at other institutions. While practice algorithms for SGH do exist in the literature, they focus on inpatient management. In addition, none have been adopted uniformly.

Methods: A twelve-question survey querying practice patterns regarding the diagnosis and treatment of SGH was electronically distributed to pediatric airway surgeons whose professional focus includes the diagnosis and treatment of vascular anomalies.

Results: Our survey resulted in responses from thirteen pediatric airway surgeons with a particular interest in the treatment of vascular anomalies. We found no consensus in modalities for diagnosis, treatment, or postoperative and follow-up practices.

Conclusion: A broad spectrum of diagnostic, treatment, and follow-up methodology exists amongst pediatric airway surgeons who commonly treat SGH. We have found that our algorithm differs from those of our colleagues at other institutions. We propose to share our algorithm, but also suggest a future interinstitutional panel discussion to create an international consensus statement for the best evidence-based approach towards SGH. It is our belief that such a consensus statement would be streamlined, promote efficiency, emphasize minimal disruption to the patient and family's daily life, and decrease length of hospital stay.

A study of the complex genetic mechanisms associated with PHACE syndrome

Dawn Siegel (Stanford University School of Medicine); Elizabeth S. Partan (Johns Hopkins University); Nirmal Vadgama (Stanford University); Francine Blei (NYU Langone/NYU Grossman School of Medicine); Sarah Chamlin (Ann and Robert H. Lurie Children's Hospital of Chicago); Beth A. Drolet (University of Wisconsin); Gifford Casey (Stanford University); Hanmin Guo (Stanford University); Ilona Frieden (UC San Francisco); Ioannis Karakikes (Stanford University); Anthony Mancini (Lurie Chidren's Hospital,

Northwestern University); Denise Metry (Baylor College of Medicine); Anthony Oro (Stanford University); Alexander E. Urban (Stanford University); Kevin C. Wang (Stanford University); Nara Sobreira (Johns Hopkins University)

Purpose: Infantile hemangiomas can be associated with multiple congenital malformations in the rare syndrome, PHACE. Complex mechanisms are increasingly associated with congenital heart disease (CHD), including oligogenic inheritance in which the phenotype is created by the combinatorial effects of multiple genes. Many of the de novo variants (DNVs) identified in CHD include RAS/PI3K pathway genes(2). These same genes also underlie RASopathies and vascular anomalies.

Methods: We analyzed whole genome sequencing (WGS) in a PHACE cohort (n=72 trios) with multiple strategies. First, we analyzed VCF files using the PhenoDB tool and DECIPHER. Next, we used exomiser, a tool that incorporates clinical data in the form of Human Phenotype Ontology (HPO) terms and ranks candidate variants based on patient phenotype similarity to known disease-gene phenotypes. Statistical analysis of the probability of observing multiple damaging DNVs in an individual gene was performed using denovolyzeR, focusing on DNV loss-of-function and missense, and comparing them against expected DNV numbers in the general population, using a Poisson framework. Using a software called Gene Combinations in Oligogenic Disease (GCOD), we examined oligogenic variants in individuals with heart defects. We used CNVnator to call CNVs (deletions and duplications) and prioritized candidate disease associated CNVs based on allele frequency.

Results: For the CNV-affected genes, we performed Gene Ontology (GO) enrichment analysis and found multiple significant enrichments for these CNV-affected genes, including cell-cell adhesion via plasma membrane (adjusted P = 0.047). Among the significant genes we identified in the combined analysis above, we first prioritized THBS2 (P = 0.009) and RASA3 (P = 0.006). As proof-of-concept, we generated mouse models carrying putative causal DNV, Thbs2D859N and Rasa3V85M. We found that Thbs2D859N homozygous mice exhibit structural brain defects with mild reduction in the frontal cortex volume.

Conclusion: These results suggest that complex genetic mechanisms contribute to the spectrum of phenotypes in PHACE.

Disparities in management of Infantile Hemangioma: Impact of social determinants of health in a large population over a 10-year period

Nicole Reynoso (University of California - San Francisco); Ana Marija Sola (University of California, San Francisco); Ilona Frieden (UC San Francisco); Nicole Kittler (UCSF); Erin Mathes (UCSF); Kristina Rosbe (UCSF); Josephine Czechowicz (University of California San Francisco - Benioff Children's Hospital)

Purpose: Research across medicine has revealed that socioeconomic and demographic factors impact care. For Infantile Hemangioma (IH), timely access to care, and treatment with propranolol/timolol when indicated, can halt growth and result in better outcomes. We investigated the impact of social determinants of health on care of patients with IH.

Methods: Clinical informatics techniques were utilized to identify patients diagnosed with IH at age 2 years or younger at a single academic institution between June 2012-2022. Data were obtained on race/ethnicity, primary language, insurance payor, age at diagnosis and therapeutic interventions.

Results: 2,215 infants (64.7% female) were included. The mean/median ages of diagnosis were 5.8 and 3.6 months, respectively. The population was 49% White, 14% Asian, 3.2% Black, 21% Hispanic and 12% other. 37% were publicly-insured and 14% were non-English speakers. 15.3% of patients received

propranolol (mean/median age 5.43/3.37 months) and 29.5% received timolol (mean/median 5.89/2.77 months). Multivariate regression analysis revealed infants with public insurance were diagnosed 1.4 months later than commercially-insured infants (p<0.0001). Publicly-insured patients were also less likely to receive timolol (OR 0.39, p<0.0001), and treatment was initiated 2.2 months later (p=0.004). Patients in non-English speaking families were less likely to receive propranolol (OR 0.50, p=0.012). Treatment with propranolol was initiated 4.2 months later in Black infants compared to White (p=0.0016). Among Asian patients, age at diagnosis was younger by 1.0 months (p=0.014), while rates of medication use were also lower (propranolol OR 0.65, p=0.003 and timolol OR 0.36, p=0.016).

Conclusion: This study is the largest to date of social and structural determinants of health and access to evaluation and treatment for IH. Disparities in care were identified in non-English speaking, publicly-insured and Black patients. The mixed data in Asian patients suggests that sociocultural factors may also influence treatment decisions. Further study is needed to understand barriers and improve care equity.

Pediatric hepatic hemangiomas: lessons learnt

Sarah P. Cherian (Hospital Saint Justine); Josee Dubois (CHU Ste-Justine, Université de Montréal); Niina Kleiber (CHU Sainte-Justine, Université de Montréal); Julie Powell (CHU Sainte-Justine, U of Montreal); Martha Dirks (CHU Sainte-Justine, Universite de Montreal)

Purpose: Define imaging characteristics for radiological diagnosis of pediatric hepatic hemangiomas and determine if the ISSVA classification for cutaneous congenital hemangiomas can be adapted to hepatic lesions.

Methods: Retrospective review of suspected cases 1992-2019 with parameters from available imaging (US, CT and MRI) used to determine significant relationship that can predict pathology. US parameters: focality, echogenicity, vessel density, venous morphology, shunt, calcification. Regression timepoints 6, 12 and >12months. Review of biopsied lesions (non regressive, AFP elevation).

Results: 55 patients, 58% congenital 42% infantile. Congenital lesions diagnosed most commonly perinatally 52% and infantile 88% postnatal age group 0.0002. AFP elevation documented in 32 patients seen more commonly in infantile vs congenital. Statistically significant relationship between focality and pathology infantile multifocal congenital unifocal 0.0; however, cases of multifocal congenital and unifocal infantile exist. Significant sonographic appearance and echogenicity: Infantile hypoechoic homogeneous vs congenital heterogeneous (echogenicity p0.0 and appearance p0.0026). Hypervascularity seen in both groups, however venous vessels (ectasia/ lakes and visible vessels) seen in the RICH group (p0.0071). Congenital lesions with contrast imaging demonstrated peripheral enhancement (p0.0) with calcification (p0.0063). Indications for biopsy: elevated AFP, non regressive with RICH, NICH and PICH diagnosed and 6 case of hemangioendothelioma. No calcification seen in the infantile group (p0.00), calcification persisting post regression in 38% of congenital lesions. Restricted diffusion can be seen in infantile and congenital lesions on MRI.

Conclusion: All are hypervascular lesions with sonographic features of appearance and echogenicity infantile hypoechoic homongenous vs congenital heterogenous. If ectasia/ lakes and visible vessels think congenital. Calcification can persist post regression. Non regressive congenital lesions exist on RICH/ PICH/ NICH spectrum with hemangioendothelioma and hepatoblastoma as differentials. Peripheral enhancement with congenital lesions may help differentiate from hepatoblastoma. MRI can show restriction, limited role of primovist.

Prospective study to assess the utility and validity of a chromameter in the assessment of infantile hemangiomas

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Purpose: To date, there are no validated tools to objectively measure changes in infantile hemangiomas (IHs). Chromameter, designed to assess color differences and reflection is a potential objective tool to predict and monitor IH proliferation and involution.

Methods: A single-center prospective cohort study was conducted in Toronto, Canada from 2019-2022 to evaluate the utility, validity and responsiveness to change of Chromameter CR-400 (Konica Minolta®) in quantifying the evolution of IHs. Statistical analyses included means, standard deviations (SD), or medians and interquartile ranges for non-normally distributed data. Correlation coefficients (Spearman rho, Cronbach alpha, ICC) were used to show reproducibility, validity, and responsiveness to change. A p-value <0.05 indicated statistical significance.

Results: This study included 34 infants [mean age-3.8 (SD=1.35) months], mostly females (84%). IHs were small [mean size=2.6 (SD=1.9) cm], uncomplicated, and superficial (88%), affecting the face and trunk. 60% received treatment; 85% systemic and 15% topical. Redness was analyzed using a 100 mm visual analog scale (VAS) (0 normal–100 intense red). The correlation between the chromameter and VAS scoring was not statistically significant (Adj. R2=0.155, p=0.317). Inter-rater and intra-rater consistency was statistically significant, showing ICC scores of 0.96 [95%CI:0.93–0.98] and 0.95 [95%CI:0.90–0.97], respectively. Correlation coefficients scores denoted a strong, and positive correlation at baseline [Spearman r(34) =0.633, p =0.000; Cronbach alpha 4 items; α=0.98], and at follow-up [Spearman r(21) =-0.275, p=0.226; Cronbach alpha 3 items; α= 0.88]. Responsiveness to change scores were VAS -0.6 [mean VAS=–13.85 (SD=22.84)], ΔE -3.55 [mean ΔE=–21.90 (SD=5.91)], and Δa -1.15 [mean Δa=–1.6 (SD=1.39)]. The chromameter was considered easy and safe to use by parents and investigators.

Conclusion: The chromameter is safe, fast, and reliable for assessing IH proliferation, and can potentially aid in treatment decision algorithms, and monitoring treatment response.

Session 2: Vascular Tumors

Single-cell transcriptional profiling identifies a LAMA4 as a potential target gene in Kaposiform hemangioendothelioma

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Purpose: To dissect the disease heterogeneity and identify the underlying cellular and molecular pathogenesis in Kaposiform hemangioendothelioma(KHE).

Methods: Single-cell RNA sequencing was performed on 3 KHE tumor tissue samples, one Congenital Hemangioma(CH) tissue sample, one Infantile Hemangioma (IH) tissue sample and normal skin. The last three served as controls. We conducted data integration and cell-type annotation based on gene expression profiling. Furthermore, we identified pathogenesis-related genes according to copykat analysis ,nichenet ligand receptor analysis, GO and KEGG analysis.

Results: A total of 29194 cells in KHE were obtained for further analysis, with a median unique molecular identifier count of 5826 per cell and a median number of 1689 genes detected per cell. Mainly eight

type cells are defined: KHE cells, fibrocyte Myeloid cell series, B cells, Tcells, mastocyte, Schwann cells, dendritic cell. Copykat analysis of KHE data indicated that the alloploid components of KHE were mainly tumor endothelial cells. By nichenet ligand receptor analysis, single-cell sequencing hemangioma data was compared with normal skin data, focusing on endothelial cells, 1253 ligand-corresponding target genes and 88 ligand and receptor pairs were obtained in KHE data. Then, the KHE data analysis results were compared with infantile hemangioma and congenital hemangioma data, and target genes LAMA4, TGFB1 and FBN1 with specific or high expression in KHE were screened out, among which the expression level of LAMA4 gene in KHE was the most different from that of IH and CH. GO and KEGG analysis showed LAMA4 associated with p38 MAPK pathway.

Conclusion: The LAMA4 is highly expressed in KHE which could be a biomarker for Immunohistochemical diagnosis. The LAMA4 might be a candidate for therapeutic targets of KHE.

PQ interval prolongation and first-degree AV block in children with infantile hemangiomas treated with propranolol

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Purpose: Propranolol is a first-line treatment for infantile hemangiomas (IH) in children. It is safe and rarely causes side effects, such as atrioventricular (AV) conduction disturbances, PQ interval prolongation, and first-degree AV block in electrocardiography (ECG). First-degree AV block is clinically mute in most children. There is a risk of progression of the first-degree AV block, therefore precaution is recommended. There are currently no dosing guidelines for propranolol in IH children with ECG abnormalities. The purpose was to evaluate of propranolol treatment protocol in children with IH where prolongation of the PQ interval and/or first-degree AV block were observed.

Methods: Retrospective analysis of the course of propranolol treatment in children with IH who had ECG abnormalities. ECHO and ECG were performed before propranolol administration and after achieving the target dose of 2 mg/kg/d. Cardiological follow-up was 1-2 months after initiation.

Results: Between 2020 and 2023, 76 children with IH were treated with propranolol. Seven children aged 2 - 11 months had ECG abnormalities. In 5 patients a PQ interval prolongation up to maximal values for age and heart rate was observed during subsequent follow-ups at time intervals from 2.5-8.8 months after initiation on doses of 1.15 -2 mg/kg/d. First-degree AV block occurred in 2 patients. In one, during the introduction, and persisted, despite a dose reduction to 1.2 mg/kg/d with normalization after withdrawal. In a second patient, it was observed after 5.8 months at a dose of 1.85 mg/kg/d and resolved after reduction to 1,09 mg/kg/d. Therapy was not discontinued in any of the patients. No deviation of PQ interval was observed after treatment.

Conclusion: The recommendation for cardiological follow-up in children with IH on propranolol is justified and allows observation of conduction disturbances. Prolongation of PQ is not an indication to withdraw the therapy. Interdisciplinary cooperation with cardiologists is essential in IH treatment.

Treatment Experience for Different Risk Groups of Kaposiform Haemangioendothelioma

Miao Miao Li (Henan Provincial People's Hospital)

Purpose: Background Kaposiform haemangioendothelioma (KHE) is a rare vascular tumor with a high risk of mortality. KHE may develop into Kasabach-Merritt phenomenon (KMP), which characterized by

thrombocytopenia and consumptive coagulopathy, the management of KHE associated with KMP is still challenging. Objectives To examine the clinical characteristics of patients with KHE and discuss the treatment experience for different Risk Groups of Kaposiform Haemangioendothelioma.

Methods: Methods Retrospective review of 70 patients diagnosed with KHE between 2017 and 2022 in our center, we classify lesions into three Clinicopathological Stages based on the tumor involving depth and divided the severity of KHE into three levels by estimating clinicopathological stages and severity of thrombocytopenia. Treatments of different severity groups were estimated with sufficient data.

Results: Results In our cohort, 27% were neonates, KHE lesion occurred at birth in 84% of patients.Common clinical characteristics included a locally aggressive cutaneous blue-purple mass, thrombocytopenia, associated coagulation disorder, local pain or joint dysfunction. 78% of our cohort patients developed KMP, 92% patients were given surgery treatment. Patients of Low-Risk Grade (8 cases) all underwent operations, all of them recovered without recurrence after maximum of 5 years follow-up. 25 out of 26 patients of High-Risk Grade underwent surgery treatment.32 out of 36 cases in High-Risk Grade underwent surgery.2 cases dead at one and three months after discharge.

Conclusion: Conclusions Our study describes the largest assessment of high-risk KHE patients who have been given an operation to date, with five years following up track of recovery, which provides an invaluable experience for the future treatment of KHE and KMP patients from different risk groups: Early surgical intervention may be the most definitive treatment option for most KHE patients; Comprehensive treatment is the best choice for the most life-threatening Extremely High-Risk Group.

Different doses of sirolimus for kaposiform hemangioendothelioma: a randomized clinical trial

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Purpose: Kaposiform hemangioendothelioma (KHE) is a rare aggressive vascular neoplasm that occurs predominantly in infancy or early childhood. Currently, sirolimus is a promising treatment modality for KHE. Most scholars consider sirolimus blood concentration of 10-15 ng/ml to be an effective therapeutic concentration. However, long-term higher dose of sirolimus treatment can cause some common complications such as oral mucositis which affects the quality of life of the patient. Therefore, we conducted this study to see if low-dose sirolimus is beneficial to the prognosis of patients.

Methods: Between 2019 and 2021, patients with KHE were clinically recruited, randomized and followed for 1 year to compare the efficacy of different doses (low-dose group: blood concentration maintained at 5-8 ng/mL, usual-dose group: blood concentration maintained at 10-15 ng/mL) of sirolimus in KHE and the incidence of drug-related adverse effects.

Results: A total of 80 patients with KHE were enrolled, including 40 in the low-dose group and 40 in the usual-dose group, with a male to female ratio of 1.3: 1. There was no significant difference in baseline data between the two groups. After 1 year of treatment with sirolimus, 32 of 40 patients (80.0%) in the low-dose group had an objective response, compared with 34 of 40 patients (85.0%) in the usual-dose group (difference 5%; 95% confidence interval, -12.0-21.8). There was no significant difference in other secondary outcome measures. During the one-year follow-up period, the frequencies of total adverse events were lower in low-dose group (2.4 events per patient in the low-dose group vs 3.5 events per patient in the usual-dose group).

Conclusion: The efficacy of sirolimus in the low-dose group was noninferior to that in the usual-dose group, while the adverse effects were lower than those in the usual-dose group.

Neurointerventional treatment of life-threatening vascular tumors in newborns
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Purpose: This abstract discusses the neurointerventional radiological approach to management and treatment of life threatening vascular tumors of the head and neck in the newborn.

Methods: We present two rare cases of newborn patients who presented with large neck and face congenital hemangiomas with rapid enlargement causing severe high output cardiac failure. Imaging revealed large disfiguring hypervascular tumors with massive dilation of feeding arteries and draining veins. Neurointerventional Radiology was consulted as part of a mulitdisciplinary team (neonatology, dermatology, otolaryngology, hematology, and cardiology) taking care of these patients. Transarterial embolization was invoked once these babies developed high output cardiac failure that became more unstable with time and not responsive to optimal medical management.

Results: Embolizations with transarterial superselective microcatheterization of the multiple feeders were performed via the umbilical artery in one baby and the femoral artery in the other. Polyvinyl alcohol particles 300-100 microns sized embolic agents were used. Embolizations were immediately followed by incisional biopsies by the pediatric otolaryngology service. Biopsies are consistent with congenital hemangioma in both patients with features of Kaposiform hemangioendothelioma in one. Both patients were treated with sirolimus. Both patients' cardiac function rapidly normalized after embolization of their tumors. The tumors also rapidly decreased in size with clinical examination and follow up imaging. The last folllow up clinic visits were at 8 and 6 months for both patients and both are healthy, thriving and meeting their developmental milestones.

Conclusion: Congenital hemangiomas of the head and neck are rare. Rarer still are the ones in newborns that rapidly grow and cause life threatening high output cardiac failure. When non-invasive medical management has met its limits in these cases, the consultation of the neurointerventional team and subsequent treatment with transarterial embolization are very helpful in the stabilization of tenuous cardiac status and involution of these large tumors.

Novel Genomic Structural Variations in Angiosarcoma
Thuy Phung (University of South Alabama)

Purpose: Angiosarcomas are malignant vascular tumors with a number of known molecular aberrations identified by standard technologies, such as FISH and next generation sequencing. However, potentially clinically significant large genomic aberrations, such as gene fusion, large amplification and deletions, may not be detectable by these technologies. To gain further insights into the genomic landscape of angiosarcoma, we performed optical genome mapping (OGM) of primary human angiosarcoma cell lines.

Methods: The genomic landscape of angiosarcoma cells were analyzed using novel optical genome mapping (OGM) technology. Whole genomic DNA from three (3) primary human angiosarcoma cell lines were isolated and fluorescent labels were added at a specific sequence motif. Labeled DNA molecules

were linearized in nanochannel arrays on the chip. Changes in the patterning of the labels were identified by software solutions to detect structural aberrations.

Results: OGM analysis of these cells revealed multiple unique structural aberrations, including large insertions/deletions, inversions, duplications, inter-chromosomal and intra-chromosomal translocations. Further analysis showed a 354-Kb deletion in Plexin D1 gene locus that regulates the migration of endothelial cells and is required for normal development of the heart and vasculature; reciprocal t(4;9) translocation in UGT8 (UDP Glycosyltransferase 8) gene locus that is involved in biosynthesis of galactocerebrosidase; reciprocal t(6;22) translocation involving HIRA (Histone Cell Cycle Regulator) and EYS (Eyes Shut Homolog) gene loci; and 14 Mb inversion interrupting RYR2 (Ryanodine Receptor 2) and TAF1A (TATA-Box Binding Protein Associated Factor) gene loci.

Conclusion: These findings demonstrate the utility of optical genome mapping as a new tool to uncover large genomic structural variations to better understand the molecular pathogenesis of malignant vascular tumors. Future studies are aimed to determine the biological significance of these structural variations in angiosarcoma.

Session 3: Venous Malformations

Endothelial cell-derived extracellular vesicles contribute to abnormal perivascular cell coverage by transferring miR-4432 in venous malformations

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Purpose: Venous malformations (VMs) are developmental vascular malformations characterized by discontinuous endothelium and sparse perivascular cell coverage. Extracellular vesicles (EVs) play vital roles in regulating vascular development and have been proven to be oversecreted in VMs. This research aims to investigate the role of increased EV secretion in the progress of VMs.

Methods: Human umbilical vein endothelial cells (HUVECs) over-expressing TIE2-L914F and TIE2-WT were constructed to simulate VM-ECs and normal ECs (as control). EVs were isolated from the conditioned media and quantified with nanoparticle tracking analysis. Protein and RNA carried by EVs were quantified with Bradford assay and ultraviolet, respectively. Differentially expressed miRNAs (DE-miR) in EV were detected using miRNA-seq, and further validated using real-time PCR. Meanwhile, the expression level of DE-miR in VM tissues was detected using in situ hybridization. Moreover, the effects of TIE2L914-EV on the proliferation, migration, and adhesion of perivascular cells were investigated by cell viability assay, transwell cell migration assay, and cell adhesion assay. MiRNA inhibitors and mimics were employed to verify the effects of DE-miR.

Results: The total EV and EV-carried RNA amount was dramatically elevated in TIE2L914F HUVEC while EV-carried protein level showed no significant difference. PCA and heatmap analysis of miRNA-seq showed that the miRNA expression profile of TIE2L914F-EV was significantly different from that of TIE2WT-EV, TIE2L914F HUVEC, and TIE2WT HUVEC. Besides, miRNA-seq analysis proved that TIE2L914F HUVEC tended to secret more miRNAs through EVs compared to TIE2WT HUVEC, and miR-4432 was the most significantly elevated in TIE2L914F-EV-miRNAs. VM tissue specimens presented sparse perivascular cell coverage and increased miR-4432 expression in perivascular areas. The abilities of proliferation, migration, and adhesion of perivascular cells were decreased after being treated with TIE2L914F-EV whereas miR-4432 inhibitor rescued these effects.

Conclusion: TIE2L914F HUVEC-EV carried miR-4432 contributes to the development of VMs by reducing perivascular cell coverage.

Aggressive phenotype of blue rubber bleb naevus syndrome caused by mosaic TEK fusion | *Roli Adollo (Genetics & Genomic Medicine, UCL GOS Institute of Child Health, UK); Alicia Lopez Bruzos (Genetics & Genomic Medicine, UCL GOS Institute of Child Health, Mosaicism & Precision Medicine Laboratory, Francis Crick Institute, UK); Aimie Sauvadet (Genetics & Genomic Medicine, UCL GOS Institute of Child Health, UK., Mosaicism & Precision Medicine Laboratory, Francis Crick Institute, UK); Davide Zecchin (Genetics & Genomic Medicine, UCL GOS Institute of Child Health, UK., Mosaicism & Precision Medicine Laboratory, Francis Crick Institute, UK); Ignacio Del Valle Torres (Genetics & Genomic Medicine, UCL GOS Institute of Child Health, UK, Mosaicism & Precision Medicine Laboratory, Francis Crick Institute, UK); Amir Sadri (Paediatric Plastic Surgery, Great Ormond Street Hospital for Children, London, UK); Claire O'Neill (Paediatric Dermatology, Great Ormond Street Hospital for Children, London, UK); Lea Solman (Paediatric Dermatology, Great Ormond Street Hospital for Children, London, UK); Mary Glover (Paediatric Dermatology, Great Ormond Street Hospital for Children, London, UK); Veronica A. Kinsler (Genetics & Genomic Medicine, UCL GOS Institute of Child Health, UK, Mosaicism & Precision Medicine Laboratory, Francis Crick Institute, UK, Paediatric Dermatology, Great Ormond Street Hospital for Children, London, UK); Satyamaanasa Polubothu (UCL)*

Purpose: Blue rubber bleb naevus syndrome (BRBNS) is a rare, multisystem disorder characterised by multifocal venous malformations (VMs) primarily affecting the skin, gastrointestinal tract and mucosal membranes. VMs increase in number and size over time and can lead to organ dysfunction and fatal bleeding. BRBNS is caused by double somatic mutations in TEK in 50% of patients, which encodes the receptor tyrosine kinase Tie21. However, several patients are wild-type for these mutations; leaving the genetic basis unsolved. The aim of this study was to identify the genetic cause of BRBNS in a patient wild-type for known mutations, to further understand the pathobiology and identify novel therapeutic targets.

Methods: A 6-year-old girl with aggressive BRBNS requiring fortnightly blood transfusions and long-term therapy with thalidomide and sirolimus was recruited for genetic studies. DNA extracted directly from affected skin was sequenced on a high-depth Next Generation sequencing panel including TEK and associated genes. RNA from affected skin underwent paired-end RNA sequencing with bioinformatics analysis for gene fusion transcripts. Fusions were confirmed by Sanger sequencing the cDNA across the fusion junction. Blood DNA was sequenced in parallel.

Results: A mosaic TEK-GRAP2 fusion was detected in affected skin in two samples from discrete lesions, confirming clonality; and found to be absent from blood confirming its somatic nature. This results in loss of the 3' phosphorylation domain of TEK but preservation of the kinase domain, with suspected auto-phosphorylation of the receptor tyrosine kinase, thus enhancing downstream signalling of the resultant fusion protein. No pathogenic somatic variants in TEK were detected.

Conclusion: Here we identify a mosaic TEK-GRAP2 fusion as a novel cause of BRBNS in a patient with a highly aggressive phenotype. In vitro modelling of this novel fusion is currently underway. This adds to the genotypic landscape of BRBNS and may have implications for future targeted therapies.

The four clinical manifestations of verrucous venous malformation
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Surgery, Shanghai Ninth People's Hospital, School of Medicine, Shanghai Jiaotong University); Rui Chang (Department of Plastic and Reconstructive Surgery, Shanghai Ninth People's Hospital, School of Medicine, Shanghai Jiaotong University); Lizhen Wang (Department of Pathology,Shanghai Ninth People's Hospital, School of Medicine, Shanghai Jiaotong University); Lin Xiaoxi (Department of Plastic and Reconstructive Surgery, Shanghai Ninth People's Hospital, School of Medicine, Shanghai Jiaotong University)

Purpose: Verrucous venous malformations (VVM) are rare and may not exhibit uniform clinical patterns. Because of its diverse behavior, they are often clinically mistaken as lymphatic malformation, angiokeratoma, etc. They are hard to diagnose clinically and diagnosis depends on pathology. Our vascular anomalies center sees as much as 3-5 new VVM patients weekly. We have observed different characteristics of VVM. The purpose of this study is to categorize and summarize their clinical diverse manifestations and add to the literature.

Methods: Since 2020, patients who were suspected as VVM were registered in our internal patient data base (Medcohort). Those who were subsequently pathologically confirmed as VVM were reviewed for this study. Patient history, lesion photographs and natural history were reviewed and documented. We then analyzed their pathological behavior and looked for commonalities as well as differentiations.

Results: This study consists of 49 VVM patients whose diagnosis was pathologically confirmed. All lesions were located on the upper (n=17, 35%) or lower limb (n=32, 65%). Lesions were clinically presented as focal (n=33, 67%) or diffuse (n= 16, 33%). Clinical manifestations included mainly a red patch with some keratinization (n=10, 20%); significant keratinization(n=21, 43%); keratinization with oozing, bleeding or infection (n=12, 24%); Or mainly a subcutaneous lump (n=6, 12%). Almost all patients experienced lesion growth or keratinization.

Conclusion: According to their different clinical manifestations, VVM can be categorized into four subtypes. This study describes the behavior and clinical manifestations of these different types of VVM. This information provides clinicians with a better understanding of the disease in order to accurately diagnose and treat VVM.

FIXED DOSING OF ALPELISIB IN CHILDREN: WHEN WILL THE MAGIC FADE?

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Purpose: An empiric and fixed dose of 50 mg of alpelisib, irrespective of weight and age, has been FDA-approved in PIK3CA-related overgrowth spectrum (PROS) in the absence of any pharmacokinetic (PK) data (blood concentration determination). However, weight is highly variable in the pediatric age range and fixed dosing may lead to highly variable blood levels (e.g., toxicity in young children). The purpose of this study is to challenge this fixed and empiric dosing.

Methods: Drug exposure was determined with an area under the curve (AUC) (concentration determined at time 0 and 0.5,1,1.5,2,3,6,8 hours after dose). Adverse effects (AE) were graded

according to CTCAE grades. Insulin resistance was assessed with measurement of glucose, glycosylated hemoglobin, and C-peptide levels. Volumetric measurements on MRI were carried out before treatment start and compared to 6 months post-treatment.

Results: Eight patients (4 with PROS and 4 with TIE2-sporadic venous malformation) were treated through Novartis compassionate use program. Median age was 12 years (range: 2.6-18) and median weight was 45.4 kg (range: 15.1-92). AUC on a 50 mg oral daily dose was highly variable (range: 3036 to 16620 ng*h/mL) and inversely correlated to weight. On alpelisib, pain decreased, coagulopathy resolved, and mobility improved. VA-lesion volume decreased by 17% after six months ($p<0.05$). This decrease did not correlate to AUC. Markers of insulin resistance developed in most patients (increase in C-peptide, pre-diabetes (n=2) and type 2 diabetes (n=1)). Other AE included stomatitis, decreased appetite, chronic transaminitis and reduced growth velocity. The severity of AE directly correlated to AUC.

Conclusion: Alpelisib exposure at a fixed empiric dosing of 50 mg is highly variable. Alpelisib improves symptoms and leads to a decrease in target-VA volume, however AE significantly correlate to alpelisib exposure. If this data is confirmed, weight-based dosing and therapeutic drug monitoring may improve alpelisib use in children.

First In-human Clinical Experience with Direct Stick Embolization of Low-flow Vascular Malformations with an mTOR Inhibitor

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Purpose: While direct stick embolization (DSE) of low-flow vascular malformations (LFVMs) with off-label embolotherapeutic compounds is first-line therapy, oral mTOR inhibition has become mainstay of treatment but results in frequent blood draws, systemic toxicity, and rebound signs/symptoms upon cessation. We, herein, present the first ever report of in-human DSE of LFVMs with an mTOR inhibitor, thus targeting the culprit mutated pathway.

Methods: Since 2020, 33 DSE cases were performed in 25 patients with LFVMs using a patented formulation and technique involving the intravenously compatible mTOR inhibitor Yale-OCR7737, used as a liquid compound and later in a collagen matrix emulsion for added viscosity and intralesional residence. Data was prospectively maintained and retrospectively reviewed for technical success (successful intralesional delivery of compound); clinical success (improvement in signs/symptoms with radiologically documented reduction in flow and/or volume of treated lesion); complications; side effects; and re-interventions.

Results: From 2020 to 2023, 33 DSE cases were performed using Yale-OCR7737 in 25 patients (10[40%] men; 15[60%] women; mean age: 28 years [range 1 -70 years]) with LFMVs involving mainly the head/neck (48%) and limbs (40%); 88% were non-syndromic while 12% had Klippel-Trenaunay Syndrome; 68% exhibited venous malformations, while 32% had lymphatic malformations. Yale-OCR7737 was given as a liquid 9 (27%) times and as an emulsion 24 (73%) times. Technical and clinical success was 100% and 93%, respectively. Mean DSE sessions per patient was 1 (range 1 to 5). Localized intravascular coagulopathy occurred in 16 (49%) cases; D-dimer improved Post-DSE in 7 (21%) cases. No perioperative or delayed complications occurred. Side-effects were 7 (21%) cases of self-limited aphthous ulcers.

Conclusion: In this first ever in-human experience with direct intralesional targeting of the culprit mutated pathway, we demonstrate that DSE of LFVMs with mTOR inhibitors (Yale-OCR7737) can be safe and effective. This represents the new embolotherapeutic frontier in the interventional treatment of LFMVs.

Outcome of Bleomycin Electrosclerotherapy of Slow-Flow Malformations in Adults and Children
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Purpose: To evaluate the safety and clinical outcome of Bleomycin Electrosclerotherapy (BEST) for treating extracranial slow-flow vascular malformations.

Methods: Patient records of three Interdisciplinary Vascular Anomalies Centers were analyzed with respect to procedural details and complications and additionally a treatment-specific, patient-reported questionnaire was evaluated, obtained 3-12 months after the last treatment. Consecutive patients with symptomatic slow-flow malformations (venous malformations, VMs; lymphatic malformations, LMs; combined malformations) treated with BEST between October 2020 and July 2023 have been included. The treatment-specific, patient-reported questionnaire included mobility, aesthetic aspects, and pain (using a visual analogue scale VAS) as well as the occurrence of postprocedural skin hyperpigmentation. All outcome parameters were compared according to patients' age.

Results: In total, 325 BEST treatments were performed with different electrodes after intravenous and/or intralesional Bleomycin injection. The mean number of procedures per patient was 1.4 (±0.7). The total procedural complication rate was 10.8% (33/325) including 29/352 (8.9%) major complications. Patient-reported mobility decreased in 10/133 (8.8%), was stable in 30/113 (26.5%), improved in 48/113 (42.5%), and was rated symptom-free in 25/113 (22.1%) patients. Aesthetic aspects were rated impaired compared to baseline in 19/113 (16.8%), stable in 21/133 (18.6%), improved in 62/113 (54.9%), and perfect in 11/133 (9.7%) patients. Postprocedural skin hyperpigmentation occurred in 78/113 (69%) patients, remaining unchanged in 24/113 (30.8%), reduced in 51/113 (65.5%), and completely resolved in 3/113 (3.8%) patients. Median VAS pain scale was 4.0 (0-10) preprocedural and 2.0 (0-9) postprocedural. Children/adolescents (0-15 years) performed significantly better in all outcome parameters compared to adults (≥16 years) (mobility, $p=0.011$; aesthetic aspects, $p<0.001$; pain, $p<0.001$).

Conclusion: BEST is an effective treatment for slow-flow vascular malformations, with few but potentially significant complications. With respect to patient-reported outcome, children seem to benefit better compared to older patients, suggesting that BEST should not be restricted to adults.

Ablation of Venous Malformations by Photothermal Therapy with Intravenous Gold Nanoshells
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Purpose: Venous malformations (VMs) cause significant disfigurement, pain, and complications such as bleeding and coagulopathy. Current treatment for patients with VMs entails life-long pharmacotherapy or surgical procedures that have limited efficacy. Here, we explored whether intravenously administered nanoparticle-based agents could be used to destroy VMs by photothermal therapy (PTT), using gold nanoshells (AuNS) that generated heat following irradiation with near-infrared (NIR) light.

Methods: AuNS were synthesized by galvanically reducing gold at the surface of cobalt seeds and were characterized. Using the HUVEC-TIE2-L914F murine model of VMs, we assessed nanoparticle accumulation within the VM and biologic effects of the photothermal therapy. Irradiation was performed using an 808 nm NIR iodine laser.

Results: Following intravenous administration of AuNS to mice with VMs, 7.1±9.6 ng elemental gold/mg of tissue was detected in VMs. VM size in response to four treatment protocols was examined: normal saline without NIR irradiation (SAL), normal saline with NIR irradiation (SAL+NIR), AuNS without NIR irradiation (AuNS), and AuNS with NIR irradiation (AuNS+NIR). In animals injected with SAL, VM size increased 3-fold over 3 weeks (from 300 to 900mm3), whether or not they were irradiated. In the AuNS group, VM size increased 2.2-fold (from 300 to 700 mm3). In contrast, in the AuNS+NIR group, VMs began regressing 48 h after irradiation and reduced in size greater than 17-fold, from 300mm3 to a mean of 17.49±18.78mm3, including two VMs that were completely eliminated, which was significant compared to SAL, SAL+NIR, AuNS groups ($p<0.0004$ or lower). While photothermal therapy significantly reduced or eliminated VMs, skin burns did occur. There was no evidence of organ injury or inflammation by laboratory data or histology.

Conclusion: This is the first demonstration of accumulation of intravenously administered nanoparticles in VMs and of intravenously administered nanoparticles used to destroy VMs by photothermal therapy (PTT).

Total Hip Arthroplasty in Extensive Venous Malformations with Intravascular coagulation disorder (= IVCD): An Experience of Four Cases

Claude Laurian (St Joseph Hospital); Emma Vuilletet (St Joseph Hospital); Pomme Jouffroy (St Joseph Hospital); Annouk Bisdorff Bresson (Hopital Lariboisiere)

Purpose: Extensive venous malformations (VM) and associated degenerative joint disease of the hip are a rare condition. The difficulty of total hip replacement depends on tissue involvement around the joint. To evaluate the feasibility and outcome of hip replacement in this disease.

Methods: Between 2010 and 2020, 4 patients underwent a total hip replacement (THR). Investigations included X-ray exams, T2 MRI with fat sat saturation, and hematologic tests. The main outcome end-points of the study were success of the procedure, post-operative complications and quality of life.

Results: Four patients underwent THR, sex ratio was (3 males, 1female) with a median age of 37 years (range 27-55). All were symptomatic, with worsening hip pain and using mechanical aid. Mri identified VM in muscles and connective tissue of the buttock. All had IVCD with elevated D-dimer levels (20x normal), 2 had low level of fibrinogen all were treated with LWMH prior and after surgery. The choice of the surgical approach depended of location of tissue involvement (anterior 2, lateral 1). Preoperative sclerotherapy (Heated Horsley's bone wax) was needed (3 patients) before orthopedic procedure to reduce blood loss (mean blood loss 1500ml). Intraarticular VM of the hip was never observed. The median follow-up time was 88 months (range24 to 120). No postoperative complications were observed. At 6 months, three patients were walking with normal gait, one was using an orthopedic walker after knee arthrodesis. No reoperation, and no orthopedic events were observed during the follow-up. All patients returned to their professional activities.

Conclusion: The difficulty of THR depends on the extent of involved soft tissue around the hip area. Conventional orthopedic procedures were associated with good functional results. A surgical procedure

scheduling including: a combined vascular and orthopedic surgical team, peroperative bone wax sclerotherapy and prior DIVC treatment with LMWH allow to reduce surgical procedural risk.

TOTAL KNEE ARTHROPLASTY IN EXTENSIVE VENOUS MALFORMATIONS: A Single CENTER EXPERIENCE OF 10 CASES

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Purpose: Extensive venous malformations (VM) and associated degenerative joint disease of the knee is not a rare condition. The difficulty of total knee replacement (TKR) depends on tissue involvement around the joint, and on intra-articular VM with the risk of severe blood loss. To evaluate the feasability and the functional results of the procedure.

Methods: Between 2007-2019, 10 patients with extensive VM of the limb had TKR. Investigations included X-ray exams, T2 fat sat saturation MRI and hematologic tests. The main outcome endpoints of the study were success of the TKR, postoperative complications and functional results.

Results: For the 10 patients, sex ratio was (8 females, 3 males) with a median age of 37 years (range 19-63). All were symptomatic with worsening pain, use of mechanical aid, and 2 had contracture of the knee after treatment of pathologic fracture of femoral shaft. Surgical indications were pain for 8 and contracture of the knee for 2 patients. 4 had cure of intra-articular VM (=IAVM) and arthroplasty at the same time, 3 had arthroplasty :2, 17 and 24 years after IAVM resection, 3 had only arthroplasty. Mean blood loss was 1400ml. There were no postoperative complications. At six months, 8 patients were walking with normal gait. The median follow-up time was 9 years (range 3-18). Three patients had orthopedic events (2 pseudarthrosis on femoral shaft, 1 fracture above TKR).All patients had incomplete functional result with limitation of knee flexion around of 90°.

Conclusion: The difficulty of KTR depends on the extent of involved soft tissue and intra-articular VM. The functional result was obtained according to involvement of muscular part of the thigh and physical reeducation. Surgical procedure scheduling should include: a combined vascular and orthopedic surgical team and prior IVCD treatment with LMWH this allows to reduce surgical procedural risk

Two Cases of Sarcomas Misdiagnosed as Venous Malformations

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Purpose: The diagnosis of a venous malformation is typically made by history with classic imaging features detected on MRI and ultrasound (increased T2 signal and enhancement, compressible slow-flow vessels). However, we present two clinical cases of misdiagnosis, where history and imaging features suggested venous malformations. However, clinical suspicion and intra-operative imaging led to biopsy for both patients, revealing a sarcoma diagnosis.

Methods: Patient 1: 25 year-old female with left thigh pain for 10 years that was worsening. Imaging findings suggested a venous malformation. Clinic ultrasound demonstrated a partially compressible focal mass in her left thigh. The patient was planned for percutaneous NBCA injection, followed by resection. Patient 2: 86 year-old male with a 3-year history of an enlarging right plantar foot mass. Upon presentation, it had become painful and began spontaneously bleeding. MRI and ultrasound

demonstrated findings consistent with a venous malformation. The patient was planned for sclerotherapy followed by surgical resection and skin grafting.

Results: Patient 1: At the time of the procedure, the mass appeared like a well-circumscribed mass with no flow and not very compressible by ultrasound. Upon excision, the surgeon was concerned that the mass could be a tumor and the specimen was sent to pathology. Pathology demonstrated synovial sarcoma. The patient required radiation and surgery for definitive treatment. Patient 2: After two weeks of wound care, the bleeding decreased, but the overlying skin appeared ulcerated. The affected area had increased in size. Tissue biopsy performed demonstrated synovial sarcoma and the patient underwent radiation therapy followed by surgical resection and reconstruction.

Conclusion: We present two cases of synovial sarcoma that were misdiagnosed as venous malformations upon presentation. The diagnosis of sarcoma should be considered in patients where imaging findings may be atypical or when clinical suspicion for a different diagnosis is high. In these clinical scenarios, biopsy should be considered.

Session 4: Arteriovenous Malformations

Oncogene targeted next-generation-sequencing in extracranial arteriovenous malformations | *Sarah M. Bernhard (Division of Angiology, Swiss Cardiovascular Center, Inselspital, Bern University Hospital, Bern, Switzerland); Aleksandra Beata Tuleja (Swiss Cardiovascular Center, Division of Angiology, University Hospital Bern); Yvonne Döring (Division of Angiology, Swiss Cardiovascular Center, Inselspital, Bern University Hospital, Bern, Switzerland; Institute for Cardiovascular Prevention (IPEK), Ludwig-Maximilians-University Munich (LMU), 80336 Munich, Germany; DZHK (German Centre for Cardiovascular Research), Partner Site Munich Heart Alliance, 80336 Munich, Germany); Erik Vassella (Institute of Pathology, University of Bern, Bern, Switzerland); Ursula Amstutz (Institute of Pathology, University of Bern, Bern, Switzerland); Christiane Zweier (Department of Human Genetics, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland); Jochen Rössler (University Hospital Bern); Laurence M. Boon (Center for Vascular Anomalies, Division of Plastic and Reconstructive Surgery, Cliniques universitaires St-Luc, Universite catholique de Louvain, 1200 Brussels, Belgium, VASCERN VASCA European Reference Centre); Miikka Vikkula (Human Molecular Genetics, de Duve Institute; Center for Vascular Anomalies, Division of Pathology, University Clinics Saint-Luc, UCLouvain, Brussels, Belgium; VASCERN VASCA European Reference Centre; WELBIO department, WEL Research Institute, avenue Pasteur, 6, 1300 Wavre, Belgium); Fabian Haupt (Department of Diagnostic, Interventional and Pediatric Radiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland); Györgyi Hamvas (Division of Angiology, Swiss Cardiovascular Center, Inselspital, Bern University Hospital, Bern, Switzerland); Rafael Kammer (Division of Angiology, Swiss Cardiovascular Center, Inselspital, Bern University Hospital, Bern, Switzerland); Iris Baumgartner (Division of Angiology, Swiss Cardiovascular Center, Inselspital, Bern University Hospital, Bern, Switzerland)*

Purpose: Most isolated congenital vascular malformations are genetically characterized by somatic variants in various genes. However, large clinical variability challenges the analysis of correlations between genotype and phenotype. In sporadic extracranial arteriovenous malformation (AVM), mosaic-activating variants in the RAS/MAPK PTEN signaling pathways have been described. Our aim was to distinguish AVM phenotypes based on clinical and angiographic findings in relation to corresponding pathogenic variants.

Methods: Within our prospective vascular malformation cohort, that exists since 2018 and is continuously enrolling consecutive patients, we reviewed patients with angiographically verified AVM in

whom a genetic study of the affected tissue using high-throughput sequencing by the TruSight Oncology 500 panel had been performed. Each patient's initial clinical evaluation, imaging and histopathologic analysis were assessed concerning patient and family history, symptoms, longitudinal overgrowth, soft tissue hypertrophy, angiographic classification and histology.

Results: Overall, 37 patients (18 males and 19 females) were included for analysis. Most of the AVMs (73%) were located in the extremities. We detected known variants in MAP2K1 (n=9), KRAS (n=7), RASA1 (n=1), but also variants in other genes of the RAS pathway (RIT1, PTPN11). We also identified alterations in the PI3K/AKT/mTOR signaling pathway with a PIK3CA variant (n=2), and in the PTEN-Pathway with a combination of somatic variants in PTEN and GNAQ (n=1), not yet associated with extra-cranial AVM. Additional variants of unknown significance were detected in all patients. Comparing AVM with KRAS variants to AVM with MAP2K1 variants, AVM with KRAS variants were more diffuse, involving whole extremities (71% vs 22%) and were frequently associated with ulcerations (71% vs 11%) and longitudinal overgrowth (86% vs 22%).

Conclusion: Though a larger number of cases would be required to draw definite conclusions, our study contributes to characterizing the molecular landscape of extracranial AVMs and points to a genotype-phenotype correlation regarding variants in MAP2K1 and KRAS.

Trametinib prevents formation of vascular lesions in a MAP2K1 p.K57N arteriovenous malformation mouse model

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Purpose: Extracranial arteriovenous malformation (AVM) is caused by endothelial cell (EC) specific somatic activating mutations in the RAS/MAPK signaling pathway. Inducing somatic expression of MAP2K1 p.K57N, the most common AVM mutation, in murine ECs has been shown to cause AVM-like vascular malformations most prominent in brain, and intestines. The goal of this study was to determine if pharmacotherapy using a MAP2K1 inhibitor would prevent the formation of vascular lesions in MAP2K1 mutant mice.

Methods: 12 R26GT-Map2k1-GFP/+; Tg-Cdh5CreER+/- mutant pups were treated topically on the dorsal skin of the left ear with 50 µg of 4-OH-tamoxifen at postnatal day 10 (P10) to activate MAP2K1 p.K57N expression in ECs in order to generate vascular lesions. Six mice (Group 1) were not treated with a MAP2K1 inhibitor. Six mice (Group 2) were treated with the MAP2K1 inhibitor trametinib starting at P21 (weaning) (3 µg/ml ad libitum in drinking water). Both groups were followed for survival and development of vascular lesions.

Results: Group 1 non-treated mice died between P30-P45. All animals contained vascular malformations in the brain and intestines. Group 2 mice all survived long-term and were analyzed at P52 for the presence of vascular anomalies. None of the mice treated with trametinib developed vascular malformations.

Conclusion: A MAP2K1 inhibitor prevents formation of Map2k1 p.K57N induced vascular malformations in mice. These findings support the use of trametinib as a treatment for patients with extracranial AVM.

Somatic RIT1 indels identified in arteriovenous malformations hyperactivate RAS-MAPK signaling and are amenable to MEK inhibition

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Purpose: Arteriovenous malformations (AVM) are benign vascular anomalies prone to pain, bleeding, and progressive growth. Treatment is often difficult and relapse after therapy is common. AVM are mainly caused by somatic mosaicism with pathogenic genetic variants of the RAS-MAPK pathway. However, a causative variant is not identified in all patients.

Methods: Next generation sequencing was performed on AVM tissues to identify somatic mutations. We performed in vitro and in vivo biochemical and functional characterization of RIT1 mutations in HEK293T cells and zebrafish, respectively.

Results: We describe novel somatic RIT1 indel variants in lesional tissue of three AVM patients. RIT1 – not previously implicated in AVM development – encodes a RAS-like protein that can modulate RAS-MAPK signaling. Expression of RIT1 variants in HEK293T cells led to a strong increase in ERK1/2 phosphorylation. Endothelial-specific mosaic overexpression of the RIT1 indels in zebrafish embryos induced AVM formation. Both ERK1/2 hyperactivation in vitro and AVM formation in vivo could be suppressed by pharmacological MEK inhibition. Targeted treatment with the MEK inhibitor trametinib led to a significant decrease in bleeding episodes and AVM size in one patient.

Conclusion: Our findings expand the genetic spectrum of AVMs by identifying RIT1 as a novel gene involved in AVM formation, and pave the way for targeted treatment and clinical trials in patients with AVM.

Clinical Response to MEK Inhibitors in Arteriovenous Malformations

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Purpose: The use of targeted medical therapies for AVM is emerging. However, data on safety, efficacy, and optimal duration of treatment of AVMs with targeted agents is not well-established. We report our single-institution experience of AVM patients treated with oral MEK inhibitors.

Methods: We report treatment and outcomes for 11 AVM patients treated with MEK inhibitors between 2019-2023.

Results: Ten patients with complex AVMs were evaluated by an interdisciplinary team at our center. Patients presented with pain (n=8), bleeding (n=8), discoloration (n=7), anemia (n=1), epistaxis (n=1), swelling (n=4), headaches (n=1), and bruit/thrill (n=3). All patients had biopsy or resection of affected tissue; histopathology was consistent with AVM. Genetic testing of affected tissue was performed using Oncopanel. Patients had mutations in MAP2K1 (n=3), KRAS (n=1), BRAF (n=2), HRAS (n=1), SOS1 (n=3). A causative mutation was not able to be identified in one patient. AVM locations included: face and neck (n=9), lower extremity (n=2). Trametinib dose ranged from 0.4 mg to 2 mg daily. Median treatment duration16 months (range 3- 42). Five patients had marked clinical response, including improvement in pain (n=6), size (n=6), discoloration (n=4), bleeding (n=4), and headaches (n=1). Dermatologic side effects included acne (n=5) alopecia (n=1), eczema (n=1), paronychia (n=2), seborrheic dermatitis (n=1), scalp dermatitis (n=1), and xerosis (n=2). Other adverse events included diarrhea (n=4), anemia (n=1), AST elevation (n=1), CPK elevation (n=3), LDH elevation (n=1), fatigue (n=2), and creatine kinase elevation (n=1). Three patients eventually discontinued the medication due to lymphatic leakage (n=1), acne (n=2), edema (n=1), and paronychia (n=2).

Conclusion: Trametinib led to clinical improvement in most of our patients. Trametinib is a promising treatment for AVMs, though the side effects were intolerable for some, highlighting the need for further studies and the identification of other potential targeted agents.

Monocentric Pilot Trial on the use of Trametinib in refractory to standard care Arterio-Venous Malformations: follow-up after cessation of therapy.

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Purpose: This study evaluate the long-term clinical outcomes of trametinib adult patients with arteriovenous malformations. Initial findings demonstrated a 90% response rate, with notable reductions in pain (90%) and swelling (80%), as well as complete radiological resolution in 20% of cases. All patients developed acneiform rash (100%) and 40% experienced bleeding episodes. Following a one-year trametinib treatment, patients were monitored for four additional years to assess the persistence of trametinib's clinical effects after discontinuation. This represents an intermediary follow-up eighteen months after treatment cessation.

Methods: Ten adult patients received trametinib daily for a planned duration of one year (EudraCT: 2019-003573-26). Monthly clinical follow-up was conducted for the first three months, followed by assessments every three months thereafter.

Results: Of the ten patients, five patients completed the 12-month trametinib treatment (50%), one stopped due to a lack of clinical efficacy (10%), and four discontinued due to side effects (40%). The average duration of trametinib use was 7.75 months (ranging from 1 week to 12 months). After treatment cessation, patients were followed for an average of 26.7 months (ranging from 18 to 37 months). All patients experienced a gradual reduction of acneiform rash post treatment. No severe side effects were noted during the follow-up. However, the two patients with radiological resolution experienced a recurrence of the radiological nidus at 6 months and one year after treatment cessation. Ulcerations that healed under trametinib did not recur. Four patients presented with progressive evolution post treatment, with one experiencing a severe worsening of an extensive facial AVM requiring a tracheostomy.

Conclusion: Trametinib effectively regressed symptoms and halted lesions progression in AVM patients. However, the observed beneficial effects were not sustained after treatment cessation. Radiological resolution was transient, emphasizing the need for further investigation into sustaining the positive outcomes achieved during trametinib treatment.

Extracranial Vascular Anomalies Driven by RAS/MAPK Variants - Spectrum and Genotype-Phenotype Correlations

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Purpose: We aimed to correlate alterations in the RAS/MAPK pathway in vascular anomalies to clinical phenotype and therapy response for improved patient stratification and treatment.

Methods: This retrospective multicenter cohort study included 29 patients with extracranial vascular anomalies containing mosaic pathogenic variants (PVs) in genes of the RAS/MAPK pathway. Tissue samples were collected during invasive treatment or clinically indicated biopsies. PVs were detected by targeted sequencing of panels of genes known to be associated with vascular anomalies was performed on DNA from affected tissue. Subgroup analyses were performed according to the affected genes with regard to phenotypic characteristics and clinical course.

Results: Twenty-five vascular malformations, three vascular tumors, and one patient with both a vascular malformation and vascular tumor presented the following distribution of PVs in genes: KRAS (n=10), NRAS (n=1), HRAS (n=5), BRAF (n=8), and MAP2K1 (n=5). AVM patients with RAS PVs had significantly advanced disease stages according to Schobinger classification (p=0.043) and more frequent

relapses after treatment (p=0.016). Lesions with KRAS PVs infiltrated significantly more tissue layers compared to the other PVs (including other RAS PVs, p=0.046).

Conclusion: This direct comparison of patients with various PVs in the genes of the RAS/MAPK pathway reveals a broad distribution of clinical and radiological characteristics in extracranial vascular anomalies. RAS variants are characterized by more aggressive clinical phenotypes with higher relapse rates, potentially requiring individualized treatment strategies according to the underlying PV.

The VASCERN-VASCA Working Group Diagnostic and Management Pathways for Arteriovenous Malformations

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PURPOSE: To elaborate on expert consensus patient pathways to guide patients and physicians towards efficient diagnostics and management of patients with arteriovenous malformations (AVMs).

METHODS: VASCERN-VASCA (https://vascern.eu/) is a European network of multidisciplinary centers for Vascular Anomalies. The Nominal Group Technique was used to establish the pathways. A plastic surgeon (JC) was chosen as facilitator due to his specific clinical and research interest and experience.

The draft was subsequently discussed within VASCERN-VASCA monthly virtual meetings and bi-annual face-to-face meetings during 2022 and 2023.

RESULTS: The Pathway delineates a classification system for AVMs, beginning with a subdivision based on clinical manifestations or anatomical positioning. AVMs are categorized based on associated clinical signs into three groups: hereditary syndromic AVMs (1), sporadic syndromic AVMs (2), or sporadic non-syndromic AVMs (3). Hereditary syndromic AVMs include hereditary hemorrhagic telangiectasia (HHT) (1A), capillary malformation-arteriovenous malformation (CM-AVM) (1B), and PTEN hamartoma tumor syndrome (PHTS) (1C). Sporadic syndromic AVMs encompass patients with Parkes-Weber syndrome (PKWS) (2A), cerebrofacial arteriovenous metameric syndrome (CAMS) (2B), or spinal arteriovenous metameric syndrome (SAMS) (2C). Sporadic non-syndromic AVMs are further classified by location: central nervous system (CNS) either intracranial (3A) or spinal (3B), visceral or intrapelvic (3C), and peripheral (3D). The pathway examines specific clinical indicators and recommends diagnostic modalities for each AVM subtype. It also cites known genetic mutations and outlines treatment approaches for each AVM subtype.

CONCLUSION: Collaborative efforts from VASCERN-VASCA's network of 14 Expert Centers and European Patient Advocacy Group resulted in a consensus Diagnostic and Management Pathways for AVMs to assist clinicians and patients alike. The pathway underscores the crucial role of multidisciplinary expert centers in the management of AVM patients to offer precision-based care. It will be accessible on the VASCERN website (http://vascern.eu/).

Thalidomide as (neo-)adjuvant treatment to reduce postoperative recurrence of extracranial arteriovenous malformations.

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Purpose: Thalidomide, a non-specific VEGF inhibitor renowned for its anti-angiogenic and anti-inflammatory effects, has exhibited important efficacy in treating patients with arteriovenous malformations (AVMs) refractory to conventional therapies. Given the common occurrence of post-operative recurrences within the first year following AVM surgery, we postulated that incorporating (neo-)adjuvant thalidomide treatment could effectively reduce early recurrences of these fast-flow vascular malformations.

Methods: Since 2020, we have operated on 10 AVMs at our Center for Vascular Anomalies. Thalidomide was administered either before and/or after the operation, with a standardized dose of 50 mg per day.

Results: We included 10 patients, 7 males and 3 females. The median age was 31.7 years old (ranging from 13.8 to 55.2 years). All had stage 3 AVMs, predominantly located in the head and neck region (8/10). Thalidomide initiation occurred either 5 months prior to surgery (range: 1 to 11 months) or on the day following the operation, continuing for a mean duration of 7.5 months (range: 1 to 24 months). One patient exhibited early recurrence after 5 months but remained asymptomatic under thalidomide.

The mean follow-up duration was 23,2 months (range: 10 to 40 months), excluding one patient who underwent surgery in August 2023. No post-operative complications were observed.

Conclusion: Patients undergoing thalidomide treatment before surgery as a neoadjuvant therapy reported significant preoperative clinical improvement, manifested by a reduction in pulsatility or pain, confirming thalidomide's efficacy on extracranial AVMs. The antiangiogenic property of thalidomide did not cause any healing problems in the post-operative phase, indicating its safe use in the peri-operative setting. Within our limited series, we encountered only one early postoperative recurrence. We anticipate that these promising initial findings, from the combination of surgical resection and peri /postoperative thalidomide administration will be substantiated through an extended follow-up of at least five years.

Differential diagnosis of arteriovenous malformation and capillary malformation-arteriovenous malformation syndrome using two-dimensional and three-dimensional ultrasound

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Purpose: This study evaluated two-dimensional and three-dimensional ultrasound (US) features of arteriovenous malformation (AVM) and capillary malformation-arteriovenous malformation syndrome (CM-AVM), to make differential diagnosis.

Methods: Between January 2020 and October 2023, 103 cases CM-AVM and 105 AVM (45 early stage, 60 advanced) cases were reviewed. US findings were retrospectively evaluated. On US images, the depth, echotexture, echogenicity, margin, vessel density, blood flow velocity and three-dimension ultrasound pattern were recorded.

Results: AVM lesions were mixed echoic with hyper-echo and many visible vessels mainly with ill-defined. CM-AVM lesions were hyper-echo with ill-defined, sometimes showed visible vessels. There were statistical significances in the depth, diameter of anechoic lumen, vascular density, and arterial peak systolic velocity ($p < 0.05$), and AVM was all significantly higher than CM-AVM. The resistance index of CM-AVM was significantly increased compared with AVM. The three-dimension color Doppler revealed branch-shape blood flow for AVM. CM-AVM showed scattered streaked blood flow. Compared with early stage of AVM and CM-AVM, early stage of AVM showed more anechoic lumens than CM-AVM, the vascular density of early stage of AVM lesions are higher than CM-AVM ($p < 0.05$).

Conclusion: CM-AVM and AVM have distinctive two-dimensional and three-dimensional US imaging characteristics, and US has important value in distinguishing between two diseases.

The Sandwich Neoadjuvant+Adjuvant use of Bleomycin and Surgery for Limited S3 AVMs of the head and neck

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Purpose: Tailored treatment is often advisable with AVMs, and a clinical staging system can guide the management. SECg staging system is the Authors' preferred staging system. S3 AVMs can be removed

surgically but at the cost of functional or aesthetic impairment. Bleomycin has previously been studied in the management of AVMs. To minimise the detriments owed to radical surgery we have conducted a pilot study where bleomycin was used in a "sandwich" manner, before and after surgical remodelling (partial resection) S3 AVMs.

Methods: This was a prospective pilot study based on 14 patients affected by head and neck AVMs managed in the period February 2021 to June 2023. Inclusion criteria were: - patients older than 18 years; - S3 AVM, regardless of stages E, C or g; - no history of previous treatments; - no contraindications to the use of bleomycin. Patients underwent 3 sessions of interstitial bleomycin injections, with an interval of 4 to 6 weeks. After that, surgical resection of the AVM was performed with morphological intents. Three months after surgery, 3 more sessions of interstitial bleomycin injections, 4 to 6 weeks apart from one another, were done. US examination was done pre-treatment, before each session and every 3 months after the end of the protocol. A chest Xray was done before commencing the treatment and at the end of it.

Results: There were no major complications and 2 minor complications. One patient responded poorly to the first 3 bleomycin injections and the protocol was interrupted. Major improvements in terms of appearance and symptoms were always achieved. Total or near-total symmetry was restored, while pulsations, ulcerations, bleeding, or pain disappeared.

Conclusion: This is the first study where bleomycin was used in a "sandwich" manner with surgery to manage limited S3 AVMs. Data are encouraging and may suggest this as an ideal protocol in selected cases.

Research and Development of Novel Image-guided Ethanol Injection: Pre-clinical Investigations, and Clinical Application in Vascular Malformation.

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Purpose: Clinically, absolute ethanol (EtOH) has achieved satisfactory prognoses in the endovascular therapy of vascular malformations. Given ethanol's radiolucency, improper injection of high-concentration ethanol could bring about serious complications. Our study aimed to introduce a novel image-guided ethanol injection (IEI) for treating vascular malformations and evaluate its efficacy and safety in both animal and human subjects.

Methods: Iopromide is mixed with ethanol to achieve radiopacity and improve the physicochemical properties of the solution. Overall, 82 male New Zealand white rabbits are selected for in vivo radiopacity testing, peripheral vein sclerosis, pharmacokinetic analyses, peripheral artery embolization, kidney transcatheter arterial embolization, and biosafety evaluations. Then, a prospective cohort study involving six patients with peripheral venous malformations (VMs) is performed to explore the clinical safety and effectiveness of IEI.

Results: IEI contained 642.3 mg/mL ethanol (81.4% [v/v]) and 231.2 mg/mL iopromide, with an iodine concentration of 111.3 mg/mL. The viscosity of IEI was 3.6 mPa.s in 25℃ and 2.6 mPa.s in 37℃ compared with the EtOH's 1.1 mPa.s in 25℃ and 0.8 mPa.s in 37℃. IEI can be traced throughout the injection in both animals and patients. The IEI also exerts a similar effect as EtOH on peripheral venous sclerosis, peripheral arterial embolization, and renal embolization. Furthermore, the IEI is metabolized quickly without causing organ injury in the animals. No IEI-related adverse effects have occurred during sclerotherapy of VMs, and 4/6 (66.7%) patients have achieved complete response at 3-month follow-up.

Conclusion: IEI possessed the following properties: 1) being visible under X-ray; 2) minimizing the patient's iodine intake; 3) maximizing the effective ethanol content; 4) possessing excellent stability. In comparison with EtOH, IEI allowed clinicians to supervise the whole injection process in real-time and to adjust the injection speed. In conclusion, IEI is safe, exerts therapeutic effects, and compensates for the radiolucency of EtOH.

Ethanol Embolotherapy Management of Pelvic Arteriovenous Malformations (AVM)
Wayne Yakes (Vascular Malformation Center)

Purpose: To determine the curative role of ethanol endovascular and/or ethanol coils in the treatment of large pelvic arteriovenous malformations (AVMs).

Methods: 48 patients (25 females; 23 males; age range: 4 - 86 years; mean age: 37 years) underwent 315 endovascular procedures (6.5 procedure/patient) to treat their pelvic AVMs. 2 patients had bilateral pelvic AVMs (1 male; 1 female). 2 patients had traumatic lesions (2 males). Patients underwent transarterial, retro-grade transvenous, and direct puncture embolization procedures. Embolic agents included absolute ethanol and coils, at times in combination.

Results: 41 patients cured of their pelvic AVM (mean follow-up: 43 months) and 7 patients' treatments are on-going. Pelvic AVMs were cured by using ethanol, coils, or in combination. The addition of coils was particularly useful in those AVMs with aneurysmal venous outflows and in those AVMs with giant venous aneurysms. 3 patients suffered transient sciatic nerve injuries. 1 patient suffered an ipsilateral perineal numbness that completely resolved. 4 instances of perineal blistering and tissue injury with one injection, was treated uneventfully. 1 patient had a rectal wall injury requiring bowel diversion, and after healing, underwent re-anastamosis. 1 elderly patient died within 30 days of a 4th procedure from pulmonary embolus (PE). 1 patients coils eroded thru bladder wall and endoscopically removed. 1 patient had a small bleed that was self-limited not requiring transfusion.

Conclusion: Endovascular approaches to manage pelvic AVM have proven to be curative at long-term follow-up. In our cases, surgery adjunctively to remove the AVM has not been required. Despite previous embolizations with coils, glue, Onyx, and surgical ligations prior to being referred to our institution, endovascular and direct puncture approaches using ethanol, ethanol and coils, has proven to curatively manage pelvic AVMs involving soft tissue and bone with low complication rates and no recurrences. The longest arteriographic follow-up documenting cure is 24 years.

Session 5: Lymphatic Malformations

Assessing pharmacological inhibition and defining pathogenesis in KRAS-driven zebrafish lymphatic malformation models
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Purpose: RASopathies are caused by pathogenic variants that upregulate the RAS-MAPK pathway. A common feature is lymphatic dysfunction. Previously, we identified somatic pathogenic variants in KRAS in individuals affected with central conducting lymphatic anomaly and demonstrated they activate MAPK. In vitro and in vivo. Single case studies using inhibitors of KRAS effectors, MEK and ERK, have had mixed success in humans. Thus, the purpose of this study is to establish additional zebrafish lymphatic anomaly models, define disease progression, and identify therapeutic treatments for individuals affected with KRAS-related CCLA.

Methods: Using transient transgenesis in zebrafish larvae, we created models of lymphatic malformations driven by pathogenic variants in KRAS identified in research participants (p. G12D, p.A146T, p.G12C). We used live confocal imaging, drainage assays, RNA-seq and pharmacological inhibition to understand and treat overactivated-KRAS driven lymphatic anomaly.

Results: KRAS p. G12D, p.A146T, p.G12C zebrafish models impact lymphovenous development including pericardial edema (68.8%, 24.6%, 29.6% occurrence, respectively) and cystic lymphovenous malformations (65.6%, 70.6%, 42.9% occurrence, respectively). Although the lymphatic and axial vasculature appear fused, preliminary lymphatic drainage assays demonstrate these vessels retain some specialized circulatory/drainage function. Gene ontology analysis of RNA-seq from 5 days post fertilization, KRAS-expressing larvae show upregulation of angiogenesis, Ras signaling, and endothelial migration associated genes. These include angpt2a and gna14, notchl and dll4. Though angiogenesis genes were normalized by MEK inhibitor cobimetinib, downregulation is incomplete, leaving gna14, and notchl upregulated. This suggests that inhibition of Notch and alternative Ras-signaling pathways may be therapeutic targets. Furthermore, preliminary studies demonstrate increased efficacy of allele specific KRAS inhibitors compared to MEK inhibition.

Conclusion: Our zebrafish models show that angpt2a and gna14 are upregulated, enhancing understanding of KRAS pathogenesis and indicating these could be biomarkers for future clinical trials. Future work targeting prospective dysregulated pathways will identify additional clinical therapies.

A high throughput zebrafish chemical screen identifies Pan-AKT and tyrosine kinase as novel candidate treatment for Kaposiform Lymphangiomatosis (KLA)

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Purpose: Current pharmaceutical treatments for KLA have led to clinical improvement; however currently there is no cure for the disease. In recent years, a somatic activating mutation in NRAS (Q61R) in the lymphatic endothelial cells was identified as the disease cause. Therefore, we aimed to develop a zebrafish model of the disease in order to characterize the disease pathogenesis and identify new drug treatments by a high throughput zebrafish chemical screen.

Methods: We established two zebrafish transgenic lines in order to model KLA. Cconfocal imaging of developing zebrafish larvae were used to characterize the mutant phenotypes. In addition, we performed a focused drug screen based on canonical and non-canonical NRAS downstream targets. Images were automatically analyzed using Artificial intelligence-based Application. Hits were validated using zebrafish confocal microscopy, as well as immunoblotting and sprout assays on patients' endothelial lymphatic cells.

Results: The two zebrafish models reproducibly recapitulate the phenotype of KLA. Expression of mutated NRAS in the venous/lymphatic endothelium leads to pronounced pericardial edema, a phenotype largely associated with lymphatic defects in zebrafish. Confocal imaging showed bloating of the thoracic duct as well as severe morphological changes in intersegmental lymphatic vessels and the Posterior Cardinal vein (PCV). Trametinib, a MEK inhibitor, effectively reverted the Q61R mutation lymphatic phenotypes, both in terms of the bloated TD and the pericardial edema, in a dose-dependent manner. Overall, 130 drugs were tested, and 36 hits were identified, including receptor tyrosine kinase,

PI3K, and MEK inhibitors. GSK690693, a pan-AKT inhibitor, and Cabozantinib, a tyrosine kinase inhibitor, were further verified to revert the lymphatic phenotype, normalize patient's lymphatic endothelial cell sprouting, and block NRAS downstream pathways.

Conclusion: NRAS Q61R zebrafish models recapitulate KLA clinical features. Using this model, we established a pipeline for automated in vivo high-throughput KLA drug screening. Our analyses identified new therapeutic candidates for KLA.

Hyperactive KRAS/MAPK signaling disrupts normal lymphatic vessel architecture and function
Michael Dellinger (UT Southwestern Medical Center)

Purpose: Complex lymphatic anomalies (CLAs) are sporadically occurring diseases caused by the maldevelopment of lymphatic vessels. We and others recently reported that somatic activating mutations in KRAS can cause CLAs. However, the mechanisms by which activating KRAS mutations cause CLAs are poorly understood. Here, we report that inhibition of MAPK signaling in lymphatic endothelial cells (LECs) suppresses changes caused by active KRAS.

Methods: Lyve1-Cre mice were used to express an active form of KRAS (KRASG12D) or a dominant-negative form of MEK1 (Map2k1K97M) in LECs. Immunostaining was performed to visualize lymphatic vessels in tissue samples. Lentivirus particles were used to express GFP (vector control) or KRASG12D in primary human LECs. MTS assays were performed to assess cell proliferation and scratch assays were performed to assess cell migration. Changes in cell signaling were analyzed by immunoblotting and changes in gene expression were analyzed by RNA sequencing.

Results: We found that hyperactive KRAS signaling in LECs during embryonic development impaired the development of lymphovenous valves and led to the formation of enlarged lymphatic vessels. KRASG12D caused morphologic changes to LECs and stimulated their proliferation and migration. Expression of KRASG12D in LECs also stimulated PI3K/AKT and MAPK signaling and decreased the expression of genes that regulate the maturation of lymphatic vessels. To determine the effect of MEK1/2 inhibition on these phenotypes, cells were treated with trametinib. Trametinib decreased KRASG12D-induced changes in cell morphology, proliferation, and migration. It also decreased MAPK signaling and increased the expression of genes that regulate the maturation of lymphatic vessels. Blockade of MAPK signaling by expressing Map2k1K97M in LECs also suppressed KRASG12D-induced lymphatic vessel hyperplasia in embryos.

Conclusion: Our results suggest that one mechanism by which hyperactive KRAS/MAPK signaling causes lymphatic malformations is by inhibiting the maturation of lymphatic vessels. Taken together, our work further supports the testing of MEK inhibitors in CLA patients.

Precision Engineering of Patient-Specific Lymphatic Malformation Models Reveals Alpelisib Responsiveness and Unveils Non-Hot Mutations in the PI3K/Akt/mTOR Pathway
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Purpose: We aimed to determine the impact of non-hotspot mutations (NHMs) in lymphatic malformation (LM) progression, recurrence, and drug resistance. Despite the approval of alpelisib for pik3ca-related overgrowth, patient heterogeneity and mosaicism can limit the response to treatment.

Using a precision medicine approach, we reverse-engineered patient-matched LM organoids (LMOs) for in-vitro testing. Our goal was to isolate patient-specific cell lines, collect genomic data, and assess their responses to PI3K/Akt/mTOR inhibitors. This study emphasizes the importance of exploring NHMs in LMs and their potential implications in alpelisib treatment.

Methods: LM biopsies were expanded using hydrogels and lymphatic endothelial cells (LECs) were generated, followed by whole-exome and scRNA-seq. LMOs were formed from 3,000 LECs and embedded in sprout-inducing hydrogels. LMOs were treated with alpelisib (24uM), sirolimus (16uM), or vehicle control for 24h. Confocal microscopy was used to capture live/dead staining and branching data. Regression percentages were calculated, and the groups were compared using two-tailed unpaired t-tests.

Results: Treatment with sirolimus and alpelisib did not significantly affect the viability of LMOs, with most cell death occurring at the center of the organoid. Alpelisib treatment resulted in significantly higher sprout regression than sirolimus treatment for LMO3 ($p<0.05$) and 6 ($p<0.01$). Alpelisib did not significantly regress LMO5 sprouts. LMO3 exhibited over-proliferation and increased live-cell marker. Enrichment of LEC subtypes was characterized by scRNA-seq. Whole-exome sequencing identified 30 variants, including missense I391M in the kinase domain of pik3ca in LMO3, and 6. Shared NHMs (47% overlap) were also found in pik3cb, tp53, map3k1, pik3r2, and flt4.

Conclusion: We highlighted the presence of NHMs in patient cell lines and demonstrated a higher alpelisib regression response in samples with I391M in pik3ca. This in vitro platform effectively discerned drug responses, linking treatment responses to a more complex LM genetic background, which could help predict the patient's treatment response and disease outcomes.

The Antenatal and Perinatal Management of Fetuses with Extensive Lymphatic Malformations
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Purpose: To review fetuses with extensive lymphatic malformations (LMs) detected in-utero in whom consideration was given to life saving procedures (e.g. ante- and/or postnasal sirolimus, ex-utero intrapartum treatment (EXIT) to establish an airway, in-utero transfusions or amnioreduction).

Methods: A retrospective review of cases presenting between 2007 and 2023 to a regional fetal care centre with antenatally diagnosed extensive LMs of the head and neck (H&N), chest or extremities.

Results: N=18 fetuses with extensive LM involving the H&N (n=9), chest (n=7) and extremities (n=2) were managed. H&N: 9 fetuses had H&N LMs that varied in maximum estimated size between 133 and 1157 mL. Two of the 5 mothers with polyhydramnios required amnioreduction; 1 fetus required in-utero transfusion. Antenatal sirolimus was administered to 2 mothers; reducing the final estimated LM volume. There was 1 intrauterine death. An EXIT procedure was required in 6 of the remaining 8 fetuses. There were 2 additional deaths (during EXIT and postnatal withdrawal of care). Of the 5 neonates who survived, a tracheostomy was required in 4. All survivors received and responded to sirolimus and sclerotherapy. Chest: 7 fetuses had LMs of the chest wall that varied in estimated size between 38 and 360 mL. Polyhydramnios was present in 3; one required amnioreduction; another in-utero transfusions. One suffered an intrauterine death. 3/6 surviving fetuses received sirolimus and sclerotherapy. Extremities: 2 fetuses had extremity LMs that varied in size between 80 and 183 mL. In both cases, families chose termination of pregnancy.

Conclusion: Extensive LMs that are detectable antenatally require intervention especially when the airway is compromised. Typically, an EXIT procedure and eventual tracheostomy are required for survival for those with extensive H&N LM. Antenatal and early postnatal sirolimus may promote earlier regression of the malformation potentially allowing fetuses to survive with improved functional outcomes.

Predicting postnatal outcomes and therapeutic needs by combining pre- and post-natal imaging characteristics and clinical data in patients with neck lymphatic malformations versus cystic tumors
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Purpose: This study aims to (1) analyze MR imaging characteristics as predictors of lymphatic malformations (LMs) versus cystic tumors (e.g., teratomas), and (2) determine imaging risk factors associated with both invasive airway management at birth and requirements for more immediate therapeutic intervention.

Methods: A single-center 3-year retrospective analysis of prenatal fetal MR studies in patients with cystic neck masses was performed. 43 prenatal MR studies were included, and the imaging features evaluated were: macro/microcystic content, intra-cystic blood-fluid levels, calcification, tongue invasion, esophageal and tracheal compression/deviation, pattern of extension (invasion vs displacement), and mediastinal involvement. Postnatal clinical data, including delivery notes, post-natal MR imaging, and laryngoscopy results, were analyzed.

Results: The cohort comprised 37 LMs (86%) and 6 cystic teratomas (14%). Mean gestational age at time of prenatal diagnostic imaging was 29 weeks 3 days (range:19w 4d - 37w), and mean age at time of the postnatal MR imaging was 4 days. Imaging features for distinguishing between LMs and cystic tumors were: (1) pattern of lesion extension, specifically invasion (LM 96%) vs distortion (teratoma 100%); (2) tongue invasion (80% LM, 0% teratoma); and (3) presence of blood-fluid levels (60% LM, 13% teratoma). The pre-natal features most associated with invasive airway management (intubation/tracheostomy) at birth were: (1) tracheal compression (32.5% LM, 100% teratoma) and (2) tongue invasion (39% intubated) (Fig. 1). Neonatal interventions occurred in 65% and included sclerotherapy, surgical debulking, laryngoscopy, sirolimus, enteral nutrition support, or a combination.

Conclusion: Fetal MR features of neck LM such as infiltrative margins, extension to either the tongue or mediastinum, and fluid levels were the most reliable discriminators of LM versus other cystic neck masses. Prenatal detection of airway deviation and fetal tongue invasion were the best predictors of post-natal invasive airway management and need for therapeutic interventions, and thus may aid parental counseling and anticipate perinatal care needs.

An audit of the treatment costs of pediatric lymphatic malformations – a tertiary center experience
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VASCERN VASCA European Reference Center); Kristiina Kyrklund (Department of Pediatric Surgery, New Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki Finland; VASCERN VASCA European Reference Center)

Purpose: To assess care volumes and costs in pediatric vascular anomalies (VA), and to consider how healthcare resources could be optimally directed to enhance care protocols.

Methods: Case volumes and costs of care for several main VA diagnoses were retrieved from our tertiary institution's finance management database by ICD-10 codes. Nonsyndromatic pediatric lymphatic malformations (LMs) emerged as a high-cost subgroup. The records of patients <16 years of age with LMs (D18.1) managed 2018–2023 were reviewed.

Results: Care costs for LMs were EUR 3,456,000 for 265 patient care episodes. Costs ranged EUR 1,563,000–220,000/year and mainly related to long-term tracheostomy requirement and home nursing care, and multiple sclerotherapies under anesthesia. The highest costs were incurred in 2018 (Fig 1) when several patients had tracheostomies. In 2019, 2 patients were successfully decannulated and costs reduced by EUR 1,055,000. In total, 6 PIK3CA positive patients required a tracheostomy with the median decannulation time 34 (13–72) months. With increasing experience through ISSVA and VASCERN, our approach has now shifted to favor primary mTOR inhibitor treatment following initial tracheostomy in complex cases, reserving sclerotherapy only if these are not effective. Our data suggests the need for sclerotherapy has reduced in head and neck LMs. Sclerotherapies for peripheral LMs are increasingly being performed under local anesthesia, which further reduces treatment costs and simplifies the care pathways.

Conclusion: Our national health care system is predominantly based on public health care resources. Assessment of the financial perspectives of care is essential for demonstrating key targets for optimizing healthcare delivery by understanding the main cost drivers. In this analysis, LMs appear to be associated with a high financial burden, mainly from tracheostomy-related costs. Early introduction of mTOR inhibitors, when indicated, may reduce the need for sclerotherapy and permit earlier weaning from tracheostomy.

Comparisons of Clinical Features Between Pediatric and Adult Patients with Surgically-resected Abdominal Lymphatic Malformations

Min Yang (West China Hospital of Sichuan University); Cong-xia Yang (West China Hospital of Sichuan University); Yi Ji (West China Hospital of Sichuan University)

Purpose: We aimed to compare the clinical features of abdominal lymphatic malformations (ALMs) between pediatric and adult patients.

Methods: We retrospectively analyzed and compared the clinical data between pediatric (≤14 years) and adult (>14 years) patients who were surgically treated and pathologically diagnosed as ALMs at our institution from January 2009 to December 2022.

Results: Our study enrolled 162 pediatric and 158 adult patients. The male-to-female ratio for pediatrics and adults was respectively 82:80 and 52:106 (P=0.001). 42.6% pediatrics with ALMs were admitted to hospital through emergency channels, while that was 11.4% in adults (P<0.001). The mean duration of symptoms prior to admission for pediatrics was 4.69±10.9 months, which was statistically shorter than that for adults (10.93±24.19 months; P<0.001). The most common location of ALMs for pediatrics was small intestinal mesentery (42.6% VS. 6.3%; P<0.001), while that for adults was retroperitoneum (62.7%

VS. 15.4%; P<0.001). The most common clinical presentations at diagnosis for pediatrics was acute abdominal disease (45.1% VS. 12.0%; P<0.001), while that for adults was incidental health checkup (56.3% VS. 16.0%; P<0.001). There was no significant difference when comparing the maximum diameter of ALMs for both pediatric and adult patients (9.19±5.28 cm VS. 8.84±5.05 cm; P=0.118), as well as their pathological type (P>0.05). The proportion of chyliform contents of ALMs for pediatrics were significantly higher than that for adults (27.2% VS. 14.6%; P=0.006). ALMs for pediatrics combined with statistically more preoperative intestinal volvulus than that for adults (23.5% VS. 3.8%; P<0.001). The most common surgical procedure for both pediatric and adult patients was total resection of ALMs (98.8% VS. 98.1%; P=0.682), while resections with intestine were more frequently performed for pediatrics (32.7% VS. 6.3%; P<0.001).

Conclusion: ALMs between pediatric and adult patients differed significantly in gender, admission pathway, duration of symptoms, presentations, location, chyliform contents, intestinal volvulus and resections with intestine.

Kaposiform Lymphangiomatosis (KLA): Update on clinical features, treatment approach, and use of targeted medical therapy

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Purpose: Kaposiform lymphangiomatosis (KLA) is a rare and aggressive lymphatic anomaly first described as a distinct entity in 20 patients in 2014 [1]. Overall survival is very poor (51%) [1]. Historically, patients were treated with supportive care and surgical intervention. Recently, new medical therapies have emerged, including the use of mTOR and MEK inhibitors.

Methods: We conducted a retrospective review of clinical features and treatment outcomes for 57 patients diagnosed with KLA. All patients were referred to the participating treatment institutions between 1995 and 2023.

Results: The median age at symptom onset was 5.4 years (range 0-40.6). Anatomic involvement varied: lung (82%), abdominal (77%), bone (68%). Pleural effusions occurred in 72% and pericardial effusions occurred in 56%. Thrombocytopenia (platelet count <150,0000/uL) occurred in 63% and hypofibrinogenemia (fibrinogen <150 mg/dL) occurred in 50%. Sixty percent of patients required transfusions of blood products. Sixty percent of patients were treated with sirolimus for >6 months. Five-year overall survival was 56% in the non-treated group and 97% in the sirolimus-treated group (log-rank p-value=0.0013). Seven patients had genetic mutations identified: NRAS (n=5), KRAS (n=1) from tissue (n=4) or cell-free DNA (n=2). Due to toxicity (n=4) or disease progression (n=3) on mTOR inhibitors, 5 patients initiated therapy with trametinib. Three of these patients had no significant adverse events. Two patients stopped trametinib due to lower extremity swelling and are now doing well on selumetinib. Fifteen of the 57 patients died (24%).

Conclusion: Sirolimus significantly improved survival of patients with KLA. Despite this success, some patients have disease progression on sirolimus. There is emerging potential for molecular diagnostics and targeted therapies in KLA patients, particularly in those who become refractory to mTOR inhibition. Evaluating the safety and efficacy of targeted therapies in KLA will be an important area of future research.

Session 6: Combined Malformations

Genomic Characterization of Patients with Vascular Anomalies and Neurocutaneous Disorders Using Paired Exome Analysis and RNA Sequencing

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Purpose: Vascular, lymphatic, or capillary malformations, somatic overgrowth, neurocutaneous disorders, or vascular tumors, are caused by inherited and/or post-zygotic variants in the PI3K/AKT/mTOR and RAS/RAF/MEK signaling pathways. Here we describe the use of high-depth paired exome analysis to discern the genetic underpinnings of these disorders.

Methods: Comprehensive genomic profiling, including high-depth paired exome sequencing of a comparator germline sample and disease-involved tissue, and whole transcriptome analysis of disease-involved tissue, was performed across a cohort of 75 individuals affected with the disease entities. The capture panel is comprised of targets for 19,433 genes within the human genome (39 Mb of genomic space) in concert with a genomic backbone of probes, enabling the detection of SNV, CNV, and cnLOH.

Results: Among this cohort, 43 individuals had clinically significant variants (pathogenic/likely pathogenic by ACMG/AMP for germline or Tier I/II by AMP/ASCO/CAP for somatic), resulting in a diagnostic yield of 57%. Furthermore, we identified 7 individuals with germline pathogenic variation in which disease-affected tissues harbored second-hit variants, including 5 involving GLMN (glomuvenous malformation), and 1 each involving NF1 (neurofibromatosis), KRIT1 (cerebral cavernous malformations), and TSC1 (tuberous sclerosis). Second-hit variants in the form of were observed in three cases with GLMN germline variants (1p cnLOH), one case with KRIT1 germline variant (7q cnLOH), and one case with TSC1 germline variant (9 cnLOH), demonstrating the breadth of detection of disease-associated variation. We did not detect second-hit variants in the lesional tissues of three individuals

with germline pathogenic variation in GLMN, TSC1, and PTEN. The comparisons of inferred stromal and immune cell fractions derived from expression data between cases with and without the detection of second-hit variants did not show a significant difference.

Conclusion: High-depth paired exome sequencing extends the breadth of the detectable mutation spectrum in both germline and somatic vascular anomalies and neurocutaneous disorders.

Utility of cfDNA in comprehensive genomic profiling of complex vascular anomalies

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Purpose: To investigate comprehensive genomic analyses, including use of cfDNA, to aid in molecular diagnosis and guide medical therapies in complex vascular anomalies.

Methods: 358 individuals with complex vascular anomalies were evaluated from our institution. Routine exome (~80x), high coverage exome (>400x), UMI-based ultra-deep coverage targeted sequencing (~100,000x, panel of 51 genes), and blocker displacement qPCR/Sanger assay were applied to genomic DNA isolated from blood, saliva, lesional tissue, lymph node, FFPE, endothelial cells isolated from lymphatic effusions, and cell-free DNA (cfDNA) from plasma and lymphatic fluid.

Results: Pathogenic germline and somatic variants, unveiling new genotype-phenotype associations, were identified in 203 individuals (56.7%) across 40 different vascular anomaly diagnoses. All somatic variants were independently confirmed. Among participants harboring somatic variants identified in tissue DNA, 22 out of 39 participants demonstrated concordance in cfDNA (56.4%). Notably, 24 participants, for whom tissue biopsy was not possible, were found to have positive results with cfDNA isolated from peripheral blood with variant allele fraction (VAF) ranging from 0.2% to 18.2% (median 0.6%). These patients, because of lack of ability to safely obtain tissue, would have otherwise been unable to be included for genetic testing, potentially missing the opportunity for efficacious molecular-guided therapies. We found that cfDNA sampling after embolization/sclerotherapy increased molecular diagnostic likelihood in five participants with AVM, VM, PHTS, or KTS. cfDNA yielded relatively high positive rate (17/22; 77%) in participants with CM, KTS, FAVA, PROS, CLOVES, or extensive VM, suggesting its utility in patients with relatively high index in terms of disease volume and severity.

Conclusion: The use of cfDNA from plasma and chylous fluid provides a promising and less invasive alternative to resolve the genetic etiology, informing clinical diagnosis and enabling targeted therapeutics. Our comprehensive genomic platform, featuring extremely deep sequencing, has expanded our ability to discover somatic variants of VAF as low as 0.2%.

MEK inhibition restores dysregulated genes in human endothelial cells expressing the NRAS Q61R mutation identified in kaposiform lymphangiomatosis

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Purpose: Kaposiform lymphangiomatosis (KLA) is characterized by spindled lymphatic endothelial cells accompanying malformed lymphatic channels and elevated levels of Angiopoietin-2 (Ang-2). We have developed human endothelial progenitor cells (EPC) expressing the somatic NRAS Q61R mutation identified in the lesions of KLA patients. The purpose of these studies was to use RNA sequencing analysis to identify genes and pathways that were dysregulated in NRAS Q61R EPC and restored by MEK inhibitor trametinib, which is starting to be used clinically. The efficacy of three MEK inhibitors on abnormal endothelial spindling and Ang-2 expression was also assessed.

Methods: EPC were transduced with lentiviral constructs containing p.Q61R NRAS (NRAS Q61R) or wild-type NRAS (NRAS WT) under doxycycline (Dox) regulation. RNA was extracted from Dox-induced NRAS WT, NRAS Q61R, or NRAS Q61R EPC treated with trametinib (2nM) for 48 hrs. Bulk RNA sequencing analysis was performed. Additionally, EPC were treated with Dox and either trametinib (2 nM), selumetinib or cobimetinib (50, 100, and 200 nM), or vehicle for 48 hrs. EPC spindling was assessed with ImageJ and Ang-2 levels by western blot and ELISA.

Results: RNA sequencing revealed 1315 upregulated genes and 1773 downregulated genes in NRAS Q61R EPC. Trametinib corrected 19% of the upregulated genes and 8% of the downregulated genes, including genes associated with MAPK signaling, angiogenesis, and coagulation. Trametinib prevented EPC spindling morphology and reduced Ang-2 production (85%). At the highest dose, selumetinib and cobimetinib reduced Ang-2 production (82% and 90%, respectively) and inhibited spindling.

Conclusion: RNA sequencing analysis revealed dysregulated genes in the MAPK, angiogenesis, and coagulation pathways in EPC expressing NRAS Q61R. Studies using MEK inhibitors demonstrated that the MAPK pathway is driving abnormal spindling morphology and Ang-2 production in NRAS Q61R EPC. Trametinib reduced abnormal EPC spindling and Ang-2 production at a much lower dose compared to selumetinib and cobimetinib.

Clinical phenotype of the PIK3R1-related vascular overgrowth syndrome

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Purpose: The PIK3R1-related vascular overgrowth syndrome remains poorly defined clinically. We sought to determine the frequency of PIK3R1 variants in patients with segmental overgrowth, and to further describe the phenotype of patients harboring a mosaic PIK3R1 variant.

Methods: Patients were ascertained from a national cohort of skin mosaic phenotypes, including 623 patients with segmental overgrowth genotyped for PIK3CA. We searched for PIK3R1 variants by targeted NGS (next-generation sequencing) on affected tissue in 297 patients with a clinical presentation suggestive of PIK3CA-related overgrowth (PROS) negative for PIK3CA variants. We retrospectively studied the clinical phenotype of patients positive for PIK3R1 variants.

Results: We identified three missense variants and six in-phase indels of PIK3R1 in 15 patients (5.0%), exclusively in affected tissue, with variant allele fractions (VAFs) between 2.0% and 12.0%. All variants were predicted to upregulate the PI3K-AKT-MTOR pathway. We found extensive pale or dark capillary malformations (CMs) in 14 patients, segmental overgrowth in 11, venous development anomalies (varicose veins or persistent lateral marginal vein) in ten, lymphatic malformation in six, and an extensive café-au-lait macule or naevus spilus in three, thus defining phacomatosis pigmento-vascularis (PPV). Two patients had fingertip CM. One had limb hypoplasia and one had isolated hemihypertophy without VMs. Two had spinal involvement. No patients had MCAP (megalencephaly-capillary malformation) or life-threatening manifestations, and none were treated with sirolimus or alpelisib.

Conclusion: PIK3R1 variants account for a minority of patients with PROS-like phenotypes (5%). They are about 20 times less common than PIK3CA variants. Patients usually present with a Klippel-Trenaunay phenotype, whereas the MCAP phenotype appears to be absent. Whether venous development anomalies, limb hypoplasia or PPV are more common in PIK3R1-related KTS remains to be determined. We suggest that PROS be renamed "PI3K-related overgrowth spectrum" to include both PIK3CA and PIK3R1-related phenotypes.

New promising ways for sirolimus treatment: from continuous to intermittent administration of sirolimus in slow-flow vascular malformations

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Purpose: The VASE trial aims to establish sirolimus as the new standard of care for slow-flow vascular malformations. Conventionally, sirolimus is administered continuously, leading to accumulation of adverse events in some patients. There is a need for new administration schemes.

Methods: We conducted a prospective evaluation of different sirolimus regimens in patients initially enrolled in the VASE trial who experienced symptom resurgence after the 2-year sirolimus treatment. They resumed sirolimus for 3-6 months and were then allocated to various dosing schedules: 1) sirolimus for 5 days ON/ 2 days OFF (group A); 2) sirolimus for 3 months ON/ 3 months OFF (group B), 3) sirolimus as painkiller during pain episodes (group C) and 4) sirolimus as pain prevention before physical

effort (group D). The assessment focused on symptom control (pain and functional limitation) in these alternative regimens.

Results: Twenty-five patients were included in this analysis; at sirolimus reintroduction, 20 patients had pain (VAS score between 5-8) and 5 had functional limitations (VAS score between 5-7). All patients achieved symptoms control after 3-6 months of sirolimus (pain VAS between 0-2 and functional limitation VAS between 0-2). Nine patients were included in group A, 4 patients in group B, 4 in group C and 8 in group D. With a median follow-up of 9 months (ranging from 6 to 12), we observed that all patients maintained sustained symptom control without any deterioration in VAS scores. Adverse events were less frequently reported.

Conclusion: Sirolimus administration can be tailored to each patient with intermittent schedules, resulting in excellent symptom control and a reduction in adverse events.

Sirolimus for Vascular Anomalies Associated with PTEN Hamartoma Tumor Syndrome

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Purpose: PTEN Hamartoma Tumor Syndrome (PHTS) is a rare condition associated with vascular anomalies and heightened cancer risk via dysregulation of the AKT/mTOR pathway resulting from a germline mutation in the PTEN tumor suppressor gene. The use of sirolimus, an mTOR inhibitor, for managing vascular anomalies associated with PHTS remains relatively unexplored, with few documented cases. Investigating the outcomes of sirolimus treatment contributes to valuable collective experience regarding pharmacotherapy for this unique patient population.

Methods: A retrospective chart review of patients with PHTS and vascular anomalies treated with sirolimus was conducted at a single institution.

Results: The study identified six patients with PHTS and vascular anomalies, all treated with sirolimus. Their median age at treatment initiation was 12 years (range: 7 – 17). One patient had prior surgery, and another had surgery and sclerotherapy. All presented distinct germline heterozygous PTEN mutations, without discernible hot spots. All had macrocephaly, and three had developmental delay. Each had at least one arteriovenous malformation, with one displaying multiple additional venolymphatic malformations. After a median 2-year follow-up (range: 0.25 – 4), five patients (83%) exhibited a significant clinical response, including perceived reduced malformation size, pain relief, and improved function. Among the four patients with repeat magnetic resonance imaging, two showed size reduction, while two showed stability or minimal decrease. No significant adverse effects were observed, apart from mild buccal ulcers and acne.

Conclusion: This case series highlights the effective and safe use of sirolimus in managing vascular anomalies in a small group of children with PHTS. Larger studies are needed to substantiate these results. Intriguingly, sirolimus has demonstrated promise in animal PHTS models, prolonging survival,

and delaying cancer in PTEN knockout mice. While beyond this study's scope, this prompts questions about its potential dual role in treating vascular anomalies and preventing cancer in this population; long-term trials are required.

Adverse events during alpelisib and sirolimus treatment in PROS patients. A comparative study
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Purpose: Alpelisib is a PIK3CA inhibitor approved for the treatment of patients with PIK3CA-related overgrowth spectrum (PROS). Although there are many reports on adverse events (AEs) of alpelisib as adyuvant in breast cancer, there are only a few published alluding to AEs related to alpelisib in monotherapy in PROS patients.

Methods: Retrospective review of patients with PROS who received alpelisib through compassionate use was performed. Variables included age of treatment start, PROS phenotype, length of treatment, time of AEs appearance and grade of AEs.

Results: From the 39 patients included in the study, 70 AEs were recorded. Thirty-one patients presented at least one AE (79.5%) which was considered related to alpelisib, although most were graded mild or moderate (77.4%). The most frequently reported AE was alopecia (n=12), followed by diarrhea (n=10), anorexia (n=7) and fatigue (n=6). Another common AE not published before was growth retardation (n=9), found in children under 10 years old after at least one year of treatment, although every case resolved with dose adjustment or withdrawal. Most AEs were observed in the first year of treatment (64.5%), while some appeared later after dose escalation. At the time of this abstract there were 12 withdrawals (30.8%), only 3 related to AEs and due to patient/parent decision. The length of treatment was associated to the appearance of AEs (OR 9), while there were no differences with age or phenotype. Comparing these results with our previously reported experience in patients with PROS managed with sirolimus (92 patients of comparable age and phenotype), AEs were less frequent (44.5%) and less severe (83% mild or moderate) in the sirolimus group.

Conclusion: Most patients on alpelisib treatment will experience at least one AE, usually mild and/or moderate that resolve with dose adjustment or withdrawal. Sirolimus in similar patients produces less and milder AEs.

Accelerated Repurposing of Sotorasib for Vascular Malformations Associated with KRAS G12C Mutation
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Purpose: Arteriovenous malformations (AVM) are debilitating conditions caused by genetic mutations, either inherited or somatic when acquired during embryonic development. KRAS gain-of-function of mutations are frequently observed in sporadic AVM, particularly those involving the brain vasculature. Mechanism of disease progression in KRAS driven AVM are not well characterized and do not have approved treatments available.

Methods: We describe here two post-natal mouse models of KRAS G12C-vascular malformations that recapitulate patient phenotypes. We administered sotorasib, a targeted pharmacological inhibitor for KRAS G12C approved in oncology, to these models. Additionally, we treated a human patient with an AVM related to KRAS G12C mutation.

Results: Using these pre-clinical models, we demonstrate the effectiveness of sotorasib at improving vascular malformations and extending life expectancy. We further show that KRAS mutation specifically in arterial endothelial cells led to activation of the PI3K and ERK pathways in cells carrying the mutation but also in the surrounding ones, evocative of non-cell autonomous effect. On the basis of these results, we used sotorasib to treat an adult patient with a severely rapidly progressing KRAS G12C AVM. The patient experienced a rapid attenuation of disease symptoms, including the cessation of bleeding and a reduction in the size of the AVM. Imaging studies conducted at 12 and 24 months compared to the initial baseline showed a sustained reduction of 21.2% and 31.5% in AVM size, as well as a decrease in interstitial edema. Treatment did not cause any significant adverse events.

Conclusion: This study provides evidence that KRAS G12C direct inhibition may be a promising therapeutic approach for patients with KRAS G12C vascular malformations.

Percutaneous Sclerotherapy of Lymphatic and Venous Malformations with Osseous Involvement
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Purpose: Lymphatic (LMs) and venous malformations (VMs) with osseous involvement (OI) are uncommon vascular anomalies with limited literature. This study evaluates the effectiveness and safety of percutaneous sclerotherapy for treating vascular malformations with osseous involvement.

Methods: We performed a single-center retrospective review of all patients treated with percutaneous sclerotherapy from 01/2003 to 08/2023. OI was defined using MRI, based on osseous or periosteal involvement as assessed on T2 fat-suppressed sequences. We identified three and 21 cases of osseous LMs and VMs, respectively; one VM patient was excluded due to amputation of the fibula. We collected data on demographics, clinical presentation, treatment, adverse events, and clinical response. Clinical response was graded using a 7-point Likert scale assessing changes in pre- and post-treatment pain scores.

Results: Three non-Hispanic White male patients were treated for osseous LMs of the lower extremities. Patients presented with LMs between ages 10 and 18 with primary symptoms that include pain (3/3 patients), weakness (2/3) and swelling (1/3). Patients received 1, 3, and 3 sclerotherapy procedures specific to the intraosseous LM for a total of 6 procedures. Patients were embolized with bleomycin (1/6 procedures) or doxycycline (5/6). Patients reported mild (1/3) or moderate (2/3) improvement of symptoms following treatment. 20 patients were treated for osseous VMs of the lower extremities (11/20 patients), upper extremities (8/20), and face (1/20). Primary symptoms included pain (14/20), enlargement (5/20), and cosmetic deformity (3/20). Our institution performed 76 sclerotherapy procedures with bleomycin (24/76 procedures), ethanol (28/76), sotradecol (22/76), Onyx (1/76), and bleomycin/sotradecol combination (1/76). Patients reported no (7/20), mild (2/20), moderate (7/20), and significant (1/20) symptom improvement following treatment; three patients did not have follow-up notes after treatment. No major or minor adverse events were reported following sclerotherapy.

Conclusion: Percutaneous sclerotherapy is potentially a safe and effective treatment for lymphatic and venous malformations with osseous involvement.

Clinical features and advances in treatment of Gorham-Stout disease: a systematic review *Zilong Zhou (West China School of Medicine, Sichuan University); Yi Ji (West China Hospital of Sichuan University)*

Purpose: GSD is a subtype of complex lymphatic malformation, research on GSD is still very limited, making it difficult to diagnose and treat the disease clinically. The purpose of this study was to analyze the clinical features of GSD by screening the literature published in the last ten years and integrating the data.

Methods: A systematic search was conducted for all literatures on GSD from January 1, 2013 to January 1, 2023 to collect clinical information on all patients with GSD. Based on other authors' articles, we summarized the following four criteria to help diagnose GSD: (1) lymphangiectasia in lesion tissue biopsy, without cytotypy; (2) Imaging evidence of bone destruction; (3) Locally progressive bone resorption with little or no osteogenic reaction; (4) Genetic, metabolic, tumor, immune, infection etiology negative. The literature was excluded if any point was missing and the patient could not be definitively diagnosed with GSD.

Results: A total of 222 patients are included in the study, with a slightly higher incidence in males (male: female= 1.28:1). GSD mainly affect children and adolescents (73/122, 59.8%), 80% of patients are younger than 40 years old, the mean age of onset is 21.3 years old, and the mean age of diagnosis is 23.8 years old. The number of patients with axial bone invasion is more than that of appendicular bone (155 vs 105). The most affected bones are the vertebrates (43.4%), ribs (25.9%), and pelvic bones (23.4%). The most common clinical manifestation of GSD patients is pain (63.4%). After treatment, 96 patients are stable, and 12 died due to severe complications.

Conclusion: This study reveals the clinical characteristics and prognosis of patients with GSD, which is crucial for the early diagnosis and treatment of GSD. Further prospective studies are urgently needed to risk stratify complex lymphatic abnormalities and optimize the management of GSD.

Oncologic outcomes for patients with Ollier disease and Maffucci syndrome
Whitney Eng (Boston Children's Hospital/Dana Farber Cancer Institute)

Purpose: Ollier disease (OD) is characterized by multiple benign cartilaginous tumors known as enchondromas. When multiple enchondromatosis is associated with spindle cell hemangiomas it is known as Maffucci syndrome (MS). Somatic IDH1 and IDH2 mutations are identified in up to 80% of patients with OD or MS. Patients are at increased risk for chondrosarcoma and other malignancies. There are no universal or consensus oncologic screening guidelines, nor are there any FDA-approved medical treatments.

Methods: A retrospective chart review of patients diagnosed with OD or MS between 1980 and 2021 was conducted.

Results: Forty-five patients (22 males [45%], 23 females [51%]) were identified; 36 with OD, 8 with MS, 1 with multiple spindle cell hemangiomas. The median age at diagnosis was 5 years (range 2-14). Patients presented with pathologic fracture (20%) or discovery of a "lump" (33%). Functional limitation (48%) and pain (60%) were common. Five patients (4 with MS [83%], 1 with OS [17%]) developed malignancy between 10 and 29 years of age (mean 22.8 years); five are alive with an average follow-up of 7 years (range 1-24) after cancer diagnosis. One patient died from metastatic chondrosarcoma. Oncologic diagnoses included grade I/II chondrosarcoma (n=6), acute myelogenous leukemia (n=1), grade III anaplastic astrocytoma (n=1), and paraganglioma (n=1). Sequencing of tumor in 3 patients revealed IDH1 (p.R132C) mutations.

Conclusion: In our cohort, five patients (4 with MS, 1 with OD) developed malignancy prior to age 25, suggesting that cancer may develop in these patients earlier than has been reported in the literature. At our institution, patients are jointly followed by the Vascular Anomalies Center and Pediatric Cancer Genetic Risk Program and receive annual whole-body MRI and complete blood counts as well as imaging of known lesions. Larger, prospective studies are needed to assess the role of surveillance in pediatric OD/MS patients.

Analysis of related factors of functional impairment caused by fibro-adipose vascular anomaly (FAVA)
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Purpose: To investigate the factors associated with limb dysfunction in Fibro-Adipose Vascular Anomaly (FAVA) and identify independent risk factors.

Methods: Data from FAVA patients treated at our center between 2018 and 2023 were collected and divided into two groups based on functional disability. The variables analyzed included gender, age, pain history, clinical manifestations, lesion distribution, imaging examination results, laboratory test data, postoperative pathology findings, and other relevant information. The data were appropriately categorized and differences among the groups were compared to identify potential risk factors.

Results: A total of 202 diagnosed FAVA patients were included in the study, out of which 100 (49.5%) had limb dysfunction. These patients experienced an average duration of pain for 7.4 years. Additionally, 42% (n=42) showed increased D-dimer levels, 16% (n=16) had elevated fibrin degradation products (FDP), and 28% (n=28) exhibited decreased fibrinogen levels. Among those affected by FAVA in lower limbs (74%, n=74), a majority (89.1%, n=66) reported a history of claudication. In almost all cases (99%, n=99), deep tissues such as fascia, muscles, bones,and joints were involved by FAVA lesions. Prior to admission,treatment was received by approximately60%(n=60).

Conclusion: Factors contributing to limb dysfunction in FAVA patients include a history of pain lasting more than one year,pain intensity exceeding15cm2 under MRI scans,fibrinogen deficiency,and involvement of deeper tissues including muscles,bones,and joints. Early intervention targeting pain management,hemostatic abnormalities,and prevention of further progression can reduce the incidenceoflimb dysfunction.Inappropriate treatment may accelerate disease progression. Surgery currently remains the main stay of treatment for FAVA.

Session 7: Capillary Malformations

Generation of a mouse model for Capillary Malformation
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Purpose: Capillary malformation (CM), the most common type of vascular malformation, is a sporadic congenital lesion caused by a somatic GNAQ p.R183Q activating mutation in an endothelial cell (EC). Treatment for CM includes pulsed-dye laser and excision; drugs for CM do not exist. Our goal is to generate a murine CM model to study the pathophysiology of CM and to use as a preclinical model for CM pharmacotherapy.

Methods: A Gnaq p.R183Q-IRES-GFP cassette was inserted into the mouse R26 locus under control of the CAG promoter. To prevent expression a LoxP flanked gene trap (GT) was inserted downstream of the promotor. GT removal by Cre recombinase allows expression of GNAQ p.R183Q and GFP, with GFP allowing identification of mutant cells. By using a tamoxifen inducible Cre specifically expressed in ECs (Cdh5CreERT2) we activated GNAQ p.R183Q expression in ECs at a chosen developmental time.

Results: GNAQ p.R183Q and GFP was expressed in ECs of fetal and newborn mice using Tg-Cdh5Cre or Tg-Cdh5CreERT2 alleles. Tg-Cdh5Cre+/-;R26GT-Gnaq-GFP/+ animals featured a vascular phenotype at embryonic day (E) 14.5 and died by E16.5. Histology showed abnormal blood vessels, most prominently in the developing skin. Tg-Cdh5CreER+/-;R26GT-Gnaq-GFP/+ animals in which EC GNAQ p.R183Q expression was induced with tamoxifen at postnatal (P) day 1 died between P15 and P37. They displayed diffuse vascular abnormalities that were macroscopically noticeable in the intestines and skeletal muscles. Blood vessels contained both recombined (GNAQ p.R183Q/GFP expressing) and non-recombined ECs. GNAQ p.R183Q expressing cells co-localized with enlarged and tortuous areas of blood vessels.

Conclusion: We generated a conditional EC specific GNAQ p.R183Q mouse model of CM. Mutant animals developed vascular malformations in the intestines. These results support the causality of the human CM mutation. This murine model can be used to study the pathophysiology of CM as well as testing pharmacotherapy.

Endothelial permeability in mosaic GNAQ p.R183Q driven capillary malformations

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Purpose: Capillary malformations (CM) are slow-flow vascular malformations present at birth. They are most often cutaneous but in the rare neurocutaneous disorder Sturge Weber syndrome (SWS), patients additionally have leptomeningeal and ocular CMs. Ninety percent of CMs are caused by a somatic activating mutation in GNAQ, the gene encoding the α-subunit of the heterotrimeric G-protein Gαq. The p.R183Q mutation is present in endothelial cells (EC), and EC expressing the GNAQ p.R183Q mutation – designated EC-R183Q - are sufficient to recreate enlarged, CM-like vessels in mice.

Methods: We observed that blood vessels in skin and brain lesions from SWS patients exhibit extravascular fibrin and absence of the tight junction protein zona occluden-1 (ZO1), indicating a defect in endothelial barrier formation in CM. To explore this likely consequential feature of CM, we investigated the nature of the diminished endothelial barrier by measuring trans endothelial electrical resistance (TEER) in EC-R183Q compared EC-wild type (WT).

Results: We found EC-R183Q form a significantly reduced endothelial barrier in the TEER assay, which can be fully restored using a specific inhibitor of Gαq; this verifies the reduced barrier is due to constitutively active mutant Gαq. We speculate that the EC-R183Q exert a dominant effect on nearby EC-WT. To model this and examine functional consequences, we tested the effect of increasing percentages of EC-R183Q, from 5-75%, in an EC-WT monolayer. TEER measurements showed that cultures with 10% EC-R183Q:90% EC-WT formed significantly weakened barriers. This suggests that the mutant EC-R183Q negatively affect the ability of EC-WT to form an endothelial barrier. Small molecule

inhibitors and shRNA knockdown of key players such as ANGPT2 reveal signaling pathways for restoring the endothelial barrier to CM vessels and reducing vascular permeability.

Conclusion: In summary, TEER shows GNAQ p.R183Q EC exhibit reduced endothelial barrier formation and allows modeling of the somatic mosaicism, a pathological feature of CM.

Development of an AlphaLISA high-throughput technique to screen for targeted pharmacotherapy for capillary malformation

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Purpose: Capillary malformation (CM) is a slow-flow vascular anomaly characterized by clusters of dilated, malformed venule-like vessels within the papillary dermis. Lesions can be sporadic or part of a syndrome (ie. Sturge-Weber Syndrome). Nearly all CMs contain a somatic mutation in the GNAQ gene. To date, no CM endothelial cell (EC) model exhibits stable knock-in of the GNAQ p.R183Q mutation under the control of the endogenous promoters and enhancers of the gene. The purpose of this study was to: (1) create a novel, stable GNAQ mutant EC line and (2) develop a high-throughput screening (HTS) assay for identifying targeted pharmacotherapies for CM.

Methods: Utilizing CRISPR-Cas9, the GNAQ p.R183Q mutation was introduced into immortalized arterial endothelial cells (teloHAECs). Digital droplet PCR (ddPCR) and Western Blot was conducted comparing mutant and control cells. For in-vitro drug experiments, cells were plated at 20k cells/cm2 and treatments applied for 24-hours. Conditioned culture media was collected and processed for angiopoietin-2 (ANGPT2) protein levels using AlphaLISA.

Results: Phenotypic analysis of GNAQ p.R183Q teloHAECs reveal expected expression of mutant transcript and elevated levels of phosphorylated phospholipase C-beta 3. A key regulator of vessel formation, ANGPT2, was confirmed upregulated 2.4- to 7.2-fold in mutant compared to control cells. Treatment of mutant cells with Trametinib (MEK inhibition), YM 254890 (Gaq-protein inhibitor), Sotrastaurin (PKC inhibitor), and VS-4718 (focal adhesion kinase inhibitor) show reduction of secreted ANGPT2 by 3.2- to 6.8- fold. Our AlphaLISA HTS assay preliminarily reveals a Z1 factor of 0.69 and a signal to noise ratio of 51.6.

Conclusion: Our teloHAEC model is a stable, easy to use cell model for CM that recapitulates many previously published molecular findings associated with the GNAQ p.R183Q activating mutation. Our model coupled with the successful development of a robust, ANGPT2 based AlphaLISA HTS pave the way for the identification of targeted pharmacotherapy for CM.

Somatic mutations GNAQ183 do not only cause Port Wine Stain/Capillary malformation: Troncular venous abnormalities in a series of patients.

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Purpose: Geographic capillary malformations on lower limbs, as seen in conditions like Klippel-Trenaunay Syndrome or CLOVES, are often associated with a persistent marginal vein and other vein abnormalities. Pale/reticulated lower limb capillary malformations may also have associated varicosities, a condition oten referd to as capillary-venous malformation of the lower limb. However, The development of varicosities, atrophie blanche or venous ulcers, in patients with port-wine stains/capillary malformations (PWS/CM) due to GNAQ183 somatic variants is less recognized.

Methods: In this retrospective study, we reviewed electronic and photographic records from five institutions to comprehensively describe venous anomalies in patients with GNAQ183 CM of the limbs.

Results: Twenty-two patients (9 M/14 F, mean age: 24 years) with CM due to somatic GNAQp.R183Q variants in the lower extremities were included. Superficial and/or deep vein abnormalities were observed, with dilated veins typically not visible at birth but developing later (between 19 months and 10 years). Some patients exhibited atrophie blanche and darkening of CM at older ages, and four developed venous ulcers (two before 25 years). None presented with deep vein thrombosis or pulmonary thromboembolism. Imaging studies (Doppler ultrasound or MRI) in 20 patients revealed various abnormalities, including agenesis or hypoplasia in 12 cases, aberrant drainage through superficial veins in 9, and persistent embryological veins such as marginal veins in 3.

Conclusion: Patients with GNAQ183 CM of the limbs may be misdiagnosed with Klippel-Trenaunay syndrome. Recommendations include regular Doppler ultrasound, especially beyond 10 years of age, and for those with vein anomalies: monitoring of D-dimers and fibrinogen, education on thrombosis risk, avoidance of prothrombotic factors, and the use of compression stockings. Larger prospective studies are needed to fully understand the incidence of venous abnormalities in these patients.

Application of Artificial Intelligence in Quantitative Evaluation of Facial Port-Wine Stains

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Purpose: The efficacy evaluation of port-wine stains (PWSs) consists of subjective and objective evaluations. Subjective evaluation is mainly the visual analogue score (VAS) assessed by clinical doctors, while the objective evaluation includes spectrometer measurements, dermoscope measurements, and other imaging examinations. Spectrometer is the most commonly used quantitative evaluation method in PWSs quantitative evaluation, however, its accuracy is influenced by the force and measure point while measuring. This study is to accurately quantify PWSs, thus to assist both doctors and patients in efficacy evaluation and disease management.

Methods: We used the standard pictures from our patients database to build a system that were able to automatically and objectively evaluate the efficacy of PWS treatment by combining deep learning based image segmentation and three-dimension face reconstruction. To verify the reliability of this system, we then asked the system and five relevant clinical doctors to evaluate the area changes of 20 PWSs patients after receiving one session of photodynamic therapy.

Results: The system was built successfully. Pearson correlation analysis showed a good correlation between the evaluation of this AI system and the evaluation of clinical doctors ($r=0.9137$, $P<0.01$). Weighted Kappa indicates good consistency ($\kappa= 0.78$), confirming the reliability of this artificial intelligence quantification system.

Conclusion: This system could reconstruct the three-dimension model of PWSs, accurately quantify the lesion area, and evaluate the efficacy by assisting in calculating the changes of the lesion before and after treatment. Our artificial intelligence quantification PWSs evaluation system can provided an innovative model for the application of artificial intelligence in PWSs quantification evaluation.

Comparison of pulsed dye Laser Medicine and photodynamic therapy in the treatment of port-wine stain: a retrospective paired control study

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Purpose: port-wine stain (PWS) is the most common congenital vascular malformation. Pulsed dye laser (PDL) is the gold standard therapy in the world, but its therapeutic efficiency is limited. Since the application of photodynamic therapy (PDT) in PWS in 1990s, the therapeutic effect of PWS has been significantly improved. However, there are many unknowns about the efficacy, safety, application scope

and influencing factors of PDL and PDT. This study compared the clinical efficacy and safety differences between PDL and PDT in the treatment of PWS through a retrospective paired control study.

Methods: A retrospective paired control study was conducted to analyze 60 PWS patients who had been treated with PDL or PDT only for 3 times, respectively, to compare the overall efficacy and safety differences between the PDL group and the PDT group, and to compare the influence of different anatomical site lesions on the efficacy and safety of both.

Results: The overall effective rate and significant efficiency of PDT group were higher than those of PDL group. The curative effect of PDT group was significantly higher than that of PDL group in V1, V2 and V3, but there was no significant difference in neck. In the PDT group, lesion localization had no effect on the efficacy, while PDL had poor effect on the V2 lesions.

Conclusion: PDT and PDL are effective noninvasive treatment for PWS. Compared with PDL, PDT showed significantly higher efficacy for facial lesions. For PDT, different facial regions had no significant effect on the efficacy, while PDL had a poor effect on V2 region.

Staged Surgical Correction for Patients with Facial Port-Wine Stains

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Purpose: The majority of patients with port-wine stains commonly develop soft-tissue and/or bony hypertrophy leading to facial asymmetry, functional deficits and psychological problems. This study analyzes the structural deformities of facial PWS and provides corresponding surgical solutions.

Methods: We conducted a retrospective case review of facial capillary malformations patients who underwent surgical procedure(s) in our vascular anomalies center from 2010 to 2023. We assessed their medical records and photographs. Three-dimensional computed tomography was conducted to evaluate bony asymmetry, and enhanced magnetic resonance imaging was analyzed to estimate soft-tissue hypertrophy.

Results: Of the 280 patients who presented with facial port-wine stain, 231 (82.5 percent) had soft-tissue hypertrophy in one or more dermatomes, resulting in facial asymmetry. Only 25.49 percent of patients had V1 involvement and all of these cases combined with other dermatomal involvement, 38.8 percent had exclusive V2 involvement, 19.6 percent had solely V3 involvement, 17.6 percent had V2 and V3 involvement. The most common hypertrophic manifestations were macrocheilia, prominent malar complex and parotid gland hypertrophy on the affected side. In this study, surgical procedures included

fractional resection, complete resection followed by local flap or skin graft transplantation, two-staged surgery applying adjacent or free expanded flaps or expanded prefabricated flap, superficial parotidectomy combined with the dissection of the facial nerve, macroglossia reduction, genioplasty, zygomatic reduction and orthognathic surgery. The technique and incisions used for each facial zone are described in detail. In all cases, incisions were placed along existing boundaries of facial subunits. Serial pulsed-dye laser or photodynamic treatments were also performed.

Conclusion: More than 80 percent of patients with facial capillary malformation experience soft-tissue hypertrophy with or without bony remodeling. Tailored surgical designs are necessary to address different deformities. We describe staged surgical treatments for these patients to achieve the best aesthetic appearance while preserving and restoring maximum function.

Macrocephaly Associated with Sturge-Weber Syndrome: Presentation of Two Cases

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Purpose: Sturge-Weber syndrome (SWS) is a neurocutaneous disorder that associates a facial port-wine stain (PWS) and venocapillary malformations in meninges and/or eye. Complications include glaucoma and neurological symptoms, but also bony and/or soft tissue overgrowth ipsilateral to the PWS. We describe the atypical cases of two children with SWS with extensive PWS, associated with a pronounced and progressive macrocephaly.

Methods: -Patient 1: 2-year-old girl with extensive PWS. Brain MRI at one month of life did not detect indirect signs of SWS. Ophthalmologic examination was normal. At 3 months of age she started a progressive increase in head circumference (HC percentile >99). At 12 months of age she presented her first epileptic seizure. -Patient 2: 7-year-old boy diagnosed with pigmentovascular phacomatosis. Brain MRI at 2 years of age showed asymmetric enhancement of the choroid plexus. At 4 months of age, he started a progressive increase in head circumference (HC percentile >99). He has never presented epileptic seizures or stroke-like episodes. At the age of one year he required a trabeculectomy for glaucoma. Brain MRI at one year of life in both patients showed a striking bony thickening of the diploe associated with marked cerebral cortical atrophy. Genetic study performed on a skin sample, detected a somatic mutation in GNAQ183 in both patients.

Results: -In recent years, early brain MRI has proven useful in identifying indirect signs of leptomeningeal angiomatosis but they are not universally identifiable in all cases. -We present 2 exceptional pediatric cases of SWS that debuted with a risky facial PWS and progressive macrocephaly and cranium overgrowth without indirect radiological signs characteristic of leptomeningeal angiomatosis.

Conclusion: -Macrocephaly in patients with PWS is not specific to PROS syndrome. -The genetic study is useful in the diagnosis of atypical forms of complex vascular syndromes and allows the follow-up of patients with possible complications.

Session 8: Other Studies in Vascular Anomalies I

Double non allelic somatic activating oncogene variants in a series of vascular anomalies.
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Purpose: In contrast with multiple somatic alterations found in malignancies, activating somatic variants in vascular anomalies (VAs) usually involve a single oncogene. The identification of multiple non-allelic variants in tissue from vascular anomalies has rarely been reported, and their frequency and pathogenicity remain unknown.

Methods: We performed deep next generation sequencing (NGS) using a 55-gene panel in 237 affected tissue samples from 202 patients referred for various skin birthmarks, including vascular anomalies. The phenotype of patients harbouring two non-allelic somatic variants was further characterized.

Results: Three adult patients with vascular anomalies (1.5%) each harboured two non-allelic oncogene variants, previously reported as pathogenic, in affected tissue. Patient #1 had an extensive congenital melanocytic nevus on her trunk overlapping a scapular intramuscular venous malformation, harbouring NRAS and TEK variants. Patient #2 had a PIK3CA-related overgrowth spectrum (PROS) phenotype, with an extensive pale capillary malformation (CM). A darker superimposed linear CM on her neck harboured PIK3CA and GNAQ variants. Patient #3 had an extensive CM on his face, trunk, lower limbs, and right arm where GNAQ and PIK3CA variants were found. In all cases, a major variant with a VAF >10% and one with a lower VAF (<2%) were present.

Conclusion: The frequency of double non-allelic somatic variants in VAs had not previously been estimated form multiplex gene sequencing. Superimposed hamartomas ("twin spotting") involving two different cell lineages in patient #1, as well as the pattern of CMs in patient #2, suggest that both variants were early-onset drivers of the phenotype in the embryo, although different VAFs suggest that they were asynchronous. In contrast, the PIK3CA variant in patient #3 appears as a late-onset event occurring on a congenital CM harbouring a GNAQ variant, as previously reported with BRAF and NRAS variants in secondary pyogenic granulomas arising on CMs.

Assessment of gene–disease associations and recommendations for genetic testing for somatic variants in vascular anomalies by VASCERN-VASCA
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PURPOSE: Vascular anomalies caused by somatic (postzygotic) variants are clinically and genetically heterogeneous diseases with overlapping or distinct entities. The genetic knowledge in this field is rapidly growing, and genetic testing is now part of the diagnostic workup alongside the clinical, radiological and histopathological data. Nonetheless, access to genetic testing is still limited, and there is significant heterogeneity across the approaches used by the diagnostic laboratories, with direct consequences on test sensitivity and accuracy. The clinical utility of genetic testing is expected to increase progressively with improved theragnostics, which will be based on information about the efficacy and safety of the emerging drugs and future molecules. The aim of this study is to make recommendations for optimising and guiding the diagnostic genetic testing for somatic variants in patients with vascular malformations.

RESULTS: Physicians and lab specialists from 11 multidisciplinary European centres for vascular anomalies reviewed the genes identified to date as being involved in non-hereditary vascular malformations, evaluated gene–disease associations, and made recommendations about the technical aspects for identification of low-level mosaicism and variant interpretation. A core list of 24 genes were selected based on the current practices in the participating laboratories, the ISSVA classification and the literature. In total 45 gene–phenotype associations were evaluated: 16 were considered definitive, 16 strong, 3 moderate, 7 limited and 3 with no evidence.

CONCLUSION: This work provides a detailed evidence-based view of the gene–disease associations in the field of vascular malformations caused by somatic variants. Knowing both the gene–phenotype relationships and the strength of the associations greatly help laboratories in data interpretation and eventually in the clinical diagnosis. This study reflects the state of knowledge as of mid-2023 and will be regularly updated on the VASCERN-VASCA website (https://vascern.eu/).

The Mini-Multidisciplinary Vascular Anomalies Team Clinic: Steps to Improve Patient Access and Volumes

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Purpose: Multidisciplinary teams are important in the management of complex vascular anomalies as multimodal treatment approaches are employed for optimal patient outcomes. At large centers, teams can exceed over 10 disciplines with numerous providers and ancillary support. The coordination of large teams can limit the number of clinics and available patient visits although, frequently, the entire team is not required for each patient. Thus, we created a mini-multidisciplinary team (MMDVT) to improve access, reduce wait time, and execute team strategies without requiring the entire team.

Methods: A MMDVT of two providers with specialty support was developed. Evaluation of patient volumes, speed to clinic access, vascular diagnosis, and care coordination was performed with comparison to the traditional team clinic.

Results: Weekly MMVDT clinics were organized for each of the two involved team leaders with simultaneous sessions in the same hallway. Six to eight patients were scheduled per hour in each clinic session. In less than 4 months, over 200 regional patient visits were conducted with expedited access to care and included all vascular anomalies diagnosis. Coordination to appropriate treatment was performed via electronic medical record messaging and scheduling. This compares to less than 80 patients in the traditional multidisciplinary team clinic. Better directed referrals to the full multidisciplinary team was a secondary benefit.

Conclusion: Patient access and volumes can be improved with mini-multidisciplinary vascular team clinics in comparison to full teams. We herein explain the process to create and support the MMDVT using available resources and vascular coordinators.

A Precision Medicine Approach for Vascular Anomalies: Clinical Impact of Molecular Testing in 315 Patients Treated at a Single Center

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Purpose: Recent discoveries have demonstrated that vascular anomalies arise primarily due to somatic variants in cancer genes. While molecular profiling has become a mainstay of diagnostic testing in cancer, its adoption in the clinical care of patients with vascular anomalies has not been ubiquitous.

Methods: We evaluated the clinical utility of molecular profiling in vascular anomalies patients at a single institution. We report on diagnostic clarification, identification of clinically actionable variants, and use of targeted therapies. Pre-testing diagnoses were established via expert interdisciplinary review of patient presentation, imaging, and histopathology. Post-testing diagnoses incorporated genetic findings identified via molecular profiling.

Results: Variants in PIK3CA were identified in 47% (149/315) of all patients. Identification of PIK3CA variants supported the pre-testing diagnosis in 82% (122/149), namely in PROS (for example, KTS, MCM, FAVA, CLOVES) or isolated LM. Eighty-six percent of all PIK3CA variants identified occurred in one of 5 hotspots (C420R, E542K, E545K, H1047L, H1047R). Both targeted NGS and ddPCR testing identified variants at low variant allele frequencies (average VAF = 6.9%). Five patients with a pre-testing diagnosis of CLOVES had variants in PIK3R1. Several patients had variants in the RAS-MAPK pathway: MAP2K1 (n=10), NRAS (n= 5), KRAS (n= 8), BRAF (n= 6), SOS1 (n=5). Variants were also found in AKT (n=1), GNAQ (n=4), GNA11 (n=2), RASA1 (n=3), PTEN (n=6). Targeted NGS led to diagnostic reclassification (n=21) and identification of potential germline cancer predisposition (n=12). Molecular profiling demonstrated actionable variants in 72% (226/315) of patients. As a result of genetic testing, 39 patients initiated targeted medical therapy [alpelisib (n=19), miransertib (n=8), trametinib (n=16), selumetinib (n=2)].

Conclusion: Our study demonstrates the clinical utility of using a precision medicine approach in patients with vascular anomalies, as this testing provided diagnostic clarity, identified actionable variants, and provided support for the use of targeted therapies.

Improvement of histopathological diagnostics of vascular anomalies through spatial deep-phenotyping using non-destructive 3D histopathology

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Purpose: For histopathological analysis and subsequent diagnosis of diseased tissues a fast and accurate histopathological analysis of biopsied tissues or surgical specimens are essential. However, the 2-dimensional slide-based histopathological analysis does not represent tissue structures and molecular targets sufficiently, which aggravates an accurate and spatial analysis of the tissue.

Methods: To overcome these limitations, we have established a 3D histopathology approach based on non-destructive volumetric Light-sheet microscopy, which bears the potential to revolutionize the way pathological analysis are done. In comparison to conventional 2D pathology, non-destructive 3D histopathology allows rapid slide-free histological imaging of a whole tissue sample, volumetric analysis of diagnostic relevant structures such as immune cells or vessels as well as an improved spatial analysis of cells and cell distribution relevant to study e.g. the vascular microenvironment. To achieve this, we have successfully established a fluorescence-based analogue of the histological gold-standard staining method, hematoxylin and eosin (H&E) staining, suitable for Light-sheet microcopy. In combination with codon reassignment technology and nanobody-based staining protocols detecting relevant markers such as immune cells, vessels or proliferation state, this approach offers cutting-edge diagnostic phenotyping of the specimen. Due to the non-destructive nature of the optical sectioning methodology, the sample is available for downstream applications such as molecular diagnostics of the previously imaged specimen.

Results: Using this approach, we were able to identify new vascular phenotypes, which will set the basis for future improved histological classification. Newly identified spatial phenotypes of various vascular anomalies will be presented.

Conclusion: In summary, this innovative approach for 3D-histopathology allows more sophisticated and detailed diagnosis of tissue samples from patients with vascular anomalies and has the potential to become the new gold standard in histopathological analysis.

Bridging Cells and Cures: From Mechanisms to Dual Approach to Target Endothelial and Intervascular Stromal Cells for Vascular Anomaly Treatment

Johanna P. Laakkonen (Assoc. Prof, Ph.D.)

Purpose: Venous Malformation (VM), Angiomatosis of Soft Tissue (AST) and FAVA are benign congenital vascular anomalies that predominantly affect veins. More effective therapies are needed for symptomatic patients. We have identified that, in addition to mutation harboring endothelial cells driving the lesion formation, other cell types, notably fibroblasts, significantly contribute to venous lesion vascularization. Fibrous connective tissue is present around vessels in AST or FAVA, and sclerotherapy can induce secondary fibrosis in VM.

Methods: To investigate the crosstalk of endothelial cells and fibroblasts and its effect on vascular lesion growth VM/AST patient samples, RNA-sequencing, cell culture techniques, small molecule inhibitors, and a xenograft mouse model were used.

Results: Our studies demonstrated that fibroblasts induce pro-angiogenic endothelial cell phenotype via the ErbB and VEGFR2 pathways. Patient-derived fibroblasts were shown to secrete multiple factors regulating neovessel formation. Fibroblasts were further shown to increase vascularization of PI3K-driven venous lesions in mice. As a proof-of-concept we showed that treatment with afatinib, inhibitor of ErbB ligands, effectively reduced vascularization in PI3K-driven venous lesions in mice. We have further explored the the therapeutic potential of dual-targeted inhibition of both endothelial and intervascular stromal cells.

Conclusion: Our findings highlight the importance of the cellular microenvironment in regulating venous lesion formation and suggest that a dual therapeutic approach, targeting both intervascular stromal cells and endothelial cells, could be a potential strategy in treating venous lesions with a fibrotic component.

Evaluation of content and readability of ChatGPT-generated Educational Materials for Vascular Anomalies

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Purpose: ChatGPT, a large language model, uses artificial intelligence to generate human-like responses to prompts. The purpose of this study was to explore the utility of ChatGPT to generate educational content for a vascular anomalies center website.

Methods: ChatGPT was provided the prompt: "Generate medical website content about [diagnosis] with the headings "Overview," "Signs and Symptoms," "Diagnosis", "Genetics," and "Treatment", 200 words total, at a 10th-grade reading level" for three diagnoses (venous malformations, infantile hemangiomas, and PHACE syndrome). The content was scored by vascular anomalies experts and graded on accuracy, level of medical detail, writing style, and completeness on a scale of 1 (strongly disagree) to 5 (strongly agree). Reading level and word count were assessed with Microsoft Word.

Results: Eight attending physicians with expertise in vascular anomalies (three pediatric dermatologists, three pediatric hematology-oncologists, one neuro-interventional radiologist and one diagnostic

radiologist) participated. Content for venous malformations was highest-rated in Accuracy and Completeness. PHACE syndrome content was rated lowest in these categories. Specifically, readers commented on inaccuracy around imaging recommendations and a superficial writing style. Content on infantile hemangiomas lacked details about specific medications and treatment expectations. Flesch-Kincaid reading level and word counts were calculated as follows: Venous Malformations (grade 13.4, 291 words), Infantile hemangiomas (grade 13.9, 302 words) and PHACE syndrome (grade 15.4, 296 words).

Conclusion: Clinical information generated by ChatGPT has relevance and much of the content is accurate with good readability. However, our study highlights limitations including a paucity of complete and accurate information on genetics as well as diagnostics and therapies. Specifications of grade level and word count varied by up to 5.4 grade levels and 102 words. Large language models have potential for aiding clinicians in efficiently generating information for patients and other providers. However, true clinical utility currently will require heavy modification to improve content.

Case Series of Prenatal Administration of Sirolimus (Tolerance and Efficacy)

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Purpose: Present postnatal outcomes of fetuses diagnosed with complicated vascular anomalies that received prenatal sirolimus at a quaternary care center.

Methods: Four mothers pregnant with fetuses with complex vascular anomalies were treated with sirolimus starting from 27-29 weeks gestational age to delivery (range of prenatal therapy: 3-9 weeks). Babies were followed from birth to current date, 8-24 months old.

Results: Prenatal presentation: Fetus 1 - CLOVES phenotype with massive overgrowth of right upper extremity and large chylothorax, required 2 pleuro-amniotic shunts before sirolimus. Fetus 2. Klippel-Trenaunay phenotype with extensive intra-abdominal, pelvic and left lower extremity capillary-veno-lymphatic malformation. Fetus 3: cervical lymphatic malformation with airway extension. Fetus 4: Turner syndrome and large chylothorax that required 4 pleuro-amniotic shunts placement before sirolimus. All mothers tolerated sirolimus well with mild side effects (mucositis, fatigue and a vaginal fungal infection). Sirolimus daily doses ranged between 4-8mg po daily targeting trough levels of 8-12ng/ml. Postnatal outcomes: 1. CLOVES phenotype - pleural effusions responded promptly to sirolimus and did not require thoracentesis after birth. Spent 102 days in neonatal intensive care unit (NICU). Patient continues sirolimus due to large venous and lymphatic malformations. 2. Klippel-Trenaunay phenotype - Spent 7 days in NICU. Continues on sirolimus. 3. Cervical lymphatic malformation, 82-day NICU stay due to difficulty feeding. Was on sirolimus for 14 months and now off doing very well. 4. Turner syndrome with chylothorax and lymphedema, effusions decreased significantly while on sirolimus prenatally and did not require intubation, thoracentesis, or sirolimus after birth. 9 days NICU admission. Continues follow-up for lymphedema.

Conclusion: All mothers tolerated therapy well. No unexpected congenital anomalies outside of the vascular malformations known before prenatal sirolimus administration were identified in 2 years monitoring. Prenatal sirolimus is not a cure for vascular anomalies but can possibly decrease the immediate post-natal complications and invasive procedures.

How to increase the safety of surgical excision of facial vascular malformations. The role of adjuvant intraoperative technologies in avoiding complications.

Rebecca Rossener (University of São Paulo, Brazil); Dov Charles Goldenberg (University of Sao Paulo Medical School); Marilia Emi Sato Ito (University of Sao Paulo); Rolf Gemperli (University of São Paulo, Brazil)

Purpose: To evaluate surgical time, bleeding and facial palsy after surgical treatment of facial vascular malformations using ultrasonic scalpel and intraoperative facial nerve monitoring.

Methods: Cross-sectional retrospective analysis of a series of extracranial head vascular malformation operated by the same surgeon. Surgical resection was accomplished with use of harmonic scalpel and intraoperative facial nerve monitoring. Facial nerve monitor was used for dissection and protection of nerve branched during access and resection of the malformations. Patients' demographic data were studied, as characteristics of the malformation. Proposed outcomes were surgical time in hours, postoperative facial paralysis, bleeding and need for transfusion.

Results: Twenty-two cases were evaluated (2008-2023). Malformations were mostly venous (50%) and arteriovenous (40,9%). Ultrasonic scalpel was used in 12 cases (54.54%). Facial nerve monitor was used in 66.67% of cases, where the lesion was located, or surgical access crossed the territory of the facial nerve. The average procedure duration was 3.8 hours. In contrast, in cases where ultrasonic scalpel was used, it was 3.25 hours. Partial facial paralysis was diagnosed as permanent in 9.09% and transient in 4.54%. In the ultrasonic scalpel group, there were no cases of permanent facial paralysis. Despite facial nerve monitoring, 15.38% permanent facial nerve changes and 7.69% transient were observed. In all cases it was selective and related to muscular resection. In 9.09% of operated cases, there was need for blood transfusion. This rate falls to 8.33% in patients operated using ultrasonic scalpel. There were no reports of hemorrhagic intraoperative complications.

Conclusion: The ultrasonic scalpel promoted a trend for reduction in surgical time and low rate of facial paralysis. Transfusion rates seems more elated to lesion dimensions. Although there was no significant decrease in postoperative facial paralysis, the absence of cases of paralysis in branches manipulated but not primarily affected by the malformation supported the indication of nerve monitoring.

Why do adults present with new-onset Vascular Malformations? Retrospective cohort study from a Multidisciplinary Vascular Anomalies Center

Ayushi Gautam (UCSF); Josephine Czechowicz (UCSF); Erin Mathes (UCSF); Mark Mamlouk (UCSF); Arman Shoyatev (UCSF); Ilona Frieden (UCSF)

Purpose: Most vascular malformations (VMalf) are due to somatic or germline mutations and they most often present in infancy or childhood. However presentation as an adult with no previous signs or symptoms is not rare. We aimed to better characterize features in this group and consider potential pathogenetic implications.

Methods: Retrospective chart review of all adult patients presenting to our multidisciplinary VascAnom center between 2018 and 2021. Diagnosis (with clinical radiologic or histopathologic correlation), relevant past medical history including family history and recalled history of trauma or provoking factors were recorded.

Results: Of 412 total patients seen, 172/412 (41.7%) were ≥18 years and 46/412 (11.2% of total) had no history or signs or symptoms before age 18. Venous malformation (29/46; 63%), primarily intra-

muscular, was the most common diagnosis. Two had late-onset multifocal venous malformations. Also observed were arteriovenous malformations (10/46; 22%), fibro-adipose vascular anomalies (FAVA) (2/46, 4%) and acquired vascular neoplasms (3/46, 7%). Only 2 patients had lymphatic malformations, one possibly iatrogenic due to cardiac surgery. Most had no skin-color changes but many had soft-tissue swelling leading to evaluation. The mean age of onset was 34 years with mean age of presentation 43 years. Locations included the head and neck (18/46; 39%), upper extremity (11/46; 24%), lower extremity (15/46; 33%), genitourinary region (1/46; 2%) and torso (1/46; 2%). Further analysis with a larger cohort is underway.

Conclusion: Adult-onset vascular malformations are not rare. Nearly 85% had either VMs or AVMs; lymphatic or capillary malformations were far less common. Our findings suggest that many late-presenting VMalf congenital with tardive onset, but further research including genomic studies are needed to help elucidate etiopathogenesis including the role of trauma and other provoking factors.

A Decade of Bleomycin

Joseph Michael Miller (Children's Hospital Los Angeles); Shimwoo Lee (CHLA); Erin Delfosse (CHLA); Mary Timbang (CHLA); Gabriel Gomez (CHLA); Minnelly Luu (CHLA); Meagan Hughes (CHLA); Jessica Lee (CHLA); Sara Kreimer (Children's Hospital Los Angeles); Dean Anselmo (CHLA)

Purpose: While still considered a second-line agent, our practice has regularly utilized bleomycin for treatment of vascular anomalies since 2014, typically in lesions or anatomic regions unlikely to tolerate edema. We describe our experiences, successes, and complications performing 403 individual procedures with bleomycin across 188 patients during this period.

Methods: Procedural report includes 6 orbital venolymphatic malformation (four patients), 4 acral hemosideric lymphatic malformation (single patient), 127 lymphatic malformation (59 cervicofacial, 68 other), 19 glomuvenous malformation (eight patients), 1 verrucous venous malformation, 192 venous malformation (132 of the extremities, 60 other), 8 fibroadipose vascular anomaly (three patients), 11 hemangioma (single patient), and 35 arteriovenous malformation (22 head and neck, 13 other; seven patients).

Results: Clinical success rates for each group will be described in detail, however of note GVM cure rate of 89% observed and single large glabellar non-involuting congenital hemangioma debulked to allow resection without skin graft. Standard single session bleomycin dose was kept to under 15 units, but in less than 2% of cases was between 15 and 30 units. Maximum lifetime dose of bleomycin administered was less than 100 units for all patients, but was significantly higher on average for patients with AVM (9.5 units to 79.5 units lifetime). All AVM located within the head/neck showed both angiographic and clinical response to bleomycin, while none of the other AVM did ($p = 0.03$). This discrepancy did not appear to be related to dose delivered ($p = 0.17$). Few complications were witnessed across the 403 procedures. Skin ulceration: 0, flagellate erythema: 0, clinically-apparent pulmonary injury: 0 (including hypersensitivity pneumonitis and pulmonary fibrosis, although note that PFTs were not measured), hyperpigmentation: 5.

Conclusion: We discuss potential mechanisms for hyperpigmentation based on a synthesis of bleomycin's pharmacokinetics, mechanism of action, and our experience, suggesting future avenues for benchtop research.

Session 9: Difficult Cases

Lightening striking twice: patients with two distinct vascular malformations

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Purpose: The occurrence of any one vascular anomaly due to a somatic mutation is rare. Estimated incidence is 1 in 300 for capillary malformations, 1-2 in 10,000 for venous malformations, and 1 in 100,000 for arteriovenous malformations. Yet, a very small proportion of these individuals have more than type of vascular malformation due to distinct genetic mutations.

Methods: Patients with >1 vascular anomaly type were identified within a multi-site cohort study dedicated to better understanding vascular anomalies. Through this study, demographic, clinical, and genetic data are collected and entered in a centralized HIPAA-compliant database (REDCap).

Results: Two patients were identified as having two distinct vascular malformations, confirmed by genetic testing. A 41-year-old female had a port wine stain (GNAQ p.Arg183Gln) of the left temple and an arteriovenous malformation (HRAS p.Gly75_Glu76insMetArgAspGlnTyrMetArgThrGly) of the left proximal forearm. A 9-year-old male had a port wine stain (GNAQ p.Arg183Gln) affecting the right face, neck, and arm and a venous malformation (TEK p.Leu914Phe) affecting the left hemipelvis and knee.

Conclusion: Given that having just one vascular malformation is rare, what could explain the occurrence of two distinct mosaic vascular mutations within the same individual? We are curious if these individuals have a genetic susceptibility and are interested in testing that could elucidate this phenomenon.

GNA11+ Frontal Segmental Vascular Anomaly Associated With Intracerebral Vascular Malformation: A Challenging Case

Daniela Kramer (Hospital Luis Calvo Mackenna); Antonella Muñoz (Médico General Pontificia Universidad Católica de Chile); Maria Cossio (Pontificia Universidad Catolica de Chile); Camila Downey (Clínica Alemana - UDD); Paulo Zuñiga (Clinica Alemana - UDD); Lizbet Perez (Clinica Alemana - UDD); Laura Moneguini (ASST Santi Paolo e Carlo di Milano); Giacomo Colletti (University of Modena and Reggio Emilia)

Purpose: Describe a challenging case of a male born with an unusual vascular segmental facial anomaly complicated by heart failure secondary to a high flow dural fistula

Methods: Description of a unique clinical, histopathologic and genetic evaluation in a male infant observed over 6 years.

Results: A 37-week-old male newborn delivered for prenatal ultrasound findings of a forehead tumor associated with fetal congestive heart failure signs. At birth he presented a segmental, palpable, left facial, bright red vascular anomaly with sharp-defined borders, involving upper eyelid, forehead and the adjacent scalp. A remarkable venous ingurgitation on the upper chest and neck was present. Shortly after birth, he developed progressive cardiac failure and secondary pulmonary hypertension, mainly due to the presence of a high-flow dural fistula in the posterior fossa detected on MRI, which was treated

with endovascular embolizations, with resolution of cardiac involvement. No concomitant congenital anomalies were present. At 8 months of age, an oral trial of propranolol at 2.5 mg/kg/day was administered for 2 months, with no modification of the lesion. Throughout the years of observation he received periodic ophthalmologic, cardiologic, dermatologic and neurologic evaluation. He has no developmental delay and vision is diminished in the ipsilateral eye, without signs of glaucoma. Clinically, the vascular lesion remained stable, exhibiting neither consistent involution nor growth. No areas of ischemia nor ulceration developed. Only a subtle change in color and flattening, characterized by a reduction in the number and depth of surface furrows, was observed. At 4 years of age, the lesion was completely excised. Histology showed a GLUT1 negative superficial and deep dermal vascular proliferation. Genetic study of the tissue revealed a Q209P GNA11 mutation.

Conclusion: We present a challenging case involving a GNA11 vascular segmental anomaly associated with an intracerebral anomaly, contributing to the spectrum of these complex vascular anomalies

Unusual Presentation of Coronary Artery Fistula in Capillary Malformation-Arteriovenous Malformation 2 Syndrome

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Purpose: This case illustrates an atypical presentation of capillary malformation-arteriovenous malformation syndrome 2 (CM-AVM2), featuring a unique occurrence of giant coronary aneurysm requiring long-term anticoagulation and antiplatelet therapy.

Methods: Review of patient electronic health records and imaging studies.

Results: 22-day-old male presented with new cardiac murmur and was found on echocardiogram and computed tomography angiogram (CTA) to have a large fistula from the left circumflex coronary artery directly into the coronary sinus. The patient was monitored closely by echocardiogram until presentation at age 1yo with left eye exophthalmos. MR imaging and subsequent angiography revealed left-sided basilar artery to perforator venous fistula with dilation and tortuosity of the left superior ophthalmic vein, enlargement of the left cavernous sinus with a large draining vein, and prominent flow voids in the left anterior middle cranial fossa. He underwent IR embolization and coiling. Procedure was complicated by subarachnoid hemorrhage and temporary need for external ventricular drain. Patient was then noted to have several cutaneous capillary malformations and genetic testing was sent revealing a pathogenic variant in EPHB4 c.175G>A, consistent with CM-AVM2 syndrome. Spinal imaging for screening did not reveal any spinal vascular malformations. At age 3yo, the patient underwent closure of the coronary AVF. The presence of prior AVF and subsequent closure resulted in secondary massive aneurysmal dilation of the coronary artery. For prevention of coronary thrombosis, the patient was initiated on dual anticoagulation and anti-platelet therapy with warfarin and aspirin.

Conclusion: Timely cardiac auscultation and imaging led to the discovery of an unusual coronary AVF. Subsequent presentation of cerebral AVF and skin findings prompted genetic testing of pathogenic EPHB4 variant, confirming diagnosis of CM-AVM2. Whether this represents an isolated phenomenon or a new clinical feature in the spectrum of CM-AVM2 syndrome is unknown, but clinicians should consider cardiac imaging for any patients with cardiac murmur.

Difficult Case Presentation: Dual therapy with beta blockers and sirolimus in an infant with diffuse hemangiomatosis

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Purpose: Infantile hemangiomas are common, but diffuse neonatal hemangiomatosis and infantile hemangiomatosis are rare. We present the case of a now 10-month-old infant with diffuse cutaneous and hepatic hemangiomas who was initiated on intravenous beta blocker, steroid and sirolimus in the setting of critical illness. The purpose of this submission is to present the clinical use of a) dual therapy with beta blockers and sirolimus, and b) intravenous esmolol when oral propranolol is unable to be utilized in diffuse neonatal hemangiomatosis.

Methods: Our team was consulted on a 2-day-old late preterm infant with diffuse innumerable cutaneous and hepatic hemangiomas. Prenatally, fetus was noted to have a "tortuous vessel in liver." Patient was initially started on oral propranolol at 3 days of life and tolerated maximum dose. Patient remained in the NICU for respiratory distress and development of feeding skills. Infant then developed necrotizing enterocolitis requiring bowel rest and cessation of oral propranolol, with switch to intravenous steroids for management of hemangiomas. Patient developed high output cardiac failure, severe hypothyroidism, and respiratory distress due to severe tracheo-bronchomalacia. Airway evaluation did not reveal hemangiomas. Patient clinically decompensated with escalation of respiratory support and inability to give enteral medication. Hemangioma on forearm was biopsied with positive GLUT-1 staining consistent with infantile hemangioma. Infant was initiated on triple therapy with steroids, intravenous esmolol and sirolimus.

Results: Patient stabilized after starting this therapy and was weaned off steroids within two weeks. Beta-blocker therapy was transitioned to oral propranolol, which infant has remained on along with sirolimus. Hemangiomas have been stable based on clinical symptoms and imaging.

Conclusion: We present a challenging case of an infant with life-threatening diffuse infantile hemangiomatosis treated with beta blockers and sirolimus therapy. Patient benefited from intravenous esmolol when enteral beta blocker was not an option due to clinical complications.

GPR161 Unmasked: Expanding the Gene-Phenotype Relationship of an Emerging Tumor Suppressor

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Purpose: A now 15-year-old female presented for concern due to increasing hypertrophy of fatty tissue around the right hip with no inciting event. Past history was significant for detection of multiple masses in different body regions over time including the left foot (at 5y) and right elbow (at 8y). There was a family history of pediatric and adult-onset cancer. Despite prior imaging and pathologic examination, the constellation of the proband's clinical features were of uncertain etiology.

Methods: Imaging studies and biopsy of involved tissues were undertaken. To evaluate the genetic underpinnings of disease, paired exome sequencing was performed using saliva as a germline comparator along with somatic tissue from the elbow mass.

Results: MRI of the elbow demonstrated an ill-defined area of abnormal T2 hyperintense and T1 hypointense signal within the subcutaneous soft tissue. Excisional biopsy demonstrated scattered lobules of mature adipose tissue surrounded by fibroconnective tissue containing scattered vessels and nerves. These findings were consistent with benign fibroadipose and fibrovascular tissue. An ultrasound of the foot demonstrated a hypoechoic mass along the dorsum with an appearance suggestive of lymphatic malformation. Excisional biopsy was consistent with a vascular malformation. Paired exome sequencing revealed a germline pathogenic loss-of-function(LOF) variant in GPR161. Evaluation of the somatic tissue demonstrated loss-of-heterozygosity(LOH) of chromosome 1q, including the GPR161 locus resulting in reduction toward homozygosity of the variant allele.

Conclusion: Biallelic inactivation of GPR161, a putative tumor suppressor, has been recently described in medulloblastoma. In such cases, a germline LOF variant, in tandem with 1q LOH in the tumor satisfy Knudson's two-hit model of tumorigenesis. Loss of GPR161 is associated with hyperactivation of sonic hedgehog signaling, a pathway known to be dysregulated in cancer. Here, we expand the genetic spectrum associated with lipomatous and vascular disease to include GPR161. Furthermore, we define the genetic etiology enabling informed management and counseling.

Initial experience with bleomycin electro-embolotherapy (BEET) for the treatment of extracranial arterio-venous malformations

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Objective: Arteriovenous malformations (AVM) associated with capillary malformations (CM) present considerable therapeutic challenges. This study documents a successful case of managing such a patient using BEET.

Methods: We assessed a 38-year-old female with an AVM in the left nasal and upper lip regions, associated with a congenital CM. Following a COVID-19 infection at age 36, she experienced unremitting throbbing pain in these areas, which did not respond to analgesics. A whitish areola, similar to Gallo's glow, intensified the visibility of the underlying CM, corresponding to grade three on Schobinger classification. Previous treatments, including pulsed dye laser and percutaneous bleomycin sclerotherapy, had failed to alleviate her symptoms. Angiography showed the AVM primarily fed by the facial artery with a hypertrophic labial feeder. We performed a superselective intraarterial injection of 0.4 mg bleomycin in 2.0 ml contrast medium using a Magic microcatheter and .007 in microguidewire during electroporation. Reversible electroporation used finger electrodes with 15 mm length, 100 µs pulse duration and 730 V amplitude, during bleomycin injection over six minutes.

Results: Immediate and six-month follow-up angiography post-procedure indicated occlusion of the AVM vessels post-electroporation. The patient was discharged on the third day, reporting no pain and notable aesthetic improvement at one year. The high-concentration intranidal bleomycin, used relative to the vessel diameter post-electroporation, proved effective for this small AVM. This outcome aligns with in vitro effects like reduced blood flow, enhanced permeability, and prolonged Bleomycin retention at the electroporation site, producing a sclerosing and potentially embolus-like effect. Mathematical models support a 40% greater electric field impact on endothelial cells lining the vessels.

Conclusion: This pilot patient case suggests that bleomycin electro embo therapy could be an innovative electrosclerotherapy approach for CM-AVMs, justifying further investigation.

Lymphangiographic Features of Lymphedema -Distichiasis Syndrome (FOXC2 Mutation) in a Stillborn Fetus

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Abstract: Lymphedema-distichiasis syndrome (LDS) is caused by FOXC2 mutation. We demonstrate the utility of postmortem lymphangiography to illustrate the early pathologic changes in female fetus (23-week gestational age, 405 g) with hydrops fetalis and intrauterine demise. The family history was known for lymphedemadistichiasis syndrome (LDS) caused by FOXC2 mutation. The technique of direct lymphangiography included the use of 22-gauge needles, ethiodized oily contrast (Lipiodol) and serial radiographs. The striking abnormality of the lymphatic system included markedly dilated lymphatic channels (megalymphatics) throughout the skin and soft tissue with massively dilated proximal trunks, absence of valves, non-visualization of a normal thoracic duct, bilateral anomalous and ectatic paravertebral channels in the posterior mediastinum and no evidence of lymphatic-venous connections. Histologically, dilated lymphatic channels were also observed in the epicardium, lungs, and retroperitoneal connective tissue. Histologic evaluation was hindered by autolysis.

Large Pediatric NTRK-rearranged Neoplasm Mimicking a Vascular Malformation

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Purpose: Pediatric NTRK (neurotrophic tyrosine receptor kinase)-rearranged spindle cell neoplasms (NTRK-SCNs) are an emerging group of soft tissue neoplasms whose histopathological and biological characteristics continue to be studied, but whose clinical behaviors are not well understood. Here, we provide a case presentation of such a tumor mimicking a vascular malformation.

Results: Our patient is an 11-year-old female referred for a lesion clinically and radiologically concerning for a vascular malformation. The patient presented with a congenital red vascular stain, which grew larger and developed a protuberance after the patient's first menstrual cycle. A chest wall MRI demonstrated a soft tissue cutaneous and subcutaneous T1 hypointense and T2 hyperintense lesion with flow voids that uniformly enhanced post contrast. Upon excision, next-generation sequencing revealed a spindle-cell neoplasm containing an LMNA-NTRK1 fusion.

Conclusion: NTRK-SCNs commonly affect older children (median age of 13.5 years) and most cases involve superficial soft tissues of the extremities or trunk. Although these tumors are locally aggressive, they rarely metastasize. Surgical management may be the optimal choice, but some patients, like ours, require a morbid resection with a skin graft for complete resection. Importantly, many of these tumors are amenable to new targeted therapies, such as Larotrectinib, making their recognition both diagnostically and therapeutically important. They should remain in the differential diagnosis for children who present with a firm, fixed vascular lesion that has sudden, rapid growth, and early biopsy should be considered.

Session 10: Other Studies in Vascular Anomalies II

The clinical implications of readily available genetic testing in a vascular anomalies service

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Purpose: Introduction Vascular anomalies are a diverse group of conditions with significant phenotypic overlap, which complicates secure diagnosis. Improved recognition of the molecular underpinnings of these conditions and development of targeted, high read-depth genetic testing has the potential to transform diagnosis and management of vascular anomalies. While limited case reports and case series have highlighted the genomic yield and utility of genotyping in this group of individuals, no studies have investigated the impact of genotyping on larger patient cohorts. Our multidisciplinary vascular anomalies service has offered a targeted 27-gene panel test for patients since 2020 on lesional tissue. Objective To review the diagnostic yield and clinical utility of targeted high-read depth gene panel testing of children with vascular anomalies.

Methods: Methodology This was a retrospective audit that included all patients treated by our multidisciplinary vascular anomalies team, and who have undergone targeted vascular anomalies gene panel testing from June 2020 to November 2023. Genetic test reports were reviewed and reconciled with the patient phenotype. Clinical notes, imaging and histopathology informed pre-test and post-test diagnosis and treatment.

Results: Results We have a cohort of 254 patients who have undergone genetic testing in total, with 205 (81%) having a genetic variant identified. Preliminary analysis of the first 92 patients has demonstrated that 45% of patients had a result which supported their pre-existing clinical diagnosis, and that 21% had a change of diagnosis because of their genetic test result. In cases of changed diagnosis, management was changed in 47%.

Conclusion: Conclusion Molecular diagnosis permits security of management choices, meaningful genetic counselling and access to targeted treatment. Introduction of targeted high-read depth genetic sequencing at our vascular anomalies service has allowed for improved diagnosis and treatment options for our patients and should be considered in similar patient cohorts and multidisciplinary clinics.

A Highly Sensitive Genetic Panel to Evaluate Patients with Mosaic Vascular Anomalies

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Purpose: To describe early results from a highly sensitive genetic panel to evaluate patients with largely mosaic vascular anomalies

Methods: This is a single-center study utilizing a 218 gene panel that targets coding regions and intron-exon boundaries of genes associated with vascular anomalies and other disorders with overlapping features. Using unique molecular identifier (UMI) adapters and a targeted 1000X compressed read coverage, it has been validated to detect down to a variant allele frequency (VAF) of 1%. DNA was obtained from fresh, frozen or paraffin-embedded tissue, blood, buccal brushes, or cells pelleted from fluid.

Results: 24 patients were evaluated in a vascular anomalies center and 6 patients were evaluated by dermatology, genetics, or oncology. Of the 30 patients eligible for this analysis, 23 (76.7%) had identified causal variants. Mean time to result was 36 days (15-98 days). 25 variants were described: 11 PIK3CA, 4 TEK, 2 GNAQ, 2 KRAS, 1 KDR, 1 CELSR1, 1 PTEN, 1 SUFU, 1 MAP2K1, and 1 MTOR. These variants were classified as 21 pathogenic, 1 likely pathogenic, and 3 variants of uncertain significance (VUS). Of the 11 variants in PIK3CA, the kinase domain substitution at p.His1047 was the most frequently observed (36.3%). Mean VAF was 18.7%, with a minimum VAF of 1.9%, therefore most variants were consistent with somatic mosaicism. Variants in CELSR1 and SUFU were identified at VAFs suggestive of a germline origin in patients who were not known to have germline variants. 6 patients had an alteration of clinical management based on the findings.

Conclusion: This genetic panel is highly effective in identifying somatic and germline clinically significant variants in patients with vascular anomalies. The prevalence of causative variants is higher than reported in previous studies. Future directions include validation of this panel in additional specimen types to extend utility.

Somatic PIK3CA variants are associated with eccrine angiomatous hamartomas

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Purpose: Eccrine angiomatous hamartoma (EAH) is a rare vascular anomaly with mixed eccrine and vascular components, typically identified in children. While benign, EAH can cause significant morbidity and be difficult to treat. The aims of this case series were to identify all patients with EAH that have been seen at the Queensland Children's Hospital and describe their phenotypic and somatic genotypic details, in an effort to contribute to the limiting understanding and literature surrounding this condition.

Methods: Individuals with EAH were retrospectively identified through engagement in a multidisciplinary vascular anomaly clinic in a tertiary Australian children's hospital. All individuals had a previous histological diagnosis of EAH. High read-depth sequencing of a panel of 27 genes known to be associated with vascular anomalies was undertaken on affected tissue. Samples were re-reviewed by a senior pathologist and geneticist for this study.

Results: Six cases of EAH were identified. All were associated with one of three somatic PIK3CA variants (c.1633G>A;p.Glu545Lys, c.1624G>A;p.Glu542Lys and c.3140A>G;p.Histo1047Arg) in low allele fractions. These variants have previously been reported in a range of tumours and vascular anomalies, including PIK3CA-related overgrowth spectrum, but not in EAH.

Conclusion: Occurrence of somatic PIK3CA variants in EAH provides evidence for a novel gene disease association and is plausibly the cause of EAH in some individuals. This finding expands the phenotypic spectrum of PIK3CA, contributes to understanding of the pathophysiology of this rare condition and may avail molecularly targeted therapy in the future.

Patient Reported Outcome Measurement Information System (PROMIS) Measures in Action: Development of a visualization tool in Epic

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Purpose: Vascular anomalies can have a significant negative impact on a patient's quality of life, and the incorporation of patient-reported outcome measures (PROMS) into healthcare planning can provide insight into this burden. Integration of PROMs has been hindered by a lack of electronic health record (EHR) infrastructure that presented PROMs in a format that allowed for easy visualization. We present the development of an interactive display tool built within our EHR that tracks real-time changes in Patient Reported Outcome Measurement Information System (PROMIS) scores that has streamlined the inclusion of the patient experience into healthcare planning.

Methods: Customizing an existing EHR display tool, with the assistance of an electronic health record analyst, a display item was created that collects PROMIS scores and places the data within centralized locations of the medical record. The display item is interactive, allowing healthcare providers to view the graphical representation of scores over time as well as access item-level responses.

Results: PROMIS questionnaires are assigned by attaching the questionnaires to an encounter or sending via a patient message via EHR. Patient responses automatically flow into the display item, which has been placed in several prominent locations that do not require navigation to access. While the PROMIS questionnaire display tool is in the pilot stage, monitoring responses has proven beneficial in capturing the patient experience. (Figure 1, 2, 3, & 4)

Conclusion: Our center presents a method for capturing PROMIS measures that allows for efficient access to patient responses. Use of patient-reported outcome measures should be considered a part of health maintenance in patients with chronic diseases to understand the impacts on the patients and improve shared medical decision-making. Graphical representation of responses allows for real-time shared medical decision-making to improve quality of life and may help guide decisions for treatment.

Clinical Use and Adverse Effects of Bortezomib in Pediatric Patients: A Systematic Review and Meta-Analysis

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Purpose: Slow-flow vascular malformations, including lymphatic (LMs) and venous (VMs) malformations, have severe morbidities and mortality but limited pharmacotherapeutic options. Recent work in our laboratory found that endothelial cells from LM/VMs (LMECs/VMECs) were highly sensitive to proteasome inhibitors (PIs), which more effectively inhibited LM/VMEC viability than current off-label clinical therapies. Bortezomib (BTZ) was the first PI to gain FDA approval for adult malignancies and has been used clinically as an off-label treatment for pediatric oncologic and non-oncologic indications. We hypothesize that BTZ is well tolerated in pediatric patients.

Methods: We performed a systematic review and meta-analysis of the literature. PubMed and the Cochrane Database for relevant articles and included all studies that reported outcomes and adverse effects (AEs) of pediatric patients (≤21 years of age) treated with BTZ.

Results: 11 clinical trials, 4 clinical studies, and 33 case reports/case series met inclusion criteria (572 patients). Indications for BTZ in clinical trials were oncologic and included acute leukemia and relapsed/refractory solid tumors. Non-oncologic indications in clinical studies and case reports/small case series included antibody-mediated rejection after solid organ transplant, autoimmune cytopenia, and anti-NMDA receptor encephalitis. Common AEs included infection, peripheral neuropathy, gastrointestinal, respiratory, and hematologic disturbances (Table 1). Dose-limiting AEs were found in 15.6% of pediatric patients. AEs were lower in pediatric non-oncologic patients compared to oncologic patients. All non-hematological AEs ≥Grade 3 were limited to onologic patients. Patients aged ≤8 had comparable AEs to the overall pediatric population.

Conclusion: BTZ is well tolerated in the pediatric population; non-oncologic pediatric patients have less ≥Grade 3 AEs than oncologic patients. Well-controlled prospective clinical trials using BTZ treatment LM/VM patients may be warranted.

Evaluating the Impact of Sirolimus Treatment on Quality of Life in Individuals with Vascular Anomalies: A Comparative Analysis Before and After Intervention

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Purpose: This study seeks to evaluate self-reported quality of life metrics among patients diagnosed with vascular malformations (VMs) before and after undergoing a 6-month sirolimus treatment.

Methods: This study aimed to evaluate the health-related quality of life (HRQoL) of patients diagnosed with vascular malformations (VMs) before and after a 6-month sirolimus treatment using the PedsQLTM measurement. The assessment covered physical, emotional, social, and school functioning and was conducted from January 2017 to October 2023. A scale of 0 to 100 was used to score responses, with higher scores indicating better HRQOL. The study also considered variables such as age, sex, type and location of VM, pain presence and intensity, tracheostomy, and previous surgery. HRQoL was compared with that of healthy individuals and those with other chronic diseases. The study team calculated central and dispersion measures and performed uni- and multivariate analyses to evaluate the relationship between quality of life and study variables.

Results: A total of 39 patients, females (56.4%), with a median age of 12 years (4-21) were included with PROS spectrum (28.3%), venolymphatic malformation (20.5%), lymphatic malformation (20.5%), fibroadipose vascular anomaly (12.8%), venous malformation (7.7%), Gorham-Stout disease (5.1%), Generalized Lymphatic Anomaly (2.6%), and Kaposiform lymphangiomatosis (2.6%). Initially, 46.2% reported pain, with a median intensity of 8. Patients exhibited lower Health-Related Quality of Life (HRQoL) scores compared to healthy children, similar to those with chronic diseases, scoring a median of 64.56 (self-report) and 65.21 (proxy report). After 6 months of sirolimus treatment, self-report scores increased significantly to 79.89 ($p < 0.005$), and proxy report scores increased to 77.17 ($p < 0.005$).

Conclusion: Patients with VMs had lower HRQoL scores than the general population, which improved significantly with sirolimus treatment. The study highlights the correlation between pain and lower HRQoL scores at baseline.

Sirolimus: friend or enemy of surgeons dealing with vascular anomalies?
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Purpose: Sirolimus is becoming a standard of care in slow-flow vascular anomalies, effectively alleviating symptoms. Recurrence after treatment cessation still exists, with sclerotherapy or surgery being the only definite treatment options. We postulated that including sirolimus into the treatment plan could reduce post-operative complications often seen after surgical interventions for slow-flow vascular anomalies.

Methods: We conducted a multicentric retrospective review of the medical records of 27 patients who underwent surgery while on sirolimus for extensive slow-flow vascular anomalies.

Results: We operated 7 lymphatic (LM), 10 venous (VM), and 10 combined vascular anomalies (VAs). Mean age was 24 years. Mean hospitalization duration was 6 days (median: 4). Drainage was removed on average after 6 days (ranging from 1 to 21). Notably, 24 patients (89%) experienced no complications or delays in healing.

Conclusion: This retrospective study highlights the importance of continuing sirolimus treatment before and during the surgical resection of slow-flow vascular malformations. Particularly in cases of extensive lymphatic malformations, sirolimus proves beneficial in reducing healing complications by minimizing postoperative leakage and, consequently infection. Additionally, the use of sirolimus is associated with a shorter duration of hospitalization. Thus, sirolimus emerges as a valuable ally for surgeons dealing with vascular malformations, and should be considered as an adjuvant treatment, especially in the context of partial resection planning.

Fetal Magnetic Resonance Imaging of Vascular Anomalies
Riikka Schultz (Radiology, University of Helsinki and Helsinki University Hospital)

Purpose: Vascular anomalies (VAs) are the most common mass lesions in children. They may be detected in routine prenatal ultrasound examinations leading to further evaluation with fetal MRI. We aimed to evaluate the role of fetal MRI in diagnosing VAs and predicting their postnatal clinical course.

Methods: We analyzed all fetal MRI studies performed at our institution between 2006-2019, identified fetuses with VAs and compared their MRI findings with postnatal diagnoses. Patient records provided the details of delivery and postnatal management of each child.

Results: 537 fetuses were studied with fetal MRI for suspected extracranial pathology. 16 were prenatally diagnosed as VAs (5 tumors, 11 malformations). Prenatal and postnatal diagnoses corresponded in 14/16 (87,5%) cases. All malformations were simple or combined lymphatic

malformations (LMs) that displayed specific MRI findings. They grew in proportion to fetal growth during the third trimester. LMs that involved the deep neck spaces on imaging during the second trimester carried a risk for airway compromise later in pregnancy. Postnatal bleeding tendency was observed in LMs that had prenatal bleeding. Vascular tumors postnatally diagnosed as congenital hemangiomas (n=3) and kaposiform hemangioendothelioma (n=1) were indistinguishable from one another in fetal MRI. One suspected congenital hemangioma could no longer be detected in postnatal imaging. Fetal MRI findings influenced the delivery method and postnatal care. Four extensive cervical LMs were delivered with EXIT (ex utero intrapartum treatment) caesarian section and needed prolonged tracheostomy. Two families terminated the pregnancy after the diagnosis of an extensive LM. Postnatal management varied from follow-up only to surgery, radiological interventions, and pharmacological treatment.

Conclusion: Our study suggests that fetal MRI is accurate in diagnosing LMs but less specific in vascular tumors. Fetal MRI can provide valuable information for parental counseling, choosing the delivery method, and planning postnatal care.

Vascular malformations in the abdominal cavity of children
Uwe Huebner (Katholisches Kinderkrankenhaus Wilhelmstift)

Purpose: Most of VM are visible in their typical aspects and / or they are diagnosed while looking for the reasons of medical problems. VM in the abdominal cavity can be asymptomatic for a long time but also can be the reason for acute pain, major distorsion and obstruction. Most malformations are lymphatic, sometimes they are venous or diffuse.

Methods: Our report is about 16 children (newborn up to 15 years) with abdominal vascular malformations. 10 children had operative procedures to relieve pain and obstruction. One had an endoscopic procedure (Blue Rubber Bleb Syndrome). Five children needed segmental resection of the intestine. Histologically 9 of the operated malformations were lymphatic (two omentum cyts and 7 mesenteric cysts). One was a mixed type in the bladder-wall with additional malformations in liver and spleen. All other children were asymptomatic and did not need any interventions up to now. We follow them with periodic imaging (mostly ultrasound).

Results: We describe the courses from the first clinical symptoms to the diagnostic procedures (ultrasound alone in 12 cases, combined with MRI in 4 cases). When interventions were required, we could illustrate the sometimes fascinating appearance of the malformations.The clinicals courses postoperatively were uneventfull without major complications.

Conclusion: Vascular malformations in the pediatric abdominal cavity are a rare cause of abdominal pain and obstruction. In the majority of the cases they lead to surgical intervention. In others they are only a random finding and careful observation is enough.

Complete unilateral pulmonary embolisation and antiangiogenic treatment in a child with diffuse pulmonary vascular malformations and severe hypoxaemia
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Purpose: To describe a successfully improve in the oxigenation after total pulmonary embolization and antiangiogenic therapy in a 8 months years-old boy.

Methods: A 7-month-old boy was diagnosed with multiple diffuse pulmonary vascular malformations (PAVMs) predominantly in the right lung after being found hypoxaemic (75% pulse oximetry). He initially underwent an initial pulmonary embolisation in the inferior lobar branches of the right pulmonary artery without improvement. After 2 months he presented progressive reduction of his oxygenation and was hospitalized requiring mechanical ventilation (MV) followed by extracorporeal membrane oxygenation (ECMO) due to severe decrease in oxygenation. Despite this, his condition progressively worsened. A second emergency complete lower lobe embolisation was performed with a significant increase in oxygenation to 90%. After 48 hours due to a sustained decrease in oxygenation he was started on nitric oxide for suspected hypoxic vasoconstriction and 6 doses of bevacizumab 5 mg/kg dose every 15 days plus propranolol as antiangiogenic treatment. After 5 days ECMO could be withdrawn. However, after 7 days he again required MV followed by ECMO for 25 days. A third pulmonary embolisation was performed but in this case it was decided to completely occlude the right pulmonary artery using coils, plugs and histoacryl without complications. After the massive pulmonary embolisation, the ECMO and MV could be removed and he was discharged from the hospital. He currently maintains oxygen saturation of 87-92%, continuing treatment with bevacizumab every 3 months . Although HHT was the most likely, no family history, telangiectasias or vascular malformations in other organs were detected, nor were genes related to HHT or other vascular malformations.

Results: Total pulmonary embolisation improved the oxygenation. There is no evidence of antiangiogenic therapy with bevacizumab in diffuse PAVMs, nor with propranolol, but its off-label indication was based on trying to regulate pathological angiogenesis in the contralateral lung.

Facial Asymmetry Related to Vascular Malformations: Insights from Characteristics, Surgical Management, and Outcomes (2012-2022)

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Purpose: In the past decade, vascular malformations have become more common, leading to a rising number of individuals with facial asymmetry. Limited information exists regarding the clinical outlook of this deformity in China over the last ten years. This study aims to outline the clinical features and surgical approaches for these patients treated at our center from January 1, 2012, to December 31, 2022.

Methods: A retrospective chart review included 56 patients diagnosed with lymphatic malformation (LM), port-wine stains (PWS), infantile hemangioma (IH), facial infiltrating lipomatosis (FIL), arteriovenous malformation (AVM), who had facial asymmetry and underwent surgical treatment. Radiographic and clinical data were recorded.

Results: Among all patients, PWS accounted for 32.14%, FIL for 26.19%, LM for 21.43%, AVM for 10.71%, and IH for 9.93%. The zygomatic bone, maxilla, mandible, nose, and lips showed varying degrees of involvement in all patients. The most common surgical techniques are zygomatic reduction, mandibular angle osteotomy, and facial nerve dissection. Zygomatic reduction surgery is most prevalent in PWS and FIL, constituting 61.1% and 60%, respectively. IH and LM patients undergo this procedure less

frequently. Mandibular angle osteotomy is mainly concentrated in LM and FIL (25% and 26.67%, respectively), while facial nerve dissection is widely applied across all diseases. It accounts for over 90% in LM, IH, and FIL, and close to 50% in PWS and AVM. All cases involving orthognathic surgery and orbital osteotomy are performed around the age of 18y. Autologous fat grafting, liposuction, and rhinoplasty were performed based on individual needs.

Conclusion: Facial asymmetry related to vascular malformations primarily focuses on PWS, FIL, and LM. Surgical correction is inevitable to acquire facial symmetry. Facial nerve dissection is the most widely used procedure in these patients and orthognathic surgery and orbital osteotomy can be chosen to be completed before 18y.

Poster Abstracts

5 - Assessing the Association between Communication Quality and the Ability to Navigate Healthcare Systems for Patients with Vascular Anomalies

Bryan A. Sisk (Washington University School of Medicine in Saint Louis); Sunny Lin (Washington University School of Medicine in Saint Louis); Anna Kerr (Heritage College of Osteopathic Medicine)

PURPOSE: Vascular anomalies (VAs) are rare congenital disorders that can cause pain, disfigurement, coagulopathy, asymmetric growth, and disability. Patients with complex VAs experience multiple barriers to accessing expert care. In this survey study, we sought to understand which factors support these patients' ability to navigate the healthcare system.

METHODS: We surveyed adult patients with VAs using previously validated measures, recruiting participants from five patient advocacy groups and multidisciplinary VA clinics. The primary outcome was self-reported ability to access needed medical care, using a validated measure. We evaluated for factors associated with the patient's ability to navigate the healthcare system using multivariate linear regression (n=136).

RESULTS: Participants were predominantly women (n=90, 66%), White and non-Hispanic (n=109, 73%), and college-educated (n=101, 73%). The majority of participants had PIK3CA-Related Overgrowth Spectrum (n=107, 78%). Most participants reported that navigating the healthcare system was ""sometimes"" or ""usually difficult"" (mean score 16.4/30, SD 5.6). In multivariate linear regression, ability to navigate the healthcare system was associated positively with quality of information exchange (β=0.38, 95% Confidence Interval (CI) 0.22 to 0.55, p<0.001) and whether patients had VA specialists (β=2.31, 95% CI 0.35 to 4.28, p=0.021), but not associated with patient self-advocacy, anxiety, education, age, race and ethnicity, gender, or having a primary care doctor. In exploratory analysis of participants with primary care doctors, ability to navigate the healthcare system was positively associated with quality of information exchange (β=0.27, 95% CI 0.09 to 0.45, p=0.004), having a VA specialist (β=2.31, 95% CI 0.22 to 4.39, p=0.031), and primary care doctors' VA knowledge (β=0.27, 95% CI 0.04 to 0.50, p=0.023).

CONCLUSION: Patients with VAs struggle to navigate the healthcare system. High-quality information from clinicians and more knowledgeable primary care doctors might help patients to access needed care. Relying on patient self-advocacy is insufficient. Future efforts should focus on patient-directed and clinician-directed educational interventions.

7 - Genes involved in the development of arteriovenous malformations

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PURPOSE: Cerebral arteriovenous malformation (AVM) is a congenital vascular anomaly characterized by the presence of interconnected vessels between arterial and venous segments. This condition lacks a normal capillary network, leading to changes in tissue conditions around the affected vessels. The high blood flow rate in this area increases the risk of rupture, which can result in severe complications and even death.

Various factors can initiate the pathological process in the future malformation area. These factors include environmental factors that stimulate angiogenesis (the formation of new blood vessels), genetic factors, angiogenic growth factors, and inflammatory cytokines. Therefore, it is believed that the etiology of cerebral AVM is multifactorial, meaning that both the fetal genotype and environmental factors play a role in determining the risk of its occurrence.

The purpose of this study is to investigate the role of allelic polymorphism of the CDKN2A (rs7865618), CDKN2B (rs1333040), ANGPTL4 (rs11672433), VEGF (rs2010963), TNFa (rs1800629), IL-1a (rs1800587), IL-1b (rs16944), IL-8 (rs4073), and MMP3 (rs3025058) genes in the genetic predisposition to cerebral AVM development in Russian individuals.

METHODS: The study included 191 individuals diagnosed with cerebral AVM. The determination of polymorphic gene variants was performed using real-time PCR with competitive TaqMan probes.

RESULTS: For the polymorphic variant rs7865618 of the CDKN2A gene, it was shown that the risk of developing AVM for patients with the GG genotype (OR=1.915, CI=[1.158-3.167], p=0.01) is approximately twice as high as for patients with the GA and AA genotypes.

CONCLUSION: Thus, the GG genotype may be a risk factor for AVM development in Russian individuals. No statistically significant differences in the frequency of allele and genotype occurrence were found for the other investigated polymorphic loci in the control group and patient group.

13 - Infantile Hemangioma with Minimal or Arrested Growth Presented as Perianal Ulcers

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PURPOSE: Infantile hemangiomas (IH) with minimal or arrested growth are rare. They do not exhibit a proliferative phase or have one that accounts for less than 25% of the hemangioma's surface, which can make them go unnoticed or be mistaken for capillary malformations. Like other IH, they can ulcerate.

METHODS: We present the case of a 22-day-old infant who came to the emergency room with perianal ulcers of slow evolution after several topical treatments. These ulcers had appeared at 12 days of life. There was a larger ulcer adjacent to the anus on the left side and three small ulcers in the gluteal region with raised erythematous borders. Initially, diaper dermatitis with candida intertrigo were suspected. However, the fungal culture was negative, and there was no response to topical antifungals. Diarrhea improved after a change in diet. Acrodermatitis enteropathica was also suspected and immunodeficiency was ruled out. After 14 days of hospitalization with no improvement in the ulcers, the patient was evaluated by the vascular anomalies unit. A faint, reticulated, geographic erythematous patch was observed around the ulcers along the entire lower extremity, including the foot and extending up to the gluteal region, crossing the intergluteal line towards the sacrum. Biopsies of the ulcer and the reticulated patch were performed.

RESULTS: The biopsy revealed the diagnosis of infantile hemangioma, positive for GLUT-1. The diagnosis was segmental infantile hemangioma with minimal or arrested growth. Treatment with oral propranolol and local wound care was initiated, resulting in a good outcome and progressive resolution of the ulcers. An ultrasound was performed to rule out myelopathies, urogenital and vesicorenal anomalies, bone malformations, anorectal abnormalities, and arterial issues.

CONCLUSION: Segmental infantile hemangioma with minimal or arrested growth can present as ulcers in the perianal region, potentially leading to delayed diagnosis and treatment if this condition is not recognized.

14 - Case Report: Diagnostic Pitfalls - Superficial Soft Tissue Lymphoma mimicking a Venous Malformation

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PURPOSE: The diagnosis of slow-flow vascular anomalies (VAs), particularly venous malformations (VMs), relies on clinical, imaging criteria, and sometimes anatomopathological and somatic molecular gene analysis. We report three patients addressed to our vascular anomalies reference center to manage a slow-flow VA. In our three patients, the biopsy provided a diagnosis of soft tissue lymphoma. Our objective here is to highlight that a discrepancy between clinical and radiological data should suggest a differential diagnosis, and a percutaneous biopsy be considered.

METHODS: We describe three cases of patients who presented with clinical and radiological features suggestive of VM. These cases are detailed in terms of clinical history, clinical findings, and imaging data, including ultrasound and magnetic resonance imaging (MRI).

RESULTS: In all three cases, the final diagnosis revealed primary B-cell lymphomas of the soft tissues. These patients had an indolent form of lymphoma, emphasizing the importance of recognizing specific red flags, such as past medical history of lymphoma, age of onset, clinical non-depressible hard lesions, and reddish skin discoloration. Furthermore, the presence of spicules on MRI, a feature not previously described in the literature, emerged as a potential diagnostic clue in differentiating soft tissue lymphomas from common venous malformations.

CONCLUSION: The triad past medical history, clinical and imaging data (ultrasound and MRI) is mandatory for an accurate diagnosis in vascular malformations. Our small series emphasize that biopsy is required in cases presenting radio-clinical discrepancies. The presence of irregular contours and spicules on MRI might be a helpful sign in superficial soft tissue lymphomas yet not described in the literature."

15 - Consensus on Diagnostic Criteria for LUMBAR Syndrome

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PURPOSE: LUMBAR syndrome is the association of segmental infantile hemangiomas (IH) that affect the Lower body with Urogenital anomalies, Ulceration, spinal cord Malformations, Bony deformities, Anorectal malformations, Arterial anomalies and/or Renal anomalies. The underlying cause, natural history and outcomes of affected infants are unknown. Consensus on diagnostic criteria for LUMBAR is critical before additional needs for this syndrome can be met.

METHODS: These diagnostic criteria were developed by an expert multidisciplinary team based on analysis of peer-reviewed data, followed by electronic-Delphi (e-Delphi) consensus of a panel of international pediatric specialists.

RESULTS: 1. 61/81 invitees participated in the Delphi, equivalent to a 74% response rate. 2. Demographics of Delphi panelists: a. Pediatric subspecialty representation: dermatology (36, 59%) neurosurgery (5, 8%) urology (5, 8%) hematology-oncology (4, 7%) surgery (4, 7%) plastic surgery (3, 5%) interventional radiology (2, 3%) neurointerventional radiology (1) and neuroradiology (1). b. Country of practice: U.S. (47, 78%) Europe (10, 17%) Canada (2, 3%) Chile (1) and Israel (1). c. Years in practice: 0-10 (13, 21%) 11-20 (23, 38%) >20 (25, 41%) 3. The criteria underwent 2 Delphi Rounds. After Round 1, 81% agreement or higher was reached on each statement. After Round 2, 92% agreement or higher was reached on each statement, with 98% agreement on the criteria for diagnosis and 100% agreement that the criteria would be useful in clinical practice.

CONCLUSION: These criteria will enhance clinical care by improving screening, detection, and overall awareness of this neurocutaneous disorder. In addition, formal criteria will improve phenotypic uniformity among LUMBAR syndrome cohorts, allowing investigators to assess clinical features and long-term outcomes in a standardized manner. Finally, these criteria will serve as a launching point for prospective studies to establish screening and management guidelines. We expect these criteria to be modified over time as new knowledge is acquired.

16 - Screening Guidelines for Infants At-Risk for LUMBAR Syndrome

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PURPOSE: A segmental infantile hemangioma (IH) affecting the lower body is a required diagnostic criterion for LUMBAR syndrome. However, questions remain as to which infants should be evaluated for the syndrome, and how. These screening guidelines were developed by the pediatric subspecialty expert team who led the consensus project on diagnostic criteria for LUMBAR.

METHODS: For these screening recommendations, we divided the lower body anatomy into 4 defined cutaneous regions:

1. Lumbosacral = midline lower back, superior to the gluteal cleft.

2. Sacrococcygeal = top of gluteal cleft to tip of coccyx, including intergluteal cleft and immediate surrounding gluteal skin.

3. Pelvic = pubic/genital, perineal (area between the genitals and anus) and perianal skin.

4. Lower extremity = top of thigh to distal toes.

CONCLUSION: While there is a known regional correlation between segmental IH and underlying congenital anomalies, it is not absolute. The predictive value of a segmental IH isolated to the pelvic region (without lumbosacral involvement) as an indicator of spinal dysraphism is unknown, as is (conversely) the risk of renal and pelvic anomalies in an infant with an IH isolated to the lumbosacral or sacrococcygeal regions. The risk of underlying arterial anomalies when a segmental IH affects the lower limb is also unknown.

A prospective study, in which all newborns with segmental IH of the lumbosacral, sacrococcygeal or pelvic regions undergo ""complete"" imaging of the lumbosacral spine, kidneys and pelvis, and vascular imaging when the limb is affected, is needed to further refine these guidelines.

17 - Somatic MAP2K1 variant driver in a child with Rosai-Dorfman-Destombes disease and vascular anomaly

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PURPOSE: Report a case of Rosai-Dorfman-Destombes disease (RDD) and vascular anomaly in a child with a common MAP2K1 variant driver

METHODS: Case report and review of the literature

RESULTS: The patient is a 5-year-old male who initially presented at age 1 year with cervical lymphadenopathy and normocytic anemia. Physical exam was also significant for hypertrophy and vascular lesions of the left upper and lower extremities, confirmed by magnetic resonance imaging (MRI) to be arteriovenous malformations (AVM). Excisional biopsy of the lymph node revealed RDD. At age 4 he had recurrence of cervical lymphadenopathy and underwent a second excisional biopsy showing RDD. Somatic molecular analysis revealed a recurrent pathogenic MAP2K1 variant (NM_002755:c.169A>G, p.Lys57Glu). Biopsy with molecular analysis of the cutaneous vascular lesion identified the same MAP2K1 gene variant, present at an allele fraction of 5%. Germline whole exome sequencing was negative for the MAP2K1 variant. At age 5 he had a second recurrence of cervical lymphadenopathy. MRI showed left lower extremity intramedullary foci, concerning for skeletal involvement. He was treated with sirolimus but developed toxicity and showed no response. He enrolled on a clinical trial of cobimetinib, an oral MEK inhibitor (NCT04079179).

CONCLUSION: This is the first case report of a patient with multiple neoplastic conditions with a common MAP2K1 genomic driver. The MAPK pathway is known to play a role in maintaining normal cellular activity and alteration of genes along the pathway may result in over-activation and/or loss of tumor suppression. In this case a mutation of MAP2K1 caused both a lymphoproliferative disorder, RDD, and AVM in a child. A targeted therapeutic approach with MEK inhibition is being pursued on a clinical trial.

18 - Potential biomarkers of vascular anomalies related with sirolimus treatment

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PURPOSE: Intractable vascular anomalies (VAs) include several disorders of growth and expansion of VAs may cause clinical problems. An mTOR inhibitor, sirolimus, inhibits angiogenesis and lymphangiogenesis, and has shown promising results for VAs. However, there are a little known how sirolimus treatment has an effect on their conditions. This study aimed to clarify plasma cytokine profiles of patients with VAs after sirolimus treatment.

METHODS: We prospectively assessed the response to sirolimus (objective radiographic response rate) and the plasma samples were obtained from patients with VAs at pre-treatment and 6 months after administration. Twenty-two types of angiogenic and lymphangiogenic factors were evaluated for cytokine concentrations using commercially available Luminex multiplex cytokine analysis kits. Differences between groups were evaluated with nonparametric Mann-Whitney's (unpaired) or Wilcoxon's (paired) tests, as required. P-values were considered significant at < 0.05.

RESULTS: Ninety patients with VAs (50 lymphatic malformations, 19 vascular tumors, 9 venous malformations, 10 combined vascular malformations and 2 arteriovenous malformation) were registered. A total of 52.3% (45/86) of patients showed a partial response (PR) by radiological examination. Analysis of plasma cytokines levels between prior to sirolimus and six months after treatment of all patients showed that levels of Angiostatin, sTie-2, sVEGFR3, Tenascin C, Angiopoietin-2

and LEPTIN decreased significantly. In PR group, the levels of Tenascin C, sTie-2, sVEGFR3 and Angiopoietin-2 decreased significantly. Furthermore, the levels of VEGF-A of non-PR group increased after sirolimus treatment.

CONCLUSION: Our data indicates that some angiogenic cytokines might be potential biomarkers of responsiveness to sirolimus treatment.

19 - NON-HOTSPOT PIK3CA MUTATIONS HAVE HIGHER VARIANT ALLELE FREQUENCY AND ARE MORE FREQUENT IN PATIENTS WITH SYNDROMIC VASCULAR MALFORMATIONS

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PURPOSE: Many vascular malformations can harbor gain-of-function PIK3CA mutations causing activation of the PI3K/Akt/mTOR signaling pathway. We were interested in studying the localization and the variant allele frequency (VAF) of the somatic PI3KCA mutations in our cohort of patients with vascular malformations.

METHODS: Clinical data of consecutive patients with extracranial/extraspinal vascular malformations were prospectively collected from 2008 to 2022 (n=559). Since October 2020 genetic testing was performed on vascular malformation tissue biopsy samples using a Next Generation Sequencing gene panel (TSO500, Illumina). All patients with available genetic testing results until June 2022 were reviewed for eligibility (n=90); all consenting patients with a PIK3CA mutation were included in this study.

RESULTS: Clinically relevant mutations were found in 45/90 patients. PIK3CA mutations (n=25) were found in 16 patients with simple/combined vascular malformations (non syndromic) and nine patients with vascular malformations associated with other anomalies (syndromic).

Hotspot mutations in the exons 9 and 20 of the PIK3CA gene (E542K, E545K, H1047R/L) were found in 16/25 patients (3/16 syndromic vascular malformations) at a VAF ranging from 0,9 to 9,7%. The

remaining 9 patients (6/9 syndromic vascular malformations) had five non hotspot mutations (E110, R108, G118D, C420R, N1044K, H1065Lfs*5) with a VAF range of 3,6 31,7%.

Non-hotspot mutations had a higher VAF than hotspot mutations (p=0.0253) and were more frequent in syndromic than non-syndromic vascular malformations (p=0.0034).

CONCLUSION: The phenotypic and genotypic spectrum of PIK3CA-associated disorders is broad. Further studies are needed to enrich the ever-growing list of pathogenic PIK3CA variants associated with vascular malformations.

Our study contributes to the growing body of knowledge in the field of the genetic background of vascular malformations.

22 - Initial changes in blood tests in children with vascular malformations of the maxillofacial area
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PURPOSE: As an indicator of a violation of the general condition, the initial blood value level is important for preparing the patient for conservative treatment and its control. The study aimed to analyze the initial blood values in children with vascular malformations and their correlation with malformation volume.

METHODS: A retrospective analysis of 29 case histories of patients with venous malformation (VM), 20 with lymphatic malformation (LM), and compared them to a control group. Patients were 1 to 18 years old. The malformation volume, the initial level of the general, biochemical blood test and the coagulogram were assessed.

RESULTS: The VM volume was 14,97 ± 7,8 cm3 (in the range 2,0 -198,3 cm3), LM - 17,06 ± 18,12 cm3 (in the range 2,0 -176,7 cm3). The erythrocytes level in 14% ($p<0.05$), the lymphocytes in 18% (p=0.301) of patients with VM and the erythrocytes level in 26% (p=0.01), the lymphocytes in 26% (p=0.301) with LM were increased of a general blood test analysis. A decrease in hemoglobin level is observed in 21% (p=0.462) of children with LM.

The total bilirubin in 10,7% (p=0.698) (VM) and the creatinine in 10,5% (p=0.574) (LM) showed an increase according to the results of biochemical analysis. A decrease in total protein was found in 10.5% ($p<0.05$) of children with LM. The D-dimer in 28%, INR - 23.8%, APTT - 18% ($p<0.01$) were elevated of children with VM. Other blood parameters were within the age norm. Spearman's direct correlation was found between the VM volume and the D-dimer ($p<0.05$). There were no significant changes observed in the coagulogram indicators of children with LM.

CONCLUSION: When preparing the patient for treatment, it is crucial to monitor levels of erythrocytes, lymphocytes, total bilirubin, creatinine, and coagulation. The study shows a significant direct correlation between the volume of the VM and the D-dimer level.

23 - High Flow Intramuscular Vascular Anomalies (Intramuscular Capillary Type Hemangioma) of the Head and Neck: a 12 patients case series
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PURPOSE: High Flow Intramuscular Vascular Anomalies (HFIVA) are a poorly addressed entity. In the literature, and among physicians, they are usually named Intramuscular Capillary Type Hemangioma (ICTH). Reports are scant in the literature, and most are case reports. Here we present a 12 patients case series of head and neck HFIVA. Clinical Features, Imaging Characteristics, Treatment strategies and Postoperative Course are described.

METHODS: A retrospective analysis on 287 consecutive AVM was conducted. Cases compatible with HFIVA were selected based on clinical, radiological and histopathological features. Type of treatment and clinical course after that were reviewed. Histological features were analysed.

RESULTS: A total of 12 patients were found. Clinical features -All patients reported an asymptomatic tumescence enlarging slowly over several years. This involved the masseter in 9 patients and the digastric muscle in 1. In 1 patient the masseter and the temporalis muscle were involved. In 1 patient the anterior and middle scalene muscles were affected.

All but 2 cases presented the following MRI features: confinement within the involved muscle, respecting the fascial layers; T1 isointense lesion; T2 hyperintense lesion; vivid contrast enhancement; mostly minor flow voids. Treatment - Eight patients were treated with embolization followed by total resection. One with total resection alone. One with embolization and partial resection. One patient refused treatment. One patient received modified electro sclerotherapy. One patient was lost at follow up. All patients treated with total resection had no relapse over time. The patient who received partial resection had to be treated 2 more times owing to regrowth of the remnants. The patient treated with modified electro sclerotherapy had good response but the follow up is too short to make inference.

CONCLUSION: HFIVAs share common features. They can be differentiated from "typical" AVMs and other tumors. Total resection seems to be an effective way to treat them."

31 - Combined treatment with Embolotherapy, Schlerotherapy, Trametinib and Thalidomide of an infiltrative arteriovenous foot threatening malformation

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PURPOSE: Congenital vascular malformations are entities with a broad spectrum of presentations and variable prognosis. They typically present at a young age and are historically associated with extensive resection surgeries with high morbidity. Arteriovenous malformations (AVM) are rare, but highly symptomatic and very difficult to treat. We present a case of a foot AVM presenting with pain, ulceration and bleeding episodes that was treated with endovascular and pharmacological means.

METHODS: We reviewed all the clinical and imagiological data after obtaining the patient's informed consent.

RESULTS: A 22-year-old female presented with a foot ulcerative Yakes type IV AVM. (Figure 1). Pre-treatment angiography showed inflow through branches from the posterior tibial, peroneal and pedal arteries. The ulcer had been present for the last 10 years with occasional bleeding. Initially, we performed an initial transarterial nidus embolization with 3% polidocanol and posterior tibial artery obliteration with Concerto® 4x100 micro-coil and Onyx34®. As the patient showed incomplete clinical involution, we performed additional embolization through combined transvenous and transarterial approaches in another 3 settings 6 months apart, with PHIL 30% and 3% polidocanol. She remained in pain despite opioid use. Doppler ultrasound showed her popliteal artery's volume flow was 260cc/min. We proposed treatment with trametinib. After 1 month of trametinib the pain was completely controlled, without the need for any analgesic medication. After 6 months of trametinib her volume flow at the popliteal artery was 180cc/min, but the ulcer showed no signs of involution. It was decided

to switch the pharmacological treatment to thalidomide. After the switch, her ulcer started to involute and presently, the volume flow at the popliteal artery is 71cc/min.

CONCLUSION: Endovascular treatment was primarily used for symptomatic AVMs. However, thalidomide's success may shift the standard to a first-line pharmacological approach, reserving endovascular treatment for acutely symptomatic cases.

35 - Surgical treatment of head and neck arteriovenous malformation: Indications, outcome and factors related to recurrence

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PURPOSE: 1. Evaluate the outcome after surgical treatment of arteriovenous malformation (AVM) of the head and neck 2. Search for factors relared to recurrence after surgical treatment.

METHODS: We retrospectively assessed AVM recurrence among 93 patients with head and neck AVMs treated with surgical resection with or without embolization between January 2008 and December 2020 in one-single center. Totally resection was applied for small, localized AVMs and maximum resection was applied for big, diffuse AVMs. Outcome after follow-up were classified according to Wu's classification. Recurrence was defined as any evidence of AVM expansion following embolization and resection. Patient variables, including sex, age, history, AVM size, AVM location, stage, and treatment modalities, number of feeding arteries, angiographic features, occlusion after embolization were examined for correlations with the recurrence after treatment of head and neck AVMs. Statistical analysis was performed using SPSS 20.0

RESULTS: A total of 93 patients were enrolled in this study. 67 of 93 treated patients (72%) were questioned and checked at hospital: The cure rate after treatment was 62,7% (n=42), the improved rate was 29,8% (n=20). 86 patients were follow-up at least 6 months after surgical resection. During follow-up, 18 patients experienced recurrence (the long-term recurrence rate was 20.9%). Prior treatment, stage, AVM size, localization, number of feeding arteries and treatment modality were identified as independent predictors of recurrence. Recurrence was less likely following the treatment of lower-stage or smaller lesions and did not correlate with age, sex, angiographic features or embolization efficiency.

CONCLUSION: AVMs of the head and neck are among the most challenging conditions to manage due to a high risk of recurrence. Early and total AVM resection is the best method for preventing recurrence."

37 - The "low dose medicine" in the treatment of Limphatic Malformations. A twenty-year experience

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PURPOSE: To present a parallel experience in two Centers in treatment of lymphatic malformations (LMs) in head/neck area using ""low dose medicine"" (homeopathic/omotossicologic) between 2002 and 2022.

A preliminary experience has been lead using low dose remedies as effective support therapy respectively in oncologic/ORL field (Center A) and as resolving intravenous treatment in a difficult case of macroglossia, admitted for glossectomy after failure of conventional therapy (Center B).

METHODS: 79 patients (38 Center A, 41 Center B), 36 male, 43 female, aged from 0 to 22 years were included in this study. All the patients were affected by head and neck LMs staged at 1 to 5 of DeSerres classification. 35 patients (44,3 %) have previously been submitted to surgery and/or sclerotherapy with incomplete results. 58 patients (73,4 %) were suffering by inflammatory recurrent complications. All the

patients recruited in this series were submitted to low dose therapy based on echinacea plus a lymphatic tissue draining product, plus in some case others complex remedies individually tailored.

RESULTS: A clinical reduction in size was seen after 1 month of treatment in 90% of the patients. The results were evaluated on the basis of clinical observation supported by imaging. The treatments allow triggering a nearly complete regression in 30 % of the patients. In all the patients but two the “low dose medicine" was also effective in preventing recurrent episodes of tongue and respiratory inflammatory painful complications.

CONCLUSION: On the basis of a parallel experience in two Center along a 20 years period, the "low dose" outpatient treatment of LMs, for his efficacity, ease of administration and lack of side effects, can be considered a good support or alternative from traditional approach to more current therapies (i.e Sirolimus, Alpelisib). We think this new proposal is worthy for further larger controlled studies.

38 - TOPICAL SIROLIMUS TREATMENT IN VASCULAR ANOMALIES: OUR EXPERIENCE.

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PURPOSE: The oral efficacy of sirolimus (an mTOR inhibitor) has been demonstrated in the treatment of complex vascular anomalies. Its topical use in superficial vascular lesions has been established as a valid and safe therapeutic option.

METHODS: We present our case series of patients under 15 years of age with superficial vascular anomalies treated with topical sirolimus from 2017. Data were collected regarding the type of vascular anomaly, age at the start of treatment initiation, location, treatment time, side effects, clinical improvement, and pre-and post-treatment.

RESULTS: A total of ten patients treated with topical sirolimus were analyzed. The administration regimen was 1% sirolimus in Vaseline, a single nightly application. The diagnosis was tufted angioma in three patients, microcystic lymphatic malformation in six patients, and one patient presented venolymphatic malformation. The mean age at the start of treatment was eight and a half years (range between 6months and 14years).

The three patients with tufted angioma were diagnosed after performing a biopsy; two presented improvement in symptoms (coloration, pain, and/or sweating) and currently remain in treatment (mean treatment time of 24months). The remaining patient required a switch to oral sirolimus and is currently undergoing laser treatment.

Of the seven patients with microcystic lymphatic malformations, two had previously undergone surgical excision. A total of four noticed an improvement in symptoms, especially in terms of vesicle bleeding (mean treatment time 17months), and are currently undergoing treatment.

No patient reported any side effects.

CONCLUSION: The administration of topical 1% sirolimus is a valid, safe, and non-invasive option for vascular anomalies with superficial involvement.

Systemic absorption is undetectable according to the literature, and the side effects described are minimal.

Topical sirolimus has been previously described for microcystic lymphatic malformations improving size and bleeding blebs. We believe that it should also be considered as an effective therapeutic option in tufted angiomas.

40 - Intramuscular hemangioma capillary type: clinicopathological and molecular analysis
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PURPOSE: Intramuscular hemangioma capillary type (IHCT) are rare entities, refers to a fast-flow vascular lesion. The purpose of this study was to determin the relationship between clinicopathological and molecular in IHCT.

METHODS: We reviewed all IHCT cases from our institution confirmed pathologically from 2014 to 2023, and examined 10 cases by next generation sequencing (NGS) .

RESULTS: The cohort comprised 10 patients (6 males, 4 females) with a median age of 18(range:1-37) years. Lesions of disease included trunk (n=4), upper extremity (n=2), lower extremity (n=2), shoulder(n=1), and neck (n=1). IHCT was most commonly a progressive increasing mass, and was mostly painless. Histopathologically, all lesions exhibited aggregates, lobules and/or anastomosing cords of capillary-type vessels, separating or infiltrating between the skeletal muscles. 4 lesions had irregularly dilated vessels with thick walls like AVM in the periphery of the lesion. Occasional mitoses were present , however, there was no apoptosis or cellular atypia. Ultrasonography was performed in all cases describing mainly a hyperechogenic intramuscular lesion. MRI demonstrated the most common features were a well-delineated mass that was homogeneous. We detected somatic mutations in 7 of 10 IHCT cases. 4 cases had a mutation in MAP2K1 (p.Q58_E62del, p.K57_G61del, p.K57N), 2 cases had mutations in KRAS (p.Q61R and p.L56V, p.G13R), and 1 case had a mutation in HRAS (p.D69_Q70insRWYSAMRD). Mutant allele frequencies detected by sequencing ranged from 9.98% to 15.97%. All cases were followed up, and no recurrence was found after operation.

CONCLUSION: IHCT's hemodynamic and molecular genetic phenotypes are similar to those of AVM, and there are mutations in MAP2K1 or RAS gene, but there are differences in clinical pathology and treatment methods. This study provides further insight into gene-causing mutations for vascular anomalies and possible targets for developing pharmacotherapy.

41 - Regimen for Accelerated Propranolol Initial Dosing (RAPID)
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PURPOSE: Infantile hemangiomas are common vascular tumors in children. Propranolol has proven effective in treating infantile hemangiomas and while generally safe, has potential risk for more serious side effects of hypotension, bradycardia, and cardiovascular or respiratory compromise. Current prescribing guidelines recommend initiating propranolol doses at 1 mg/kg/day, with up-titration to 2 mg/kg/day. This study aims to compare the incidence of adverse events in infants and children treated with propranolol initiated at 1 mg/kg/day versus being initiated directly at 2 mg/kg/day.

METHODS: A retrospective cohort study was conducted using medical records of patients receiving propranolol therapy for infantile hemangiomas between October 2018 - March 2021. Patients were categorized by initial propranolol dosage: 1 mg/kg/day or 2 mg/kg/day. The primary outcome measures included parent-reported adverse events, hypotension (defined by the Pediatric Advanced Life Support criteria), bradycardia (defined as <1st percentile for age), and hemodynamic changes following propranolol initiation.

RESULTS: Out of the 244 patients identified, 123 were initiated at the 1 mg/kg/day dose, and 121 at the 2 mg/kg/day dose. There was no significant difference in the incidence of adverse events between the two groups (p = 0.074). Additionally, among patients initiated at 2 mg/kg/day, there were no significant differences in the incidence of age-related or weight-related adverse events for those younger than 2 months or those in the 1st or 2nd quartile for weight (p = 0.66).

CONCLUSION: Infants and children initiated at 2 mg/kg/day did not demonstrate an increased incidence of adverse events associated with propranolol compared to those initiated at 1 mg/kg/day. These findings provide clinical evidence for the practice of accelerated propranolol initiation dosing.

42 - Case Report of an infant with components of LUMBAR syndrome, who was successfully managed with a combination of Propranolol, Bleomycin Sclerotherapy and Neurosurgery

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PURPOSE: To present an infant with an extensive infantile hemangioma (IH), components of LUMBAR syndrome (lumbosacral hemangioma, intraspinal lipoma - spina bifida, perianal skin tag), who responded to a combination therapy of propranolol, sclerotherapy with bleomycin, which permitted surgical correction to occur safely.

METHODS: We reviewed the patient's medical records.

RESULTS: A 7-month-old girl presented to our clinic with extensive superficial and deep segmental IH in the lumbosacral region and an underlying lipoma (intraspinal lipoma type IV – chaotic), compressing the cauda equina. The cutaneous lesions were noted shortly after birth and then started enlarging progressively. She remained neurologically intact. Due to the presence of IH at the anticipated incision site she initiated therapy with propranolol (final dose 3 mg/kg/day). Patient demonstrated improvement to the extent, color, size of the IH lesions, but due to persistence at the area of planned surgery received one session of localized percutaneous sclerotherapy with 0.2 mg/kg of bleomycin at 3 months post start of therapy. The procedure yielded further improvements locally and was deemed appropriate to undergo surgery after approximately 5 months of propranolol therapy at 12 months of age. Surgery was successful at removing the lipoma and she did not experience undue healing or bleeding complications at the site. Medical therapy and sclerotherapy were well tolerated.

CONCLUSION: Propranolol is a well-known therapy modality for IH, and its initiation is recommended by 4 weeks of life. Although the medication was started at the late age of 7 months, she still showed a moderate clinical response. Sclerotherapy is not often considered or utilized in IH, but in this case it served as a rapid and effective aid in IH regression at the specific site of a planned surgical intervention. The multi-disciplinary management led to a successful outcome for the patient.

47 - Targeted next-generation sequencing for detection of PIK3CA mutations in archival tissues from patients with Klippel–Trenaunay syndrome: A retrospective study of 14 patients

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PURPOSE: We aimed to demonstrate the clinical utility of targeted next-generation sequencing (NGS) in identifying PIK3CA mosaicism in archival formalin-fixed paraffin-embedded (FFPE) tissues from patients with Klippel–Trenaunay syndrome (KTS).

METHODS: This retrospective study involved 14 patients with vascular malformations with lower limb hypertrophy who underwent resection of the vascular malformations between 2011 and 2020. KTS was diagnosed based upon the triad of capillary malformation, venous malformation, and hypertrophy of the affected limb. We used an order panel to perform targeted sequencing of all PIK3CA gene coding sequences. The panel consisted of 64 amplicons with an overall coverage of 87.9%.

RESULTS: Participants were 9 female and 5 male patients with KTS diagnosed as capillaro-venous malformation (CVM) or capillaro-lymphatico-venous malformation (CLVM). Median age at resection was 14 years (range, 5–57 years). Median archival period before DNA extraction from FFPE tissues was 5.4 years (range, 3–7 years). NGS-based sequencing of PIK3CA achieved an amplicon mean coverage of 119,000x. PIK3CA missense mutations were found in 12 of 14 patients (85.7%; 6/8 CVM and 6/6 CLVM), with 8 patients showing the hotspot variants E542K, E545K, H1047R, and H1047L. The non-hotspot PIK3CA variants C420R, Q546K, and Q546R were identified in 4 patients. Overall, the mean variant allele frequency for identified PIK3CA variants was 6.9% (range, 1.6%–17.4%). All patients with geographic capillary malformation, histopathological lymphatic malformation or macrodactyly of the foot had PIK3CA variants. No genotype–phenotype association between hotspot and non-hotspot PIK3CA variants was found.

CONCLUSION: Amplicon-based targeted NGS could identify low-level mosaicism from low-input DNA extracted from FFPE tissues, potentially providing a diagnostic option for personalized medicine with inhibitors of the PI3K/AKT/mTOR signaling pathway.

48 - Fluoroscopy and endoscopy-guided transoral sclerotherapy using foamed polidocanol for oropharyngolaryngeal venous malformations in a hybrid operation room: A case series

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PURPOSE: This study evaluated the effectiveness and safety of fluoroscopic and endoscopic sclerotherapy for oropharyngolaryngeal venous malformations.

METHODS: Patients with venous malformations involving the oropharynx who underwent transoral sclerotherapy in a hybrid operation room were enrolled in this retrospective study. All patients were examined with MRI before the first session and at least 6 months after the final session, and treatment outcomes were graded using MRI before and after treatments as follows: excellent (>66% volume

reduction), good (>33% volume reduction), fair (<33% volume reduction), and poor (no change or worse).

RESULTS: Fourteen consecutive patients (6 female, 8 male; mean age at presentation, 32 years) were analyzed. Major clinical symptoms were breathing difficulties (n = 3), snoring (n = 2), sleep apnea (n = 1) and swallowing difficulties (n = 1). Lesions were extensive in face and neck (n = 9), and limited in oropharyngolarynx (n = 5). Treated regions were soft palate (n = 8), pharynx (n = 7), the base of the tongue (n = 4) and epiglottis (n = 1). Permanent tracheostomy was placed in 2 patients at presentation. The mean number of sclerotherapy sessions per patient was 4.6 (range, 1–14). The mean follow-up duration after the first sclerotherapy session was 77 months (range, 6–141). A prophylactic tracheotomy was performed in 2 patients, and post-procedure tracheostomy was performed in 3 patients, including 1 patient with bleeding with urgent placement of a tracheostomy. Effectiveness of treatment was rated as excellent (n = 2), good (n = 7), and fair (n = 5).

CONCLUSION: Hybrid transoral sclerotherapy can be effective and safe for oropharyngolaryngeal venous malformations, enabling intraoperative assessment of the distribution of sclerosant mixed with contrast material using fluoroscopy, endoscopy and CT.

50 - Maternal and Paternal Factors as Predictors of Sturge-Weber Syndrome and Neurological Outcome: A First Look

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PURPOSE: Few studies have investigated prenatal factors and assessed their influence on the development of Sturge-Weber syndrome (SWS) and neurological outcome in a SWS population. Thus, the aim of the present study was to retrospectively identify potential prenatal risk factors influencing SWS and neurological outcome in individuals with SWS.

METHODS: Sixty-nine subjects, seen between 2019 and 2023, were consented for research and met inclusion criteria. Medical records and a clinical intake questionnaire were retrospectively analyzed to create a database. The questionnaire inquired about the patient's medical, familial, and birth history. Variables were analyzed as either symptoms or potential predictors of SWS.

RESULTS: Higher paternal age at conception was associated with a range of cognitive dysfunctions in offspring with SWS brain involvement. Indeed, paternal age was associated with low IQ (n=25, p=.004), strokes or stroke-like episodes (SLEs) (n=34, p=.030), gross and/or fine motor delay (n=34, p=.036), delays in ability to perform activities of daily living (n=30, p=.012), and delayed learning compared to peers (n=31, p=.027). Furthermore, paternal age was correlated with worse cognitive outcome, as measured by cognitive Neuroscore (r=.575, p<.001, n=32). When maternal thyroid disease and hypertension were present during pregnancy, offspring were more likely to experience low IQ (n=30, p=.041) and the regression of any abilities (n=37, p=.045), respectively. Logistic regression confirmed the association between paternal age and severe cognitive Neuroscore (β=.300, p=.033, OR: 1.35 95% CI: [1.02, 1.78]), even when controlling for the effects of seizures and strokes or SLEs.

CONCLUSION: In this study, prenatal factors were associated with neurological symptoms in subjects with SWS. Older paternal age, in particular, may predict worse neurocognitive outcome. Further research is needed in a larger cohort to determine their value as prognostic tools. Likewise, genetic animal models may be used to determine the impact of prenatal factors on the severity of outcome.

55 - Rapidly growing congenital hemangioma resulting in life-threatening, intra-lesional hemorrhage requiring surgical resection

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PURPOSE: A 14-day old male presented to the Vascular Anomalies Clinic with a 6cm x 5.5cm, partially ulcerating vascular mass emanating from the posterior right peri-scapular region. The mass was diagnosed via prenatal ultrasound. No fetal MRI was obtained. Due to the size of the lesion, presumed to represent a congenital hemangioma based on clinical presentation and post-natal ultrasound, echocardiogram was performed (which was normal), and close follow-up was scheduled. 5 days following initial presentation, patient was taken to the Emergency Department with some external bleeding from the mass with increasing size of the lesion. Hemoglobin = 5.2g/dL at presentation. The patient responded to transfusion. An MRI and percutaneous biopsy were performed to evaluate for possible kaposiform hemangioendothelioma versus congenital hemangioma.

The biopsy and MRI were consistent with a congenital hemangioma (GLUT-1 negative, D2-40 negative). Baby was discharged after a 4-day admission. Two weeks after discharge, however, the patient was readmitted with recurrent bleeding and hgb = 5.9 g/dL. The mass had continued to grow rapidly, and interventional radiology was consulted for possible embolization. Unfortunately, arterial supply to this lesion was primarily from the right vertebral artery, precluding endovascular embolization. However, since the patient was at high risk for continued bleeding, percutaneous gelfoam embolization was attempted with minimal effect. The patient stabilized and was discharged after a 7-day hospitalization, in hopes that the mass would begin to rapidly involute.

Two weeks later, the patient was again seen in the Vascular Anomalies Clinic. At that time, the mass had continued to grow to a massive size with down trending hgb. The patient was subsequently scheduled for surgical excision with plastic surgery.

Pathology confirmed a hypermitotic, GLUT-1 negative, hemangioma. Genetic testing confirmed pathogenic variants of both GNAQ and PIK3CA. The patient is 2 months post-op and doing well with no evidence of recurrence.

56 - A Potential Role for Topical Sirolimus in Patients with KHE/TA and a significant Superficial Component

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PURPOSE: Systemic sirolimus has previously been shown to be effective in the treatment of KHE/TA. There are limited studies to date on a role for topical sirolimus in patients with KHE/TA with significant superficial skin involvement.

METHODS: Retrospective review of medical records since January 2020 identified 3 patients with KHE/TA with a significant superficial component treated with topical sirolimus as adjunct therapy during oral sirolimus taper at a single pediatric institution. Two out of the three patients initially had KMP, while the third patient had dropping platelets and fibrinogen prior to oral sirolimus initiation. Response was determined by clinical subjective and objective measures.

RESULTS: Two of the three patients with KHE/TA and substantial superficial components were successfully weaned off of oral sirolimus using topical sirolimus as adjunct therapy. There were no issues with pain or clinically significant change in laboratory work during oral sirolimus taper or the subsequent 3 months.

CONCLUSION: Topical sirolimus may serve a valuable role in helping to successfully wean off of oral/systemic sirolimus in a subset of patients with KHE/TA who have significant surface area to volume ratio of their lesions, by delivering medication locally through the skin. Future studies on the use of topical sirolimus in this population would provide guidance on optimal timing and duration of therapy. While 1% topical sirolimus may not be sufficient for drug delivery in all such, newer agents with higher concentrations or improved absorption might show further benefit for these patients.

57 - PIK3CA-related isolated macrodactyly: therapeutic approach.
Marta Marí Muro (Hospital 12 de Octubre)

PURPOSE: We aim to present 3 clinical cases of macrodactyly where we found an activating mutation in PIK3CA gene.

METHODS: We reviewed three cases seen and treated in our hospital during the last 3 years. The first case, a 2-year-old male, presented a single overwrought of the 3rd and 4th left fingers creating a simple syndactyly which was operated at 1st year of life. Physical examination revealed further development of overgrowth, together with radial deviation of medium and distal phalanges on both affected fingers. Our second case is a 4-year-old male who showed overgrowth of 2nd and 3rd fingers on his left foot, as well as expansion of fat tissue on the plantar region. A dermolipectomy was performed, but further progression was observed in spite of it, restraining de use of certain types of footwear. The third case is a 14-year-old woman with macrodactyly affecting her right thumb exclusively. She also underwent a dermolipectomy, and developed further growth despite the treatment.

RESULTS: All three patients underwent an MRI where we observed an isolated overgrowth of adipose tissue. No vascular malformations or other kind of associated tumours were found in those imaging studies. The genetic tests of our patients showed a positive activating mutation in PIK3CA.

CONCLUSION: Macrodystrophia is one of the diseases included in PIK3CA-related overgrowth spectrum. In this group of diseases, surgery represents an adjuvant treatment that could enhance functional adaptation of the patient, but it does not always provide a permanent solution. The selective PIK3CA inhibitor Alpelisib, offers a therapeutic alternative for these patients. Its effectiveness has already been proven in several articles. Nevertheless, more long-term experience is required to properly establish the stability of its results, as well as its security profile.

66 - Sequential Endovenous Laser Ablation Followed by Sclerotherapy in the Management of Klippel-Trenaunay Syndrome
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PURPOSE: Klippel Trenaunay Syndrome (KTS) poses unique challenges due to the diffuse nature of subcutaneous vascular anomalies, making complete surgical excision unfeasible. Consequently, sclerotherapy is often the preferred treatment choice. However, the constraints on the volume of sclerosant per session pose limitations, especially in the presence of extensive lesions. In this study, we report successful outcomes with a combination therapy approach that involves the sequential use of Endovenous Laser Ablation (EVLA) followed by Sclerotherapy for KTS patients.

METHODS: We present the case of a 14-year-old female with KTS, displaying capillary malformations and widespread low-flow vascular anomalies since birth. She sought treatment due to severe pain in the lateral aspects of her left lower leg and left foot dorsum. Preoperative imaging confirmed the presence of lateral megaveins and deep venous patency.

Our treatment strategy encompassed the sequential application of EVLA, targeting lateral megaveins outside the affected limb, followed by Sclerotherapy for other lesions.

RESULTS: After 6 months, the patient experienced pain relief, accompanied by a significant reduction in the size of foot dorsum lesions, ultimately improving her shoe comfort and enabling a return to her regular daily life.

CONCLUSION: In conclusion, EVLA effectively addresses lateral megaveins in KTS patients, and the sequential addition of Sclerotherapy further enhances therapeutic efficacy. This study underscores the benefits of a combined EVLA and Sclerotherapy approach in the comprehensive management of Klippel Trenaunay Syndrome.

69 - Evidence of Congenital Hemangioma Causing Breast Hypoplasia and Therapeutic Strategies

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PURPOSE: Congenital hemangiomas (CH) is rare cutaneous vascular tumors of intrauterine onset. To date, two cases of infantile hemangiomas (IH) combined with breast hypoplasia have been reported. CH exhibits distinct behavior compared to IH, and relationship of CH to breast development remains uncertain.

METHODS: We present a patient with CH lesions in the breast, accompanied by ipsilateral breast hypoplasia. Magnetic resonance imaging(MRI) assesses the extent of lesion involvement and the size of bilateral breasts. The lesion was surgically excised and CD31, GLUT-1 were histopathologically examined.

RESULTS: Congenital hemangiomas involving the right breast resulted in pronounced hypoplasia of the affected breast in a 12-year-old patient. Homogeneous subcutaneous masses (43 × 12mm) were observed with parenchymal contrast enhancement on T1-weighted images. The lesion was surgically removed. Histologic characteristics of resected specimens included numerous small vessels form lobular collections and hobnailed endothelial cells tested positive for CD31 and negative for GLUT-1, confirming the diagnosis of CH.

CONCLUSION: This case demonstrates that the presence of CH may cause breast hypoplasia and that surgical intervention prior to puberty should be considered in an attempt to minimize this adverse sequela.

70 - Pathogenic Analysis of Angiogenesis and Adipogenic Differentiation of adipose derived stem cells in angiolipoma

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PURPOSE: Angiolipoma is a type of benign soft tissue tumor characterized by the presence of mature adipose tissue and abnormal proliferation of blood vessels. These tumors are usually asymptomatic, but they can cause pain or tenderness if they compress nearby nerves or tissues. The exact pathogenesis of angiolipomas is not fully understood. In this study, we attempted to elucidate the role of adipose-derived mesenchymal stem cells (ADSCs) in the pathogenesis of angiolipoma.

METHODS: Primary adipose-derived stem cells of angiolipoma were isolated and cultured. Mesenchymal marker expression were confirmed by flow cytometry. Differentiation potential was evaluated by Oil Red O staining. The expression of PPAR γ, C/EBP α, FABP4, VEGF,TGF β, HGF and PDGFD were examined by RT-qPCR. ELISA kits were further used for evaluation of angiogenic factors (HGF/VEGF).

RESULTS: The adipocytes from angiolipoma were more hypertrophic than those observed in normal adipose and abnormal vascular proliferation was found in lesion. Furthermore, comparative to normal ADSCs, ADSCs of angiolipoma exhibited lower adipogenic potential. The mRNA expression of PPAR γ, C/EBP α, and FABP4 was also down-regulated in angiolipoma. Interestingly, ADSCs of angiolipoma express and secrete a variety of angiogenic factors such as VEGF, TGF-β, HGF, and PDGFD.

CONCLUSION: ADSCs of angiolipoma express and secrete a variety of angiogenic factors, which can partly explain the abundant abnormal blood vessels in angiolipomas. The mature adipocytes in angiolipomas may do not originate from adipogenic differentiation but are rather associated with the proliferation of pre-existing adipocytes.

71 - Postoperative Scarring in PROS Patients: Unraveling Normal Scarring Patterns in Clinical Cases

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PURPOSE: The current belief is that Excessive scarring occurred frequently in patients with PIK3CA-related overgrowth syndromes. This might impact the formation of surgical indications. However, we have observed that a certain proportion of facial infiltrating lipomatosis (FIL) patients developed normal scaring outcomes after surgery. In this study, we observed and recorded the scarring outcomes in patients with FIL.

METHODS: A retrospective chart review included 18 patients diagnosed with facial infiltrating lipomatosis (FIL), who had underwent surgical treatment at our center from 2012.1.1 to 2022.12.31. A multidisciplinary team comprising members from the dermatology, plastic surgery, and genetics departments conducted an analysis of medical records and photographs. Next-generation sequencing is employed to confirm mutations in the PIK3CA gene.

RESULTS: A total of 18 FIL patients with were analyzed and all patients had taken preoperative and postoperative photographs. Among all 18 patients, we observed that 4 cases (22%) exhibited normal scarring outcomes. We detected PIK3CA mutations in the scar tissues of these patients, and the mutation frequency in scar tissues was consistent with that in the affected tissues. Among these, 3 patients underwent multiple surgeries involving facial nerve dissection and mandibular osteotomy. However, 7 cases (38.8%) developed excessive scarring. Among these 7 patients, 5 cases involved mandibular osteotomy and zygomatic reduction. The remaining patients' scar conditions fell between these two categories.

CONCLUSION: The proportion of Excessive scarring in FIL patients is lower than reported in the literature in our center, but cases of hypertrophic scars still exist. We recommend performing staged surgery for PROS patients and opting for incisions that are less prone to scarring for the first-stage surgery.

72 - ARTERIAL ANEURYSMS IN PEDIATRIC POPULATION. SINGLE CENTER EXPERIENCE. IS IT POSSIBLE TO ESTABLISH CLINICAL MANAGEMENT CRITERIA BASED ON GENETIC TESTS RESULTS?

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PURPOSE: Pediatric arterial aneurysm is complex disease than can affect children in every range of age and multiple vascular territories. Current literature suggests that the management of this pathology must be individualized, although the data regarding the optimal timing and the treatment of choice remain limited. We aim to present our series of children with arterial aneurysms, to analyze our outcomes and the possible roll of genetic analysis as a starting point to define the clinical management.

METHODS: An observational retrospective study was performed including all patients <18 years of age diagnosed with arterial aneurysms and treated in our center between 2001-2022. Demographic data, genetic analysis, treatments and outcomes were analyzed.

RESULTS: Fifteen aneurysms in seven children (3 boys), ranging from 3-9 years old were included. Genetic alterations were identified in 4 patients (WDR19/TTC21B variants, COL3A1 mutation in two children and ETV6-NTRK3 rearrangement, respectively). Arterial aneurysms were located in abdominal aorta (3), renal artery (2), celiac trunk (1), inferior mesenteric artery (1), hypogastric artery (1), subclavian artery (1), axilar artery (1), humeral artery (2), cubital artery (1), femoral superficial artery (1) and posterior tibial artery (1). Four aneurysms were treated with resection alone, 7 with resection and bypass reconstruction using biosynthetic material (n=3) or autologous vein (n=4) and 1 with percutaneous embolization (hypogatric artery aneurysm). Thrombosis was observed in 4 distal bypass reconstructions, clinically well tolerated. Two aneurysms underwent conservative treatment, observing a decrease in their size. One patient died from a renal aneurysm rupture.

CONCLUSION: The management of pediatric arterial aneurysms is a challenge due to their heterogenicity in terms of clinical features, locations, etiologies, child age and coexisting structures involved. Multi center studies and further investigations should be performed in order to stablish when management should be more aggressive. Genetic test results could be a promising starting point that guide management.

73 - LYVE1-Driven Expression of NRAS Q61R in Mouse Embryos Causes Edema, Hepatic Vascular Defects, and Abnormal Lymphatic Structures Incompatible with Life

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PURPOSE: Kaposiform lymphangiomatosis (KLA) is a complex lymphatic anomaly characterized by "kaposiform" spindled lymphatic endothelial cells and abnormal lymphatic vessels. The prognosis is poor and severe complications include hemorrhagic effusions and coagulopathy. The NRAS Q61R mutation has been identified in the lesions of patients with KLA; however, its role in the pathogenesis of KLA is unclear. The goal of this study was to develop a novel mouse model of KLA with NRAS Q61R expression targeted to the lymphatic endothelium.

METHODS: To drive the expression of NRAS Q61R in developing lymphatics, LYVE1-Cre+/+ mice were mated to Lox-Stop-Lox-NRAS Q61R+/- (LSL-NRAS Q61R+/-) mice in which the mutant gene was knocked into the endogenous NRAS allele. The pups did not survive birth and so whole embryos were collected and imaged at embryonic day 15.5. Tails were collected for genotyping, and whole embryos were fixed in 4% PFA and embedded in paraffin for histology.

RESULTS: There were two litters of 16 embryos. Eight were LSL-NRAS Q61R+/-/LYVE1-Cre (NRAS Q61R embryos) and eight were LYVE1-Cre only (control embryos). NRAS Q61R embryos had 14.5% lower body weight, significant edema around the exterior of the embryos, abnormal blood-filled vessels with hemorrhage, and abnormalities in abdominal organs. Hematoxylin and eosin staining showed blood-filled cavernous vascular defects throughout the liver and abnormal clusters of cells within the jugular lymph sacs.

CONCLUSION: Constitutive LYVE1-driven expression of NRAS Q61R during embryonic development leads to hepatic vascular anomalies and irregular jugular lymph sacs that are incompatible with postnatal life. This novel mouse model can be utilized to better understand the role of NRAS Q61R in the pathogenesis of KLA during prenatal development

74 - Overgrowth syndrome: challenging clinical case with uncontrollable progression
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PURPOSE: Overgrowth syndromes encompass a group of clinical entities with variable phenotypic expression and different impact on the patient's quality of life. The determination of activating mutations allows, in selected cases, to use targeted systemic therapies.

We present the case of a patient with progressive lipomatous overgrowth of the limb, and unidentified activating mutation.

METHODS: Clinical case presentation.

RESULTS: 17-year-old woman with asymmetric progressive overgrowth of the left lower limb (thigh, calf and foot) since the first year of life, accompanied by plantar colagenoma. Imaging tests show lipomatous infiltration of the posterior compartment of the leg. Due to the significant limitation of her quality of life, several dermolipectomies have been performed as a palliative measure. However, overgrowth has reappeared in the same areas.

Histological analysis of the resected tissue reveals mature fibroadipose tissue growth with patchy hamartomatous areas. The study of the genetic panel for vascular anomalies has not found any activating mutations related to overgrowth syndromes.

Despite the negative genetic tests, treatment with oral sirolimus was started a year and a half ago. Systemic therapy has reduced pain in the affected area, but has failed to stop the progressive overgrowth of the limb, as evidenced by a volume increase in control imaging tests.

CONCLUSION: The asymmetric and progressive overgrowth observed in this patient represents a condition that remains unidentified, despite histological and genetic tests. Treatment approaches in such cases are individualized and primarily focused on palliation. However, numerous debulking surgeries and systemic treatment with sirolimus have failed to stop disease progression. As a result, we currently lack therapeutic alternatives that could provide symptomatic stability and enhance the patient's quality of life.

75 - Ulnar distribution pattern is predominant in upper extremity lymphatic malformations
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PURPOSE: Lymphatic malformations are a common vascular anomaly in the pediatric population. Although the most frequent location is the cervical region, they can appear in any location where lymphatic tissue is present. The locoregional distribution patterns of these lesions in the upper extremity have been studied by Spanish team in Madrid. In cooperation with previous authors we decided to study the group of polish patients.

METHODS: We reviewed the medical records, radiological images and clinical photographs of 12 patients with upper extremity lymphatic malformation that were admitted to the Clinic in the years 2021 - 2023. The locoregional distribution of the lesions, treatment applied and clinical course were assessed. Statistical analysis of the collected data was performed using FactoMineR and factoextra R v.4.1 packages.

RESULTS: Of the 12 patients included in this series, 10 (83%) presented lymphatic malformation in the ulnar segment of the upper extremity, and 2 (17%) in the radial segment. In 7 of the patients (58%) the involvement was of the left upper limb, whereas in 5 (42%), of the right upper limb. In 100% of patients with proximal arm involvement, the lesion was on the posterior side. No differences were found in clinical presentation or evolution between patients with ulnar and radial distribution.

We evaluated the clinical course of treatment and their current and ongoing effects.

CONCLUSION: Upper extremity lymphatic malformations characteristically follow an ulnar distribution pattern, although the radial localization may also be affected, especially at distal level. A detailed characterization of these patterns may contribute to a better and earlier diagnosis of the pathology.

76 - An unusual case of hypertrophic capillary malformation.

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PURPOSE: We report the case of a 76-year-old patient presenting with facial capillary malformation that became hypertrophic within 6 months.

METHODS: This patient had a flat, stable capillary malformation, never treated since birth. Within 6 months, this patient experienced a rapid major hypertrophic and nodular change on the chin and lip area, associated with repeated bleeding. An important chin pendulum appeared within 2 months. MRI of the facial mass revealed hypertrophy of the soft parts of the chin and lip area with muscle infiltration. This rapid evolution was not explained by underlying AV fistula but cervical doppler US showed a 90% stenosis of the left internal carotid artery. CT angiogram showed involvement of the external carotid artery and the facial artery supplying the malformation. To prevent a thromboembolic stroke, the patient underwent emergency angioplasty of the internal carotid artery.

RESULTS: Angioplasty allowed of the nodules to be stabilized and the bleeding episodes to stop. Recruitment of the external carotid and facial arteries explains the rapid growth of capillary malformation. The stabilised sequelae were treated surgically: removal of bulky nodules and reconstruction with a cervical flap.

CONCLUSION: In the case of an unusual development of a capillary malformation the underlying vascularization must be examined in order to understand the aetiology: vascular malformation or ageing.

80 - A case of a giant scrotal AVM complicated by life-threatening intermittent hemorrhage and severe pain

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PURPOSE: Vascular anomalies involving the male genitalia, especially arteriovenous malformations (AVMs), are rare. However, they can cause considerable distress, including pain, life-threatening hemorrhage, and negative impacts on urinary, sexual, reproductive, and emotional function. Successful management of scrotal AVMs is often exceptionally difficult.

METHODS: A 18-year-old male presented to an outside hospital with a 1-year-history of scrotal swelling and pain. Computed tomography demonstrated AVM involving the right gluteal muscles and scrotum. Over the next year, he underwent angiogram with coil embolization x3. This was complicated by skin necrosis, intermittent bleeding, and recurrent infection, prompting presentation to our vascular anomalies center (VAC) for a second opinion.

RESULTS: On presentation to our VAC, examination revealed a massively enlarged scrotum with extensive ulceration and necrosis, active fluid leakage, and severe tenderness. The patient was now unable to work due to pain and intermittent life-threatening hemorrhage, dependent on narcotics, and engaging in polysubstance abuse due to the severity of his pain. Given his extremely poor quality of life and risk for life-threatening bleeding, an extensive interdisciplinary discussion was held to develop a treatment plan. We elected to pursue serial embolization followed by surgical debulking with skin grafting if necessary. Additionally, Trametinib was added. Over the following 6 months, he underwent embolization x4 with glue, STS, and ethanol, complicated by recurrent purulent infection and foreign body reaction. However, he achieved substantial improvement in the overlying scrotal skin. He was taken to the operating room for extensive surgical debulking with primary closure (EBL 1400 mL, operative time 368 min). The bilateral testicles and cord structures, urethra, and penis were preserved. His pain, bleeding, and scrotal bulk is significantly improved following operative intervention.

CONCLUSION: This case highlights the importance of taking an interdisciplinary approach to patients with challenging, life-threatening vascular anomalies who otherwise may not have any viable treatment options.

84 - Coexistence of lumbosacral segmentary hemangioma and sacral neuroblastoma

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PURPOSE: The objective of this presentation is to raise awareness about the possibility that anomalies other than those previously described are associated to lumbosacral segmentary hemangiomas.

METHODS: A clinical case of a newborn with a lumbosacral segmentary hemangioma is presented.

RESULTS: A 17 days-old girl with no significant personal or familial history was attended due to two painful ulcers in her right buttock. The patient presented a very light red macule in the right buttock since birth, which had become progressively more evident, and had recently ulcerated. The physical examination revealed an erythematous plaque, affecting the S3-4 metameres, with two ulcers of 1 and 0.7 cm on it. Considering the possibility of a lumbosacral segmentary hemangioma, a magnetic resonance imaging was performed to evaluate associated locoregional anomalies, revealing a probable neuroblastoma of 4 cm that originated in the left S1-2 neural foramina. A MIBG scintigraphy did not show tracer uptake in any location other than the aforementioned lesion, and a core needle biopsy confirmed the diagnosis of neuroblastoma. Taking into consideration that the patient presented favorable prognostic factors, it was decided to follow a watch-and-wait approach. Regarding the ulcers, given the suspicion of an underlying hemangioma, propranolol was started. Fifteen days later, the plaque on the patient's buttock had lightened and both ulcers had completely resolved, supporting the

clinical suspicion. At present, the patient is 3 months old, the hemangioma has markedly involuted, and the neuroblastoma has slightly reduced its volume by ultrasound imaging.

CONCLUSION: Even though lumbosacral segmentary hemangiomas have been related to neurological, genitourinary, or anorectal anomalies, there are no reports of association with pelvic neuroblastoma. Therefore, although the present is a single case, it may help raise awareness about the possibility that neuroblastoma could be an additional manifestation associated with segmentary hemangiomas. Nonetheless, further research is needed to evaluate this hypothesis.

86 - Blue Rubber Bleb Nevus Syndrome: Can Medical Therapy Replace the Surgeon?
Claire A. Ostertag-Hill (Boston Children's Hospital); Cameron Trenor (Boston Children's Hospital); Melisa Ruiz-Gutierrez (Boston Children's Hospital); Tishi Shah (Boston Children's Hospital); Victor L. Fox (Boston Children's Hospital); Meghan J. O'Hare (Boston Children's Hospital); Steven J. Fishman (Boston Children's Hospital)

PURPOSE: Blue rubber bleb nevus syndrome (BRBNS) commonly leads to severe chronic anemia secondary to gastrointestinal (GI) bleeding. Meticulous surgical resection can achieve successful control but requires tedious procedures, sometimes so lengthy that staged operations are necessary. Sirolimus has recently emerged as an effective therapy for many vascular anomalies, but its efficacy in managing BRBNS-related GI bleeding remains poorly understood. We aim to examine tolerability, duration of needed therapy, and efficacy of Sirolimus as a potential alternative to surgery.

METHODS: A retrospective review of patients treated with Sirolimus for BRBNS-related GI bleeding was performed.

RESULTS: To date, twelve patients have been treated with Sirolimus for BRBNS-related GI bleeding at our center. Patients were median of 13.1 (IQR 11.0, 17.8) years at Sirolimus initiation and had a median hemoglobin nadir of 5.8 (4.4, 8.3) g/dl prior to Sirolimus. During the median follow-up period of 4.0 (2.0, 5.2) years, two patients (16.7%) experienced refractory GI bleeding, necessitating frequent blood transfusions and ultimately major surgical intervention. Additionally, one patient (8.3%) discontinued Sirolimus after 4 months due to intolerable side effects. Nine patients (75.0%) experienced significant improvement in their GI bleeding with a most recent median hemoglobin of 13.0 (12.0, 13.3)g/dl, remaining blood transfusion free since treatment initiation. However, attempts to discontinue Sirolimus in 4 of these 9 patients after a median of 17 months on therapy resulted in recurrent GI bleeding and anemia in all patients, requiring medication reinitiation.

CONCLUSION: Daily sirolimus can lead to remarkable improvement in BRBNS-related GI bleeding. However, a subset experiences side effects requiring medication discontinuation or severe bleeding refractory to Sirolimus, necessitating surgery. Additionally, maintenance of symptom relief requires long-term medication continuation, which may not be possible or desirable for all patients. Given these challenges, a thorough discussion between patients and their interdisciplinary provider team regarding medical therapy versus surgery is paramount.

88 - Management of Splenic Vascular Anomalies: A Review of 15 Pediatric Cases at a Single Institution
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PURPOSE: Splenic Vascular Anomalies (SVA) are rare lesions that can be difficult to diagnose in the pediatric population. Clarity is needed on how to optimally work-up and follow these patients. The aim of this study was to create a management algorithm that effectively utilizes imaging modalities to achieve quality clinical outcomes.

METHODS: We retrospectively reviewed the medical records of pediatric patients diagnosed with SVA from 2012 to 2022. Demographic and clinical history, available imaging findings, pathology results, operative information, and clinical outcomes were collected and summarized descriptively.

RESULTS: Fifteen patients met inclusion criteria for this study. SVA was identified incidentally in 13/15 (86.7%) patients. The median SVA diameter (maximal diameter) was 4.2 cm (range, 1 – 7). Imaging modalities used to identify or work-up SVA included: Ultrasound imaging (US) in 14/15 (93.3%) patients, Magnetic Resonance Imaging (MRI) in 12/15 (80%) patients, and Computed Tomography (CT) in 4/15 (26.7%) patients. Five patients (33.3%) received laparoscopic splenectomy as definitive treatment. The median maximal SVA diameter for the five surgical patients was 5.2 cm (range, 5 – 7) and 3.2 cm (range, 1 – 5.7) for 10 nonsurgical patients. Splenectomy was performed for one patient (20%) due to persistent abdominal pain; surgical indications for the other four (80%) surgical patients included SVA imaging size or concern for splenic rupture from participation in contact sports. Preoperative imaging correlated with postoperative pathology in 2/5 (40%) surgical patients. Among all patients, the median number of days between the first imaging study to identify the SVA and the last study monitoring the SVA was 709.5 days (range, 37 – 2163). The median change in SVA maximal diameter during that time period was 0.2 cm (range, -0.9 – 1).

CONCLUSION: SVAs are stable lesions that do not require intensive imaging follow-up. Most operative interventions are performed based on SVA size on imaging.

91 - Cutaneous ulcer with osteomyelitis secondary to Alpelisib in PROS

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PURPOSE: Alpelisib is approved by the FDA for the treatment of patients aged 2 and older with severe manifestations of PROS syndrome and PIK3CA mutation. We present the case of a CLOVES syndrome patient treated with Alpelisib who developed a complication of a cutaneous ulcer with osteomyelitis.

METHODS: A 57-year-old male with a diagnosis of CLOVES syndrome (activating mutation of PIK3CA detected through NGS), had overgrowth of the left lower limb as well as deep venous malformations along the entire extremity. To reduce pain and improve ambulation, treatment with Alpelisib was initiated in a compassionate use program at a dose of 250 mg per day.

RESULTS: Baseline laboratory tests and follow-up were strictly normal. The only adverse effect reported by the patient in the third week was a grade 1 nocturnal headache, which spontaneously resolved. In the fourth week, the patient experienced a significant worsening of a preexisting weight-bearing ulcer on the lateral plantar side of the left foot. In two weeks, the ulcer increased in size and depth fourfold, with an additional ulcer appearing on the dorsal side of the foot. At this point, Alpelisib was discontinued. SPECT-CT and bone scintigraphy showed septic arthritis/osteomyelitis of the first metatarsophalangeal joint, leading to treatment with oral Moxifloxacin and Linezolid, along with local wound care and surgical and enzymatic debridement. After 4 weeks of discontinuation of the drug, the patient experienced significant improvement.

The main adverse effects reported in Alpelisib product information are hyperglycemia, stomatitis, and diarrhea. In our case, none of these events were observed. We have not found any previous cases reported with Alpelisib regarding the development or worsening of ulcers.

CONCLUSION: The absence of other factors contributing to the worsening of the ulcer, along with the significant improvement after discontinuation of the drug, suggests a causal relationship between the ulcer and Alpelisib.

92 - OVERGROWTH SYNDROME ASSOCIATED WITH PIK3CA TREATED WITH ALPELISIB: EFFICACY AND SAFETY RESULTS AFTER TWO YEARS OF TREATMENT

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PURPOSE: The overgrowth syndrome associated with PIK3CA (PROS) represents a spectrum of conditions sharing the same etiopathogenic mechanism, caused by mutations in the PIK3CA gene. We present efficacy and safety results of Alpelisib in a patient with PROS after two years of treatment.

METHODS: A 64-year-old woman, followed in our center for a clinical presentation characterized by overgrowth of the left half of her body associated with multiple vascular malformations, both in the skin and various organs (cerebral, bone, pericardium, spleen). Genetic testing performed on skin confirmed the diagnosis of PROS, detecting a mosaic mutation in the PIK3CA gene (c.1357G>A). This alteration was not detected in blood, confirming its somatic origin. Given the patient's progressive systemic symptoms, with an increase in her shortness of breath, it was decided to initiate treatment with Alpelisib in compassionate use program.

RESULTS: Alpelisib was started at a dose of 250 mg per day. On the fifth day of treatment, the patient developed cellulitis in her left lower limb, requiring antibiotic treatment and discontinuation of alpelisib. One month later, the treatment was reintroduced at the same dose, but the patient reported hair loss, metallic taste and digestive discomfort, leading to discontinuation of alpelisib again. Four months later, Alpelisib was reintroduced at 50 mg per day, with a subsequent escalation to 100 mg per day, a dose she has continued since. The latest angio MRI shows an improvement in the lesions with a clear improvement in respiratory symptoms. The patient can walk for a longer time, climb stairs, and no longer requires crutches. Cutaneous lesions have improved, and angiomatous lesions on her knees have decreased. No new episodes of phlebitis have occurred.

CONCLUSION: Long-term results of Alpelisib in PROS are reported. Our patient has shown significant improvement in symptoms, and adverse effects have been controlled by lowering the Alpelisib dosage.

93 - Patau syndrome with multiple hemangiomas: a trisomy through the skin

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PURPOSE: Patau syndrome is a chromosomal disorder characterized by trisomy of chromosome 13, which presents as a polymalformative syndrome with distinctive features such as microcephaly, microphthalmia, mental retardation, cleft lip and palate, polydactyly, and heart and kidney diseases. Among the specific malformations associated with this condition, skin defects such as aplasia cutis, glabellar region spots, deep palmar creases, nail hyperconvexity, and multiple hemangiomas have been reported.

METHODS: We present the clinical case of a male newborn male who, at birth, exhibited agenesis of the corpus callosum, dextrocardia, renal abnormalities, hepatomegaly, skeletal anomalies, and parietal aplasia cutis. Additionally, a Dermatology consultation was sought for the progressive appearance of reddish skin lesions in various locations. Due to all these alterations and with a suspected diagnosis of Patau syndrome, a genetic study was requested to confirm the clinical picture.

RESULTS: On the skin, 12 erythematotelangiectatic macules of varying sizes were observed in different body areas, with the largest being 5 mm in diameter. A biopsy of one of the lesions was performed, revealing dermal telangiectatic vessels with GLUT-1 positivity, confirming the diagnosis of hemangiomas. Massive DNA sequencing confirmed trisomy of chromosome 13. Unfortunately, the patient passed away at 2 months of age due to complications arising from the malformations.

CONCLUSION: Patau syndrome has an incidence of 1 in 10,000 live births, and in 80% of cases, survival is less than one year. Infantile hemangiomas can occur in up to 40% of patients affected by this syndrome, so it should be part of our differential diagnosis for a newborn with a polymalformative syndrome and multiple hemangiomas.

97 - Phenotypes-Genotypes Analysis Revealed PIK3CA H1047R Mutation is A Predictor of Severity and Recurrence of Facial Infiltrating Lipomatosis

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PURPOSE: Facial infiltrating lipomatosis (FIL) is a rare congenital disorder characterized by unilateral facial enlargement, for which surgery is the prevailing therapeutic option. Several studies have shown that the FIL is caused by PIK3CA mutations. This study aimed to further identify phenotype-genotype correlation in FIL.

METHODS: We reviewed the data of patients diagnosed with FIL and underwent genetic testing at our center, and analyzed the phenotype-genotype correlation.

RESULTS: A series of 27 patients were included in this study, and all patients had presented infiltrative manifestations of adipose tissues confirmed by magnetic resonance. We observed that macrodactyly, polydactyly, hemimegalencephaly and hemihyperplasia could also be seen in patients with FIL. In total, 11 different PIK3CA mutations were detected in tissues obtained from 25 patients, respectively, missense mutation p.His1047Arg (n=6), p.Cys420Arg (n=4), p.Glu453Lys (n=4), p.Glu542Lys (n=2), p.Asn345Lys (n=1) p.Glu418Lys (n=1), p.Glu545Lys (n=1), p.Gln546Lys (n=1), p.His1047Tyr (n=1) and deletion mutation p.Glu110del (n=3) and p.Pro449_Leu452del (n=1). The GNAQ p.Arg183Gln mutation was also detected in the epidermal nevus tissue of one patient. Furthermore, three patients harbored an additional mutation, including IDH1 or GNA14 mutation. Imaging revealed that patients carrying hotspot mutations had more severe adipose infiltration and skeletal deformity. Besides, patients with the PIK3CA H1047R mutation demonstrated the most severe involvement of soft/hard tissues and were most prone to have postoperative recurrence.

CONCLUSION: PIK3CA hotspot mutations tend to lead to more severe cases of FIL, specifically characterized by a increased number of affected soft/hard tissues. In particular, patients carrying the

PIK3CA H1047R mutation should be given special attention, as these individuals exhibit the most severe maxillofacial deformities and are highly prone to postoperative recurrence.

101 - PIK3CA Gain-of-Function Mutations Enhance the Adipogenic Capacity of ADSCs in Facial Infiltrating Lipomatosis through Down-Regulation of TRPV1

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PURPOSE: Facial infiltrating lipomatosis (FIL) is a rare congenital disease characterized by unilateral facial enlargement. Although next-generation sequencing has revealed that the pathogenesis of FIL is associated with phosphatidylinositol 3-kinase catalytic subunit alpha (PIK3CA) mutations, the underlying molecular mechanisms remain undetermined.

METHODS: Histological features and lipid accumulation of FIL and controls were observed using H&E and Oil Red O staining. The influence of PIK3CA on adipogenesis was evaluated through lentivirus-mediated PIK3CA knockdown and the dual-target PI3K/mTOR inhibitor WX390 in FIL adipose tissue-derived mesenchymal stem cells (FIL-ADSCs). Downstream target genes were identified through RNA sequencing (RNA-seq).

RESULTS: We found that he adipose tissue in FIL patients demonstrated tissue infiltration accompanied by increased lipid accumulation. All adipose-derived stem cells isolated from FIL (FIL-ADSCs) harboured PIK3CA mutations. Compared to ADSCs obtained from normal subcutaneous adipose tissue, FIL-ADSCs exhibited a greater capacity for adipogenesis. Suppression of PIK3CA resulted in a reduction in the adipogenic potential of FIL-ADSCs. Furthermore, PI3K/mTOR double-target inhibitor WX390 was found to impede PIK3CA-mediated adipogenesis both in vivo and in vitro. RNA-seq revealed that the expression of transient receptor potential vanilloid subtype 1 (TRPV1) was upregulated after PI3K pathway inhibition, and overexpression and activation of TRPV1 both inhibited adipogenesis of FIL-ADSCs.

CONCLUSION: Our study showed that PIK3CA mutations promoted adipogenesis in FIL-ADSCs and that this effect was achieved by suppressing the expression of TPRV1. Pathogenesis experiments suggested that WX390 may serve as an agent for the treatment of FIL.

106 - RECURRENT SPONTANEOUS FRONTAL ECCHYMOSIS PHENOMENON ASSOCIATED WITH HEADACHE VERSUS RARE VASCULAR ANOMALIES: A CASE REPORT.

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PURPOSE: Despite specific complementary tests and advances in somatic genetics, reaching a definitive diagnosis in certain childhood vascular anomalies is challenging due to their great clinical variability. This requires a proactive approach to find appropriate treatment and prognosis.

METHODS: An 8-year-old healthy girl experienced sudden onset of 4 episodes in 12 months of extensive facial lesions from the middle forehead to preauricular and fronto-parieto-temporal regions of the left scalp. The lesions appeared erythematous-hemorrhagic, with central elevation, accompanied by a headache rated 8/10 on a numerical pain scale. The episodes were triggered by environmental heat and completely resolved within 12 days. Complementary tests performed in response to this peculiar lesion associated with headache included complete blood count, biochemistry, hemostasis assessment, genetic study with 60k Array CGH, contrast-enhanced MRI, and two skin biopsies, the first from healthy skin and the second from the lesion.

RESULTS: Prior to the result of the second biopsy, all complementary tests were normal. We investigated whether we were dealing with the so-called RECURRENT SPONTANEOUS FRONTAL ECCHYMOSIS PHENOMENON ASSOCIATED WITH HEADACHE, characterized by recurrent episodes of intense trigeminal headache associated with the sudden appearance of severe facial ecchymosis. This phenomenon has been more frequently described in Indian women, with normal complementary tests and non-specific pathological findings such as capillary dilatations or extravasated red blood cells in the dermis. Despite the clinical similarity with our patient, her second biopsy is consistent with two entities: Acquired Progressive Lymphatic Malformation or Targetoid Hemosiderotic Hemangioma, both different from the patient's clinical presentation.

CONCLUSION: - Clinical correlation between symptoms and specific tests is of great importance in vascular anomalies.

- Currently, our patient remains without a definitive diagnosis due to the discrepancy between clinical and histopathological findings.

- Therefore, expert meetings and the existence of multidisciplinary teams are essential.

107 - Downregulation of glycolysis promotes premature senescence of endothelial cells in venous malformations

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PURPOSE: Venous malformations (VMs), prevalent among congenital developmental vascular anomalies, are present from birth and show ongoing growth, while previous studies highlight diminished proliferation and impaired tight junctions in VM endothelial cells (ECs). However, the lesions do not spontaneously shrink, indicating a distinctive pathological state in VM ECs. This research aims to unveil the regulatory pathways underlying this state in VM ECs, emphasizing metabolic processes.

METHODS: Histological analyses were conducted to validate increased expression of senescence-related proteins in VM lesions, accompanied by a down-regulation of multiple glycolytic proteins. Cells overexpressing TIE2-L914F were constructed with Human Umbilical Vein Endothelial Cells (HUVECs) to simulate VM ECs, followed by function evaluation after regulating senescence and glycolysis in vitro. In vivo, VM models were established in nude mice to investigate the role of glycolysis-mediated senescence in VM development.

RESULTS: In VM tissue specimens, a series of glycolysis-related proteins were downregulated in VM ECs, with a notable decrease in PFKFB3, a pivotal rate-limiting enzyme of glycolysis. Additionally, there were significant alterations in senescence-associated proteins. Compared to normal ECs, the expression of PFKFB3 was significantly reduced and senescence-associated proteins were upregulated in TIE2-L914F ECs. This was accompanied by weakened cell proliferation, arrested cell cycle, and enhanced anti-apoptotic ability, which were typical features of premature senescence. Moreover, TIE2-L914F ECs

exhibited increased sensitivity to the administration of senescence inhibitor dasatinib. In vivo, dasatinib effectively inhibited the growth and development of VM in animal models.

CONCLUSION: This study establishes a direct connection between glycolysis, premature senescence in VM ECs, and the sustained growth of VMs. The suppressed glycolysis in VM ECs emerges as a critical factor in initiating premature senescence, which in turn promotes VM development. Significantly, interventions targeting cell senescence show promise in alleviating premature senescence and inhibiting the ongoing development of VMs.

113 - Recurrence and restart of sirolimus in vascular anomalies after withdrawal

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PURPOSE: To assess the long-term effect after withdrawal of sirolimus in patients who responded to sirolimus.

METHODS: Patients from a large cohort were reviewed in this study who were eligible for the followings: a) underwent sirolimus at least 6 months; b) discontinued sirolimus at least 3 months (not due to adverse effect); c) responded to sirolimus.

RESULTS: 3 patients were included in this study. Patient 1 with a congenital large lymphatic malformation responded to sirolimus after 1-year treatment. After a 2-year suspension of sirolimus, his lesion regrew and several times of ulcers with effusion happened. Patient 2 had a diffuse vascular lesion on her right face causing exophthalmos and facial disfiguration. After 2-year treatment, her lesion regressed and exophthalmos and disfiguration partially improved. After 2-year suspension, the lesion regrew and conditions got worse. She underwent serval times of severe seizures. We continued sirolimus therapy and the seizure was temporarily controlled. Patient 3 with a large diffuse lymph-venous malformation on her left chest and abdomen responded to sirolimus after 1-year treatment. After a 5-month withdrawal, lymphatic follicles rebounded even more server than the initial. The continued low-dose sirolimus therapy was sufficient to reduce the lesion. After a 12-month restart of sirolimus, the lesion achieved optimal regression and remained it

CONCLUSION: Our cases observed quick recurrence after withdrawal. Sirolimus may reduce lesions in the first 3 to 6 months and remain in long-term use. Prolonged use did not increase the risk of AEs in our cases under monitoring. Once the drug is withdrawn, the dormant lesion may progress and cause more severe damage. Restarting the drug is still effective in cases of recurrence with no signs of progression, which indicates that drug resistance did not happen. Our cases emphasized the importance of continuing the long-term use of sirolimus under monitoring in patients with potential complications.

114 - Correlation between CM-AVM Gene Mutations and Clinical Phenotypes: an Exploration Study

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PURPOSE: To investigate the clinical manifestations of patients diagnosed with capillary malformation-arteriovenous malformation (CM-AVM), with an emphasis on identifying a correlation between the functionality of gene mutation sites and related conditions.

METHODS: We looked at 74 patients who were clinically diagnosed with AVM and conducted NGS or WES sequencing at our center from March 2021 to October 2023; 48 patients with a clinical diagnosis of CM-AVM were screened. A comprehensive review was conducted on the patient's molecular genetic findings in conjunction with their clinical features and medical history.

RESULTS: Out of a total of 48 patients diagnosed with CM-AVM (M=27, F=21), 14 were identified as carrying RASA1 mutations, of which 8 proved germline mutations and 2 were with other mutations; 16 were identified as carrying EPHB4 mutations, of which 15 proved germline mutations and 7 contained other mutations; 19 patients lacked RASA1 or EPHB4 mutations, and 4 were identified as carrying additional mutations. All had at least one skin erythema during the course of the disease, 12 had scattered erythema throughout the body. 13 presented with tortuous dilated blood vessels when first diagnosed, and 14 had at least soft tissue hypertrophy beneath the erythema. Additionally, patients may present with comorbidities such as pyogenic granuloma, ossifying fibroma, or others. There was a higher probability of uncommon combined symptoms, including mesenchymal tumors, craniocerebral vascular malformations, Kaposi-type hemangioendothelioma, overgrowth, etc., among patients who had RASA1 and EPHB4 detected ($p<0.05$). The severity, progression, and distribution of mutation sites' functional segments were also subjected to statistical analysis.

CONCLUSION: This research investigates the association between gene mutations and the course of CM-AVM in patients, contributing to a more comprehensive understanding of the disease's clinical manifestations and genetics. In-depth molecular genetic investigations and larger sample sizes are required to confirm it.

116 - CM-AVM Patients With Dual-locus Mutations: Locus Function and Clinical Manifestations

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PURPOSE: To explore a case series of capillary malformation-arteriovenous malformation (CM-AVM) patients with dual-locus genetic mutations, focusing on the correlation between the function of the mutation site and clinical manifestations, and to gain a deeper understanding of the genetics and clinical characteristics of this rare disease.

METHODS: We reviewed patients who were both clinically diagnosed with AVM and underwent NGS or WES sequencing in our center from January 2021 to November 2023 (a total of 74 patients). 8 patients with double mutations, diagnosed as CM-AVM were screened out. A review of the data pertaining to this cohort of patients was conducted, followed by a thorough investigation into the functional implications of the mutation loci. Subsequently, we integrated the genetic findings with the patients' clinical manifestation and medical records.

RESULTS: Among CM-AVM patients, dual-locus gene mutations are relatively rare. Each of the selected patients had at least one gene mutation in RASA1 and EPHB4. Among them, one person had two mutation sites in EPHB4, one person had one in each RASA1 and EPHB4, and 6 people have one site mutation in other genes, including GNA11, GNA14, ACVRL1, PIK3CA, and MTOR. Mutations in genes encoding G protein subunits all occur in the GTP-binding domain. All patients showed erythema that tended to be thickened by soft tissue, but the distribution throughout the body was irregular ($p>0.05$). A patient carrying EPHB4 and ACVRL1 mutations developed intracranial AVM and extremely rare internal carotid artery occlusion.

CONCLUSION: Study reports the possible situation of dual-locus gene mutations in CM-AVM patients and suggests a possible link between these mutations and disease severity, which contributes to a more comprehensive understanding of the genetics and clinical aspects of CM-AVM. Characteristics provide useful information for early diagnosis. Larger sample sizes and in-depth molecular genetic studies are needed to explore the association between mutations and phenotypes.

117 - Scalp AVM-related Hair Loss: Solved by Absolute Ethanol Treatment

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PURPOSE: To investigate the impact of absolute ethanol on the restoration of hair growth in the treatment of scalp arteriovenous malformations.

METHODS: A cohort of 4 individuals presenting with localized hair loss resulting from scalp arteriovenous malformation (AVM) underwent interventional therapy involving the administration of absolute ethanol in our center. The subsequent progress of hair regrowth was closely observed and documented. Throughout the course of the treatment, the administration of absolute ethanol was accomplished by the utilization of a microcatheter or direct puncture technique under the guidance of digital subtraction angiography (DSA). The quantity of ethanol utilized in each experimental condition was recorded, and the imaging data was maintained. We conducted a comparison between the condition of the lesions and the rate of hair growth prior to and subsequent to the treatment.

RESULTS: In comparison to the pre-treatment phase, the post-treatment phase exhibited a notable reduction in the local size of the lesions, improved angiographic pictures, and a considerable improvement in hair growth among all 4 patients. There was a substantial increase in hair density in the region where hair loss initially occurred, and there was a notable reduction in hair loss associated with AVMs.

CONCLUSION: This study demonstrates that the use of absolute ethanol as an interventional treatment strategy is efficacious for scalp AVMs. Additionally, it exerts a beneficial impact on the restoration of hair development in cases of AVM-related localized hair loss. It is anticipated that this treatment will enhance the quality of life for individuals with scalp AVMs; however, additional research is required to substantiate these initial findings.

121 - Large Mixed Venous Lymphatic Malformation Conferring Airway Compromise and Speech Impairment

Dawn Z. Eichenfield (Rady Children's Hospital-San Diego); Wynnis Tom (Rady Children's Hospital-San

Diego); Deborah Schiff (Rady Children's Hospital-San Diego); Hilda Ding (Rady Children's Hospital-San Diego)

PURPOSE: To obtain treatment recommendations for a 14 year old trach-dependent female with a large mixed venous lymphatic malformation of the tongue, lips, floor of mouth, TMJ, masticator, pharynx and infratemporal fossa, and scalp with bleeding, airway compromise, and speech impairment.

METHODS: Patient established with Rady Fresh Start in 2012 and had sclerotherapy x2 with regrowth and sirolimus trial for 6 months, but ultimately lost access to care with pandemic and visa expiration.

RESULTS: Patient re-established with Rady Fresh Start in 10/2023 and restarted sirolimus. Foundation One testing from peripheral blood VUS: AMER1 (FAM123B or WTX), CDKN2A/B, MTOR, NOTCH1.

CONCLUSION: Our team would like input on sclerotherapy options and approach, as well as the feasibility of surgical treatment. We are also wondering whether tissue biopsy would be safe to attempt for genetic testing and whether a trial alpelisib or other targeted therapies would be reasonable.

123 - Outcome of new treatment strategy based on modified "Cho-Do type IIIb AVM": Korean referral vascular anomalies center experience.

Sang Yub Lee (Department of Radiology, Samsung Medical Center); Kwang Bo Park (Depatment of Radiology, Samsung Medical Center); Young Soo Do (Department of Radiology, Hallym University Sacred Heart Hospital); Jun Gon Kim (Department of Radiology, Samsung Medical Center)

PURPOSE: The 'Cho-Do' angiographic classification type IIIb AVM consist of multiple hypertrophied fistulae directly connected artery to vein. Traditionally, transarterial (TA) or direct puncture (DP) ethanol embolization was used to treat this type of AVM. However, we experienced numerous feeding arteries entering into the vein walls and there are complex vascular connections among feeding arteries. Thus, we suggest a modified concept of type IIIb AVM which is focused on venous coil embolization followed by ethanol injection from venous side to feeding arteries. To identify safety and efficacy of this new treatment strategy, a retrospective study was performed.

METHODS: Type IIIb peripheral AVMs were retrospectively reviewed and patients were divided into transarterial embolization (old) group and venous coil embolization followed by ethanol injection (new) group. AVM characteristics, embolization techniques including embolic materials and access techniques, number of treatment sessions, angiographic outcome, and procedure related complications were reviewed.

RESULTS: A total of 117 type IIIb AVM patients (55 males, median age 27 years, interquartile range; 18-36 years) were enrolled in this study. They underwent a total of 515 procedures. Forty one were new group (172 sessions) and 76 were old group (343 sessions). Demographics and AVM characteristics were not different in both groups. New groups showed significantly higher treatment outcome (36/41 [88%] of over 90% of lesion improvement) than old group (39/76 [51%]) (p=0.001). Total treatment sessions (4.2 sessions per patient vs. 4.5 sessions) and use of ethanol amount (129ml vs. 141ml) were lower in new the group, however, there was no statistical significance. Procedure-related complications were significantly lower in new group (18/171, 11%) than old the group (80/342, 23%) (p=0.001).

CONCLUSION: We suggested a modified concept of ‘Cho-Do' type IIIb AVM. Treatment based on modified concept demonstrated better treatment outcome and less complication than previous embolization technique

124 - Analysis of cardiomegaly in peripheral arteriovenous malformation and factors affecting cardiac size change after embolization.

Sang Yub Lee (Department of Radiology, Samsung Medical Center); Kwang Bo Park (Department of

Radiology, Samsung Medical Center); Young Soo Do (Department of Radiology, Hallym University Sacred Heart Hospital); Jun Gon Kim (Department of Radiology, Samsung Medical Center)

PURPOSE: To evaluate percentage of cardiomegaly in peripheral arteriovenous malformations (AVMs) and to find factors that contribute to improve cardiomegaly after endovascular embolization of peripheral AVMs.

METHODS: A retrospective review of patients who underwent embolization of peripheral AVMs in a single vascular anomalies center, from 2000 to 2022 was performed. Four-hundred-thirty-seven patients (median age: 32 years, interquartile range, 22 – 45 years) received 1238 sessions of AVM embolization. Cardiothoracic ratio (CTR) on chest radiography over 0.5 was considered cardiomegaly. The prevalence of cardiomegaly in peripheral AVMs and factors influencing changes in cardiac size after AVM embolization were analyzed.

RESULTS: One-hundred-eight patients showed cardiomegaly (24.7%) at initial presentation. In univariate analysis, type I or II AVM, diffuse involvement, and bone involving AVM showed significantly associated with cardiomegaly. In multivariate analysis, AVM type I or II (odds ratio [OR], 2.08; 95% confidence interval [CI], 1.28 - 3.33; P = .00030), diffuse AVM (OR, 2.02; 95% CI, 1.16-3.51, P = .0127), bone AVM (OR, 2.27; 95% CI, 1.12 – 4.55, P = .0217), and abdomen & pelvic AVM (OR, 3.1; 95% CI, 1.82 – 5.26) and thorax-neck AVM (OR, 2.44; 95% CI, 1.17 – 5.10) had higher risk than extremity AVMs (P < .0001). Among 84 of cardiomegaly who had follow-up chest radiography, 77% (65/84) showed decreased cardiac size and 58% (49/84) showed normalized (CTR < 0.5). Bone involvement (OR, 19.35; 95% CI, 1.82 – 206.22, P = .0141) and over 90% angiographic devascularization (OR, 6.1; 95% CI, 1.39 – 26.7, P = .0163) were independent factors of decreased cardiac size.

CONCLUSION: In present study, 24.7% of peripheral AVM patients represented cardiomegaly on initial presentation and the majority of patients (77%, 65/84) showed decreased heart size after AVM embolization. Bone involvement and over 90% angiographic devascularization were predicting factors of decreased cardiac size.

136 - Ulcerated hemangiomas in pediatrics - a challenge in wound care management
Dania Eisenring (University Childrens Hospital Zurich)

PURPOSE: Infantile hemangiomas (IH) are the most common vascular tumors in infants. IH with a risk of ulceration are treated with beta-blocker therapy. These ulcerated IH pose a challenge for wound treatment, as the wound healing process is prolonged, leading to repeated painful dressing changes. Up to now, ulcerated IH have been treated with octenidine wound gel in combination with a polyurethane foam dressing at our center. In a proportion of patients, we observed an unsatisfactory course with these measures. A wound gel containing organic cellulose (Nanogen Actigel®) has been shown to support healing of complex wounds. We present our experience with organic cellulose on a series of infants with ulcerated IH.

METHODS: Case series of infants with ulcerated IH locally treated with an organic cellulose gel. The following data were assessed: duration until healing, recurrence rate, and pain during dressing changes. All ulcerated IH were photo documented.

RESULTS: The organic cellulose gel was applied on 7 ulcerated IH. All affected children were under 6 months of age.

5 children had an ulcerated IH in the diaper area, while the other two lesions occurred on the thigh and upper lip respectively. All children were treated with beta-blockers. Four children received oral propranolol, while three IH were treated with topical timolol 0.5%. In 6 children, the organic cellulose gel was used in combination with a polyurethane foam. In one child, only the organic cellulose gel

(upper lip) was used. In all children the ulceration healed completely within 6 to 22 days. The parents reported little to no pain during dressing changes.

CONCLUSION: All infants with ulcerated IH showed an excellent and rapid response to local wound care with the organic cellulose gel. Although there is no comparison group and the sample is small, these results are encouraging and should be verified in a larger study.

137 - Venous malformation, possibly a type of ciliopathy
Hou-Fu Xia (School of Stomatology Wuhan University); Gao-Hong Chen (School of Stomatology Wuhan University); Gang Chen (School of Stomatology Wuhan University)

PURPOSE: Abnormal endothelial cells (ECs) have been regionalized as the initial trigger of venous malformation (VM). This study aims to reveal the key change of mutant VMECs.

METHODS: Human umbilical vein endothelial cells (HUVECs) were firstly transfected with lentivirus coding TIE2-WT or mutant TIE2 (L914F) to construct control (HUVEC-TIE2-WT) or VM ECs (HUVEC-TIE2-L914F), respectively. The next-generation sequencing and bioinformatics analysis were employed to compare the transcriptome difference between HUVEC-TIE2-WT and HUVEC-TIE2-L914F. The cilia of VMECs were characterized by immunofluorescence staining, scanning electron microscopy (SEM) and transmission electron microscopy (TEM). The effects of disturbing cilia with specific inhibitor or siRNA on cell proliferation, migration, apoptosis and tube formation were studied in HUVEC-TIE2-L914F.

RESULTS: HUVEC-TIE2-L914F were characterized with abnormal p-TIE2/p-AKT activation and VM lesion-formation ability. Gene ontology enrichment analysis revealed that the up-regulated genes were mainly concentrated in cilia-related gene sets, while the down-regulated ones were extracellular matrix related sets. The results of immunofluorescence staining, SEM and TEM showed that both the number and length of cilia in HUVEC-TIE2-L914F were increased significantly compared with the HUVEC-TIE2-WT. More than that, blocking cilia formation significantly inhibited the proliferation, migration and tube formation, but promoted the apoptosis in HUVEC-TIE2-L914F. Treatment with cilia inhibitor or rapamycin also disturbed the cilia formation and improved the progression in murine VM models.

CONCLUSION: Excessive cilia formation in ECs is possibly a typical characterization and a key target in VMs.

143 - Long-term outcomes of sirolimus treatment for kaposiform hemangioendothelioma Continuing successes and ongoing challenges
Siyuan Chen (West China Hospital of Sichuan University)

PURPOSE: Treatment with sirolimus, an inhibitor of the mammalian target of rapamycin pathway, has improved the prognosis of patients with kaposiform hemangioendothelioma (KHE). However, the efficacy, durability, and tolerability of long-term sirolimus treatment in patients with KHE have not been well elucidated.

METHODS: We performed efficacy and safety assessments based on more than 4.5 years of follow-up in patients receiving sirolimus therapy for KHE.

RESULTS: One hundred sixty-seven patients were analyzed, including 102 (61.1%) patients with the Kasabach-Merritt phenomenon (KMP). Follow-up was conducted after a median of 56.0 months. A total of 154 (92.2%) patients had a durable response to sirolimus treatment. No difference in durable response was found between patients without KMP and patients with KMP (95.4% vs. 90.2%; difference, 5.2%; 95% confidence interval [CI], -4.0% to 13.1%). Rebound growth occurred in 17.3% of patients upon sirolimus discontinuation. Early treatment discontinuation (odds ratio [OR]: 3.103; 95% CI: 1.529-6.299; P=0.002) and mixed lesion type (OR: 2.271; 95% CI: 0.901-5.727; P=0.047) were associated with tumor rebound growth. No KHE-related deaths occurred in this cohort. At the last follow-up, approximately

17.4% of patients had active disease and/or changes in body structures to a variable extent. Serious adverse events occurred most commonly during the first year of sirolimus therapy.

CONCLUSION: Follow-up of almost 4.5 years demonstrated that the efficacy of sirolimus persisted over time and that long-term treatment of sirolimus was not associated with unacceptable cumulative toxicities. However, nonresponse, tumor relapse and long-term sequelae remained as challenges despite intensified and prolonged sirolimus therapy.

144 - A prospective multicenter study of sirolimus for complicated vascular anomalies
Yi Ji (West China Hospital of Sichuan University)

PURPOSE: Complicated vascular anomalies (VAs) may be intractable and uncontrollable by conventional treatments and may result in lethal outcomes. We undertook a prospective, multicenter phase II trial to evaluate the efficacy and safety of sirolimus in pediatric patients with complicated VA.

METHODS: Eligible patients had to be aged 0-14 years and to have complicated VAs. Patients were treated with daily oral sirolimus for 12 months. The primary endpoint was the response measured by sequential volumetric MRI. The secondary endpoints were the disease severity score and quality of life (QOL).

RESULTS: Ninety-eight of 126 (77.8%) patients, enrolled on an intention-to-treat basis, had an objective response to sirolimus, with a 20% or more decrease in lesion volume. Compared with arteriovenous malformation, response rates were higher (>80%) in patients with common lymphatic malformation, venous malformation, kaposiform hemangioendothelioma, and combined malformations with a prominent venous and/or lymphatic component ($P<0.05$). In total, improvements in the disease severity score and QOL were obtained in 83.3% and 79.4% of patients, respectively. The most common adverse event was mucositis (47 patients). More serious adverse events included reversible grade 4 pneumonitis (3 patients) and grade 4 upper respiratory infection (1 patient). All of these adverse events were considered at least possibly treatment-related.

CONCLUSION: Sirolimus is an apparently effective option in pediatric patients with various types of complicated VAs. Close monitoring of possible adverse events is needed. This trial is a basis for future prospective studies using new therapeutic approaches.

145 - Novel organoid construction strategy for non-involuting congenital hemangioma for drug validation
Yi Ji (West China Hospital of Sichuan University)

PURPOSE: Non-involuting congenital hemangiomas (NICHs) are fully formed vascular tumors at birth, with distinctive clinical, radiologic, and histopathological profiles. In the literature, there is no effective therapy strategy for patients with NICH except surgery. Currently, no cell line or animal model exists for studying the mechanism of NICH and drug validation.

METHODS: We plan to construct a new strategy by constructing NICH organoids for further study.

RESULTS: Here, we report a novel NICH organoid system construction and optimization process. Both HE and immunohistological staining exactly matched NICH tissue. We further performed transcriptome analysis to elucidate the characteristics of NICH organoids. Both NICH tissue and NICH organoids manifested similar trends in download sites. NICH organoids display novel features to new cells derived from organoids and show spectacular multiplication capacity. In the preliminary verification, we found that cells splitting from NICH organoids were human endothelial cells. Drug validation demonstrated that trametinib, sirolimus, and propranolol showed no inhibitory effects on NICH organoids.

CONCLUSION: Our data show that this new NICH-derived organoid faithfully captured the features of this rare vascular tumor. Our study will boost further research on the mechanism of NICH and drug filtering in the future.

146 - Noninvoluted midline capillary malformation for which potential awareness should be raised

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PURPOSE: Salmon patches (SPs), also called "angel's kiss", are midline capillary malformations (MCMs) that involve the nape, eyelid or glabella and occur in approximately 40% of newborns. Most SPs will involute within 5 years. Because of their self-limited natural history, clinical follow-up with no intervention is often prescribed at the first clinic visit. However, some MCMs never involute and even progress to Sturge–Weber syndrome (SWS) or fast-flow vascular malformations (FFVMs). Misdiagnosis may lead to the progression of diseases, including disfigurement, bleeding, ulceration in AVMs, and blindness and cerebral apoplexy in SWS. Here, we report 24 noninvoluted MCMs and propose an optimized diagnosis algorithm.

METHODS: From 2020 to 2023, 24 noninvoluted MCMs were retrospectively evaluated by clinical manifestations, genetic analysis, and radiology analysis in our centers. Capillary malformation-arteriovenous malformations (CM-AVMs) were diagnosed by genetic sequence or clinical manifestations, such as family history or multifocal high-flow erythema on ultrasound. Arteriovenous malformations (AVMs) were diagnosed by physical examination and radiology analysis. SWS was diagnosed by glaucoma, former seizure attack, or abnormal magnetic resonance imaging (MRI) results in the brain.

RESULTS: The diagnosis of enrolled patients was list as follows: 11 patients with CM-AVMs, 7 with AVMs, 1 with an unclear FFVM, 3 with SWS and 2 with port-wine stains (PWSs).

CONCLUSION: Despite significant differences in later manifestations, SPs, CM-AVMs, AVMs, and SWS could all present as MCMs in the early stage, making them challenging to distinguish in clinical practice. Our study raised the awareness of CM-AVMs, AVMs, and SWS among MCMs, emphasizing that MCMs should not be automatically diagnosed as SPs. Indiscriminate follow-up until the age of 5 for MCMs might lead to progression to FFVMs. A midterm evaluation at 2 years of age was crucial. A new diagnostic algorithm for MCM was advocated to prevent potential risks." Salmon patches (SPs), also called "angel's kiss", are midline capillary malformations (MCMs) that involve the nape, eyelid or glabella and occur in approximately 40% of newborns. Most SPs will involute within 5 years. Because of their self-limited natural history, clinical follow-up with no intervention is often prescribed at the first

clinic visit. However, some MCMs never involute and even progress to Sturge–Weber syndrome (SWS) or fast-flow vascular malformations (FFVMs). Misdiagnosis may lead to the progression of diseases, including disfigurement, bleeding, ulceration in AVMs, and blindness and cerebral apoplexy in SWS. Here, we report 24 noninvoluted MCMs and propose an optimized diagnosis algorithm. From 2020 to 2023, 24 noninvoluted MCMs were retrospectively evaluated by clinical manifestations, genetic analysis, and radiology analysis in our centers. Capillary malformation-arteriovenous malformations (CM-AVMs) were diagnosed by genetic sequence or clinical manifestations, such as family history or multifocal high-flow erythema on ultrasound. Arteriovenous malformations (AVMs) were diagnosed by physical examination and radiology analysis. SWS was diagnosed by glaucoma, former seizure attack, or abnormal magnetic resonance imaging (MRI) results in the brain.The diagnosis of enrolled patients was list as follows: 11 patients with CM-AVMs, 7 with AVMs, 1 with an unclear FFVM, 3 with SWS and 2 with port-wine stains (PWSs). Despite significant differences in later manifestations, SPs, CM-AVMs, AVMs, and SWS could all present as MCMs in the early stage, making them challenging to distinguish in clinical practice. Our study raised the awareness of CM-AVMs, AVMs, and SWS among MCMs, emphasizing that MCMs should not be automatically diagnosed as SPs. Indiscriminate follow-up until the age of 5 for MCMs might lead to progression to FFVMs. A midterm evaluation at 2 years of age was crucial. A new diagnostic algorithm for MCM was advocated to prevent potential risks.

147 - Oral antibiotic prophylaxis for infection in patients with vascular anomalies receiving sirolimus treatment: a multicenter retrospective study

Siyuan Chen (West China Hospital of Sichuan University)

PURPOSE: Patients with vascular anomalies (VAs) receiving oral sirolimus may at high risk of infectious complications. Antibiotic prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMZ) has been advocated. However, there have been few evidence-based analyses on this topic. This study evaluated the effect of prophylactic TMP-SMZ on the incidence of infections in patients with vascular anomalies (VAs) receiving sirolimus monotherapy.

METHODS: A multicenter, retrospective chart review was performed on all patients with VA receiving sirolimus treatment from August 1, 2013 to January 2021. Before January 2017, all patients were treated with sirolimus without antibiotic prophylaxis. In the subsequent period, all patients were treated with TMP-SMZ for at least 6 months during sirolimus therapy. The primary outcome was the percentage of patients with at least one serious infection during the initial 6 months of sirolimus treatment.

RESULTS: One hundred and Ninety-five patients receiving TMP-SMZ was compared a previous cohort of 112 patients without antibiotic prophylaxis. The demographics, type of VA, and severity of disease were similar between the groups. The incidence of serious infection did not differ between group. We saw no difference in the incidence of individual infection and incidence of total infection between groups. No symptomatic PJP or sirolimus-related death were detected. The rate of sirolimus discontinuation due to adverse events did not differ significant between groups.

CONCLUSION: We demonstrated that prophylactic TMP-SMZ did not decrease the incidence of infection nor improve the tolerance in patients receiving sirolimus monotherapy.

148 - Screening for infantile hepatic hemangioma in patients with cutaneous infantile hemangioma: a multicenter prospective study

Yi Ji (West China Hospital of Sichuan University)

PURPOSE: Abdominal ultrasonography has been proposed for screen infantile hepatic hemangioma (IHH) in patients with multiple cutaneous infantile hemangiomas (IHs). The aim of this study was to establish the optimal cutoff point for the number of cutaneous IHs needed to screen for IHH.

METHODS: We performed a prospective, multicenter study to screen for IHH in patients younger than 9 months of age who had multiple cutaneous IHs (n ≥3) on ultrasonography. For comparison, a group of patients with 1 to 2 focal cutaneous IHs was also recruited.

RESULTS: In total, 676 patients with at least 3 cutaneous IHs, and 980 patients with 1 to 2 focal cutaneous IHs were enrolled. Thirty-one patients were found to have IHH. A higher number of cutaneous IHs was associated with an increased risk of IHH (R = 0.973, P < 0.001). Receiver operating characteristic curve analysis revealed that 5 cutaneous IHs was the optimal cutoff point to screen for IHH, with an area under the curve of 0.872 (P <0.001; 95% CI, 0.789-0.955).

CONCLUSION: Screening for IHH is recommended in patients younger than 9 months of age who present with 5 or more cutaneous IHs.

150 - COMBINED VASCULAR MALFORMATION WITH POLYOSTOTIC FIBROUS DYSPLASIA: A NEW ENTITY?

FELIPE E. VELASQUEZ-VALDERRAMA (PEDIATRIC DERMATOLOGIST); ROSALIA BALLONA-CHAMBERGO (PEDIATRIC DERMATOLOGIST)

PURPOSE: To present another kind of combined vascular malformation with another clinical features

METHODS: We collect clinical file from our institution. We asked informed consent from parents

RESULTS: Female, 3 years old . Medical History caesarean section (C-section), Gestational Age (GA): 39 weeks, Birth Weight: 3900gr, No complications, interprofessional discharge Prior illnesses: Congenital lymphedema of the right lower limb at 1 month Suspected Albright Syndrome at 8 months. Allergies: metamizole Age onset: 2 years, insidious onset, progressive downhill course

Tumor in the right supraclavicular, months before admission a greenish-purple area was noticed that bled slightly and was itchy (pruritus).

Examination: vascular tumor in the right supraclavicular region with areas of scabbing, mild tenderness on palpation and a nodular appearance.

Asymmetry of lower limbs with a slight increase in volume in the right lower limb. X-rays of lower limbs and right ischial bone: findings suggestive of fibrous dysplasia or enchondromatosis, a biopsy examination is recommended. Left lower limb is 1.5cms longer than the right one.

Magnetic resonance angiography: Ovoid shaped, intense contrast-enhancing lesion 2.8cm in diameter in the right posterior cervical region, at the C4 and C5 level above the trapezius muscle, reliant on the right subclavian artery.

Skin histopathology: Focally thinned out epidermis. Vascular dilatations of varying sizes with capillaries, arterioles and veins extending into the dermis and hypodermis. Dilated venous vessels containing thrombi in a process of formation. Doppler ultrasound of the vascular lesion: tumor in the right supraclavicular region, suggestive of AVM (arteriovenous malformation); it is recommended that the evaluation is expanded with a peripheral angiography to better examine the area.

CONCLUSION: We concluded to be a combined vascular malformation in the right suprascapular and polyostotic fibrous dysplasia probably McCune Albright syndrome and lymphedema on the right side of the body and macrocephaly

152 - Dilation of persistent sciatic vein after endovascular laser ablation of marginal vein

Iryna Benzar (Pediatric Surgeon); Boris Koval (vascular surgeon of Bogomolets National Medical University); Anatolii Levytskyi (Head of Pediatric Surgery department of Boomlets National Medical University)

PURPOSE: Complications and treatment of the marginal vein are described in the literature, but little attention is usually paid to the persistence of other embryonic veins, in particular, the sciatic vein.

METHODS: Endovenous laser ablation (EVLA) performed in 10 children aged 3-14 years with low extremities embryonal veins. Pretreatment visualisation was performed using ultrasound in grayscale and Doppler mode, and dynamic MRI angiography. For EVLA 1470-nm diode laser was used. EVLA was performed under general anaesthesia and permanent US control. In the early postoperative period patients received LMV heparin and limb compression.

RESULTS: Persistent both marginal and sciatic veins were found in 8 children, including bilateral lesion in one case, and isolated persistent sciatic vein in two children. Underlying overgrowth syndromes were Klippel-Trénaunay (n=4) and CLOVES (n=3). All patients were symptomatic at the time of treatment. In two patients, previously performed embolisation of the marginal vein mouth lead to a significant expansion of the distal vein segment and collaterals. In our first patient EVLA of only the marginal vein resulted in dilatation of the sciatic vein and its tributaries, so sciatic vein ablation was performed during the reintervention. In the next 7 patients, targeted MRI imaging of the sciatic vein was performed and simultaneous ablation of the marginal and sciatic veins provided a good result. In two patients, EVLA was performed of only the sciatic veins. The result of the treatment: a significant reduction in limb girth (n=10), cessation of bleeding from skin lesions (n=5), decrease in pain and increase in tolerance to physical activity (n=10), disappearance of orthostatic collapse (n=3).

CONCLUSION: Persistence of the lateral marginal vein can be combined with persistent sciatic vein, their simultaneous ablation reduced the number of surgical interventions and ensured a good postoperative result.

155 - Giant facial AVM controlled by embolotherapy made feasible thanks to thalidomide pretreatment

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PURPOSE: Arteriovenous malformation AVM is due to direct communication between dysplastic arteries and veins creating a nidus. AVMs can be congenital, or seem acquired in adulthood. Superficial AVMs usually appear as warm angiomatous blumps with pulsations, thrill and bruit. Ultrasonography with colodoppler UCD is the best diagnosis tool, CT angiography, magnetic resonance angiography MRA, describe the nidus and the involved vessels. Resorting to partial excision aggravate AVMs. Therefore embolization with various agents followed by surgical resection is recommanded. Molecules with anti angiogenic properties were recently used. We report the case of a giant facial AVM that could only be embolized after thalidomide treatment.

RESULTS: A 68 years old man presented an enormous angiomatous mass of the left cheeck. He suffered from pain and bleeding from endojugal mucosa. The lesion expands with thrill after a facial trauma ten years ago. UCD showed high velocity of the left, facial and internal maxillary arteries. Angiogramm revealed 2 arterio venous fistulas AVF, in the lip and the check. Rapamycine was tried for 3 months without any improvement. The patient was transferred to St Luc hospital in Brussels where an embolization attempt failed due to the very high flow of the AVF. To reduce the AVM flow, thalidomide treatment started at 100mg/d for 2 months then reduced at 50 mg/d for 1 month. The second attempt of embolization with coils and ethanol was successful. Surgery was ruled out because or renal failure. A follow up for 7 years good evolution.

CONCLUSION: Management of complex bleeding AVMs is challenging. Failure of endovascular therapy necessitates the implementation of medical management. Using thalidomide to treat AVMs is novel but can lead to adverse events. In our patient because of renal failure the dosage was only 50mg/d. Despite this, thalidomide was able to decrease the AVM flow enabling embolization with success.

156 - Bilateral whole lung irradiation for severe pulmonary involvement of generalized lymphatic anomaly

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PURPOSE: Describe two adult cases of generalized lymphatic anomaly with severe pulmonary involvement treated with bilateral whole lung irradiation (BWLI).

METHODS: Case 1: A 31-year-old female with lymphatic anomaly involving the lungs, mediastinum, and retroperitoneum was diagnosed in 2014 via lymphangiograms and pleural biopsy. Genetic testing was negative. Initial management included pleurodeses and lymph channel ligation. In 2021, her disease progressed and she was treated with sirolumus. In 2022, she was admitted for respiratory failure, which was refractory to noninvasive ventilation. BWLI was recommended.

Case 2: A 61-year-old male was diagnosed with lymphatic anomaly diffusely involving the lungs and mediastinum in 1998 via CT and mediastinal biopsy. Later genetic testing was negative. Mechanical pleurodesis was performed. The patient was managed supportively until his condition worsened in 2023. He initiated sirolimus, but was admitted one month later for respiratory failure requiring intubation and ventilation. IR bronchial artery embolization followed by BWLI was recommended.

RESULTS: Case 1: The patient completed BWLI, 1500 cGy in fifteen fractions. She was discharged with nocturnal ventilation the day following treatment completion. She has experienced no radiation toxicities to date. At most recent visit, ten months after RT, she reports significant functional improvement. She only utilizes supplemental oxygen with exertion.

Case 2: The patient underwent IR bronchial artery embolization followed by BWLI, 1200 cGy in eight fractions. He was extubated after two treatments and discharged after seven, on 1 L O2. Four weeks later, he was admitted and eventually intubated for respiratory decline. He died nine days later. Autopsy revealed diffuse alveolar damage and organizing pneumonia, possibly due to radiation injury. There was also a pulmonary artery thromboembolism with hemorrhagic infarction.

CONCLUSION: In absence of relief from conservative measures, BWLI should be considered in adults with generalized lymphatic anomaly with severe pulmonary involvement after careful consideration of potential risks and benefits.

160 - Somatic Genetic Exploration of Superficial Vascular Malformations by cfDNA Liquid Biopsy in a Cohort of 88 Patients from a Monocentric French Hospital

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PURPOSE: Superficial vascular anomalies (SVAs) are complex disorders characterized by abnormal vascular growth. Recent advances in Next Generation Sequencing (NGS) have revealed genetic somatic alterations associated with vascular malformations. Traditionally, SVA treatment relies on clinical follow-up, embolization, surgery, or sclerotherapy. However, some cases present challenges with temporary relief and complications. Targeting genetic alterations could enhance treatment outcomes, but obtaining tissue samples for genetic testing can be invasive and challenging. Liquid biopsy, a non-

invasive approach, offers a promising solution by detecting genetic mutations in cell-free DNA (cfDNA). This study aims to assess the feasibility and sensitivity of detecting pathogenic genetic variants in SVA patients using cfDNA from liquid biopsy.

METHODS: The study enrolled 88 patients : 55 with arteriovenous malformations (AVM) and 33 with lymphatic malformations (LM). For AVM patients, liquid biopsy samples were collected from peripheral blood, efferent veins, afferent arteries, and AVM nidus. For LM patients, lymphatic fluid was obtained by direction punction during diagnostic procedures. Molecular analysis was performed using a panel genes involved in solid tumors. LM patients with pathogenic variants detected by NGS on cfDNA underwent validation through digital PCR.

RESULTS: In AVM patients, pathogenic variants were detected in 24% of cases, predominantly in MAP2K1 and KRAS genes. Proximity to the AVM nidus or efferent vein showed higher sensitivity for variant detection. Peripheral blood samples, though exhibiting lower VAF, proved effective when validated by available tissue analysis. A pathogenic variants were identified in 30% of LM patients, showing the efficacy of liquid biopsy in low-flow lesions.

CONCLUSION: The study provides valuable insights of liquid biopsy for the genetic analysis in superficial vascular malformations, demonstrating technical feasibility and sensitivity. Liquid biopsy offers a simple way to access molecular information, for improved diagnosis and treatment strategies. Further research may explore its applicability in cerebral AVMs and optimizing sequencing conditions for peripheral blood samples.

171 - Dentition development anomalies in facial segmental hemangiomas not related to PHACES.
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PURPOSE: In recent years, the association between infantile hemangiomas (IH) affecting the maxillary or mandibular area and different alterations in dental development have been described, especially in the context of PHACES syndrome.

METHODS: We present the cases of two female patients aged 8 and 6 years respectively who were followed by our team because of segmental facial hemangioma with subsequent studies which did not reveal any abnormalities; therefore, they did not meet the criteria for PHACES syndrome.

Both patients were treated with oral propranolol, achieving an optimal and fast response.

RESULTS: In the first case, a delay in eruption of deciduous teeth was observed in the left inferior hemiarch, where the hemangioma was more intense. At the age of 5 years, enamel hypoplasia was observed, along with caries and tooth fusion. An orthopantomography was performed at the age of 7 years, showing agenesia of permanent incisives in the left inferior hemiarch, as well as other dentition anomalies. In the second case, on the right upper and inferior hemiarchs, where the hemangioma was located, hypoplasia and cavities on some primary and permanent molars, and one supernumerary tooth, were observed.

CONCLUSION: We present two patients with facial segmental IH not related to PHACES, who developed multiple dentition abnormalities. To our knowledge, some of these abnormalities have not even been reported in the context of segmental IH.

Evidence of an association between IH and developmental anomalies seems to be strong. These anomalies may be severe, and not only in PHACES-related cases, as shown in these cases.

This association is probably underdiagnosed owing to the lack of protocolized dental studies on IH patients and follow-up. Therefore, we suggest screening for these anomalies with X-ray imaging during transitional dentition in cases of IH affecting the maxillary and mandibular areas.

178 - Persistent Pyogenic Granuloma in Infant's Temporal Region: A Case of Post-Excision Expansion

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PURPOSE: Pyogenic granuloma (PG), a benign vascular tumor also known as lobular capillary hemangioma, is commonly acquired postnatally. Despite its prevalence, the exact etiology remains elusive, with proposed associations with trauma, infection, and preceding dermatoses. While surgical excision with primary closure is a universally employed treatment, some reports suggest the potential for PG recurrence.

METHODS: A 10-month-old female infant presented with a 1.5 cm pedunculated red de-epithelialized exophytic lesion, suggestive of infantile hemangioma. Parental preference led to early surgery due to frequent massive bleeding. Microscopic examination, including negative GLUT-1 staining, confirmed the diagnosis of pyogenic granuloma. Despite initial successful healing, recurrence manifested after five months, presenting as numerous small 1-3 mm red papules around the matured scar. Incisional biopsy confirmed the PG diagnosis, with negative GLUT-1 staining and a low MIB-1 index (10%).

RESULTS: In fear of wider recurrence, surgical excision with reconstruction was avoided. Pulsed dye laser was unsuccessful. Cryosurgery, though partially effective, required weekly sessions for over a year until complete resolution. After six months of post-treatment observation, no recurrence was observed.

CONCLUSION: The recurrent form of PG with satellite lesions, previously identified as Warner and Wilson-Jones syndrome (WWJS), lacks a known etiology, with limited literature and only three reported cases. While recent reports suggest gene mutations (BRAF, RAS, GNA 14) in PG, their specificity to this unique recurring characteristic in WWJS is unknown. Surgical resection is the conventional treatment, but considering trauma as a trigger for PG, especially in exposed hair-bearing locations, alternative approaches should be considered. Persistent cryosurgery, though time-consuming, proved effective and painless for the patient. Further research is needed to understand the genetic basis and optimal management of recurrent PG.

181 - How to Minimize the Severe Complications Associated with the Absolute Ethanol Treatment of Hand AVMs

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PURPOSE: To investigate the particular difficulties associated with the use of absolute ethanol for treating hand arteriovenous malformations (AVMs); to present a series of strategies employed during treatment and afterwards to mitigate the risks of ischemia, necrosis, and other severe complications resulting from the absolute ethanol treatment, and the corresponding outcomes observed in patients.

METHODS: Data from June 2022 to October 2023 were collected from patients diagnosed with hand AVM who underwent absolute ethanol treatment at our center. All interventions, conducted under DSA and general anesthesia, employed endovascular techniques using direct puncture or microcatheter for fistula treatment. Ethanol administration rates were regularly monitored through hand-push angiography, ensuring the absence of extraneous arteries. Throughout treatment, variables such as skin color, lesion temperature, and pulse were observed, with ischemia indicators prompting intervention adjustments. If it shows a suboptimal blood flow recovery, change the treatment area or end the treatment immediately, keep the affected limb warm, and administer 30mg/100ml papaverine by intravenous drip to alleviate spasm. The quantity of ethanol used in all treatments, the dermal temperature of the impacted region pre- and post-operation, and the patients' symptom complaints inside a three-month period subsequent to the treatment were documented and subjected to statistical analysis.

RESULTS: In comparison to patients who solely underwent angiography as a means of preventing reflux to unrelated arteries, patients who received a supplementary series of preventative measures exhibited a reduced likelihood of experiencing ischemia-induced edema, pain, and skin necrosis during a three-month postoperative period ($p<0.05$).

CONCLUSION: In the management of hand AVMs, it is imperative to meticulously evaluate the condition of the affected limb, promptly suspend the treatment, and administer measures such as warmth and antispasmodic therapy. These measures aim to mitigate the occurrence of treatment-related complications and enhance the patient's postoperative quality of life.

184 - Kaposiform Hemangioendothelioma and Tufted Angioma: A Multicenter Case-Control Study
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PURPOSE: The purpose of this study is to identify predictors of whether to treat or not in cases of Kaposiform Hemangioendothelioma (KHE) or Tufted Angioma (TA).

METHODS: This is an international multicenter study currently enrolled with 71 patients with KHE or TA treated at 3 sites between 2000 and 2021. Fisher's exact test was used for statistical analysis ($p<0.05$). Data collected includes demographics; clinical and laboratory and imaging characteristics, treatment and patient outcomes.

RESULTS: Preliminary data includes 71 patients- 57 were treated (patients were treated with combinations of sirolimus (56%), systemic steroids (52%), embolization (10%), laser ablation (14%), vincristine (47%), surgical excision (15%), cryoablation (10%), propranolol (25%), and interferon (9%)), and 14 were not treated. Predictors of treatment included depth of the lesion (superficial, mixed or deep), Kassabach-Meritt Phenomenon (KMP), mass effect, rapid increase in size, severe pain, functional impairment, disease reactivation, joint invasion, deep cavitary involvement and leg-length discrepancy ($p<0.05$). Long term sequela were more prominent in the treated group (untreated lesions predominantly developed residual changes like redness and violaceous color change (71%) vs dyspigmentation (22%), scarring from surgical resection (16%) and chronic pain (9%) in the treated group; $p<0.05$).

CONCLUSION: Our cohort of KHE and TA patients showed similar clinical characteristics to those reported in the literature. While identified predictors of treatment mostly match US consensus criteria established in 2013, the introduction of Sirolimus as a highly efficacious treatment highlights the need to further characterize these predictors in a larger cohort (n=200) .We want to collect more data and

conduct further analysis using a regression model to determine the parameters that may specifically guide treatment. We also want to understand efficacy and safety of specific therapies.

185 - Use of 3D printing in pre-surgical planning in severe cases of pediatric patients with vascular anomalies

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PURPOSE: The treatment of vascular anomalies is characterized by a multidisciplinary approach. Presently, there is a growing preference for non-invasive methods and systemic targeted treatments. However, there remain instances where a surgical intervention is deemed appropriate, proving to be the most straightforward means to enhance the patient's quality of life.

Employing volumetric geometry reconstruction and 3D printing of the vascular lesion and its surrounding anatomical structures serve as suitable tools for more precise pre-surgical planning.

The objective of this study is to assess the benefits of 3D printing in the pre-surgical planning in severe cases involving pediatric patients with various types of vascular anomalies.

METHODS: The assessment included two patients with vascular anomalies: a 2-month-old infant with a lymphatic malformation of the left side of the neck and chest, and a 4-year-old girl with a venous malformation of the left supraclavicular region. In both patients, the multidisciplinary committee endorsed surgical treatment of the lesion because of the formation of skin necrosis due to insufficient perfusion of the skin cover caused by the pressure of the rapidly growing affection. Significant limitations in the mobility of the child's neck and upper extremities further justified surgical treatment.

Based on MRI data sets, 3D models of lesions, including the surrounding anatomical structures (soft and hard tissues), was created. This facilitated the visualization of the surgical intervention and pre-definition of all procedural steps.

RESULTS: The average duration of both surgical procedures was 6 hours, with no complications observed during intraoperative and postoperative periods. The actual anatomical proportions aligned with the predefined 3D printed models of vascular lesions, and the use of 3D models in the pre-surgical planning enhanced the safety of surgical procedures.

CONCLUSION: 3D printing of vascular anomaly models proves to be a valuable tool for pre-surgical planning, particularly in severe cases involving pediatric patients with vascular anomalies.

186 - Treating a complicated arteriovenous malformation (AVM) with trametinib in a pediatric patient who failed other treatments.

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PURPOSE: Arteriovenous malformations (AVM) are difficult to treat lesions and typically progressive over time.

Since the discovery of mosaic pathogenic variants along the MAPK pathway being the cause of sporadic AVM, a limited number of reports showing a improvement to targeted treatment with MEK inhibitors has been published.

We report here a pediatric case of a refractory AVM treated with trametinib.

METHODS: Case report.

RESULTS: An 11-year-old boy with a congenital AVM involving his left upper back was referred to our Vascular Anomalies Center. As the lesion was growing, two sessions of embolisations (ethanol) were performed at an external institution in 2021. These interventions led to severe ulceration that never healed. In March 2022, the lesion was embolized (Onyx34® and Glubran/Lipiodol®) at yet another institution. However, this was followed by anterior spinal ischemia leading to motor and sensory impairment of the lower extremities. Moreover, hemodynamics of the AVM was not improved, and the ulceration persisted.

Molecular analysis revealed the post-zygotic pathogenic variant p.Q61R in KRAS (VAF 12.17%). On angio-MRI, the lesion was located mainly in the subcutis with feeding vessels emerging from the external carotid, the subclavian, and the intercostal arteries.

With this large, ulcerated lesion being at risk for life-threatening bleeding and superinfection, targeted treatment with trametinib was initiated in June 2023 (0.025mg/kg qd). After 4 months size had decreased and the ulceration reduced by more than 50%. Complete healing is expected within the next weeks. Follow-up MRI is scheduled for December 2023.

CONCLUSION: This observation adds to the growing body of literature suggesting that AVM are amenable to genotype-guided medical therapy. MEK inhibitors have the potential to profoundly change the therapeutic landscape of these challenging lesions.

Current evidence suggests that use of trametinib in patients with AVM is well tolerated with an acceptable safety profile. However, long-term data are currently not available.

191 - Blue rubber bleb nevus syndrome (BRBNS) with recurrent bloody stool treated by endoscopic sclerotherapy– case report

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PURPOSE: Blue rubber bleb nevus syndrome (BRBNS) is a rare syndrome characterized by multiple vascular malformations of varying appearance and size, occurring mainly on the skin and in the gastrointestinal (GI) tract. Gastrointestinal lesions of BRBNS can be the cause of recurrent acute or chronic bleeding and treatment is challenging.

METHODS: The patient has taken Sirolimus 1.25ml bid since 3 months. In the colonoscopic examination, numerous bluish submucosal lesions were found in rectum. The size of the lesions was estimated from 0.3 mm to 2.5 cm. Under general anesthesia, the patient was treated with colonoscopic sclerotherapy for the hemangiomas in the rectum. By polidocanol injection, most of the vascular formation were treated (1~3 ml per lesion). However, after the sclerotherapy, bloody stool still existed. Two weeks later, for the residual lesions observed in the next colonoscopy, an additional injection was given.

RESULTS: The patient received therapeutic sclerotherapy 2 times for the vascular malformations in the rectum by colonoscope, in which all the hemangiomas were treated by polidocanol. After two sessions of therapy in our hospital, bloody stool have been absent. No severe therapy-related adverse events such as postoperative reactionary hemorrhage, embolism or perforation was noticed.

CONCLUSION: Repeated endoscopic sclerotherapy, combined with Sirolimus, can be effective, safe, simple to perform, and quick to recovery in the clinical management of GI manifestations of BRBNS.

194 - "Drug-loaded foam" or absolute ethanol: which is the better choice for the sclerotherapy of venous malformations?

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PURPOSE: To evaluate and compare the efficacy and safety of bleomycin-polidocanol drug-loaded foam and absolute ethanol for the sclerotherapy of venous malformations.

METHODS: We conducted a prospective analysis of cases treated with bleomycin-polidocanol drug-loaded foam (BPF) and absolute ethanol (AE) for venous malformations at our center from February 2018 to January 2020. Comparative indices included the number of treatment sessions, the reduction rate of lesion volume (based on magnetic resonance images), patient satisfaction, and the incidence rate of complications.

RESULTS: 37 patients treated with BPF and 35 patients treated with AE were included in the study. There were no statistical differences in gender, lesion location, and symptoms between the two groups of patients. In terms of treatment sessions (1.6 vs 1.7 times) and lesion volume reduction rate (-80.4% vs -82.3%), there is no statistical difference between BPF and AE groups. While BPF group had higher patient satisfaction rate (7.1 vs 5.9) and less complication rate (35.1% vs 68.6%), with statistically significant differences.

CONCLUSION: With the better safety and equivalent efficacy, Bleomycin-polidocanol drug-loaded foam may be a better choice for the sclerotherapy of venous malformations than the absolute ethanol.

195 - Modified integral subunit expanded flap for medial mid-face birthmark: a retrospective study

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PURPOSE: To assess the effectiveness of a modified integral subunit expanded flap technique for treating congenital birthmark including port-wine stain and melanocytic nevus lesions in the medial mid-face, with a focus on minimizing scarring.

METHODS: 22 patients, aged 4-46 years, with medial mid-facial congenital birthmark were included in the study. The procedure involved 3 stages: tissue expander insertion and expansion, subunit repair with the expansion flap, and long-term repair and adjustment. The extent of resection, complications, and outcomes were recorded and analyzed.

RESULTS: Between 2012 and 2020, all patients were successfully treated and followed up for 12 months to 4 years. The resection area involved up to 90.7% of normal skin within the midface subunit. Major complications included hematoma, expander leakage, incision infection, skin necrosis, palpebral separation, and hypertrophic scars. However, the outcomes were generally favorable, with improved aesthetics. Detailed patient results and case illustrations are presented.

CONCLUSION: The modified integral subunit expanded flap technique for treating medial mid-face lesions demonstrated promising results in terms of minimizing scarring and achieving a natural subunit division effect. Although concerns exist about the extent of normal skin resection, the procedure's overall aesthetic benefits outweigh potential drawbacks. Further prospective studies should assess the

method's comparative scope and burden against traditional reconstructions and include objective measurements.

196 - Bleomycin, nab-paclitaxel, and temsirolimus, which is the best choice for the drug-loaded foam in the sclerotherapy of vascular anomalies?'

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PURPOSE: With different drug combinations for drug-loaded foam, including the selection of the loaded drug at different concentrations, try to find the optimal combination and ratio of drug-loaded foam to explore its potential in the sclerotherapy of vascular anomalies.

METHODS: Bleomycin, nab-paclitaxel, and temsirolimus were selected as the potential drugs to be loaded in the foam. Different concentration gradients were chosen for each drug and mixed with Polidocanol to prepare drug-loaded foams, namely Bleomycin Polidocanol Foam (BPF), nab-Paclitaxel Polidocanol Foam (PPF) and Temsirolimus Polidocanol Foam (TPF), with Polidocanol (POL) and absolute ethanol (AE) as the control groups. In vitro experiments were conducted to compare foam stability and quality, and animal experiments were performed to assess vascular tissue damage capability.

RESULTS: The optimal concentrations for foam stability were 0.5%, 1%, and 0.25% for BPF, PPF, and TPF, respectively. The vascular tissue damage capability was the strongest for 0.5% BPF.

CONCLUSION: A concentration of 0.5% Bleomycin Polidocanol Foam (BPF) may be the optimal concentration and ratio for drug-loaded foam in the sclerotherapy of vascular anomalies.

204 - Low Prevalence of PHACE Syndrome in Facial Segmental Hemangiomas in China

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PURPOSE: PHACE syndrome is a neurocutaneous syndrome with large facial segmental hemangiomas as the most typical manifestation. Compared with the higher prevalence of Caucasians, PHACE syndrome has rarely been reported in Chinese. In order to confirm the prevalence and clinical characteristics of PHACE syndrome in Chinese, we conducted a retrospective single-center study.

METHODS: We reviewed 1375 patients with facial hemangiomas between April 2021 and September 2023, including 126 patients with segmental hemangiomas. Finally, this retrospective study was

conducted with 98 infants who had facial segmental hemangiomas and completed brain MR, cardiac ultrasound and ophthalmology examination. The clinical photographs were reviewed to determine the localization by segment, and the criteria for definite and possible PHACE was used to diagnose. The prevalence and clinical characteristics of PHACE were calculated.

RESULTS: Five (5.1%) of 98 patients were diagnosed with "definite" PHACE, no patient (0.0%) was diagnosed with "possible" PHACE. The average time of patients with PHACE who first found hemangioma on face and visited the dermatology or plastic surgery were 7 days and 20 days. Two of the patients had structural anomalies of the brain, four had cerebrovascular anomalies, four had cardiovascular anomalies, and two had ocular anomalies. The most common anomalies were tricuspid valve regurgitation, atrial septal defect and aortic stenosis.

CONCLUSION: The prevalence of PHACE syndrome in facial segmental hemangiomas is only 5.1%, significantly lower than the 20%-33% that reported in Caucasians. PHACE patients mainly manifested in the anomalies of cerebrovascular system and cardiovascular system in China.

207 - LUMBAR Syndrome-OEIS Complex Overlap: A Case Series

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PURPOSE: We present 3 cases with overlapping features of OEIS (Omphalocele, Exstrophy, Imperforate anus, and Spinal defects) complex, also known as cloacal exstrophy, and LUMBAR (Lower body hemangioma, Urogenital anomalies, Myelopathy, Bony deformities, Anorectal/Arterial anomalies and Renal anomalies) syndrome.

METHODS: Case series and literature review.

RESULTS: Case 1 is an 8-week-old girl with a segmental infantile hemangioma (SIH) of the lumbosacral back extending to the left leg, and multiple congenital anomalies including bladder exstrophy with an omphalocele, rectovestibular fistula, duplicate vaginas and didelphic uterus, a solitary right kidney with a small low-lying left kidney, and lipomyelocele with severe sacrococcygeal dysplasia and spinal dysraphism.

Case 2 is a 4-week-old boy with a SIH of the buttocks, groin, perineum and perianal skin, and multiple congenital anomalies including omphalocele, bladder exstrophy, absent right kidney, right lateral abdominal hernia, bilateral inguinal hernias, undescended testes, tethered cord, small and mildly bifid glans penis and epispadias, and bilateral talipes equinovarus.

Case 3 is a 9-week -old boy with a SIH affecting the lumbosacral area, buttocks, perineum, and both legs and multiple congenital anomalies including omphalocele, bladder exstrophy, recto-bladder fistula, tethered spinal cord, bifid scrotum, absence of an identifiable phallus and undescended testicles.

CONCLUSION: Our 3 cases are the first to demonstrate a connection between OEIS complex and LUMBAR syndrome, which we propose represent a phenotypic spectrum with likely shared pathogenesis. We hypothesize that OEIS complex and LUMBAR result from a somatic pathogenic variant(s) very early in embryologic development. The involvement of structures in the caudal developmental field and the likely differences in embryologic timing of OEIS and LUMBAR suggest there may be a disruption of spatiotemporal gene expression in the same or separate genes affecting the same pathway.

211 - Does Somatic Gene Mutation Causing Venous Malformations Differ in Anatomical Regions?
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PURPOSE: Venous Malformation (VM) is one of the most common vascular anomalies with the incidence of 1 to 2 in 10.000 and prevalence of 1%.1 Although most of VM are sporadic, they can be inherited as an autosomal dominant trait and is known as 'familial mucocutaneous venous malformations. Most venous malformations are on the head and neck area,2 but when VM affects lower extremities, it could increase the morbidity. There is still no review regarding the genetical phenomena in venous malformations that occurred on lower extremities. The authors reviewed whether the genetic mutation in venous malformation is different regarding anatomical regions to have better insight on etiology.

METHODS: Literatures were searched from online PubMed, Cochrane and Scopus databases added with manual searching strategy using relevant keywords and MeSH terms. All papers were then appraised for their validity, importance, and applicability using Oxford CEBM etiology tools. The studies included systematic review, RCT, cohort, case control, and case series, which discuss only pure venous malformation without involving syndromic diseases.

RESULTS: Eight articles were reviewed and appraised. Somatic mutation of TIE2, TEK, and PIK3CA genes was found to contribute to venous malformations. Venous malformation in any anatomical region can be caused by somatic mutation of TIE2/TEK or PIK3CA gene which can overlap with germline mutation in inherited/ familial VM.

CONCLUSION: We concluded the location does not have significant association with the mutated genes.

217 - Preoperative Transarterial Embolization and Targeted Therapy Using Larotrectinib in Treating Infantile Fibrosarcoma Mimicking Kaposiform Hemangioendothelioma: A Case Report
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PURPOSE: To assess the efficacy of targeted Therapy using larotrectinib and transarterial embolization (TAE) in treating a one-month-old male infant with a progressively growing infantile fibrosarcoma in the right chest.

METHODS: We present the case of a one-month-old male infant with hypovolemic shock due to intratumoral hemorrhage in the right chest. The mass was present since birth, and its size progressively increased within 1 month, from approximately 5x2x2cm in size to 20x15x7cm. Magnetic resonance imaging (MRI) revealed a heterogenous solid lesion with a hemorrhagic component, and Doppler ultrasonography revealed a heterogenous hypervascular solid lesion, mimicking Kaposiform Hemangioendothelioma (KHE). The patient underwent two rounds of TAE with Polyvinyl alcohol (PVA), gelfoam, and coils, targeting the internal mammary, superior thoracic, and right thoracoacromial arteries. These interventions were performed to reduce tumor vascularity before tumor removal surgery. After surgery, the patient underwent 3 cycles of chemotherapy using Vincristine and followed by targeted therapy with Larotrectinib.

RESULTS: Following the second embolization, Doppler ultrasonography confirmed a significant reduction in vascularity. Tumor removal surgery with skin-grafted closure was successfully performed six days after embolization, with approximately 350 cc of intraoperative blood loss. No post-procedural complications were observed. Molecular diagnostic studies resulted in TPR::NTRK1 fusion, which has been reported in spindle cell mesenchymal neoplasms. The patient was given 3 cycles of chemotherapy

using Vincristine and followed by Larotrectinib. No residual lesion was found in follow-up MRI and PET-Scan. During monitoring, no residual mass has been observed to date.

CONCLUSION: This case report demonstrates that pre-operative embolization and Larotrectinib therapy are effective treatments for infantile fibrosarcoma resembling KHE. Larger-scale clinical research investigations are necessary to validate this finding.

218 - R183Q GNAQ Sturge-Weber syndrome Leptomeningeal and Cerebrovascular Developmental Mouse Model

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PURPOSE: Sturge-Weber syndrome (SWS), a rare neuro-vascular malformation disorder with abnormal leptomeningeal and cortical vessels, is usually caused by the R183Q GNAQ somatic mosaic mutation enriched in brain endothelial cells. A new developmental mouse model of SWS brain involvement was recently created to investigate mutation impact upon brain vascular development and to facilitate preclinical drug studies.

METHODS: A new Tet-ON R183Q GNAQ (tetO-Gnaq*R183Q+/+) transgenic mouse line was backcrossed for three generations, then paired with rtTA tet transactivator mice under the Tie2 promoter (Tie2-rTA/TRE-βGal+/-) to generate mice expressing endothelial R183Q GNAQ in the presence of a doxycycline-based diet. Litters were perfused at P14-17, with a subset perfused with Evans Blue. Half received a sub-seizure dose (1.5 mg/kg; i.p.) of kainate. Fixed mouse brains were stained with X-gal, DAPI, and antibodies for Gαq, Tie2, phosphorylated-S6, and claudin-5; image scoring for vessel staining intensity or pattern in the leptomeninges and cortex was completed by an investigator blinded to genotype.

RESULTS: X-gal localized to leptomeningeal endothelial cell membrane/cytoplasm, and excluded Tie2 and Gαq. In cortical microvessels, X-gal colocalized to nuclear/perinuclear regions with prominent Tie2 and Gαq expression. Leptomeningeal X-gal staining was more frequent in kainate-treated mice, versus non-treated mice ($p = 0.023$). Phosphorylated-S6 vessel scores were significantly higher in leptomeningeal vessels of mutant mice ($p = 0.035$), but decreased in mutant cortical microvessels. Claudin-5 staining was discontinuous in X-gal positive mutant cortical microvessels, demonstrating abnormally irregular vascular caliber. Only mutant brains had severe Evans Blue staining ($p = 0.028$).

CONCLUSION: The new R183Q GNAQ Tet-ON developmental mouse brain model demonstrates endothelial expression of mutant Gαq associated with decreased blood brain barrier integrity with abnormal claudin-5 expression, altered Tie2 and Gαq cellular localization, abnormal microvascular caliber, and increased leptomeningeal, but decreased microvascular, mTOR activity. Further study is ongoing investigating later time-points, other targets, and triggers of neurovascular progression.

220 - PK/PD characterization of pimasertib in a mouse model of KRAS-driven vascular malformations

Guillaume CANAUD (Hôpital Necker Enfants Malades)

PURPOSE: Arteriovenous malformations (AVM) are debilitating conditions caused by genetic mutations when acquired during embryonic development. KRAS gain-of-function mutations are frequently observed in sporadic AVM, particularly those involving brain vasculature. While KRAS signals through the MAPK pathway in normal cells, mechanism of disease in KRAS-driven AVM is not well characterized and no approved treatments are available.

METHODS: A post-natal mouse model of KRAS G12C-vascular malformations that recapitulates patient phenotypes was used in this study. Pimasertib, an allosteric inhibitor of MEK1/2, was used in this study.

We generated 12 mice including 7 males: 4 controls (carrying wild type KRAS alleles but expressing the GFP in Cdh5 positive cells, KRASWT) and 8 KRASG12C-Cdh5 mice. Vehicle was administered to KRASWT (n= 3) and KRASG12C-Cdh5 (n=2) mice and pimasertib at a twice daily dose of 1 or 3 mg/kg/dose to KRASG12C-Cdh5 mice. Mice were sacrificed 5 days after treatment initiation. The day before the sacrifice, plasma was collected at 2, 4 and 6 hours post last dose, snap frozen and shipped to the sponsor for PK analysis. The spleen and lung tissues from KRASWT and KRASG12C-Cdh5 mice were collected for Phosphoflow analysis.

RESULTS: At the time of sacrifice, CD31+GFP+ cells were FACS sorted from the lungs and the spleen and explored for AKT/mTOR and ERK pathways activation. Compared to the controls, a dramatic activation of both pathways was observed in endothelial cells derived from KRASG12C-Cdh5 mice. Following treatment with pimasertib, a notable reduction in ERK phosphorylation was evident in endothelial cells. In addition, pimasertib also reduced AKT and S6RP phosphorylation. We observed a dose-dependent effect, but even the lower dose of pimasertib significantly inhibited phosphorylation events. PK analyses are ongoing.

CONCLUSION: This study demonstrates that pimasertib inhibits ERK, AKT and S6RP phosphorylation in endothelial cells of a mouse model of KRAS G12C-driven arteriovenous malformations.

225 - Multicenter study of long-term outcomes and quality of life in PHACE syndrome, ages 10 and up.
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PURPOSE: To characterize long-term outcomes of PHACE Syndrome

METHODS: Multicenter study with cross-sectional interviews and chart review of individuals with definite PHACE ≥10 years of age. Data from charts were collected across multiple PHACE-related topics. Data not available in charts were collected from patients directly. Likert scales were used to assess the impact of specific findings. Patient-Reported Outcomes Measurement Information System (PROMIS) scales were used to assess quality-of-life domains.

RESULTS: A total of 104/153 (68%) individuals contacted participated in the study at a median of 14 years of age (range 10-77 years). There was infantile hemangioma (IH) residua in 94.1%. Neurocognitive manifestations were common including headaches/migraines (72.1%), participant-reported learning differences (45.1%), and need for individualized education plans (39.4%). Cerebrovascular arteriopathy was present in 91.3%, with progression identified in 20/68 (29.4%) of those with available follow-up imaging reports. Among these, 6/68 (8.8%) developed moyamoya vasculopathy or progressive stenoocclusion leading to isolated circulation at or above the level of the circle of Willis. Despite the prevalence of cerebrovascular arteriopathy, the proportion of those with ischemic stroke was low (2/104; 1.9%). Nineteen (18.3%) had endocrine disease including hypothyroidism, growth hormone deficiency, early/delayed puberty, hypopituitarism, and gonadotropin releasing hormone insufficiency. There were three patients who had been pregnant resulting in 7 healthy, full term deliveries. PROMIS global health scores were lower than population norms by at least 1 standard deviation.

CONCLUSION: PHACE syndrome is associated with long-term mild to severe morbidities including IH residua, headaches, learning differences, and progressive arteriopathy. Primary and specialty follow-up care is critical for PHACE patients into adulthood.

226 - Under pressure: Neonatal nasal tip necrosis mimicking infantile hemangioma

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PURPOSE: Pressure necrosis along the nasal tip can mimic an ulcerating infantile hemangioma. We present our case as well as a review of the literature of these challenging lesions. In our case, the ultrasound and MRI highly suggested an infantile hemangioma along the nasal tip and the patient was started on very low dose oral propranolol as a precaution. The patient's propranolol was discontinued within 2 weeks and the lesion continued to heal without any further intervention. A similar case had been previously reported in the literature secondary to nasal tip necrosis from continuous positive airway pressure (CPAP). The purpose of this poster is to bring awareness to pressure necrosis as it has a very distinct contour and to highlight that imaging (ultrasound and MRI) at these sites may look similar to infantile hemangioma thus leading to unnecessary treatment.

METHODS: Case report and review of the literature

RESULTS: Pressure necrosis on the nasal tip has a distinct clinical appearance and can mimic infantile hemangioma on ultrasound and MRI imaging.

CONCLUSION: It is important to recognize the distinct features of pressure necrosis on the nasal tip, especially in infants who may have been exposed to CPAP, as a mimicker of infantile hemangiomas clinically and radiologically, to avoid unnecessary radiological work-up and management with oral propranolol.

228 - Long-term sequalae of large segmental infantile hemangiomas in PHACE syndrome

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Cotter (Harvard University); Eulalia Baselga (Department of Dermatology. Hospital Sant Joan de Deu); David Bosquez (Hospital Sant Joan de Deu); Surabhi Neerendranath Jain (Stanford University); Jordan K. Bui (Stanford University); Irene Lara-Corrales (The Hospital for Sick Children and University of Toronto, Toronto, Canada); Tracy Funk (Oregon Health and Science University); Alison Small (Oregon Health and Science University); Wenelia Baghoomian (Oregon Health and Science University); Albert C. Yan (Children's Hospital of Philadelphia); James R. Treat (Children's Hospital of Philadelphia); Griffin Stockton Hogrogian (Children's Hospital of Philadelphia); Charles Huang (Children's Hospital of Philadelphia); Anita Haggstrom (Indiana University); Mary List (Indiana University); Catherine McCuaig (University of Montreal; CHU Sainte Justine); Victoria Barrio (University of California San Diego); Anthony J. Mancini (Northwestern University); Leslie P. Lawley (Emory University); Kerrie Grunnet-Satcher (Emory University); Kimberly A. Horii (Children's Mercy Hospital and Clinics); Brandon Newell (Children's Mercy Hospital and Clinics); Amy Nopper (Children's Mercy Hospital and Clinics); Maria Garzon (Columbia University); Margaret E. Scollan (Columbia University); Erin Mathes (UCSF)

PURPOSE: To describe infantile hemangioma (IH) sequelae in PHACE syndrome in individuals ≥10 years of age.

METHODS: Multicenter study with cross-sectional interviews and medical record review of individuals with definite PHACE ≥10 years old. Information on initial IH characteristics (subtype, morphology, location), treatments, and complications were collected. Patient interviews characterized sequelae by collecting data on location, size, type of residua, treatments, satisfaction with IH appearance, and impact on self-confidence. Logistic regression analyses were run to identify associations between IH features and long-term outcomes.

RESULTS: 103/104 had a facial IH. In infancy, 78/104 (75%) received systemic treatments for their IH. 13/78 that received systemic treatments received oral beta-adrenergic blockers alone, 43/78 received systemic steroids alone, and 15/78 received both. Residua was present in 98/104 (94.2%) including most commonly color change (74/104; 71.2%), textural change (41/104; 39.4%), and swelling/bulk (23/104; 22.1%). 15/104 (14.4%) had persistent IH of the intraoral mucosa. Most reported being very satisfied or satisfied with IH appearance (93/104; 89.4%). Half (52/104) received treatments for residua, especially laser (46/104; 44.2%). The majority of those who underwent laser reported improvements, though it was not associated with self-confidence (OR 0.377 [0.135-1.057] p=0.064) or satisfaction of the IH appearance (OR 0.602 [0.171-2.1], p=0.43). Self-confidence was inversely associated with surgical treatment in infancy (OR 0.145 [0.045-0.465], p=0.0012) and ulceration (OR 0.291 [0.104-0.812], p=0.018).

CONCLUSION: This is the largest cohort studying PHACE syndrome in adolescence and adulthood. Treatments for IH residua is common in PHACE. No patients who desired treatments went without them, and most report satisfaction with the IH appearance. Self-confidence was decreased in those who had ulceration or surgical treatments in infancy, likely secondary to scarring. Efforts to prevent both should be prioritized with early systemic treatment in infancy and close follow-up.

231 - Single stage embolization and resection of a large cutaneous infantile hemangioma causing pulmonary hypertension

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Case: 9-month-old infant with a large cutaneous infantile hemangioma (IH) over the left shoulder that was first noticed at 3 week of age The lesion was progressively increasing in size but was otherwise asymptomatic and patient started on oral propranolol at 6 months of age Patient with clinical signs of heart failure with poor growth and increased work of breathing At 8 months, echocardiographic evidence of severe pulmonary hypertension and SpO2 of 90% and patient admitted to cardiac ICU The exact etiology of the pulmonary hypertension was unclear and cardiac catheterization performed with overall findings suggestive of high output cardiac state secondary to IH Given that this represented a possible reversible cause of pulmonary hypertension, a multidisciplinary team reached a consensus to attempt pre-operative embolization and primary resection under a single anesthetic

Conclusion: Pulmonary hypertension and heart failure secondary to a cutaneous infantile hemangioma is an atypical clinical presentation Other recommendations for management of this lesion included embolization alone, oral sirolimus, and continued beta blocker therapy with addition of systemic steroids Multidisciplinary approach to these complex lesions is critical to achieving favorable clinical outcomes

233 - **Review of Integration of Patient Reported Outcome Measures in the Paediatric Vascular Anomalies MDT.**

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PURPOSE: To assess the ease of integration of the Patient Reported Outcome Measures (PROMs) assessment into the clinic time from the perspective of patients and/or patient's care givers and clinicians. A second purpose is to review clinical progression of paediatric vascular anomalies from the patient and/or patient's care giver's perspective using PROMs.

METHODS: The PedsQL form was chosen to assess PROMs. PedsQL assesses physical, emotional, social and school functioning. A printed-out version of the age appropriate PedsQL was handed to the patient and/or patient's care giver whilst in the waiting room. Depending on the patient's condition, a Dermatology Life Quality Index or PedsQL Paediatric Pain questionnaire were given to the patient as an additional assessment tool. During the MDT clinic, one clinician would read the PROMs and then raise any issues highlighted by the form during the consultation.

RESULTS: The vascular anomalies MDT was started in July 2020 and the use of PROMs was introduced in November 2021. In the 2-year period between this time and November 2023, 70 patients were seen over 13 clinics. From this total, 90% (63/70) of patients completed a PROMs form. A PedsQL Paediatric Pain questionnaire was filled out in 6% (4/70) patients. 8 patients were seen more than once during this period. From these 8 patients, PROMs were able to highlight an overall improvement in scores in 50% (4/8) patients and an overall decline in 50% (4/8) over time.

CONCLUSION: This audit can conclude that PROMs can be easily integrated into the vascular anomaly MDT clinic as shown by the high completion rate. Additionally, it aides a patient focused consultation by identification of wider issues relating to vascular anomalies. PROMs can assess the clinical progression by showing an improvement or worsening of patient's overall wellbeing related to their vascular anomalies.

234 - Single-stage treatment of vascular malformations utilizing glue embolization and surgical excision in pediatric and adult patients

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PURPOSE: To describe a diverse patient cohort and associated outcomes following single-stage glue embolectomy and surgical excision for vascular malformations (VMs).

METHODS: Patients with VMs treated via single-stage glue embolectomy and surgical excision at a single institution were retrospectively reviewed. Following percutaneous access and venography, VM embolization was performed with cyanoacrylate glue (1-4 or 1-3 dilution with lipiodol). After cessation of blood flow was demonstrated, the VM was surgically resected under general anesthesia.

RESULTS: Ten patients (4 females, 6 males; age range: 6-42 years, median 21 years [IQR 12.3-28 years]) with VMs (n=11) underwent glue embolectomy and excision. VMs were associated with pain (n=11), swelling (n=5), and bleeding (n=1). VMs were diagnosed via imaging, and included venous, as well as combined lymphatic-venous, and capillary-lymphatic-venous malformations. VMs involved the extremities (n=7), neck/shoulder (n=2), back (n=1), and hip (n=1), and were predominantly subcutaneous (n=9), while two were intramuscular. A single case included excision of cutaneous vascular blebs. Following excision, one case was diagnosed as a solitary fibrous tumor via histopathologic examination. In addition to glue embolectomy, two patients also underwent coil embolization. Complications were uncommon—one patient developed a reaction to residual glue in an adjacent superficial vein which required excision of feeding veins. A second patient experienced increased swelling, which resolved without intervention within 2 weeks. All patients with confirmed VMs (n=10) underwent successful single-stage glue embolectomy and surgical excision, determined by ongoing resolution in pre-procedural symptoms, at a median interval of 2.2 months (IQR 0.6-4.7 months) of follow-up.

CONCLUSION: The reported cases support single-stage glue embolectomy and immediate excision as a safe and effective therapeutic modality for VMs in both pediatric and adult patients. This combination therapy may reduce the risks associated with excision alone by decreasing intra-operative bleeding and allowing for better identification of the extent of the VM, resulting in more complete removal.

236 - Novel Treatment Approach for Lymphatic Malformations Using NTRK Inhibitors

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PURPOSE: Lymphatic malformations are non-cancerous masses composed of clusters of abnormally growing lymphatic vessels. Treatment typically consists of a combination of sclerotherapy and sirolimus. However, response to sclerotherapy can be sub-optimal and may require multiple treatments and surgical debulking. We report a finding of an ETV6-NTRK3 chromosomal mutation in a patient with a lymphatic malformation. This indicates that patients with lymphatic malformations may respond to NTRK inhibitors.

METHODS: Reported a case report of an 18-year-old patient with multiple lymphatic malformations. Phoenix Children's Hospital Electronic Medical Record was reviewed.

RESULTS: 18-year-old male with a history of multiple lymphatic malformations presented with shortness of breath. He was found to have a right sided chylothorax secondary to a lymphatic malformation. The patient had previously been on sirolimus, but it was discontinued due to side effects. During the admission, he had a chest tube placed for 1 month, restarted sirolimus, and had sclerotherapy performed twice. However, despite sirolimus and sclerotherapy, the patient's chylothorax continued to accumulate. Genetic testing from a biopsy revealed an ETV6-NTRK3 chromosomal rearrangement. Patient was started on Larotrectinib, an inhibitor of tropomyosin kinase receptors. After two weeks of therapy, the patient's pulmonary effusions completely resolved. His chest and abdominal lesions have also decreased in size.

CONCLUSION: Lymphatic malformations are difficult to treat when they do not respond to conservative management. They may require consecutive sclerotherapy treatments and catheter drainage. This case

represents a novel treatment approach to a treatment refractory lymphatic malformation. Our patient's response to Larotrectinib can be seen in Figure 1, where the picture on the left was at presentation and the picture on the right represents two weeks of being on an NTRK inhibitor. NTRK inhibitors may be an effective treatment option for lymphatic malformations that could prevent the need for invasive procedures.

237 - Macrocystic lymphatic malformations of the head and neck: A retrospective comparison of treatment verses watchful waiting.

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PURPOSE: To compare the likelihood of recurrent swelling after initial presentation between treated and untreated patients with macrocystic lymphatic malformations of the head and neck not involving the airway. The frequency and timing of emergency department accesses related to the event of swelling were analysed to provide data on efficacy and ideal timing of treatment.

METHODS: A 5-year retrospective review of a hospital database was conducted reviewing 35 patients with multi-cystic lymphatic malformations of the head and neck not involving the airway. An event was defined as an incident of recurrent swelling of a neck lymphatic malformation after initial presentation that required urgent admission to the emergency department. A Cox regression analysis was conducted which included age, gender, diameter of lymphatic malformation at presentation, and echogenicity on US evaluation. This was used to predict the recurrence of the lesion in the treatment and non-treatment groups. Fisher's test and mean comparisons were performed to correlate the number and the frequency of emergency department accesses.

RESULTS: The mean age at presentation was 3.9 years old. Mean follow-up time was 2.7 years. Thirteen patients underwent treatment after their initial presentation. A total of 20 events occurred after the initial presentation, and only 2 of these events occurred in patients within the treatment arm (p=0.02). There were 11 patients in the non-treatment group and 2 patients in the treatment group who accessed the emergency department after initial presentation for a subsequent swelling event (p=0.42). The average number of emergency department accesses in the non-treatment group was significantly higher (p=0.04).

CONCLUSION: Sclerotherapy of macrocystic lymphatic malformations of the head and neck after initial presentation significantly reduces the chance of a subsequent swelling event. Leaving the patients untreated may increase the morbidity of the patient and may burden the emergency department.

239 - The classification of facial hypertrophic port wine stains

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PURPOSE: As a common manifestation of the natural course of port wine stains, the lesions become thicken with age and have different clinical manifestations especially in face. Currently there is no clear classification method for hypertrophic port wine stain to distinguish the clinical manifestations. It is important to propose a new classification method to refine subtype of facial hypertrophic port wine stain.

METHODS: 47 patients with facial hypertrophic port wine stains were enrolled between August 2014 and December 2021. Retrospective analysis of the clinical features and imaging data was performed for each case.

RESULTS: Based on the statistical results, a new classification was proposed for 47 patients with hypertrophic port-wine stains, namely, congenital hypertrophic port-wine stain (n=26) and acquired hypertrophic port-wine stain (n=21), and acquired hypertrophic port-wine stain was further divided into early-onset (n=15) and late-onset (n=6). All 26 patients with congenital hypertrophic port-wine stain were complicated with bone and soft tissue hyperplasia. 16 of 21 patients with acquired hypertrophic port-wine stain had soft tissue thickening accounted for 76.19%, and only 4 patients had maxillary changes.

CONCLUSION: Through retrospective analysis, we classified the clinical subtypes of patients with hypertrophic port-wine stains into congenital hypertrophic port-wine stains and acquired hypertrophic port-wine stains. Patients with different subtypes have different treatment strategies, which should be distinguished clinically.

245 - Propranolol in Treating Pediatric Airway Hemangiomas: A Literature Review and meta-analysis

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PURPOSE: Purpose: Hemangiomas are prevalent vascular tumors that present substantial challenges when they involve the airway. This comprehensive literature review explores the effectiveness, safety, efficacy, dosing protocols, and potential adverse effects of propranolol in the treatment of pediatric airway hemangiomas.

METHODS: Methods: Embase, PubMed, Cochrane, and Web of Science were thoroughly searched for articles from their inception up to August 2023 by two independent reviewers, following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. The quality of the included studies was evaluated using the Newcastle-Ottawa scale (NOS) criteria. In this review paper, successful treatment was defined as achieving full airway clearance to the extent that it no longer posed a threat to the patient's airway, prompting the attending physician to discontinue medication.

RESULTS: Results: From the initial pool of 824 screened abstracts, this review incorporated 7 full-text articles, encompassing a total of 74 patients. The patients exhibited an average age of 2.3 years, spanning from 4 weeks to 7 years. Approximately 59% of the patients were female (n=34), and the average treatment duration was 7.9 months. The pooled data indicated an overall airway clearance rate of 85.5% (95% CI 0.803, 0.951, I2 0%). Notably, the most commonly reported method of medication delivery was 2 mg/kg/body weight/day divided into 3 oral doses. Furthermore, a comprehensive analysis of post-treatment complications was conducted, revealing a pooled complication rate of 9% (95% CI: 0.008-0.120; I2=0%, n=4).

CONCLUSION: Conclusion: Our review strongly suggests that propranolol provides a safe and effective approach to managing this challenging condition, thereby mitigating potential risks and complications associated with airway hemangiomas in pediatric patients.

246 - Efficacy and Safety of Lasers in Treating Head and Neck Capillary Malformation: A Systematic Review and Meta-Analysis

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PURPOSE: Purpose: Laser therapy has emerged as the primary treatment modality for capillary malformation (Port Wine Stain) showing promising results. This systematic review and meta-analysis aim to evaluate the comparative effectiveness and safety of frequently employed lasers in the management of capillary malformations of head and neck.

METHODS: Methods: Embase, PubMed, Cochrane, and Web of Science were comprehensively searched for articles from their inception up to August 2023 by two independent reviewers. The quality of the included studies was assessed using the Newcastle-Ottawa scale (NOS) criteria. In this meta-analysis, patients achieving 25-100% clearance were categorized as successful treatment, while those with 0-25% clearance were considered non-responsive to the treatment.

RESULTS: Results: 725 abstracts screened, 14 full-text articles were included, comprising a total of 714 patients with a mean age of 19.5 years . The mean number of laser treatments per patient was 6.8 sessions, with 80% of patients undergoing Pulsed Dye Laser (PDL) treatment, 12% receiving Nd:YAG laser treatment, and 8% opting for 577 nm Yellow laser treatment. The pooled overall success rate was 91% (95% CI 0.96-0.983, I2 0%). Subgroup analysis for overall response showed that the pooled response rate for PDL was 90% (95% CI: 0.94-0.973; I2=0%, n=486), 99% for Nd:YAG (95% CI: 0.979-1.008; I2=0%, n=119), 86% for Yellow 577 (95% CI: 0.7621-0.964; I2=0%, n=43).Furthermore, a subgroup analysis of post-treatment complications revealed a pooled complication rate of 10% for PDL (95% CI: 0.031-0.147; I2=87.9%, n=63) and 4.2% for Nd:YAG laser (95% CI: 0.007-0.080; I2=0%, n=5).

CONCLUSION: Conclusion: Our meta-analysis reveals that laser treatment is a safe and effective procedure for managing capillary malformation in the head and neck region. Nd:YAG exhibits a higher overall treatment response and fewer post-laser complications when compared to PDL and 577 Yellow laser treatments.

248 - FEATURES OF SURGICAL TREATMENT OF CHILDREN WITH VENOUS MALFORMATIONS OF THE HEAD IN THE PRESENCE OF DIRECT COMMUNICATION OF THE MALFORMATION WITH THE CRANIAL CAVITY

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PURPOSE: To identify the features of treatment of children with venous malformations of the head in the presence of direct communication with the cranial cavity.

METHODS: Treatment was given to 5 patients with venous malformations of the head aged 1 to 11 years. All children were diagnosed with the aspect of venous malformation of the head, the bone defects of the skull vault and base were found; it has been established that the abnormal tissues of the malformation were partially supplied with the blood due to the ""reflux"" of venous blood from the cranial cavity through the bone defects. In 4 children, the bone defects were localized in the calvarial bones. In 1 patient - in the bones of the skull vault and base. A surgery was performed to remove the abnormal tissues to the maximum possible extent, interrupting the pathological ""reflux"" of venous blood into the malformation tissues through defects in the skull bones.The bleeding was stopped using a medical wax by impression of the latter into defects of the skull bones. For children with defects in the area of the calvarial bones, complete interruption of the ""reflux"" with the closure of all bone defects using wax was performed.

RESULTS: In 4 patients, a good clinical outcome was achieved. In 1 patient, an unsatisfactory outcome was achieved: continued growth of the abnormal tissues was noted due to the persistent pathological "reflux" of venous blood into the area of the malformation tissues through a defect in the sphenoid bone.

CONCLUSION: In children with venous malformations of the head in the presence of direct communication of the malformation with the cranial cavity, the puncture-sclerogenic treatment mode is not effective. Removal of the abnormal tissues without interrupting the blood ""reflux"" from the cranial cavity into the malformation tissues leads to continued growth of the abnormal tissues.

249 - Treatment of Symptomatic Kaposiform Hemangioendothelioma with MR-guided ablation
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PURPOSE: Kaposiform Hemangioendothelioma (KH) is a locally aggressive vascular tumor with the potential for serious complications; Over 70% of KHEs develop coagulopathy (Kasabach-Merritt phenomenon [KMP]). KHE can also cause pain, mass effects, or functional impairment. There is no consensus on the treatment of KHE.

MR-guided cryoablation (MRC) and MR-guided laser ablation (MRL) are novel minimally invasive techniques safely adopted for the effective treatment of low-flow vascular malformation. There are no reports of MR-guided ablation for the treatment of KHE.

Here in, we report the successful application of MR-guided cryotherapy and MR-guided laser ablation in two patients with treatment-resistant Kaposiform hemangioendothelioma

METHODS: Retrospective Case series

RESULTS: Patient 1 is a male with deep right lower flank and retroperitoneal KHE complicated by KMP at one month, initially controlled with a combination of prednisone x4 months and 14 months of oral sirolimus. At four years of age, he developed a rapid and painful recurrence of KHE with deep muscular and retroperitoneal involvement. He received a session of MRL with excellent control of pain and stable disease for more than a year of follow-up to date.

Patient 2 is a male with extensive KHE of the right chest and abdominal wall complicated by KMP. The coagulopathy was controlled with prednisone, but he continued to have rapid painful growth of KHE despite medical treatment with sirolimus, propranolol, and vincristine. He received MRC at the age of 2, resulting in symptomatic and radiologic improvement of KHE. He required four subsequent MRC treatments at the age of 3, 4, and 6 years. At 10 years, He remains stable and asymptomatic to date.

No procedure-related side effects were noted in the patients.

CONCLUSION: MRC and MRL are valuable minimally invasive techniques for treating medically resistant, rapidly progressive, symptomatic KHE.

251 - Central lymphatic phenotype in Noonan Syndrome using MR lymphangiography
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PURPOSE: In Noonan Syndrome (NS), pathogenic variants hyperactivate Ras/MAPK pathway, impeding Lymphatic Endothelial Cell (LEC) branching. Patients are prone to central conducting lymphatic anomalies (CCLA), however, MR lymphangiography (MRL) results differ between variants. This multicentre study explores genotype-phenotype correlations in NS patients with diverse pathogenic variants using MRL

METHODS: 17 cases with lymphatic symptoms (chylothorax, Protein Losing Enteropathy, or lymphedema) from three institutions were included. Ages at MRL ranged from 1 month to 35 years, with a mean age of 13 years. Patients harbored (likely) pathogenic variants in KRAS(2), PTPN11(6), RIT1(4), SOS1(1), SOS2(3), or SHOC2(1). MRL featured dynamic imaging with intranodal contrast. A systematic rating system evaluated contrast enhancement in central lymphatic vessels and flow. Fisher's exact test analysed differences among pathogenic variants. Limited by sample size, potential trends related to clinical significance were observed.

RESULTS: The CCLA manifested in diverse features across pathogenic variants. There were no significant variant-related differences in thoracic duct assessment, flow direction, or fluid collections. Trends include thoracic duct anomalies: no contrast (24%), full-length contrast (35%), and partial contrast with dilation or tortuosity (41%). Notably, pathogenic PTPN11 variants exhibited 50% dilated duct, 33% tortuous duct, and 50% ascites. Pathogenic RIT1 variants had 25% dilated duct, 50% tortuous duct, with 25% ascites. Pathogenic KRAS variants (50%) showed ascites and retroperitoneal retrograde flow. Pathogenic SHOC2, SOS1, and SOS2 variants showed no thoracic duct dilation or tortuosity, and no ascites, or retroperitoneal retrograde flow. Mesentery retrograde flow was absent in PTPN11, RIT1, and SHOC2 variants, while present in KRAS, SOS1, and SOS2 variants.

CONCLUSION: This study presents the complex variations of CCLA among NS with diverse pathogenic variants. Notable differences exist, but a larger multicentre prospective study is essential to establish genotype-phenotype correlations conclusively.

252 - Efficacy and safety of DOAC in painful venous malformations in children
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PURPOSE: Low molecular weight heparins improve the coagulopathy and symptoms of venous malformations (VMs). Subcutaneous injections are a matter of discomfort especially in children. Our group (ISSVA 2021) reported that direct oral anti-coagulants (DOAC) such as dabigatran were an efficient and safe alternative option in adults. We describe the use of DOAC in children in this context.

RESULTS: Patients 1 (F, 17 yo) and 2 (F, 12 yo) present with a painful VM involving the entire lower left (1) and right (2) limb and associated with truncular deep ectatic veins at risk of pulmonary embolism. Patient 1: D-dimer 3000ng/ml, fibrinogen (fg): 2.2 g/L. Tinzaparine 4500 IU/d achieved pain relief and D-dimer <270ng/ml, maintained for 1 year now with dabigatran 110 mg x2/d. Patient 2: D-dimer 6100 ng/ml, fg: 1.5 g/l; fondaparinux 5 mg/d lowered d-dimer to 970 along with complete pain relief, then dabigatran 150 mgx2 led to D-dimer lowering to 430ng/ml and fg increase to 3.38g/l, for a year. Patients 3 (M, 10 yo) and 4 (M, 12 yo) have extra-truncular VMs involving the foot, d-dimer =

8683 mg/ml (⍰3), and the foot, ankle and leg, D-dimer level: 3430 ng/ml (⍰4). Platelet count and fg level are within normal range. Both have severe pain, sport limitation and limping, dramatically improved by enoxaparin 4000 UI (⍰3) and fondaparinux 2.5 mg/ (⍰4), and lowering of D-Dimer level to 2.262 ng/ml (⍰3) and 540 ng/ml (⍰4). Rivaroxaban 10mg/d maintains complete symptoms relief with D-dimer level below 1000 ng/ml for both, for 6 and 24 months respectively.

CONCLUSION: No bleeding manifestations were observed even in patients ⍰1 and ⍰2 for whom coagulation normalization was mandatory for the risk of pulmonary embolism, requiring higher dosage. In this condition, Dabigatran was chosen based on previous data in adults, otherwise rivaroxaban is the most studied DOAC in children.

254 - Intracranial hypotension, cerebral spinal fluid leak, and neurosurgical urgency in a case of generalized lymphatic anomaly

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PURPOSE: To describe the case of a child with a complex generalized lymphatic anomaly (GLA) with spinal involvement, and to present the current relevant literature pertinent to this case.

METHODS: A case report and review of the literature was completed.

RESULTS: This patient presented at 9 months of age with a small, non-tender lump in the flank. MRI revealed intra-abdominal and retroperitoneal lymphatic malformation , with splenic changes, borderline low-lying tonsils, lumbar vertebral changes, and an L4 compression fracture. Sirolimus was started at 3 years of age. Intravenous zoledronic acid was added to prevent focal osteolysis. While his bone density in the lumbar vertebrae appeared to stabilize (-3.6 at 4 years, -2.6 at 7 years), a signal change in the upper cervical spine developed in conjunction with the development of headaches and worsening cerebellar ectopia between 6 and 7 years of age. Tonsillar herniation significantly worsened over a short interval, in conjunction headaches. Symptoms of intracranial hypotension evolved, with positional headaches, vomiting and parasthesias. Craniocervical decompression and duraplasty were needed. A CSF leak was suspected due to reports of postural changes in headache severity. This was addressed with an epidural blood patch during craniocervical decompression. Multiple hospital admissions were required, with polypharmacy for pain management. Importantly, this child's quality of life and mental health have been appreciably affected.

CONCLUSION: GLAs with spinal involvement require diligent attention. There is a paucity of cases with spinal involvement described in the literature. GLA poses significant risk of morbidity when anatomically complex locations, particularly the spine, are affected. Spinal involvement in any vascular malformation highlights the importance of screening for signs and symptoms that suggest changes in CSF pressure. Risk for Chiari malformation should be considered. This case highlights that the optimal combination of therapies has not yet been established.

256 - Characterization and Tumor Risk in PIK3CA-related Overgrowth Spectrum (PROS)

Kim M. Keppler-Noreuil (University of Wisconsin School of Medicine and Public Health)

PURPOSE: Genetic and epigenetic syndromes associated with lateralized overgrowth have been associated with increased risk of primarily embryonal tumors, including Wilms tumor (WT), with frequency of tumor development between 3.3 -6%. The PI3K-AKT-mTOR comprise a critical signaling pathway regulating cellular growth, proliferation, and angiogenesis. Many different solid and hematological tumors or cancers are caused most commonly by somatic activating variants in PIK3CA

hotspot codons H1047, E542, and E545. Tumor risk and surveillance for patients with PROS is currently controversial. The objectives of this systematic review are to characterize and determine the estimated risk for tumorigenesis and development of malignancies in PROS.

METHODS: Retrospective review of the literature for PROS phenotypes and reported tumors/malignancies.

RESULTS: There have been 11 reports of PROS in the literature, including 12 individuals, who have developed tumors. Frequency ranged from 1.4% (6/419), 1.6% (4/258) to 3.3% (4/122). Clinical diagnoses included 6 with CLOVES, 2 with MCAP, 2 with KTS, 2 with lateralized overgrowth. The tumor types included: 7 (~60%) with WT, 4 (33%) with indeterminate WT vs Nephroblastomatosis (NB), and 1 (8%) with NB. Six (50%) had somatic PIK3CA hotspot variants. Age at tumor diagnosis was 27.4 months (mean), and 9-119 months (range). Urine cell-free DNA detected low level PIK3CA in these reported patients with NB or WT compared to those without renal involvement (P <0.05).

CONCLUSION: Proposed surveillance and clinical management will be reviewed. Further longitudinal data is needed to support relationship between tumor risk and genotype/ clinical phenotypes to guide recommendations for surveillance.

267 - A new variant anatomy of lateral marginal vein of Sevelle as the sole venous drainage of the left lower limb in Klippel-Trenaunay Syndrome

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PURPOSE: We report a case of Klippel-Trenaunay Syndrome with a variant lateral marginal vein anatomy which was not described before.

METHODS: MRI of the lower limb with MR angiogram and venograms performed.

Conventional Contrast venogram with compression of lateral marginal vein at different levels was also done.

RESULTS: The lateral marginal vein, in our case, does not drain thorough the ipsilateral gluteal vein and the iliac segment of the vein is completely absent. Rather it drains via a large subcutaneous vein anteriorly, coursing from the left common femoral vein joining with the right common femoral vein, akin to the femoral-femoral bypass.

On conventional venogram with occlusion of the lateral marginal vein at various points confirmed that the marginal vein is the sole draining vein of the left leg.

CONCLUSION: Persistent lateral marginal vein is usually managed with surgical intervention, embolization, radiofrequency ablation or sclerotherapy. However, in the case described, the venogram showed that the no venous drainage of the leg if the lateral marginal vein were to be embolised. Therefore, intervention is contraindicated as the lateral marginal vein is the sole drainage vein of the left lower limb.

282 - Alpelisib attenuates lymphatic malformation endothelial cell proliferation through upregulation of Angiopoietin-2 and inhibition of VEGFR3 signaling

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PURPOSE: Alpelisib, a PI3K inhibitor, reduces disease burden in patients with lymphatic malformations (LMs), but its specific mechanisms of action downstream of PI3K are not well understood. This study elucidates a relationship between Angiopoietin-2 (Ang-2), a lymphatic homeostatic factor, and VEGFR3 in the pathophysiology of cystic LMs and characterizes a potential mechanism for alpelisib: targeting the Ang-2/VEGFR3 axis.

METHODS: Patient-derived LM endothelial cells (LM-ECs, n=16) were isolated and cultured from cystic LMs. EC identity was confirmed using RT-PCR and western blot with human dermal lymphatic endothelial cells (HDLECs, n=6) as controls. Ang-2 overexpression in 2 LM-EC lines and 2 HDLEC lines was achieved with lentiviral transduction and validated with western blot following puromycin selection. WST-8 and single-cell clonogenic assays were performed over 4 and 7 days, respectively. Cell-surface VEGFR3 expression was assessed in trypsin-treated cells with western blot. Alpelisib (2.5 μM), rapamycin (10 nM), or vehicle (0.01% DMSO) treatments were performed in full serum and serum starvation conditions in LM-ECs.

RESULTS: Ang-2 mRNA (-4.4x) and protein (-3.5x) were significantly downregulated in LM-ECs compared to HDLECs. Ang-2 overexpression in LM-ECs and HDLECs significantly attenuated proliferation ($p<0.0001$). Ang-2 overexpressing LM-ECs and HDLECs showed downregulation of total and cell-surface VEGFR3, p-Akt, and p-ERK1/2 but no changes in Angiopoietin-1 and p-Tie2 expression. Alpelisib, but not rapamycin, increased Ang-2 expression in LM-ECs in a dose-dependent manner and downregulated VEGFR3. Alpelisib in combination with Ang-2 overexpression displayed a synergistic reduction in LM-EC proliferation compared to Ang-2 overexpression or alpelisib treatment alone ($p<0.0001$).

CONCLUSION: Ang-2 is significantly downregulated in hyperproliferative LM-ECs, and Ang-2 overexpression using lentiviral transduction downregulated VEGFR3 and suppressed LM-EC proliferation. Alpelisib, but not rapamycin, also increased Ang-2 and suppressed VEGFR3 expression. This suggests that Alpelisib may reduce LM growth by targeting the Ang-2/VEGFR3 axis, and that synergism of VEGFR3 inhibition may allow for smaller doses of targeted treatments.

283 - LUMBAR Syndrome: A Study of Prenatal Risk Factors in Comparison to PHACE Syndrome and OEIS Complex

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PURPOSE: A shared pathogenesis between LUMBAR syndrome with PHACE and OEIS complex (Omphalocele, Exstrophy, Imperforate Anus, Spinal anomalies), is supported by recent reports of LUMBAR/PHACE and LUMBAR/OEIS overlap. All are sporadic in occurrence with negative family history. These rare syndromes are unlikely to co-occur by chance alone. Infants with PHACE syndrome are more likely to be female, born at term, and a result of single-gestation pregnancy. In contrast, infants with OEIS are more likely to be low birth weight, premature, and the product of multiple gestation pregnancy, with an equal gender distribution. This is the first study of prenatal risk factors in LUMBAR syndrome.

METHODS: Retrospective review of a database of 146 published reports used to establish diagnostic criteria for LUMBAR syndrome. Fisher's exact test was used to compare statistical significance between categorical variables.

RESULTS: Patient gender was reported in 109 cases: 40 (37%) boys and 69 (63%) girls. 36/37 (97%) infants were born at term, defined as ≥ 37 weeks gestation ($p < .0001$). Birth weight was normal in 21/22 (96%), defined as ≥ 2500 grams ($p = .0002$). 6/15 (40%) mothers were primigravids. The average maternal age was 30.2 years (n =13). Most pregnancies were uncomplicated. Family history was negative for congenital anomalies in 13/14 (93%). There were no reports of parental consanguinity and

no reports of twins or other multiple births (p = .0605). There was no statistically significant difference in the incidence of anomalies between girls and boys.

CONCLUSION: Like PHACE, LUMBAR is significantly more common in full-term, normal birth weight, singleton girls. We hypothesize that in utero hypoxia, possibly with genetic susceptibility, at a specific early embryologic timepoint could explain the association between LUMBAR, PHACE and OEIS. Prospective studies in LUMBAR syndrome are needed to evaluate maternal pre-pregnancy and pregnancy characteristics, and other maternal risk factors for prenatal hypoxia.

287 - Combined treatment of extensive lymphatic-venous malformation of neck and upper mediastinum.

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PURPOSE: The aim of the study is to present treatment of a girl with complex LVM, including systemic treatment and surgery.

METHODS: One month baby girl was admitted to the surgical clinic with a tumor extenting to the entire left side of the neck. Diagnostics began with ultrasound and MRI, where complex LVM was visible, which was situated along and among the jugular artery, vein, vagus nerve, modeling the vessels, trachea, pharynx, extending from the parotid gland to the superior mediastinum. The maximum size of the lesion was 11x8x7xcm. After completing the diagnostics, treatment with Sirolimus was proposed. The parents initially did not consent to this. Local treatment with Bleomycin was initiated.

RESULTS: Three injections of the drug were performed into the cysts among the LVM, which resulted in a moderate effect at the injection sites. The parents changed their mind and treatment with Sirolimus was started. The lesion decreased by 1/3 after 7 months and further treatment had no effect although continued for another 3 months. The mean drug concentration was 11.18 ng/dL. No significant complications related to the treatment or LVM itself were observed, apart from a transient increase in blood triglyceride levels. After re-analyzing all the data, it was decided to excise the lesion. On the day of the procedure, the child was 2.5 years old. Intraoperative ultrasound and neuromonitoring were used to precisely identify the LVM and the structures surrounding it. The LVM was completely removed, separating it from the vessels, nerves, sympathetic plexus, salivary glands, pharynx and prevertebral space. No complications or recurrence were noted. The child has been under observation for 11 months after the procedure. She is fully functional, without any deficits.

CONCLUSION: Developing systemic therapies and using techniques to assist the surgeon during surgery improves treatment outcomes in patients with LVM.

288 - Capillary Malformation-Arteriovenous Malformation Consensus Guidelines

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PURPOSE: Evaluation and treatment guidelines and multidisciplinary, expert consensus-derived diagnostic criteria are lacking for capillary malformation-arteriovenous malformation syndrome (CM-AVM). Evidence-based, multidisciplinary consensus guidelines for the diagnosis and management of CM-AVM syndrome were developed.

METHODS: A modified Delphi Process was used to attain consensus. A group of experts in the fields of pediatric dermatology, genetics, neurosurgery, radiology, and hematology-oncology were assembled and divided into 3 working groups: clinical findings, genetics, and treatment. An extensive literature review was completed for each topic and proposed statements were drafted based on the relevant articles and expert opinion. The Strength of Recommendation Taxonomy was used to grade the strength of recommendation and level of evidence of the individual articles. The proposed statements were compiled and anonymously reviewed by all members. Statements that reached 80% agreement (7-9) were included in the final recommendations.

RESULTS: Agreed upon clinical characteristics of capillary malformations in CM-AVM syndrome include having multiple (> 3), congenital and/or acquired, small, oval or round, pink to red-brown macules or patches. AVM/AVF features include appearance congenitally or early in life with variable onset of symptoms. Recommended genetic testing includes RASA1 and EPHB4 with consideration for testing for HHT genes. Radiologic screening is suggested after clinical or genetic diagnosis and should include MRI with and without contrast of the head and spine, and MRA of the head.

CONCLUSION: These evidence-based consensus statements on CM-AVM syndrome offer guidance for diagnosis, evaluation, and treatment for CM-AVM patients.

290 - Photoacoustic microscopy for imaging of venous malformations

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PURPOSE: Vascular malformations, which can be high-flow or slow-flow, are mostly benign but can potentially be life or function-threatening when involving vital structures or when associated with overgrowth syndromes. For malformations that are predominantly cutaneous, diagnostic techniques like ultrasonography and magnetic resonance imaging may be inadequate in characterization of these lesions. Photoacoustic microscopy is a fairly new non-invasive imaging technique that relies on optical properties of tissues. It is able to detect hemoglobin, water, lipids, and other light absorbing chromophores, allowing for greater contrast and spatial resolution compared to conventional ultrasonography.

METHODS: We describe a case series of photoacoustic microscopy performed on 8 pediatric patients with venous malformations managed at our Vascular Anomalies Clinic. The photoacoustic device (Hadatomo Z WEL5200) was applied to lesional and control skin with measurements taken twice for each site. Two- and three-dimensional images were captured, and the lengths and diameter of all vessels were measured using the device.

RESULTS: Across the 8 patients, the overall medians of vessel diameter and length were larger in the venous malformation compared to non-lesional skin. Of these 8 patients, 6 had median vessel diameters that were larger in the venous malformation compared to non-lesional skin, with a mean positive difference of 12.8 µm. In 5 of the 8 patients, median vessel length was longer in the venous malformations compared to non-lesional skin, with a mean positive difference of 115.1 µm.

CONCLUSION: Photoacoustic imaging is able to provide high-resolution visualization and accurate characterization of vessel architecture in venous malformations.

293 - A hard case of heart failure: Embolization of a pelvic AVM with high-output heart failure

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PURPOSE: A 47-year-old male was referred to interventional radiology (IR) for a pelvic arteriovenous malformation (AVM) diagnosed in adulthood with previous outside embolization. He endorsed no pelvic symptoms but had worsening high-output heart failure requiring optimization for renal transplant evaluation.

METHODS: Pelvic AVMs are an uncommon vascular malformation, especially in males. They may be asymptomatic or can present with symptoms such as venous congestion, hematuria, or high-output cardiac failure. Embolization is often the initial therapy for symptomatic AVMs, although successful treatment can be difficult due to extensive AV communications.

RESULTS: Pre-treatment CT demonstrated an extensive pelvic AVM with hypertrophied feeding arteries arising from the bilateral internal iliac artery (and embolization material present proximally on the right), dilated veins draining to right iliac venous system, and a dysplastic vascular nidus. Digital subtraction arteriography confirms the AVM; he underwent 3 embolization sessions over a 3-month period due to persistent AVM filling on imaging, as follows:

1. Transarterial embolization of median sacral (n-BCA glue, coils) and right internal iliac (n-BCA glue, coils, Amplatzer II plug) feeding arteries

2. Transarterial embolization of distal inferior mesenteric (n-BCA glue) and right internal iliac (n-BCA glue, coils) feeding arteries, and unsuccessful Coda balloon occlusion of the right internal iliac vein for either stasis or retrograde embolization of the nidus

3. Transarterial embolization of distal left internal iliac feeding arteries (n-BCA glue), followed by percutaneous embolization of the right internal iliac artery (n-BCA glue, coils) under dual fluoroscopic and CT guidance, with decreased AVM filling on completion aortogram

CONCLUSION: This rare case of a pelvic AVM in a male patient with high-output heart failure demonstrates the difficulty of treating this high-flow lesion despite multiple embolization sessions with a variety of materials and techniques. Furthermore, the imaging and clinical endpoints are difficult to define, with little evidence defining the best next steps.

296 - Novel Dosing Schedule of Propranolol Improves Sleep Patterns in Patients with Infantile Hemangiomas

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PURPOSE: Propranolol is the first-line therapy for infantile hemangiomas (IH). Sleep disturbance constitutes the most common reason for early propranolol discontinuation by parents. Propranolol is typically administered BID, but in patients who report sleep dysfunction we adjust to TID dosing. This study aimed to compare the impact of propranolol on sleep when administered in BID or TID dosing regimens.

METHODS: This was a prospective single center pilot study. Patients with multiple hemangiomas or a single hemangioma >2cm were randomized into BID or TID dosing. Patients with an isolated hemangioma <2cm were prescribed timolol as the control. Parents were offered the Brief Infant Sleep Questionnaire (BISQ) at each clinic visit (every 3 months) until termination of the medication (18 months of age).

RESULTS: A total of 158 BISQ surveys were given to 128 patients: 88 at the time of initiation and 70 at the time of follow-up. The BID group reported the fewest nighttime sleep hours with 8.52 ± 1.90 compared to the TID group with 9.76 ± 0.89 and the timolol group with 9.56 ± 1.59 (p=0.05). The BID group had significantly more nighttime awakenings at 1.67 ± 1.05 compared to the TID group at 0.81 ± 0.75 and timolol at 1.44 ± 1.13 (p=0.05). Subjectively, parents report the most problems with sleep in the BID (1.87 ± 1.15) group compared to the TID (1.18 ± 0.40) and timolol (1.22 ± 0.44; p=0.05) groups.

CONCLUSION: The novel TID dosing strategy exhibits sleep patterns more consistent with the control group indicating less overall sleep disturbance. Improvements in sleep patterns are likely to have increases in long term drug adherence leading to maximum treatment efficacy, but barriers to TID dosing still exist. Ongoing enrollment of patients is crucial to provide better recommendations in the dosing regimens for beta blockers in the management of infantile hemangiomas.

297 - Multi-institutional study on the efficacy and safety of wearing a custom-made compression elastic garment for 6 months for Klippel–Trenaunay syndrome with venous malformation

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PURPOSE: Klippel–Trenaunay syndrome (KTS) is a congenital vascular malformation syndrome characterized by low-flow vascular malformation as a capillary affliction as well as venous malformation (VM) potentially causing limb asymmetry from the overgrowth of soft tissue and/or bone. Compression therapy with an elastic garment is a suitable conservative and minimally invasive first-line treatment for KTS. However, such therapy for limb VM including KTS has not yet been sufficiently assessed. Our prior study of 15 KTS patients showed that wearing a custom-made elastic garment for one month could significantly decrease lower thigh circumference with no adverse events. Accordingly, this prospective, multi-center investigation evaluated the efficacy of this treatment for KTS with VM.

METHODS: After measurement of the affected limb, a custom-made elastic garment with 30 mmHg of compression was manufactured by THUASNE (France). A total of 20 patients (7 male and 13 female; mean age: 10.9 years) received compression therapy for 26 weeks at among 5 affiliated institutions. The primary outcome was lower thigh circumference. Secondary outcomes included body water content, pain, modified Rankin Scale, vital signs, and elastomeric force change of the elastic garment.

RESULTS: All 20 patients completed the treatment program. Among the four measurement points in the lower limb, the ratio of affected limb to healthy side circumference was significantly lower at the superior end of the tibial tuberosity (p=0.039) and at the transition of the calcaneal tendon and the gastrocnemius muscle (p=0.000) at the study endpoint. The elastic force of the garment had decreased by half during the 26 weeks. No serious adverse events related to the intervention were recorded.

CONCLUSION: Compression therapy with a custom-made elastic garment may be an effective and safe method for limb overgrowth in KTS with VM. Replacement of the garment is advised every six months to maintain a stable treatment effect.

299 - Expansion of the Phenotype of Lymphatic Anomalies Caused by Somatic Activating BRAF variants

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PURPOSE: The somatic activating variant in BRAF (p.V600E) was recently described as a novel cause of macrocystic head and neck lymphatic malformations in three individuals (Zenner, 2022). Other recent studies profiling the genetic causes of more complex lymphatic anomalies identified this same pathogenic BRAF variant (Liu, 2022; Li & Sheppard, 2023). Our aim was to expand the phenotypic description of the somatic BRAF p.V600E variant in individuals with vascular anomalies.

METHODS: We searched the database of individuals with vascular anomalies at our institution for those identified as having somatic BRAF p.V600E variants via clinical or research-based genetic testing. Three

patients were previously reported. A comprehensive retrospective review of identified individuals' electronic health records was performed.

RESULTS: Five individuals with vascular anomalies had the BRAF p.V600E variant. All patients had complex lymphatic anomalies with mixed macrocystic/microcystic lymphatic malformations in the abdomen; other anatomic involvement included the retroperitoneum, pelvis, and chest. All patients also developed central conducting lymphatic dysfunction though it occurred in 4 patients only after procedural interventions; 3 had surgeries in the areas of their malformations over a decade prior to symptom onset, while 1 developed symptoms shortly after biopsy of the malformation at 1 year of age. Thus, it is unclear if the conduction disorder was a primary central conducting lymphatic anomaly (CCLA) versus secondary dysfunction from traumatic disruption of the lymphatics.

CONCLUSION: All identified individuals with the pathogenic BRAF p.V600E variant had complex lymphatic anomalies, including lymphatic malformations involving the abdomen and other body compartments and organs not previously reported, as well as abnormal conduction of the central lymphatics. This is an important new phenotype of the pathogenic BRAF p.V600E variant that has not been previously described. Further investigation is needed to better understand the etiology of the conduction problems associated with this pathogenic variant to inform the mulitidisciplinary approach to treatment.

301 - Multifocal cutaneous infantile hemangioma and focal hepatic congenital hemangioma: in the search of new links

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PURPOSE: The presence of multiple cutaneous infantile hemangiomas (IH) is frequent and one the main markers of visceral involvement, typically presenting as multifocal or diffuse lesions. On the other hand, congenital hepatic hemangiomas (CHH) are rarely multiple and usually present as focal hepatic lesions without cutaneous involvement.

METHODS: We describe two patients with coexistence of multiple cutaneous IHs and focal CHH. Both patients were born at 37 weeks of gestation without prenatal diagnosis and no relevant clinical history.

RESULTS: Case 1 presented at third week of life with progressive millimetric cutaneous IH localized in trunk and extremities. Blood analysis were normal and abdominal ultrasound revealed a focal vascular lesion in segment 4 of the liver (2.5x2cm). Close follow up with ultrasound without pharmacological treatment was decided. Cutaneous IH disappeared completely at 6 months of life, while it took until 14 months for the CHH to involute entirely.

Case 2 presented at first week of life with multiple IH in left lower limb, trunk and head. Two of the lesions were bigger, one in right knee (1.5cm) and one in abdomen (1cm). Blood analysis were normal and abdominal ultrasound found a focal vascular lesion in segment 6 (1.5x2.2cm). Due to the size of the cutaneous lesions, topical therapy with Timolol® was started without response, changing to Propranolol® after 4 weeks. Cutaneous IH disappeared completely at 9 months of life, however CHH remains stable in ultrasound follow-up (2 years).

CONCLUSION: The association of different vascular tumors in the same patient will continue to be a subject worthy of investigation. There is a link between IH and CHH? Are there any focal CHH GLUT-1 positive? Could some focal CHH respond to pharmacological therapy? The association of multiple cutaneous IH and focal CHH has not been published so far.

302 - GAIN OF FUNCTION PATHOGENIC VARIANTS IN RIT1 CAUSE CENTRAL CONDUCTING LYMPHATIC ANOMALY

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PURPOSE: Central conducting lymphatic anomaly (CCLA) is a devastating lymphatic disorder and only 40% of individuals receive a genetic diagnosis. Identification and validation of novel genetic causes are essential for driving personalized therapies.

METHODS: The IRB determined the retrospective cohort study meets exemption criteria and one participant enrolled in an IRB-approved protocol. Deep vascular anomaly panel was performed. Spheroid sprouting assay using HDLECs was performed. Mrca1-driven transient zebrafish transgenic model induced mosaic expression of wildtype(WT)-RIT1 or RIT1-p.Met90Ile in the venous and lymphatic endothelium. Larvae were treated with MEK inhibitors cobimetinib, mirdametinib, and pimasertib to evaluate efficacy. RNA-sequencing was performed.

RESULTS: We identified a mosaic pathogenic variant in RIT1 p.Met90Val (VAF1.22%) from cfDNA isolated from lymphatic fluid in one participant with CCLA. RIT1 is a RAS GTPase lacking a CAAX domain. Five additional individuals with RIT1-Noonan syndrome and CCLA were identified. CCLA manifested as pulmonary lymphangiectasia, protein losing enteropathy, pleural effusions, chylopericardium, plastic bronchitis, and ascites. DCMRL demonstrated abnormalities of the thoracic duct, dermal backflow, retrograde mesenteric flow, and hepatopulmonary connections. Spheroid sprouting assay demonstrated significantly increased number of sprouts and cumulative sprout length compared to control ($n=3, p<0.05$). Zebrafish larvae have pericardial edema (69%;68/98), cystic malformations of the caudal plexus (20%;20/98), and disorganized vasculature (67%;66/98) significantly increased compared to control ($p<0.0001$). Cobimetinib treatment resulted in a significant reduction in the fraction of larvae with pericardial edema, but mirdametinib and pimasertib treatment did not. Pathway analysis from RNA-sequencing showed increase in lymphatic vessel development, sprouting angiogenesis, lymphangiogenesis, and lymph vessel morphogenesis in the RIT1 overexpression model compared to control.
CONCLUSION: Somatic pathogenic variants in RIT1 cause CCLA. Models show increased lymphangiogenesis, pericardial edema, dilations and disorganization of the vasculature which is supported by transcriptional profiling. Ongoing work is evaluating the cellular and molecular mechanisms of lymphatic dysplasia due to RIT1 activation and response to therapeutic treatment.

303 - Efficacy and safety of sclerotherapy of congenital venous malformations involving the tongue in children

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PURPOSE: Evaluate the efficacy/safety of sclerotherapy of congenital low-flow venous malformations (CVMs) involving the tongue of children, and identify anatomic factors that require planned intubation/admission following procedures.

METHODS: IRB-approved, retrospective review of patients receiving sclerotherapy for CVMs of the tongue between 2014–2023 was performed. Patients with congenital lymphatic malformations were excluded. Patients with veno-lymphatic malformations were included, only if the tongue component was venous.

RESULTS: 13 patients (7F/6M), avg age at first treatment = 10.6y (median = 11.3; range: 2-18.5), avg weight at first treatment = 42.7kg (median = 40.3; range: 10.2-111.5) were identified. Presenting

symptoms included: swelling (n=13), pain (n=7), speech abnormalities (n=9), and bleeding (n=2). 59 total procedures were performed (avg=4.5; median=3; range: 1-9). 8 patients (61.5%) had complete resolution and 5 patients had improvement in tongue-related symptoms. Avg clinical follow-up = 32.8 mos (median=27; range: 2-74). All patients (n=7) with MRI follow-up had improvement on imaging. Avg imaging follow-up = 61.3 mos (median=44; range: 18-163). 2 patients remained intubated post-procedurally. 1 had diffuse involvement of the tongue (3 procedures). The other had involvement of the left hemi-tongue, tongue base, and floor-of-mouth (7 procedures). Patients were extubated within 48 hours. 1 patient (2-year-old with left hemi-tongue involvement) was admitted for observation (not intubated) after her 1st of 5 procedures. 1 patient was tracheostomy dependent due to diffuse head/neck venolymphatic malformation, and thus did not need admission after her 3 procedures. The remaining 9 patients (45 procedures) were treated as outpatients. 58/59 (98.3%) procedures were performed with intravascular bleomycin foam. 1 procedure was performed with 3% STS. There were no complications.

CONCLUSION: Sclerotherapy of CVMs of the tongue in children is safe and efficacious. Diffuse tongue and tongue base involvement in patients without a tracheostomy may require post-procedure intubation. CVM's isolated to the anterior tongue did not require post-procedure intubation after sclerotherapy.

305 - Streptococcal and Haemophilus Bacterial Infections in Children with Vascular Malformations on Sirolimus

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PURPOSE: Sirolimus, an inhibitor of mTOR, is an immunosuppressive medication used in the treatment of some vascular malformations (VMs). mTOR inhibitors are used in other disorders where an increased risk of infection has been reported. The level of risk to patients with VMs on sirolimus is not clear. By examining patients with VMs on sirolimus who developed bacteremia, we aim to inform treatment decisions for this patient group.

METHODS: A retrospective chart review of 150 children with VMs treated with sirolimus was conducted at a single institution.

RESULTS: We identified five children with VMs that developed bacteremia (4 streptococcal; 1 H. influenzae) while on sirolimus. Median age at sirolimus initiation was 2 years (range:0-8 y). 3/5 children received complete pneumococcal and H. influenzae vaccinations; 2 did so whilst on sirolimus. Initial dose of sirolimus was 2.5 mg/m2/daily or 0.8 mg/m2/twice daily and then adjusted according to levels. Mean duration of treatment prior to developing bacteremia was 2.7 years. At presentation, 4/5 children had fever, one had severe VM pain and then developed fever. One recently had three pyogenic granulomas excised. All had blood cultures drawn at presentation and were treated with ceftriaxone, with antibiotic adjustments made later based on bacterial susceptibilities. One patient died of septic shock while in the emergency department; the other 4 were all hospitalized for a median of 4 days (range:3-6). One child subsequently discontinued sirolimus.

CONCLUSION: This review highlights 5 cases of bacteremia in children. Two were associated with vaccine preventable infections. Three were caused by encapsulated bacteria associated with hyposplenism. This raises the question of the role of sirolimus in vaccination response and whether patients on sirolimus would benefit from adopting targeted vaccination and antibiotic prophylaxis. Larger studies are required to inform infection precaution guidelines for this patient group.

308 - Education videos for the prevention and management of skin toxicities of targeted therapies
Rebecca Levy (Hospital for Sick Children); Irene Lara-Corrales (Hospital for Sick Children)

PURPOSE: The mitogen-activated protein kinase (MAPK) pathway, also known as the RAS/ RAF/ MEK/ ERK signal cascade, is one of the main intracellular signaling pathway that regulate normal cellular proliferation. This pathway is a new target for the management of selected vascular anomalies and thus MEK inhibitors (MEKi) have been used by vascular anomalist as new treatment options for some patients. Most patients started on a MEKi develop skin toxicities that might lead to treatment modification or discontinuation that could impact patients care. Skin toxicities include skin xerosis, dermatitis, angular cheilitis, paronychia, and acneiform rash among others. (1-3) Acneiform eruption (67%) and paronychia (51%) are among the most common side effects encountered in children treated with MEKi. (4). The skin toxicities secondary to MEKi may significantly impact quality of life with significant physical and emotional discomfort that may lower adherence to therapy (5,6).

Education and prevention strategies are key to minimize and, in some cases, prevent skin toxicities of targeted therapies. As treating physicians, we need to learn to recognize, grade and manage these toxicities.

METHODS: We have created education videos on the following topics:

1. Preventing Skin Side Effects in Children Taking Targeted Therapies

   a. Gentle Skin Care for Children Taking Targeted Therapies

   b. Nail Care for Children Taking Targeted Therapies

   c. Sun Protection Tips for Children Taking Targeted Therapies

2. Assessment and Management of Skin Toxicities in Children Taking Targeted Therapies

   a. Estimating Body Surface Area for the Assessment of Skin Toxicities in Children Taking Targeted Therapies

   b. Skin Side Effects in Children Taking MEK Inhibitors

   c. Skin Side Effects in Children Taking BRAF Inhibitors

RESULTS: We would like to present these as an interactive poster at ISSVA to make these resources available to the ISSVA community.

CONCLUSION: Education resources are needed to minimize the impact of skin toxicities of targeted therapies

309 - First Use of Selumetinib in the Treatment of High-Risk Vascular Anomalies with RASopathies—A Retrospective Case Series with Emphasis on Safety and Efficacy
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PURPOSE: Selumetinib is a MEK inhibitor approved for the treatment of Neurofibromatosis Type 1 (NF1) secondary to its effectiveness and tolerability. We report the efficacy and safety of selumetinib in a population of vascular anomaly patients with RASopathies.

METHODS: Seven patients are included for retrospective analysis. Safety evaluation is based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Efficacy evaluation is based on individual response criteria, including clinical response and radiologic imaging.

RESULTS: Clinical response was reported in 6 of 7 cases (85.71%). Case 3 discontinued selumetinib within a week due to severe adverse events and an overall clinical response could not be determined. Case 2 discontinued after 2 months secondary to prolonged grade 2 abdominal pain. Dermatologic toxicity was seen in 85.71% patients. 5 patients remain on treatment.

Table 1: Clinical characteristics and toxicities of patients treated with selumetinib

CONCLUSION: Selumetinib appears to be effective and safe for patients with RASopathies. Further investigation is necessary to validate these early findings

312 - Outcomes of live virus vaccination in patients with vascular anomalies being treated with sirolimus

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PURPOSE: Describe outcomes of administration of live virus vaccines (MMR, Varicella) in patients with vascular anomalies receiving sirolimus.

METHODS: In this retrospective study, patients with vascular anomalies < 4 years old, treated with sirolimus and incompletely vaccinated were included. An immunologic evaluation on sirolimus was performed, including immunoglobulins, lymphocyte subpopulations, and vaccine titers to diphtheria and tetanus. Patients were grouped by normal, abnormal, or no evaluation. Patients were either recommended to proceed with vaccination or referred to immunology for further evaluation. Outcomes of vaccination were reviewed. Results are presented descriptively.

RESULTS: Forty-six patients were included and 29/46 (63%) had an immune evaluation. The evaluation was normal in 16/29 (55%) and vaccination was recommended; 8/16 (50%) were vaccinated while on sirolimus without complication. 13/29 (45%) had abnormal evaluations: 6/13 (46%) were recommended to vaccinate and 4 proceeded; 1 of these patients developed vaccine-strain varicella infection with 10 days of fever and rash that resolved without acyclovir, so MMR was not given. 5/13 (38%) were advised not to vaccinate of which 1 proceeded without complication, and 2/13 (15%) are still undergoing evaluation and have not been vaccinated. 17/46 (37%) had no evaluation: 7/17 (41%) were vaccinated while on sirolimus without complications. All together 23/46 patients (50%) were vaccinated (20 while on sirolimus, 3 held sirolimus prior to vaccination) with 1/23 (4%) experiencing a complication.

CONCLUSION: The risk of vaccine-strain varicella infection appears low in patients with vascular malformations receiving sirolimus and is similar to rates observed in solid-organ transplant patients receiving sirolimus or other immunosuppressive medications. An immune evaluation on sirolimus can be helpful in identifying potentially high-risk patients. It is our practice to proceed with varicella vaccination first due to the availability of treatment if an adverse reaction occurs. The risk of community infection must be weighed against the potential risk of a vaccine reaction.

314 - Targeted therapy with sirolimus in a PTEN-associated high-flow vascular malformation

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PURPOSE: mTOR inhibitors proved to be beneficial in selected cases of vascular malformations, particularly in the case of low flow. However, reports on their efficacy in high-flow malformations are scarce and results controversial.

METHODS: We present a patient with a pathogenic PTEN mutation and a vascular malformation with an arteriovenous (AVM) component, who benefited from treatment with sirolimus.

RESULTS: A 3-year-old female patient presented with a diffuse and progressive vascular malformation on her right leg, with disabling pain, progressive knee valgus and significant walking impairment. Initial magnetic resonance imaging showed a diffuse deep suprafascial malformation on the right leg measuring 18cm on its largest axis. Due to clinical worsening, the case was discussed with an international reference centre and was classified as a diffuse vascular malformation with both low and high flow components, the latter behaving in a diffuse pattern with multiple nidus and sirolimus was suggested. Long term therapy with sirolimus (0.8 mg/m2 twice daily) was instituted when the patient was 9 years old, resulting in complete remission of symptoms and significative remission of deformity. No side effects were reported. Genetic testing revealed a pathogenic PTEN variant (c789_790del).

At 35 months of follow-up, the patient presented with pain recurrence and non-disabling walking impairment for long distances. Treatment with sirolimus was maintained and the patient kept under close vigilance as the complaints now were only sporadic non-disabling pain.

CONCLUSION: mTOR inhibitors were safe and provided effective palliation in this patient as intervention was not deemed possible. In this case, there was no reduction in size of the malformation. Despite a prolonged initial period of great improvement, symptoms recurred, although not as severe as at presentation. However, due to the extension of the lesion, adjunctive direct and/or interventional measures will likely have to be instituted.

319 - Periocular Arteriovenous Malformations:Clinical Classifications and Treatment Strategies

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PURPOSE: This study proposed a new clinical classification and treatment strategies for periocular arteriovenous malformation (AVM).

METHODS: A retrospective analysis of the cases of periocular AVM from 1st Jan 2015 to 1st Jan 2019 was included in this study. According to the DSA angiography results, three classifications were divided: type 1 is unilateral ophthalmic artery blood supply the lesion and the central retinal artery is not involved; type 2 is bilateral ophthalmic artery blood supply and the central retinal artery is not involved; type 3 is unilateral or bilateral ophthalmic artery blood supply and the central retinal artery is involved.

Type 3 can be divided into 3a and 3b subtypes according to the visual acuity of the affected eye. Type 3a is the presence of vision; type 3b is the loss of vision. Type 1 patients were treated with super-selective onyx embolisation of the feeding arteries of AVMs through the ocular arteries and then treated with ethanol embolotherapy; Type 2 patients were treated with bilateral super-selection onyx embolisation of the feeding arteries of AVMs through the ocular arteries and then were treated with ethanol embolotherapy; type 3a patients were treated with ethanol embolotherapy combined with surgery; type 3b patients were treated with enucleation and orbital reconstruction.

RESULTS: A total of 32 patients were enrolled. There were 6 cases of type 1, 8 cases of type 2, 13 cases of type 3a, and 5 cases of type 3b. 5 cases were cured, 1 case improved in type 1 patients; 3 cases were cured, 5 case improved in type 2 patients; 3 cases were cured, 10 case improved in type 3a patients; 2 cases were cured, 3 case improved in type 3b patients

CONCLUSION: The classification of periocular arteriovenous malformations has guiding significance for the selection of treatment strategies.

323 - Stereotactic body radiotherapy for the treatment of extracerebral pelvic arterio-venous malformation

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PURPOSE: Stereotactic body radiotherapy (SBRT) is a recognized treatment of cerebral and spinal arterio-venous malformation (AVM). The experience with SBRT for extracranial AVM is low, restricted to a few reports and only one previous case report for pelvic AVM. We report a second case of a pelvic AVM treated with SBRT.

METHODS: We describe the case of a 61-year-old man suffering from a 12-month disabling left sciatic pain and weakness, compatible with a L5-S1 radiculopathy. The ENMG confirmed a L5-S1 radiculopathy with acute denervation of the calf muscles. Imaging (MRI) diagnosed a pelvic AVM of 36x55x55mm adjacent to the sciatic nerve and with main arterial afferences from the internal iliac artery.

RESULTS: Following multidisciplinary discussion, surgery was ruled out because of major intra-operative bleeding risks due to the deep pelvic localization. Embolization was not considered due to its perceived unpredictable effect on the sciatic nerve. We opted for a treatment with a pelvic SBRT. Three-dimensional treatment planning was performed with a planning treatment volume which covered the radiographically identifiable lesions plus a 3mm margin. We delivered 24Gy in 3 fractions of 8Gy, with the CyberKnife, using 6MV photons. The patient did not have acute toxicity. At 4 months, the echo-doppler estimated AVM flow was reduced from 700-900ml/min to 460ml/min. At 6 months, a repeat arteriography showed a clear reduction of the AVM size and its nidus, and an occluded internal iliac vein. We observed a marked clinical improvement: the proximal left sciatic pain disappeared, with a persisting but decreased left foot neuropathic pain and a partial motor improvement. There was no SBRT side-effect. We expect vascular effects from SBRT up to 2 years after the initial treatment, with a planned repeat arteriography then.

CONCLUSION: SBRT may be an option for extracranial AVM with refractory or non-possible standard interventional therapies.

325 - A nationwide population-based cohort study: increased risk of cardiovascular disease in extracranial vascular malformations

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PURPOSE: Extracranial vascular malformations affect vessel inflammation, clotting, and ischemia. However, the relationship between extracranial vascular malformations and myocardial infarction (MI) or stroke has not been fully elucidated. Limited studies have investigated the association between extracranial vascular malformations and cardiovascular diseases.

METHODS: A total of 48,701 patients with extracranial vascular malformations and a control cohort with 487,010 age- and sex-matched participants from the [--------] National Health Insurance database were included. The incidence and risk of MI, ischemic stroke (IS), and hemorrhagic stroke (HS) between participants with extracranial vascular malformations and the control cohort was then compared.

RESULTS: After adjusting for other cardiovascular disease risk factors, the adjusted hazard ratios (aHRs) for venous malformations (VMs), capillary malformations (CMs), arteriovenous malformations (AVMs), and lymphatic malformations (LMs) in patients with acute MI were 1.25 [confidence interval (CI) 1.04–1.50], 1.41 [CI 1.24–1.61], 1.68 [CI 1.18–2.37], and 1.40 [CI 1.31–1.48], respectively. For IS, the aHRs were 1.55 [CI 1.35–1.77], 1.92 [CI 1.74–2.11], 1.13 [CI 0.78–1.64], and 1.51 [CI 1.44–1.58], respectively. For HS, the aHRs were 1.51 [CI 1.12–2.05], 5.63 [CI 4.97–6.38], 2.93 [CI 1.82–4.72], and 1.34 [CI 1.20–1.50], respectively.

CONCLUSION: Independent of cardiovascular risk factors, extracranial vascular malformations were associated with an increased risk of MI, IS, and HS. For patients with CMs and AVMs, intracerebral hemorrhage risk was particularly high, accounting for 563% and 293%, respectively. Therefore, even in patients with extracranial CMs or AVMs, performing diagnostic evaluations for cerebral AVMs and employing measures to prevent intracerebral hemorrhage are very crucial.

329 - Initiation of APP Hemangioma New Patient Visit Type in Pediatric Dermatology Clinic

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PURPOSE: Infantile Hemangioma's (IH) are benign vascular tumors that occur in approximately 5% of infants. IH are vascular birthmarks that are made up of abnormal blood vessels and can occur anywhere on the body. IH occurring in cosmetically sensitive areas or those at risk for functional impairment warrant early treatment with an oral beta blocker.

Accessing a provider with expertise in hemangiomas and obtaining an appointment within a short time frame remains to be a challenge. Long wait times for patients with rapidly proliferating hemangiomas can lead to disfigurement and functional impairment. Addition of hemangioma NPV was created to improve access to care and improve patient outcomes.

METHODS: Pediatric Dermatology Clinic created a Hemangioma new patient visit type (Hemangioma NPV) when a 2nd advanced practice provider was added to the team. This new visit type allowed the call team to offer appointments within 1-2 weeks to anyone indicating a diagnosis of hemangioma or rapidly growing birthmark. Prior to adding Hemangioma NPV type patients were placed in a physician NPV slot. Timing of which patients were able to be evaluated as a NPV was variable due to potential wait list unless visit was indicated as urgent.

RESULTS: Retrospective analysis of patients evaluated over 18 months 7/1/20-1/1/22 (Pre) and 1/1/22-7/1/23 (Post) creation of new visit type. 327 patients were evaluated by physicians (pre) with diagnosis

of hemangioma compared to 604 patients with addition of Hemangioma NPV App (post) (p<.0001). Creation of this new visit type lead to an increase number of patients started on an oral beta blocker at a younger age.

CONCLUSION: Creation of a specific visit type specified APP NPV hemangioma increased access to care and led to earlier treatment of IH presumable improving patient outcomes.

331 - Assessment of Percutaneous Vascular Laser Treatment in Venous Malformations: A Ten-Year Retrospective Analysis

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PURPOSE: Introduction - Venous malformations are vascular anomalies resulting from errors in embryonic development, characterized by the presence of anomalous blood vessels that are dilated, twisted, or enlarged. These malformations can affect various areas of the body, including the skin, subcutaneous tissues, joints, and internal organs. They can cause a range of symptoms, from aesthetic issues to medical complications, often requiring specialized evaluation and treatment such as percutaneous vascular laser, intravascular laser, surgery, or sclerotherapy, among others.

METHODS: Materials and Methods - We present a retrospective series of N cases treated from 2013 to 2023 of patients with venous malformations exclusively treated with vascular laser (Nd-YaG 1064 nm) or sequential vascular laser (PDL 585nm + Nd-YaG 1064nm), both used percutaneously or in combination with subsequent surgery. The results are assessed by blinded observers and a retrospective patient satisfaction survey.

RESULTS: Discussion - Percutaneous vascular laser treatment is a highly accessible, effective, and safe option for addressing localized venous malformations, especially those affecting the skin and oral mucosa. Another significant advantage of the treatment is its non-invasiveness, often performed on an outpatient basis.

It's important to note that vascular laser treatment typically doesn't provide immediate results, and multiple sessions are often needed to achieve satisfactory results. Furthermore, if redundant fibrovascular tissue remains after the laser, it can be removed by surgery in a more comfortable and safe way for the surgeon. The side effects of laser treatment are temporary, mild and transient. Through this retrospective review, we aim to present and evaluate the results obtained with patients treated at our center using this technique.

332 - Experience in the treatment of warty venous malformations (VVM) using a combined method (laser photothermolysis on a device with a wavelength of 595 nm and infiltration with the drug Bleomycin)

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PURPOSE: Prove the safety and high efficiency of this method. Verrucous venous malformations (VVM) are a group of rather rare hyperkeratotic vascular abnormalities that affect the epidermis, dermis and even subcutaneous fat and therefore cause frequent relapses after any type of treatment. Patients with this disease often suffer for life. The question of treatment currently remains current.

METHODS: In our department from October 2020 to January 2022. 23 children with VVM were treated, 13 girls, 10 boys. Ages from 1 to 17 years.

In 8 cases there was extensive damage to the entire upper limb, in 6 cases there was extensive damage to the lower leg, in 2 children there was damage to the anterior abdominal wall, in 3 cases to the thigh, in 1 case there was damage to the upper and lower limbs, and in one case each there was damage to the frontal region, hand and foot.

Laser correction was carried out using a device with a wavelength of 595 nm using liquid dyes, infiltration was carried out with the drug Bleomycin 15 mg.

The procedure was performed in 9 children over 10 years of age without anesthesia, and in the remaining 14 children under inhalation anesthesia (Sevoran). The procedure time is on average 3-5 minutes. On average, 4 procedures were performed. The interval between procedures is 3 months.

RESULTS: In all cases, there was significant improvement due to a reduction in the volume of the lesion, which was assessed by photographs; in 4 cases of non-extensive lesions, the pathological tissue completely disappeared. No complications were noted.

CONCLUSION: The method of laser photothermolysis and infiltration with Bleomycin showed high efficiency of treatment, a low recovery period after treatment and a reduction in hospital stay. Can be considered as an alternative to surgical treatment. The method requires further research.

333 - A NOVEL CONGENITAL CERVICAL VASCULAR MALFORMATION IN A ROTHMUND THOMPSON PHENOTYPE PATIENT WITH A RARE GENE CRIPT MUTATION

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PURPOSE: To present a case of girl with a gene CRIPT pathogenic bialelic variant and a congenital vascular anomaly as a novel manifestationn in the Rothmund-Thompson phenotype.

Gene CRIPT (Cysteine-Rich PDZ Domain-Binding Protein) encodes a protein (PDZ) that has been mainly related to serve as a bridge between the cytoskeleton and the synaptic proteines. Only 6 cases with alterations in this gene and Rothmund-Thompson phenotype have been described until now.

METHODS: A 7-year-old girl, daughter of healthy cosanguineous parents of arabic origin. The common manifestations were prenatal growth delay, moderate developmental delay, microcephaly, particular facial features (very thin and scarce hair, low eyelids, short eyelashes, facial hyperqueratosis, wide forehead, short nose with a prominent tip, long and plain filtrum) and diffuse spotted pale skin. She also had bilateral cutaneous syndactyly between 4th and 5th toes and a complex congenital cervical vascular malformation consisting on superficial cervical aneurysmatic veins that infiltrate the right submandibular glands, a focal aneurysmatic dilatation of the right subclavian vein. Severe atrophy of both parotid glands, predominantly the right one. Severe dilatation and tortuosity of the left vertebral and basilar arteries.

RESULTS: The molecular study(TruSight One Expanded (Illumina) included 6699 genes): the homocygotic variant was identified (c.132delA; p.Ala45GlnfsTer86) in gene CRIPT (NM_014171.6). From the functional point of view, she had a good quality of life and good learning ability. This novel vascular anomaly findings did not generate any symptoms, so the treatment considered was conservative.

CONCLUSION: We describe a new case with a bialelic variant in gene CRIPT with typical clinical features associated to a novel vascular anomaly never described in this genetic disorder. This genetic variant is

related to ClinVar database 4 other cases with a similar common phenotype, but no vascular anomaly registered.

335 - Effective sirolimus use in prenatal and postnatal management of large complicated lympho-venous malformation – a case report.

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PURPOSE: To evaluate the effectiveness and safety of prenatal and postnatal use of sirolimus in a patient with extensive complicated lympho-venous malformation (CLVM).

METHODS: Here we report a third worldwide and first in Poland successful management of a large fetal CLVM with sirolimus taken orally by the mother during pregnancy and then by the newborn postnatally. The CLVM was detected prenatally by ultrasonography and confirmed by magnetic resonance (MRI) to involve the abdomen, pelvis, both buttocks and left lower limb. Bleeding to the CLVM cysts caused the fetus' hemodynamic compromise, manifested by increased peak systolic flow (59-77cm/s, 1.3-1.7 multiples of median) in the middle cerebral artery (MCA), indicating moderate fetal anemia. This prompted the decision to treat the fetus with sirolimus given to the mother from the 32nd week of pregnancy until the delivery in the 35th gestation week. The starting dose of oral sirolimus was 2 mg/day and resulted in through serum level of 3,8 ng/ml, so the dose was increased to 4mg/day. The serum level of sirolimus in the mother at delivery was 6,4 ng/ml, in the umbilical cord blood 3,8 ng/ml and in the newborn 4,2 ng/ml.

RESULTS: MCA peak systolic flow significantly decreased within 2 days of sirolimus treatment, suggesting reduced bleeding to the CLVM. Since the delivery, sirolimus treatment has been continued in the child, with significant reduction in the size of the malformation within the abdomen, pelvis and the left leg, which was confirmed by ultrasonography and MRI. No adverse events occurred in the mother and the fetus during the prenatal treatment period and four months of subsequent postnatal treatment.

CONCLUSION: Administration of sirolimus during pregnancy with maternal serum drug levels monitoring seems to be an efficient and safe treatment option which should be considered in high-risk fetal CLVMs."

336 - Disparities in the Molecular Diagnosis of Vascular Malformations in Clinical Practice: A Comparative Analysis of Specimen Types and Depth of Coverage

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PURPOSE: Although guidelines for genetic testing in vascular malformations are well-established, uniform implementation in the clinical setting is hindered by practical challenges including logistical,

insurance, and technical limitations. This study aims to compare the molecular diagnostic yield of genetic testing in vascular malformations between different specimen types and depth of coverage (DOC) to provide patients with realistic expectations for diagnosis.

METHODS: A retrospective chart review of patients who had an exome or panel on a biopsy for vascular malformations and/or somatic overgrowth was performed. Diagnostic yield was calculated based on specimen type (core biopsy of affected tissue or skin biopsy) and average DOC of the test (deep being ≥1000x).

RESULTS: 58 genetic tests were reviewed for 47 patients with vascular malformation(s) and/or somatic overgrowth from 1/2017 to 11/2023. Across all specimen types, deep DOC testing resulted in a significantly higher diagnostic yield, 75%, than low DOC testing, 21% (p=0.0017). Preliminary data (not statistically significant) on this small sample size show the diagnostic yield of deep DOC testing on core biopsies was 82%, compared to a 57% yield of deep DOC testing on skin biopsies. The lowest diagnostic yield was 16% from low DOC testing on skin biopsies with low DOC testing on core biopsies higher at 33%.

CONCLUSION: In the clinical setting of a vascular anomalies center with limited access to specialty genetic testing, patients whose only option is low DOC testing are significantly less likely to receive a molecular diagnosis. Preliminary results show yield is even lower among those receiving skin versus core biopsies. Given that many patients are unable to access deeper DOC testing and/or core biopsy due to practical barriers, this suggests a disparity in the molecular diagnosis of certain patients with vascular malformations. Expansion of this study will analyze this potential disparity as it relates to access to targeted medications.

338 - Integrated cfDNA methylation and peripheral blood mononuclear cell (PBMC) RNA sequencing identify genes linked to dysregulated immune responses in patients with venous malformation

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PURPOSE: Venous malformations (VMs) are congenital vascular anomalies affecting 1% of the population. These exhibit somatic variants in genes governing vascular cell processes including proliferation, differentiation and apoptosis. Rapid growth of VMs may be mediated by hormonal changes, trauma or infection. Our aims are to further understand disease mechanism and to identify potential biomarker in peripheral blood using whole genome bisulfite sequencing (WGBS) and RNA sequencing (RNAseq). Cell-free DNA cfDNA has recently emerged as a noninvasive diagnostic tool, prompting our hypothesis on its potential in studying abnormal DNA methylation patterns as disease drivers.

METHODS: RNAseq was completed from PBMCs of patients with VMs, lymphatic malformations (LMs) (n=5) and healthy controls. WGBS was conducted on plasma cfDNA from peripheral blood of patients with VM (n=7) and age/sex-matched healthy controls.

RESULTS: RNAseq on PBMCs revealed upregulated pathways in VMs related to leukocyte-mediated cytotoxicity and cell killing, linked with T cell regulation, and down regulated response to chemokines suggesting differences in cell-mediated immune responses. LM patients exhibited upregulation in B-cell receptor signaling and downregulation of leukocyte and mononuclear cell migration, aligning with humoral immune responses. WGBS on plasma cfDNA in patients with VM's revealed numerous differentially methylated regions related to cell adhesion, migration, signal transduction, and small GTPase-mediated signaling. These pathways are relevant to angiogenesis. Deconvolution analysis indicated altered immune responses in VMs as evidenced by increased macrophages, monocytes,

dendritic, and endothelial cells. We identified 29 differentially expressed genes which overlapped with DMR-associated genes in VMs. These included GNAL, IL1RL1, FASLG, and DOK2 which relate to signaling transduction, endothelial cell apoptosis, immune and inflammatory responses.

CONCLUSION: Our results validate involvement of cell signaling and transduction pathways in VM's. It supports the role of pathways associated with cell-mediated immune response. Methylation analysis of cfDNA could be a promising clinical application to enable biomarker and therapeutic target discovery.

341 - Characterization of Disease Burden for Patients with Microcystic Lymphatic Malformations
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PURPOSE: Microcystic LM is a serious, rare, and chronic disease of the lymphatic system characterized by lymphorrhea, acute cellulitis, and significant patient morbidity. Treatment options are limited with no FDA approved therapies. Understanding the patient disease burden, including signs and symptoms that are most relevant to patients is critical to support future clinical trials.

METHODS: Patients with microcystic LM were invited to participate in qualitative interviews to collect patient-specific information on disease burden. Transcripts were analyzed by qualitative coders using emerging codes.

RESULTS: Qualitative interviews revealed that for all patients (n=5) the microcystic LM had a significant impact on quality of life. All patients reported at least one surgery and most patients have had multiple surgeries with the microcystic LM returning for all patients following surgical intervention. Patients reported that the microcystic LM limited daily activities and had a negative impact on mental health, including increased anxiety and depression. The symptoms that had the most impact on quality-of-life include leaking, bleeding, and infections. Reported long-term challenges include increased mental load, doctors not understanding disease burden, reduced mobility, and financial hardships.

CONCLUSION: Microcystic LM has a significantly negative impact on quality of life. All patients reported surgeries to treat their microcystic LM with recurrence of disease in all patients. The most common symptoms reported were leaking, bleeding, and infections. Using qualitative interviews represents a novel approach to determining disease burden in rare diseases for which there are no approved therapies.

345 - Orbital Lymphatic Malformations are Associated with Intracranial Vascular Anomalies
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PURPOSE: Orbital lymphatic malformations (OLMs) are a rare type of lymphatic malformation involving the bony orbit. OLMs present specific treatment challenges and cause significant morbidity. The contribution of pathologic genetic variants and potential association of intracranial vascular anomalies with OLMs has yet to be described. We hypothesized that (1) OLMs are indicators of underlying cerebrofacial vascular metameric syndrome (CVMS) and are associated with intracranial vascular anomalies, and (2) OLMs are caused by PIK3CA variants and are candidates for targeted medical therapy.

METHODS: Retrospective case review was performed for patients with OLMs treated at a single institution from 2000-2021. Patients were identified from an Institutional Review Board approved prospectively collected quality improvement vascular anomalies database. Diagnosis of CVMS was made via magnetic resonance imaging (MRI) based on established criteria of segmental distribution of ocular, facial, and cerebral vascular malformations. Clinical outcomes including orbital and intracranial symptoms, surgical/medical interventions, and morbidity data were analyzed.

RESULTS: Seven of 412 patients with head and neck lymphatic malformations had OLM. Common symptoms included eye swelling (n=7), ptosis (n=3), and headache (n=5). Intracranial morbidity included intraventricular hemorrhage (n=2), severe headache (n=1), and seizure (n=1). All patients were diagnosed with CVMS on MRI. All patients underwent surgical resection including external excision (n=4), endoscopic orbital decompression (n=3), and orbital exenteration (n=1). All patients underwent biopsy and 100% were identified as candidates for targeted medical therapy after tissue-based DNA sequencing revealed ""hotspot"" PIK3CA variants p.E542K (n=4) and p.H1047R (n=3). Five patients were started on alpelisib, resulting in resolution of ocular symptoms and headache at six months of treatment.

CONCLUSION: In this study, OLMs were associated with intracranial vascular anomalies, meeting radiographic criteria for CVMS. All patients underwent tissue-based genetic diagnosis, revealing ""hotspot"" PIK3CA variants. Screening for intracranial vascular anomalies and targeted medical therapy with PI3K/AKT/mTOR pathway inhibitors should be considered in OLM management.

347 - Dissecting the Genetic Underpinnings of Kaposiform Hemangioendothelioma (KHE)

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PURPOSE: Determine if the application of spatial transcriptome profiling can reveal the molecular etiology of patients with Kaposiform Hemangioendothelioma (KHE), a rare vascular neoplasm involving both abnormal angiogenesis and lymphangiogenesis that often develop life-threatening complications.

METHODS: We performed spatial transcriptomics in two KHE cases to reveal new insights into disease etiology. While single-cell profiling of dissociated cells in suspension was relatively uninformative, the GeoMx platform from NanoString was successful in analysis of FFPE samples from KHE lesions. FFPE samples from 2 participants underwent region of interest (ROI) selection guided by the following markers: CD31 (PECAM1), podoplanin (PDPN) and nuclear staining. Segmentation of ROIs allowed comparison of CD31+/PDPN+ (double positive) neoplastic regions to CD31+ regions marking normal vasculature. A total of 26 ROIs were profiled. More than 16,000 genes were successfully detected across all ROIs.

RESULTS: Several markers were differentially expressed in the KHE neoplastic lesions compared to controls, with most prominent expression differences involving endothelial cells and smooth muscle cells/myofibroblasts. Of those, PROX1, FLT4, MGLL and MAP4K4 were enriched in the KHE neoplastic cells. KDR, PDPN, and VEGFC are also highly expressed. FLT4 encodes for VEGFR3, a ""master"" receptor for lymphangiogenesis, that can be directly targeted by several approved tyrosine kinase inhibitors. PROX1 is considered the ""master switch"" for lymphatic endothelial cell specification and sprouting. MGLL is a serine hydrolase that is also implicated as either an oncogene or a tumor suppressor depending on the cancer type. MAP4K4 specifically activates the JNK pathway. Considerable heterogeneity in the expression signatures was observed between the two KHE patients, consistent with the known heterogeneity of KHE, illustrating the importance of profiling each subject separately.

CONCLUSION: Spatial transcriptome profiling in KHE cases reveals new disease etiology of KHE with several biomarkers demonstrating marked upregulation in the neoplastic endothelial cells, presenting potential new therapeutic targets for this life-threatening disease.

349 - Spatial Transcriptomic Analysis of Lymphatic Endothelial Cells in Macrocystic Lymphatic Malformations

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PURPOSE: Lymphatic malformations (LMs) are caused by defective morphogenesis of lymphatic vessels and surrounding tissue overgrowth. The majority are caused by somatic activating PIK3CA mutations that are present in a small fraction (<10%) of cells within the lesion. Intralesional paracrine signals from lymphatic endothelial cells (LECs) must play a primary role, but few studies have examined transcriptional profiles of LECs within their native architectures in an unbiased manner.

METHODS: Spatial analysis of RNA expression was obtained using the NanoString GeoMx Whole Transcriptome Atlas (18,269 genes) on four different macrocystic LM tissue sections from four individuals with hotspot PIK3CA mutations. Expression profiles were obtained from 190 independent regions of interest (ROIs), including LECs from the same cyst, from different cysts, and from non-endothelial stromal cells at varying distances from LECs.

RESULTS: An average of 85 cells were captured per ROI, reflecting a total of ~16,000 cells. A variety of cell types were identified including LECs, arterial endothelial cells, venous endothelial cells, adipocytes, and fibroblasts. LECs show upregulation of genes involved in cell-cell and cell-matrix signaling, fat metabolism, inflammation, and hypoxia, as well as targets in the PI3K/AKT and RAS/MAPK pathways.

CONCLUSION: We demonstrate the utility NanoString-based spatial transcriptomics to characterize mosaicism in LM microarchitecture. LEC expression programs demonstrate evidence of PI3K-AKT pathway hyperactivation and upregulation of inflammatory pathways, consistent with prior publications. By applying this approach to microcystic LMs and LMs caused by mutations in genes other than PIK3CA, we will improve our understanding of LM cell biology and identify intralesional paracrine signals that can be targeted for novel therapies.

350 - Identification of Activating KRAS Variant in Verrucous Venous Malformation

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PURPOSE: RAS/MAPK/ERK signaling pathway, known for cell proliferation, differentiation, and survival, is one of the primary molecular mechanisms for vascular anomalies. Verrucous venous malformations (VVMs) are a subtype of simple venous malformations that are commonly associated with somatic pathogenic variants in MAP3K3. Despite this distinctive clinical presentation, VVMs are frequently misdiagnosed at the time of initial evaluation as a lymphatic malformation. KRAS [MIM: 190070] is a proto-oncogene also a part of the RAS/MAPK/ERK signaling pathway. Activating somatic variants in KRAS have been observed in arteriovenous malformations, but not standardly in VVMs. There has been an expansion in the phenotype of mosaic RASopathies resulting from activating somatic KRAS pathogenic variants as well as treatment strategies.

METHODS: Our patient is an 11-year-old male who presented after nine stable years with a two-week history of new onset swelling, pain, and bleeding from a vascular malformation of his left medial thigh. An MRI of the femur demonstrated a 9.1 x 9.3 x 3.7 cm lesion with increased STIR and PD fat signals within the subcutaneous tissue supportive of a VVM diagnosis. The patient underwent resection of the lesion with local flap reconstruction.

RESULTS: At his 4-month postoperative visit, the incision was well healed and he denied pain, bleeding, or swelling. The resected tissue was sent to pathology, where an overgrowth panel with next-generation sequencing revealed a pathogenic missense variant (c.38G>A, p.Gly13Asp) in KRAS at variant allele fraction of 6.5%.

CONCLUSION: The literature identifies numerous case reports of patients with overgrowth phenotypes harboring somatic variants in the same or adjacent amino acid in KRAS as our case. There is extensive and rapid research regarding understanding the underlying genetic etiology of vascular malformations, which in turn, opens the opportunity for targeted gene therapy through repurposing of cancer drugs at different points of the RAS/MAPK/ERK and PI3K/AKT/mTOR pathway.

351 - Embolization for recanalized pulmonary arteriovenous malformation: feasibility and safety
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PURPOSE: The purpose of this study is to evaluate the safety and feasibility of re-embolization for recurrent pulmonary arteriovenous malformation.

METHODS: Eleven patients (7 male, 4 female, age 48-60 years) with recanalized pAVM are included in this study. A total of 15 lesions of recurrent pAVM were re-embolized between 2017 and 2023. Recurrent forms, embolization methods, complications, and recanalization after re-embolization were evaluated.

RESULTS: Of the 15 lesions, feeder embolization had been performed in 12, sac and feeder in 3. Recanalized through previous placed embolic materials were observed in 13 lesions. In 2 lesions, reperfusion via adjacent pulmonary artery was observed in addition to recanalization through previous placed embolic materials. In 10 lesions, additional coil embolization between sac distal to the existing coil and feeding artery was perfomed. In 5 lesions, only feeding artery embolization was performed. In 2 lesions of reperfusion via adjacent pulmonary artery, adjacent pulmonary arteries were also embolized.

No complication was observed during procedure. In follow-up study, one recanalization was observed.

CONCLUSION: Re-embolization of recurrent pulmonary arteriovenous malformations after embolization can be safely performed.

353 - Novel Anesthetic Protocol for PDL-treated Capillary Malformations

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PURPOSE: Pulsed-dye laser (PDL) therapy is the treatment of choice for capillary malformations (CM). Patients with extensive CMs, or ones located on the face, frequently require anesthesia. The vasodilatory effects of sevoflurane can reduce the laser's ability to capture the hemoglobin chromophore, necessitating the use of a non-hypotensive anesthesia. The following study aimed to compare the efficacy of our novel anesthetic protocol with standard inhalation anesthesia during PDL therapy.

METHODS: This was a prospective single center study of pediatric patients with CMs who were treated with PDL therapy. Patients received the traditional anesthetic technique of inhaled sevoflurane gas (SEVO) or our non-hypotensive protocol of inhaled nitrous oxide for peripheral intravenous catheter placement, followed by total intravenous anesthesia (TIVA) of ketamine, dexmedetomidine, and fentanyl boluses. Heart rate, blood pressure, and the erythema of the CM was measured prior to induction, post-induction, and at the end of the case. A univariate analysis was performed.

RESULTS: Nine patients underwent a total of 19 rounds of laser ablation. The median age at the time of treatment was 2 years and 63.2% of the patients were female. The 9 patients (47.4%) in the SEVO group had a mean reduction in their HR of 9.67bpm, DBP of 15.13mmHg, and the erythema of their CM by 11.74, following induction. Whereas the 10 patients (52.6%) in the TIVA group had a mean reduction in their HR of 21.67bpm, DBP of 0.11mmHg, and erythema of their CM by 5.56 (Table 1).

CONCLUSION: Following induction with SEVO, patients experienced a significant reduction in their DBP and the erythema of their CM. This difference was lessened in the TIVA group. Not all patients undergoing PDL therapy for CMs need anesthesia, but the ones that do, should use a normotensive protocol to strengthen treatment efficacy.

354 - The Surgeon is Not Obsolete: Management of Vascular Anomalies of the Head and Neck

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PURPOSE: Vascular anomalies (VAs) of the face and scalp can cause aesthetic and clinical concerns. While the majority of treatment is laser or medically based, there are opportunities for surgical intervention. We need to understand indications for surgical resection and reconstruction for facial VAs.

METHODS: A retrospective single institution review was conducted of patients with vascular anomalies of the head and neck who were treated surgically at a large urban academic hospital from 2015-2023. Patients were identified from the billing database using current procedural terminology (CPT) codes for vascular resection and reconstruction and the records were reviewed for type and location of lesion, prior medical and operative interventions, age at intervention, indication for surgery, type of reconstruction.

RESULTS: Of the 135 patients that received surgical treatment for a VA, 52 patients (38.5%) had lesions located on the head and neck. The median age at the time of surgical intervention was 3 (1.75, 6.50)

years and 63.5% of the patients were female. Hemangiomas were the most common lesion and the cheek/chin/neck area was the most common location for all lesions, followed by perioral, then periorbital. Nearly 80% of patients had undergone previous treatment. Medical therapy was the most common prior intervention, with 92% of these patients taking oral propranolol. Thirty-one patients underwent surgical resection, 15 patients had laser ablation of their VA, and both surgical resection and laser ablation were performed during the same case for 6 patients.

CONCLUSION: VAs are relatively rare, and an understanding of the approach to the cosmetically and functionally sensitive area of the face is important, as medical management is not always successful. Creating a database, evaluating treatments and outcomes, and creating an algorithm for the facial subunits will help provide this insight and further education on treatment, clinical course, and outcomes.

355 - Rapid Response to Sirolimus in Patients with PIK3CA-Related Overgrowth Spectrum (PROS)

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PURPOSE: Advancements in genomic analysis has led to the discovery of casual genes underlying many vascular anomalies (VAs), providing the basis for targeted gene therapy. The umbrella term PROS, PIK3CA-Related Overgrowth Spectrum, unifies a group of overgrowth disorders linked by somatic pathogenic variants in PI3K, a regulator of mTOR. Given that patients with PROS have a known, or likely, gene mutation in the PI3K/AKT/mTOR pathway, this study aimed to compare their response to treatment with sirolimus, an mTOR inhibitor, to patients with non-PROS VAs.

METHODS: A retrospective single institution review was conducted of patients with VAs initiated on sirolimus therapy from 2019 to 2022. Records were reviewed for patient demographics, VA type, associated symptoms, measurements, and duration of treatment on sirolimus. A positive response to treatment was defined as patient/parent report of improvement in symptoms, quality of life, and/or reduction in size of the lesion via imaging or clinical assessment.

RESULTS: Of the 21 patients initiated on oral sirolimus, 14 (66.7%) met the criteria for a diagnosis of PROS. The median age at the start of treatment was 1 year and 52.4% of the patients were female. Swelling or overgrowth was the most commonly reported symptom by both groups, followed by bleeding in the non-PROS group and functional impairment in the PROS group. The median time to positive treatment response was 52.0 (46.5,113.0) and 35.0 (29.5,52.5) days in the non-PROS and PROS groups, respectively (p=0.06).

CONCLUSION: In this study, patients with PROS experienced a positive response to treatment with sirolimus faster than those with non-PROS VAs. While sirolimus is an established treatment modality for VAs, its effect on PROS patients is often rapid and profound. As alternative candidates become available for the treatment of VAs, studies should continue to evaluate the relationship between genetic status and time to treatment response.

356 - Translation and validation of the OVAMA questionnaire to Portuguese

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PURPOSE: The purpose is describing the process of translation and validation of the OVAMA questionnaire into Portuguese, along with the difficulties faced due to the influence of socioeconomical disparities on the questionnaire's comprehension by the patients of the Brazilian Public healthcare system.

METHODS: The translation was carried out after prior request from the authors (OVAMA consensus group), and consisted of 4 phases:

In phase 1, a translation from English to Portuguese was performed by two translators fluent in both languages (one with medical knowledge about vascular malformations and one without it). The independent versions were later compared and a consensus version was created.

In phase 2, a backward translation from English to Portuguese was carried out by a second team of two translators. After comparing the two translations and the original version available, a final version in Portuguese was produced, in consensus of the four translators.

In phase 3, the final in Portuguese was submitted for approval by a panel of experts in vascular malformations from our institution.

Finally, in phase 4, the Portuguese version of each questionnaire was applied to a heterogeneous group of 7 patients (with different malformations, in different locations, undergoing different treatments), at the Vascular Anomalies outpatient clinic of the Brazilian Public Healthcare System.

RESULTS: The OVAMA questionnaire (Outcome measures for vascular malformations) focuses on subjective evaluation of the results of treatments for vascular malformations. To date, there are no other questionnaires focused on vascular malformations.

The main difficulty faced by our team was the questionnaire's comprehension by the patients of the Brazilian public healthcare system (mainly due to socioeconomical disparities) and a few adaptations were required.

CONCLUSION: The OVAMA questionnaire can provide important information about the treatment of vascular malformations and the impact on the quality of life of patients, to provide the best aesthetic and functional result.

361 - RNA Sequencing Analysis of Head and Neck Lymphatic Malformation Tissue: An exploration of microenvironmental and immunologic factors

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PURPOSE: Biology of neoplasms has demonstrated that the microenvironment and immunologic milieu within cancer cells impacts clinical course and can provide therapeutic molecular targets. The objectives of this study are to delineate mRNA genetic expression within head and neck lymphatic malformation (LM) tissue and correlate differences based on LM clinical characteristics.

METHODS: Formalin-fixed paraffin-embedded sections of 12 head and neck LM excised from distinct patients were run through the Nanostring IO360™ panel to RNA sequence 770 genes expressed within the tissue. The nCounter™ platform was used for data analysis and comparison of gene expression between mucosal and non-mucosal LM, microcystic and macrocystic LM, and those lesions that had a previous inflammatory event (sclerotherapy, surgery and/or infection).
RESULTS: Mean patient age at the time of surgery was 4 years (range: 4 months–24 years). The tissue samples were composed of 3 neck, 6 oral cavity, 2 parotid and 1 scalp LM. Eight of 12 samples were

identified clinically and radiologically as macrocystic LM and 6/12 samples had a prior inflammatory event. There was clustering of genetic expression between the macrocystic and microcystic LM groups within categories of angiogenesis, cell proliferation, myeloid compartment and Wnt signaling. There was no significant clustering identified based on mucosal status or inflammatory event history. There was significantly increased expression of S100A8, S100A9, and IL1RN mRNA in the microcystic versus macrocystic LMs ($p<0.05$).

CONCLUSION: This study identifies differences in gene expression in LM based on clinical characteristics and sheds light on the role of the microenvironment in LM presentation. The increased presence of the S100 and IL1RN mRNA in the microcystic LM suggests increased activation of the PI3K/AKT/mTOR pathway and an increased immune response. Larger powered studies will determine if differentiating mRNA expression based on clinical characteristics can provide useful biomarkers for prognosis and treatment targets.

366 - MicroRNA-135b-5p upregulation contributes to pathophysiologic mechanism in the endothelial cells of arteriovenous malformations

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PURPOSE: Arteriovenous malformations (AVMs) are the congenital vascular anomalies with a poor prognosis. AVMs are considered intractable diseases, as there is no established approach for early diagnosis and treatment. Therefore, this study aims to provide new evidence by analyzing microRNAs (miRNAs) associated with AVM. We present fundamental evidence for early diagnosis and treatment of AVM by analyzing miRNAs in the endothelial cells of AVM.

METHODS: Endothelial cells (ECs) isolated from AVMs and normal tissues and cultured. Both ECs were used for profiling and validation of miRNAs. Comparative analysis of miRNAs expression differences between normal and AVM tissues was performed. Selected miRNAs were subsequently analyzed under hypoxia and VEGF treatment.

RESULTS: Fourteen up-regulated and seven down-regulated miRNAs were detected in profiling assay. Among them, miR-496, miR-135b-5p, miR-132-3p, miR-193a-5p and miR-193b-5p in up-regulated group and miR-137 and miR-30a-3p in down-regulated group were selected based on a literature review related to angiogenesis. miR-135b-5p, miR-193a-5p and miR-137 identified as candidate miRNAs with statistically significant differences in validation assay in ECs. Under hypoxic conditions, a comparison revealed a marked upregulation of miR-135b-5p in AVM compared to normal, correlating with increased endothelial activity. VEGF treatment demonstrated no significant increase in miR-135b-5p in normal, however, a surge in AVM. Under both hypoxia and VEGF treatment, comparison indicated a down-regulation of miR-135b-5p in AVM, although not reaching statistical significance.

CONCLUSION: Through this study, it was determined that miR-135b-5p is implicated in the pathophysiological processes of AVM and might play an important role as a potential biomarker on AVMs for application in diagnosis and treatment.

367 - Higher degree of response to VEGF in arteriovenous malformations

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PURPOSE: Arteriovenous malformations (AVMs) that result from abnormal connections between artery and vein are rare but potentially life-threatening condition. This research aimed to explore and assess the impact of vascular endothelial growth factor (VEGF) on the pathophysiological processing of AVMs. Additionally, the findings are being used to formulate an innovative strategy for treating AVMs.

METHODS: Endothelial cells (ECs) were cultured from normal and AVM tissues and treated with VEGF. Immunofluorescence imaging and tube formation assay were performed to evaluate EC proliferation and angiogenesis. Real-time PCR was used to analyze gene expression.

RESULTS: Immunoreactivity of CD31 was found in 82.00±0.52% of the AVM ECs area, which was significantly higher than normal ECs (78.23±0.84%). In the tube formation assay performed after VEGF treatment on the endothelial cells of each group, the number of junctions and total vessel length in each condition were significantly greater in AVM ECs group than in normal ECs group. In relative expression analysis of angiogenesis-related genes using real-time PCR, FSTL1, MARKS, and CSPG4 showed significantly higher expression in AVM ECs group than in normal ECs group under all conditions. Among them, the expressions of MARCKS and CSPG4 significantly were increased in AVM ECs group under VEGF treatment condition. Therefore, the angiogenic effect of VEGF in AVM ECs was increased compared to normal ECs.

CONCLUSION: Through this study, it is demonstrated that the higher degree of response to VEGF in AVM ECs than normal ECs could be an important factor for stimulating downstream angiogenesis in AVMs. These results are expected to help understand the pathophysiological processing of AVMs and provide basic knowledge for new treatment strategies.

374 - Factors Associated with Management Decision in Infantile Hemangiomas

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PURPOSE: The management of infantile hemangiomas (IH) has fundamentally changed with the use of beta-blockers. We conducted a large scale retrospective study of patients with IH which demonstrated

that a majority of patients (68%) with IH presenting at tertiary referral centers receive active therapy. This represents a departure from previous recommendations to observe a majority of patients with IH.

This is a follow-up analysis on this cohort with the goal of correlating demographic and clinical factors with the management decision in patients with IH.

METHODS: Multicenter retrospective study at 3 tertiary referral centers from 2012 to 2016. Data on management decision and type of treatment were correlated with demographic features, clinical characteristics, hemangioma severity score (HSS) and the American Academy of Pediatrics (AAP) risk stratification categories

RESULTS: A total of 1,722 patients were enrolled in the study. Details of management decision and type of therapy was available in 1,701 subjects. Treatment was pursued in 1,156 subjects (68%), while observation was recommended in 545 subjects (32%). The median age at presentation was significantly different between patients who received treatment [98 days (IQR 67,153)] and patients in the observation group [164 days (IQR 107, 280)]. Analysis correlating treatment decision (treatment vs observation) and type of treatment (topical beta-blocker vs systemic beta-blocker) with demographic features, clinical characteristics, HSS and AAP risk categories is in progress.

CONCLUSION: The use of beta-blockers as well as improved knowledge of the natural history and risk of complications of IH have altered management of IH. Age at referral to a hemangioma specialist is one critical factor in their management. This study further explored how demographic and clinical characteristics affected management with a goal to uncover knowledge gaps and provide more objective recommendations in the management of IH.

376 - Developing a Needs Assessment Tool to Establish Multidisciplinary Vascular Anomalies Clinics (VAMCs) in Low and Middle Income Countries (LMICs).
Jay Shah (Emory University)

PURPOSE: To develop a tool for the need assessment of VAMCs in LMICs.

METHODS: Vascular Anomalies (VA) are relatively common in LMICs. Management of VAs can vary regionally. Treatment options include surgery, interventional radiology, and medical management and some combinations thereof. Given the complex nature of VA management, VAMCs improve patient outcomes because they allow providers to collaborate on care and streamline the experience for the patient. We present a study where we aim to develop a tool that can be used in low resource settings to assess the need of and preparedness for the implementation of a VAMC.

RESULTS: Providers at Muhimbili National Hospital in Dar Es Salaam, Tanzania were surveyed from specialties including interventional radiology, pediatric general surgery, ENT, pediatric hematology/oncology, and OMFS. This survey, administered as semi-structured-interviews and adapted from the Consolidated Framework for Intervention Research, aimed to assess the current care of VAs in Dar as well as readiness and potential challenges for development of a VAMC. Several themes emerged: (1) surgical management was often more common than medical management; (2) the current referral system between VA care disciplines at MNH could be inconvenient for patients/families and take a financial toll; (3) the social stigma of VAs was high and could prevent patients/families from seeking care; (4) belief in religious explanations of disease and/or traditional healing systems was common and could often coexist with biomedical treatment.

CONCLUSION: Our research, in combination with prior literature, provides support for the necessity and possibility of VAMCs in Tanzania. Moreover, our results thus far enable us to further refine our needs assessment in accounting for the common themes identified in VA care in LMICs. Overall, this research underscores the necessity of developing comprehensive and culturally relative needs assessment tools for resources that may improve care in LMICs.

377 - Clinical and Imaging Outcomes of Serial Doxycycline Exchange for Lymphatic Malformations of the Extremities

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PURPOSE: Evaluate serial doxycycline exchanges (SDE) as a treatment for lymphatic malformations (LM).

METHODS: In SDE therapy, a percutaneous drain is placed into the LM cavity, the patient is admitted to the floor, and multiple sessions of doxycycline instillation and drainage are performed at the bedside. We conducted a retrospective, single-center chart review of patients undergoing LM sclerotherapy with SDE from April 2003 through March 2023. We assessed improvement between pre- and post-treatment clinical notes by the resolution of patient-specific presenting symptoms and lesion volume change between pre-treatment and final scans using three-dimensional ellipsoidal approximation. Patient charts were reviewed for 30-day adverse events, classified by the Society of Interventional Radiology Adverse Event Criteria.

RESULTS: Forty-six patients received an average of 1.7 ± 0.9 SDE admissions with 3.8 ± 2.3 exchanges per placement following the initial infusion. Patients presented at a median age of 5.85 years (range: 2 days - 77 years). Swelling/mass (28/46; 60.9%) and discomfort (8/46; 17.4%) were the most prevalent initial symptoms. 52.2% of patients (24/46) had one SDE admission, 30.4% (14/46) had two separate admissions, and 17.4% (8/46) had at least three separate admissions. Eight 30-day adverse events were observed, characterized as three mild, four moderate, and one severe. 9.1% of patients (4/44) experienced full clinical remission, 61.4% (27/44) experienced improved clinical symptoms, and 29.5% (13/44) experienced steady/increased symptoms. LM size was reduced by a median of 63.4% ± 63.9% after one series and by an additional 64.4% ± 69.5% after a second series. 79.4% of patients (27/34) experienced a reduction in median lesion size after all treatments, whereas 20.6% (7/34) experienced an increase.

CONCLUSION: SDE therapy is a safe and effective treatment of LMs that allows for multiple sessions of sclerotherapy with a single fluoroscopic procedure, which has the potential to reduce radiation, procedure, and anesthesia-associated risks for the patient.

378 - The Impact of Alcohol Embolization on Pain Relief in Patients with Peripheral Venous Malformations: a comparative study.

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PURPOSE: Various treatment modalities have been applied for symptomatic venous malformations, with alcohol embolization being a common approach. However, the benefits and complications of this therapy require rigorous evaluation in the face of emerging new, targeted treatments. The aim of this study was to evaluate the efficacy of alcohol embolization in pain management compared with conservative treatment, and to explore associated complications.

METHODS: A retrospective cohort analysis was performed at the Vascular Malformation Center, University Hospital Bern, from 2008 to 2022. Patients with peripheral simple venous malformations were included, one group underwent alcohol embolization and the other group received conservative treatment. Pain levels were measured using the Numeric Pain Scale (NRS). Inverse Probability of Treatment Weights (IPTW) were used to adjust for confounders such as severity of malformation indicated by number of tissues affected, localization, presence of hypertrophic tissue, history of thrombophlebitis, age, pain level at the initial visit. Primary and secondary outcomes included changes in maximum, average, and minimum pain levels.

RESULTS: Of 236 eligible patients, 93 underwent alcohol embolization and 143 received conservative treatment. Both groups showed a reduction in pain over time, with alcohol embolization resulting in a more pronounced reduction in average and minimal pain levels. However, there was no statistical evidence of an advantage of alcohol embolization in reducing maximum pain. Complications occurred in 14% of treated patients, but were generally manageable and did not lead to serious outcomes.

CONCLUSION: Alcohol embolization demonstrated a faster and more significant reduction in mean and minimum pain levels, but its efficacy in relieving maximum pain compared with conservative treatment remains inconclusive. The study highlights the need for a broader perspective on treatment outcomes beyond pain reduction. Future research should focus on holistic measures to improve the overall quality of life of patients with venous malformations and explore alternative therapies.

379 - Sinus pericranii: a case series and review of the literature

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PURPOSE: Sinus pericranii (SP) is a rare vascular anomaly characterized by abnormal communication between the intracraneal venous sinuses and extracranial venous system with the presence of either single or multiple dilated venous structures. It is typically manifested in pediatric patients and despite its benign nature, SP is not exempt from complications like thrombosis or haemorrhage.

SP may be asymptomatic or lead to symptoms such as pain, headache, or dizziness. The typical cutaneous lesion presents as a subcutaneous nodule or tumor on the scalp, exhibiting normal to reddish-blue coloration, soft, depressible and non-pulsatile, emphasized in Valsalva situations.

The diagnosis of this pathology is challenging. It relies on clinical evaluation and imaging studies confirmation.

The objective of this study is to describe the dermatologic features of SP in a series of patients diagnosed at a tertiary Childre's Hospital.

METHODS: A retrospective observational study was carried out, with radiologically confirmed SP from 2000 to 2022. Demographic, clinical, radiological and management data were collected.

RESULTS: Results from our study included a total of 19 pediatric patients (10 females and 9 males) aged between 2 months and 17 years. All of them had cutaneous lesions with different presentations,

including the classical tumor (11), snake's nest plaque (3), hair collar sign (3) and cutis aplasia (2). Only 4 of the patients had headache without other neurological symptoms.

CONCLUSION: In conclusion, we present a series of 19 pediatric patients with SP, one of the longest in the literature. SP may be underdiagnosed because of its various forms of presentation and the possibility to be asymptomatic. The cutaneous lesion was the clue sign for the diagnosis in 13 of the patients. Knowledge of SP will enable to request appropriate imaging studies, facilitating diagnosis and avoiding possible complications.

381 - Utilizing Telemedicine for Hemangioma Management – a Two Year Comparison
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PURPOSE: The use of telemedicine visits (TMV) in outpatient practices significantly increased with the onset of COVID-19. Our team initially implemented TMV March 2020, and has continued its use to present. The purpose of this study is to compare the clinic's usage of telemedicine between the initiation of the pandemic and two years later, as well as discuss optimization for patients, pitfalls, and where improvements can be made.

METHODS: This retrospective study of 174 patients diagnosed with infantile hemangiomas (IH) was conducted between March 1, 2022 and May 31, 2022 to investigate how many patients were seen via telemedicine and if the number has significantly changed since our initial analysis in 2020. Patients were stratified into new and established, and then further categorized by treatment type, discontinuation, or observation.

RESULTS: From the original review in 2020, out of the 30 IH TMV, nine were new-patient visits and 21 were established patient visits, with 20 on propranolol therapy. Of the 174 patients seen in the VAC between March 1, 2022 and May 31, 2022, 31 patients were seen via telemedicine, with 30 patients already established in care and 22 on treatment with propranolol.

CONCLUSION: While the number for telemedicine visits were similar between these time periods, these visits are now integrated in a full in person clinic, where in 2020, all visits in that time period were converted to TMV due to the shut-down. Many lessons were learned during this time period including utilization of alternative methods of communication for patient care, psychosocial and financial effects of TMV for families, barriers of technology. Review of this data also shows that TMV can be further utilized to improve office efficiency and quality of patient care.

382 - Venous malformation is the abnormal development and pathological expansion of superficial or deep veins (a modern approach to treatment in rare locations).
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PURPOSE: To show a clinical case of treatment of a patient with venous malformation of the penis by sclerotherapy with bleomycin-polidocanol solution.

METHODS: The patient is teenager of 13 years old (weight 77 kg, height 176 cm). At 5 years old a vascular formation was first noticed. The patient pediatric was consulted by surgeon at the place of residence and dynamic monitoring was recommended. From 9 years old a vascular formation was noted to increase. The teenager experienced episodes of pain and single bleeding from the malformation during spontaneous erections. Upon admission to our clinic, a comprehensive examination was carried

out, including ultrasound examination with dopplerography of the kidneys and bladder, organs of the scrotum, penis, urethrocystoscopy and consultation of urologist.

The sclerotherapy with a bleomycin-polidocanol solution in the form of foam was chosen as the treatment method of the venous malformation. The patient underwent 2 stages of sclerotherapy with a break of 1.5 months. This operation was performed under local application anesthesia. In the early postoperative period, swelling was noted in the area of the operation. The patient was discharged from the hospital the next day after surgery.

RESULTS: 10 months after 2 stages of treatment, the pathological vessels of the venous malformation are not identified, the patient has no complaints of pain.

CONCLUSION: Conclusion: The preferred method of treatment for venous malformation of the penis is sclerotherapy. Bleomycin-polidocanol solution can be used as a highly effective sclerosant. Taking into account the age category of patients, these treatment methods can be performed under local anesthesia. Minimally invasive treatment methods can reduce the time of hospitalization and rehabilitation of the patient.

385 - Pain Management in Patients with Vascular Anomalies

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PURPOSE: For most vascular anomalies (VA), chronic multimodal approach/treatment is indicated, with surgical, laser, interventional radiological and/or medical management; full resolution is rare. VA can cause pain and/or psychological distress, interfering with quality of life (1, 2, 3). The purpose of this study is to investigate methods of pain management used by patients at our VA clinic, with particular interest in treatments often not specifically prescribed, e.g. cannabinoids and opioids.

METHODS: Participants consented to and completed a survey on pain management options utilized and their subjective experience of pain improvement.

RESULTS: Of 95 participants, 47% identified as Hispanic/Latinx, 42% as White and 16% as Native American (option to choose multiple). Average age was 22.12 years (sd=18.43). Venous malformations were most common (46%), followed by lymphatic (22%). Regardless of type, 48% experienced pain at least 1-2 days/week; average daily pain rating (0-10) was 2.10 (sd=1.364). Most common medications tried were: oral NSAIDs (32%) and acetaminophen (15%). Of those who used these, more than half reported moderate to major relief. Nine percent of the cohort reported using cannabinoids (oral and topical). Of those using tetrahydrocannabinol (THC), 83% had moderate-major relief and 33% using cannabidiol (CBD) reported moderate relief. Eight percent of patients reported using oral opioid-containing medications, with 75% reporting moderate-major effect on pain. Other methods reported were: injections, ""topicals"", massage, warm/cold compresses and physical/occupational therapy.

CONCLUSION: In conclusion, nearly half of our patients with VA experience pain at least weekly, emphasizing the importance of pain management as part of a multimodal treatment plan. There may be utility in exploring anti-inflammatory effects of cannabinoids for this population. Opioids provided notable relief, and use could be underreported. Given rising legalization status of cannabinoid products and the current opioid epidemic in the US, it is important that pain management strategies are discussed/screened for in the VA population.

386 - Treatment of children with extensive infantile hemangiomas of the head, neck and respiratory tract lesions. Clinical observation

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City Clinical Hospital of the Moscow Department of Health); Alexander Zhigulin (St. Vladimir Children's City Clinical Hospital of the Moscow Department of Health); Dmitriy Komelyagin (St. Vladimir's Children's Clinical Hospital. Research Institute of Pediatric Surgery named N.I. Pirogov.); Svetlana Iamatina (doctor); Alexey Petukhov (St. Vladimir Children's City Clinical Hospital, Moscow Department of Health); Grigory Mileev (St. Vladimir Children's City Clinical Hospital, Moscow Department of Health); Svetlana Arefieva (St. Vladimir Children's City Clinical Hospital, Moscow Department of Health)

PURPOSE: Demonstrate a clinical case of treating a complex patient.

METHODS: Anamnesis morbi: at 3 weeks old a spot appeared in the occipital region of the head with a transition to the neck, and growth of the spot in volume was noted.

Upon admission, an ultrasound of soft tissues, head and neck was performed, in which hemangioma was detected only in soft tissues. A comprehensive cardiological examination was carried out and beta-blocker and hormonal therapy were prescribed. The child was discharged home with improvement under.

At 4 months old the child had an aggressive growth of vascular formation, and symptoms of airway obstruction appeared. The child was readmitted to our department, where the scope of the examination was expanded.

Diagnostics and treatment:

1. Magnetic resonance therapy and multislice tomography with contrast had showed that the hemangioma spread from the head to the anterior mediastinum with damage to the neck and displacement of the esophagus, trachea and went around the great vessels like a cuff.

2. Fibrolaryngotracheoscopy visual that the hemangioma blocked the trachea by 2/3.

3. Biopsy with immunohistochemistry was also performed. The diagnosis of infantile hemangioma was confirmed.

RESULTS: The dose of the beta-blocker Atenolol was increased to 3 mg/kg/day and long-term hormonal therapy was prescribed. During the treatment symptoms of airway obstruction had disappeared at 7 months and hormone therapy was discontinued. The hemangioma completely involuted at 1.5 years and the beta-blocker was discontinued. Residual manifestations of the hemangioma were eliminated by laser treatment sessions using a laser device with a wavelength of 595 nm; complete recovery was established after 3.5 years.

CONCLUSION: Patients with infantile hemangiomas of the head, neck and upper respiratory tract have a varied clinical features and risk of complications, which makes it necessary to develop an algorithm for the examination and treatment of these patients

387 - Focal Venous Malformations Complicated by Chronic Intralesional Extensive Thrombosis: From Clinical and Imaging Presentation to Surgical Excision Using Preoperative Sonography and Hookwire Localisation

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PURPOSE: Background: Clinical and imaging presentation as well as therapeutic management of focal VM complicated by chronic intralesional extensive thrombosis (CIET) has been poorly described. CIET

precludes sclerotherapy, which represents the gold standard for first-line VM treatment. In such a condition, CIET acts as a painful foreign body, justifying surgical excision in the majority of the cases.

METHODS: We reviewed the clinical, imaging and pathological features of 49 patients (14 males, 35 females), mean age 20 yo (range 8-57 yo) treated in our referral center for superficial vascular anomalies with CIET within focal VM over a 12-year period (2011-2023).

RESULTS: Our 49 cases were located mainly in muscle (n=43, 88%) of the lower limb (n=47, 96%), especially the quadriceps (n=13), soleus (n=12) and gastrocnemius (n=9). All patients were symptomatic with characteristic painful trigger point. Medical history included sclerotherapy in 22 cases and surgery in 1 case. Sonographic examination showed a non-compressible hypoechoic focal lesion in all cases, measuring a mean of 32 x 13 mm, surrounded by echogenic tissue suggestive of perilesional fat, demonstrating hyperintensity on T2-weighted MR images, suggestive of low-flow malformation. In all cases, imaging led to diagnose focal VM complicated by CIET. Painful or/and disabling symptoms related to CIET, acting as a foreign body, justified surgical excision despite deep location. Difficulties in perioperative lesion identification (focal induration at perioperative palpation in 37 cases without any cleavage plane in 16 cases) were overcome by using pre/peri-operative sonographic examination (n= 49/2) but also hookwire localisation in 10 of our most recent cases. In all cases, symptoms resolved after surgical excision with uneventful post-operative course, except in one case (hematoma). Pathological examination confirmed the diagnosis of VM complicated by CIET except in one case, which revealed a sarcoma.

389 - Extreme case of 15 years old patient with venous malformation of a left lower limb with hip- and knee-joint arthropathy

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PURPOSE: Clinical case - We present a case of 15-year-old boy with venous malformation of the left lower limb and left side of the pelvis. He has been treated from early childhood. Patient suffers from complex coagulation disorders with dominant of severe hypofibrinogenemia, factor XIII deficiency and constant high level of D-dimers (> 36,22 mg/L!). Ultrasound and MRI of the left lower limb and pelvis was done; diagnosis of the venous malformation was made. He was treated with multiple sclerotherapies, endovascular laser ablations, he underwent surgery of the partial removal of the malformation and Nd-YAG lasers with unsatisfactory results. Despite the physiotherapy contractures of the left hip- and knee-joint and ankle have progressed and became more painful. Patient has had problems with loading left lower limb and uses crutches. In January 2022 he started treatment with sirolimus, which he continued with nearly non - effect for 6 months (sirolimus was suspended because of the cardiac hypokinesis - probably unrelated to sirolimus). Patient was consulted with the orthopedic team and was elected for the mid-thigh amputation, but because of the hematological disorders, surgery was never performed. In summer 2023 during a multidisciplinary meeting decision was made to restart treatment with sirolimus (hasn't started yet).

Issues to discuss - Are there any other options of treatment for this patient? Is a mid-thigh amputation a good idea in patient with hip-joint contracture? How to improve healing process after amputation?

394 - Overgrowth in PIK3CA-induced Conditions with Oral Involvement

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PURPOSE: The effect of PIK3CA on the lower face and oral cavity in lymphatic malformations (LM) and other conditions has not been systematically described. We studied the longitudinal effects of this genotype on locoregional bone and soft tissue.

METHODS: Clinical data was abstracted for a retrospective case series of patients with oral PIK3CA-induced LM or other conditions, with complete datasets, seen at a pediatric hospital (2000-2017). Patient photographs at Birth, <2y, 2-10y, >10y, were rated by otolaryngologists for tongue involvement, macroglossia, mandibular overgrowth, and Wiegand classifications. Orthodontists measured radiographs and classified occlusion. Data were summarized, and associations with mandibular overgrowth tested.

RESULTS: Of 38 LM, 1 megalencephaly-capillary malformation syndrome and 1 lip and tongue segmental overgrowth patients, 23 were female (56%). Mean age at diagnosis was 1.7y (SD 2.7). LM were unilateral in 24 patients (60%). Tongue LM was superficial in 6 (15%, Wiegand I-II) or deep in 20 (51%, Wiegand III-IV) patients. Macroglossia (length/width/height extension beyond the dental arch), was present in 19 patients (46%) and developed after 2yo in 4 patients. Patients without macroglossia did not have tongue involvement. Mandibular overgrowth (atypical size of ramus/condyle/alveolar process) was present in 25 (61%; unilateral 13, 32%; bilateral 12, 29%). Associated malocclusions included midline discrepancy and/or openbite (34,68%). Patients complained of bleeding (7, 17%), pain (19, 46%), which occurred after 2yo. Diet was modified (10, 24%), or needing a gastrostomy tube (3, 7%). Seven patients had mandibular overgrowth without macroglossia. Mandibular overgrowth was associated with macroglossia, tongue involvement, and modified diet ($p<0.05$).

CONCLUSION: Oral involvement in PIK3CA-induced conditions presents at a young age and is frequently associated with macroglossia and mandibular overgrowth. Patients are commonly symptomatic. Prospective studies are needed to assess how surgery or targeted therapies impact bone and soft tissue overgrowth in the lower face.

395 - RICH or not, that was the question
Uwe Huebner (Katholisches Kinderkrankenhaus Wilhelmstift)

Clinical Problems: Cardiac failure, Shunting, Anaemia, Ulceration, Failure to thrive

Histology: First Investigator: -No expression of Glut1 - Only partial reduction of WT1-expression in endothelial cells **Diagnosis**: complex vascular malformation

Second Investigator: -Only focal positivity for Glut1 -WT1 is negative -Closely packed but wellformed vessels, highlighted in stains for SMA and CG31, no endothelial atypia **Diagnosis**: RICH

Therapy: -*Propranolol* (cardiac failure) - *Sirolimus* (supected VM) - *Surgical* (near total resection)

397 - Expanding the Phenotype of Capillary Malformation – Arteriovenous Malformation (CM-AVM) Type 1 and 2
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PURPOSE: CM-AVM1 and CM-AVM2 are autosomal dominant disorders caused by mutations in RASA1 and EPHB4 respectively. Phenotype includes multifocal capillary malformations, arteriovenous

malformations (AVM), and lymphatic anomalies (1-3). However, dysmorphic features and cardiac anomalies are much less described in the literature (4). We present a series of CM-AVM1 and 2 cases with dysmorphisms and cardiac anomalies.

METHODS: A retrospective review of charts and photographic databases from dermatology and genetics clinics was performed. CM-AVM 1 and 2 cases diagnosed from 2020 to 2023 with confirmed molecular diagnosis were analyzed.

RESULTS: 15 cases of CM-AVM1 and 11 of CM-AVM2 were analyzed. Among CM-AVM1 (RASA1) cases: 8 had facial dysmorphism (descending palpebral obliquity, pointed palate, prominent forehead), 6 macrocephaly (2 delayed neurodevelopment), 9 acral dysmorphism (clinodactyly, brachydactyly), 2 cardiac anomalies (wide ASD, ventricular systolic dysfunction, mitral stenosis), 2 perinatal lymphatic anomalies (polyhydramnios, pleural effusion, non-immune hydrops fetalis, chylothorax), and 3 women had recurrent abortion and perinatal lymphatic anomalies (2 deceased postnatally). Among CM-AVM2 (EPHB4) cases: 8 had facial dysmorphism (epicanthus, pointed palate, prominent forehead, low nasal bridge), 2 macrocephaly, 1 acral dysmorphism (fusiform fingers), 3 cardiac anomalies (left ventricular aneurysm, aortic stenosis, bicuspid aortic valve), and none had lymphatic anomalies. Multifocal capillary malformations were present in all 26 patients; internal AVMs in 1 CM-AVM1 (pulmonary); epistaxis in 2 CM-AVM1 and 7 CM-AVM2; and telangiectasia in all CM-AVM2 patients.

CONCLUSION: Although RASA1 and EPHB4 are part of the Ras-MAPK pathway, and can be classified as RASopathies, associated dysmorphisms have not been described (4,5). Considering both syndromes have variable expression and penetrance, even among members of the same family (6), and some may have severe life-threatening complications, we believe that searching for dysmorphism as well as screening for cardiac anomalies should be included in our routine workup when facing these patients.

401 - Lower Limb Length Discrepancy in Patients with Lower Extremity Capillary Malformation: A Single Institution Retrospective Study

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PURPOSE: Lower extremity capillary malformations (CMs) are associated with lower limb length discrepancy (LLD) that can cause gait abnormalities, lower back and hip pain. Limited research exists on LLD prevalence in these patients. We assessed the frequency of LLD in various types of CMs.

METHODS: We conducted a single-institution, IRB-approved retrospective chart review of patients diagnosed with a lower extremity CM, including regional CM (RCM), capillary-venous malformation (CVM), diffuse capillary malformation (DCM), and capillary malformation-arteriovenous malformation (CM-AVM). We evaluated demographics, clinical characteristics, treatments, and conducted clinical assessment or radiographic evaluation for LLD.

RESULTS: We studied a total of 1008 patients. Types of CM included: RCM (n=717, 71.1%), CVM (n=123, 12.2%), DCM (n=119, 11.8%), and CM-AVMs (n=49, 4.9%). By age 4, 41/1008 patients (4.1%) developed LLD ranging from one to two centimeters. Severe LLD (defined as ≥ 2 cm) was determined in 108/1008 patients (10.7%) at any age. The Kaplan-Meier survival estimates identified a 31.4% probability of developing severe LLD at age of 15 or older in patients with CM of any type. Subgroup analysis showed a RCM (21.7%), CVM (30%), DCM (67.5%), and CM-AVM (25.9%) probability of developing a severe LLD.

Epiphysiodesis was undertaken in 88/1008 patients (8.7%), but 12/108 patients (11.1%) with severe LLD missed the opportunity for epiphysiodesis. Chi-square and logistic regression analyses identified DCM (OR 2.634), combined medial and lateral lesion position (OR 2.618), and full-length-leg involvement (OR 4.83) as major risk factors in developing significant LLD.

CONCLUSION: Leg length discrepancy is a common sequela of a lower extremity CM. Patients with DCM, combined medial and lateral CM, and full-length-leg involvement have the highest probability of developing a major leg length difference. Understanding the prevalence of LLD in lower extremity CM is important for optimizing follow-up, patient care, and planning surgical intervention, particularly epiphysiodesis.

405 - Intracranial congenital hemangioma with consumptive coagulopathy

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Clinical History

• Full term infant admitted at 19 days of age for hemodynamic instability, anemia and thrombocytopenia in the setting of excessive blood loss after circumcision
• Initial admission: - Coagulopathy evaluation due to severe hemorrhage: Fibrinogen activity undetectable, Factor XIII activity low - Brain MRI due to abnormal rhythmic extremity movements during admission, which showed an extra-axial vascular mass with hemorrhage
• Outpatient management following initial admission: - Cryoprecipitate transfused as needed for Fibrinogen < 150 - Prednisolone and Sirolimus initiated - Increasing Head circumference and fullness of fontanelle
• Ultimately underwent surgical resection at 3 months of age with transfusion support (red cells, cryoprecipitate). Surgery was tolerated well.
• Pathology: Hemangioma, expressing CD34, ERG and vimentin (GLUT1 negative)
• Subsequent vascular anomaly panel testing of lesional tissues showed pathogenic mutations in PIK3CA, GNAQ, and VUS DCHS1
• Factor XIII and Fibrinogen deficiency resolved after hemangioma resection, genetic testing for FXIII and FG variants negative, presumed that he had a consumptive coagulopathy due to the vascular tumor. No further bleeding.

Case Discussion

• Unique combination of clinical, histopathologic and genetic factors in a vascular mass - Lesion pathology was distinct from kaposiform hemangioendothelioma (KHE), which is more commonly associated with consumptive coagulopathy than congenital hemangioma
• Unusual for hemangiomas to have two distinct pathologic mutations (PIK3CA and GNAQ) as well as a third of unknown significance (DCSH1) - GNAQ and GNA11 mutations are frequently found in congenital hemangiomas, while GNA14 mutations are seen in KHE1 - PIK3CA mutations have been described in congenital hepatic hemangioma2, however, they are most often found in overgrowth syndromes, lymphatic and venous malformations1 - DCHS1 mutations have been associated with lymphedema and mitral valve prolapse3, with no known history of these findings in patient or family
• Now 14 months old, since hemangioma resection his coagulopathy resolved and developmental milestones are being met. Should the lesion recur, targeted medical therapy such as alpelisib (PIK3CA) could be considered. In addition, coagulopathy evaluation at time of recurrence is recommended.

406 - Screening of Capillary Malformation–Arteriovenous Malformation Syndrome in Pediatric Patients with Central Nervous System Arteriovenous Malformations: An Observational Study on Prevalence and Treatment Opportunity

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PURPOSE: Background: Capillary malformation–arteriovenous malformation (CM-AVM) is a genetic disorder characterized by cutaneous capillary malformations (CM) and high-flow arteriovenous malformations (AVM) in the peripheral or central nervous system (CNS). Pre-symptomatic diagnosis of CNS AVMs could prevent dismal neurological complications.

Objective: To determine the prevalence of the CM-AVM syndrome in children with a history of non-traumatic intracranial AVMs; to estimate the number of patients that could be diagnosed prior to CNS symptoms with a skin exam; and to estimate in how many patients prophylactic sclerotherapy/neurosurgery would have been advised.

METHODS: Observational, and prospective study, including pediatric patients (aged 0-18 years) with symptomatic intracranial AVMs from January 2021 to November 2023 at one reference pediatric hospital. The study was approved by the Hospital's Ethical Committee.

Patients and first-degree relatives referring cutaneous lesions through telephonic interview were invited to conduct a physical examination. Those meeting clinical criteria for CM-AVM phenotype were offered genetic testing for RASA1 and EPHB4 genes, according to standard clinical practice. Pediatric relatives with the cutaneous phenotype were offered a cerebral magnetic resonance imaging (MRI) to rule out intracranial AVMs; adult relatives were referred to their primary care physician.

RESULTS: Among 107 eligible patients, 93 were contacted (52% male, median age 13,0 years). Sixty-seven (72%) had undergone surgical treatment. Cutaneous lesions suggestive of CM-AVM were referred by 15 patients and 13 first-degree relatives (7 were simultaneously referred in the patient and family). Patients are currently undergoing physical examination that will end in December 2023. Definitive results will be available by then.

CONCLUSION: 1. All families referring cutaneous lesions agreed to undergo screening.

2. Anamnesis and physical examination alone do not confirm the diagnosis of CM-AVM syndrome but are a useful screening tool to identify families at risk of intracranial AVMs who could benefit from further genetic testing and/or MRI.

408 - Experience in the Use of Alpelisib in PIK3CA-related disorders in children

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PURPOSE: PIK3CA-related disorders are rare, benign but often morbid conditions managed by multidisciplinary teams involving oncologists, interventional radiologists, surgeons, and dermatologists. Previously, medical options are limited. With identification of the causative PI3K/AKT/mTOR pathway,

the use of pharmacological inhibitors of the pathway is a game changer in the management of these patients.

Alpelisib is an inhibitor of PI3K and has been used successfully on PIK3CA-mutated breast cancer. We describe our experience of alpelisib in paediatric PIK3CA-related non-oncologic disorders.

METHODS: Three children, aged 2 to 8 years old, were given alpelisib on a compassionate managed access program for proven PIK3CA-mutated CLOVES (Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevis, Skeletal anomalies), giant VLM (venolymphatic malformation) and KTS (Klippel-Trenaunay Syndrome). All children were treated previously with multiple therapies including sclerotherapy, surgery and sirolimus or everolimus, with variable success. Mean duration of treatment was 17 months, ranging from 3 to 36 months.

RESULTS: Response is demonstrated in the significant reduction of rectal bleeding episodes for the child with KTS and the reduction in size of the lipomatous tumours in the child with CLOVES. For the child with VLM, even though the duration of treatment is short, there was appreciable reduction in size of the malformation. Adverse effects include mucositis and diarrhoea, necessitating a reduction in dose or temporary cessation of the medication. The child with KTS could only tolerate Alpelisib 50mg two to three times a week due to mucositis, whilst the other children are on daily 50mg. No hyperglycaemia was demonstrated. Therapy is ongoing for all 3 children.

CONCLUSION: Alpelisib is tolerable and is showing promise in the management of paediatric PIK3CA-related disorders in our centre. Molecular characterization of vascular anomalies is crucial to identify causative signaling pathways and targetable molecules within the pathways, thus expanding the therapeutic armamentarium of these conditions, and improving patients' quality of life.

409 - Strengthening Care: Patient Advocacy and Knowledge Sharing through a National Vascular Anomalies Consortium

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PURPOSE: To outline opportunities in our national health care system that strengthen knowledge about vascular anomalies, and provide options for patient and family support.

METHODS: Descriptive statistics were used to summarize the consortium's characteristics, by member specialty and geography. Qualitative methods were used to report advocacy initiatives. This analysis was taken through an educational framework unique to our country, that identifies and describes the abilities physicians require to effectively meet needs of the people they serve. This consortium has established a national multidisciplinary membership representing both Pediatric and Adult providers, allied health providers, and students.

RESULTS: The national consortium is represented by 92 members, including practitioners from seven vascular anomalies clinics in our nation. Membership is comprised of interventional radiologists (24%), hematologists/oncologists (15%), pediatrics (15%), dermatologists (15%), nursing (13%), and surgeons (7%). Geneticists, pathologists, internists, physiotherapists and radiology technicians comprise 10%. Initiatives in education, clinical care, advocacy and research are underway, with seven educational lectures, and five ""interesting case rounds"", each facilitated by internationally recognized experts. The accredited educational program reflects educational pillars that underly medical education in our country namely, medical expert, communicator, collaborator, leader, health advocate, scholar and professional.

The consortium has facilitated successful advocacy to obtain Alpelisib through the managed access program in our nation. There are national studies underway. Importantly, there have been direct and indirect impacts on patient care.

CONCLUSION: While there are only seven vascular anomalies centers in our nation, a relatively large number of patients with vascular anomalies are seen across the country. Despite a paucity of resources, multidisciplinary, national care delivered to this patient population has flourished. After two years of operation, significant success in attracting and retaining members, delivering a substantial members education program, the Alpelisib victory and an active health care provider membership, have all raised awareness of this field, and impacted patient care.

411 - A Case of Kaposiform Lymphangiomatosis (KLA) Complicated by Kasabach-Merritt Phenomenon (KMP), Recurrent Pericardial Effusions, Multifocal Lytic Bone Lesions, and Pneumococcal Meningitis
Deborah Schiff (UCSD); Hilda Ding (UCSD); Peter Kruk (Rady Children's Hospital San Diego)

PURPOSE: KLA is a complex lymphatic anomaly with a poor prognosis. Diagnosis can be challenging, and treatments, including mTOR inhibitor sirolimus and MEK inhibitor trametinib, are often only partially effective. Additional diagnostic and therapeutic options are needed.

METHODS: Case Report

RESULTS: A 6-year-old boy was diagnosed with KLA after presenting with bleeding symptoms, multifocal lytic bone lesions, pulmonary lymphangiectasia, and hypoechoic splenic lesions. He started therapy at age 6 with mTOR inhibitor sirolimus. Bisphosphonate zoledronic acid was added to treat the multifocal lytic bone lesions. At age 7, he developed recurrent pericardial effusions with tamponade physiology that was treated with repeated pericardial drain placement. Sirolimus was discontinued and MEK inhibitor trametinib was started at age 7 after FoundationOne Liquid CDX testing of blood showed an activating NRAS Q61R mutation. At age 9, prednisone was added for additional treatment of KMP. At age 10, he developed Streptococcal pneumoniae meningitis and sepsis. Pneumococcal meningitis was complicated by generalized tonic-clonic seizure and transient right hemiparesis. Subsequently, he received meningococcal and pneumococcal booster vaccines for functional asplenia, and started amoxicillin for asplenia prophylaxis. His most recent skeletal survey showed resolution of previously noted multifocal lytic lesions and no new lytic lesions.

CONCLUSION: This case report illustrates the diagnostic challenges of KLA, the risk of functional asplenia secondary to KLA, and options (including targeted therapy) for treatment of KLA-associated complications.

412 - Isocitrate dehydrogenase is a novel genetic cause for lymphatic malformations
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PURPOSE: Lymphatic malformations are low-flow malformations that arise from errors in vascular development. Understanding the molecular cause of lymphatic malformation may allow for targeted medical therapies that target underlying signal pathway dysregulation. This study therefore aimed to identify and validate novel genetic causes of lymphatic malformation.

METHODS: Clinical genetic testing was performed on lymphatic malformation tissue. To test the hypothesis that this pathogenic variant in IDH1 can cause lymphatic malformations, we utilized the zebrafish model and the Tol2 system to create transient transgenic that simulate the mosaicism seen in these patients. Digital droplet PCR for recurrent IDH1 and IDH2 variants is ongoing to screen an additional 150 lymphatic malformation samples from 39 individuals.

RESULTS: We identified recurrent somatic variants (p.R132H, p.R132C) in IDH1 in human lymphatic malformation tissue at 1.17-1.56%VAF and 14%VAF. We identified a recurrent somatic variant (p.R172S) in IDH2 in human lymphatic malformation tissue at 8%VAF and 8.5%VAF.

IDH1 encodes the enzyme isocitrate dehydrogenase which catalyzes the oxidative dephosphorylation of isocitrate to alpha-ketoglutarate in fatty acid synthesis. Pathogenic variants of IDH1 have been found in a variety of cancers, spindle cell hemangiomas and enchondromas, but have not been previously identified in lymphatic malformations.

Using the mrc1a promoter, wild-type IDH1, and IDH1 c.395G>A were expressed in venous and lymphatic endothelium. This resulted in lymphovenous cysts and dilated intersegmental vessels by 3 days post-fertilization (dpf) (26.25%, n=53, p=0.0292) and pericardial edema by 5 dpf (20%, n=70, p=0.0097). This experiment was repeated with the second IDH1 c.394C>T variant and was found to induce cystic and vessel malformations by 3 dpf (66%, n=9, p<0.0001).

CONCLUSION: We identified a novel cause of lymphatic malformations validated by a zebrafish assay. This model will allow us to better understand the variety of disease mechanisms and evaluate potential new treatments for individuals with these rare conditions.

413 - Comprehensive Characterization of Coagulation Parameters in Venous Malformations
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PURPOSE: Localized intravascular coagulopathy (LIC) is a well-recognized though poorly characterized complication of low-flow venous malformations (LFVMs) that can lead to bleeding and thrombosis. LIC is classically defined using D-dimer and fibrinogen. However, no comprehensive studies of other coagulation parameters in LFVMs exist to date. We conducted the first comprehensive characterization of coagulation parameters in patients with LFVMs.

METHODS: Since 2021, patients with LFVMs undergoing LIC evaluation at the Yale Vascular Malformations Program were subjected to an extensive set of coagulation tests: von Willebrand Factor antigen, VWF activity, factor VIII, alpha-2 antiplasmin, plasminogen activator inhibitor-1, thrombin-antithrombin complex (TAT), D-dimer, fibrinogen, prothrombin time, international normalized ratio and partial thromboplastin time. We reviewed their charts retrospectively, using their test results to comprehensively characterize LIC.

RESULTS: We included 44 patients with LFVMs (10 [23%] men, 34 [77%] women; mean age, 36 years). There were more isolated (77%) than syndromic (23%) cases. Limbs were the most common location (52%), while the muscle was the most frequently involved tissue (45%). High D-dimer and TAT were observed in most patients (54% and 63%, respectively); 50% of patients with normal D-dimer had high TAT; 7% of patients had low fibrinogen. High TAT and/or D-dimer were more frequent in patients with deep tissue involvement (muscle [82%], viscera [80%], bone [80%]) than with skin involvement (63%). Different patterns of TAT/D-dimer levels were seen in each group of tissue involvement. Derangements in factor VIII and alpha-2 antiplasmin were seen in 39% and 31% of patients, respectively.

CONCLUSION: This first-ever comprehensive characterization of LFVM-related coagulopathy demonstrates derangements in TAT, factor VIII, and a2AP; high TAT was more frequent than high D-dimer and low fibrinogen was uncommon; this all suggests that LIC screening with D-dimer and Fibrinogen alone may be incomplete. Different patterns of coagulation derangements are seen based on the extent of LFVM tissue involvement.

414 - Safety and Technical Success of Percutaneous Sclerotherapy of Vascular Anomalies of the Hands and Digits

Chase Mahler (University of Alabama Birmingham); Jake DiFatta (University of Alabama Birmingham); Rachel Oser (University of Alabama Birmingham); Junjian Huang (University of Alabama Birmingham); Andrew John Gunn (University of Alabama Birmingham); Junaid Raja (University of Alabama Birmingham)

PURPOSE: This study aims to evaluate the safety and efficacy of using percutaneous sclerotherapy and/or embolization to treat vascular malformations in the hand and digits.

METHODS: After institutional IRB approval at a large tertiary academic medical center, data for patients with vascular anomalies in their hands and digits was extracted. This included classification of type including arteriovenous malformations (AVMs), venous malformations (VMs), and venolymphatic malformations (VLMs) as well as baseline characteristics of the anomaly, treatment protocols and response, and safety metrics of treatment including documentation of unexpected or untoward effects following sclerotherapy according to the Society of Interventional Radiology (SIR) criteria. Technical success of the procedures was defined as achieving pre-procedural goals in delivering the sclerosant to the targeted area of tissue. Clinical outcome data included assessment of symptomatic and objective improvement or resolution of symptoms following treatment as well as imaging performed and follow-up clinic visits.

RESULTS: Technical success was achieved in all (100%) patients. Eight of nine patients (89%) followed up at six weeks and all reported at least partial reduction of symptoms. Imaging conducted in follow up was available for four patients and all four showed decrease in the size of the malformation. There were no intra-operative complications or major adverse events. Four patients (44%) reported SIR grade A/B minor adverse events such as swelling (n=3), pain (n=3), and poor capillary refill (n=1). Two of these patients required treatment with antibiotics and steroids which successfully abated their symptoms. All adverse effects resolved within six weeks.

CONCLUSION: Sclerotherapy appears to be a safe and effective treatment option for vascular anomalies in the hand and digits. Appropriate patient counseling regarding monitoring for potential skin discoloration, swelling, and pain maybe beneficial.

415 - Evaluation and Analysis of Free Flap Reconstruction in Post-Arteriovenous Malformation (AVM) Excision

Yuki Iwashina (Kyorin University at Tokyo); Mine Ozaki (Department of Plastic Surgery, Kyorin University School of Medicine)

PURPOSE: Reconstruction with free flap is necessary after the excision of AVM to address tissue defects. Recurrence may occur post-excision, and this study retrospectively investigates the impact of free flap reconstruction on the pathophysiology of AVM based on our cases.

METHODS: Twenty-three cases involving 24 sites where AVM was excised and reconstructed with free flaps from 2009 to 2020 were analyzed. The study included 17 male and 6 female patients with an average age of 32.4 years. The AVM locations were 11 cases in the head and neck (12 sites), 11 cases in the limbs, and 1 case in the trunk.

RESULTS: The average follow-up period was 5.9 years. Recurrence or relapse of the lesions was observed in 7 cases (3 in the head and neck, 4 in the limbs). In head and neck cases, one recurrence (ear) was from subcutaneous tissue around the flap, one case was due to the expansion of residual intracranial lesion's draining vein, and one case involved an increase in the size of remaining lesions in the oral floor and jaw bone. Recurrence under the flap was not observed in any of these cases. In limb cases, recurrence of shunts under the flap was observed in 4 cases.

CONCLUSION: We observed an increase in residual lesions and recurrence around the flap in head and neck cases, but no recurrence of shunts under the flap. Conversely, in upper limb cases, recurrence under the flap was observed. This difference was attributed to variations in the excision due to the hemodynamics of AVM. While it is possible to excise the dominantly supplied area of inflow arteries distally in head and neck lesions, in the upper limbs, tissue of the dominantly supplied area remains as long as the "length" is preserved. Therefore, in excision, it is considered essential to plan surgery considering hemodynamics.

416 - Safety and Feasibility of Direct Puncture Sclerotherapy in Perineal Arteriovenous Malformations
Jake DiFatta (University of Alabama Birmingham); Chase Mahler (University of Alabama Birmingham); Rachel Oser (University of Alabama Birmingham); Junjian Huang (University of Alabama Birmingham); Andrew John Gunn (University of Alabama Birmingham); Junaid Raja (University of Alabama Birmingham)

PURPOSE: To evaluate direct puncture sclerotherapy as a treatment option for arteriovenous malformations in the perineum. Arteriovenous malformations (AVMs) in the area between the anus and genitalia, the perineum, are frequently associated with pain, swelling, bleeding, and impaired quality of life and are difficult to treat given the complex adjacent anatomy, increased neural innervation, end terminal vascularity, and physical environmental factors (friction, humidity, hair, etc).

METHODS: Following IRB approval a single center retrospective analysis of patients who underwent direct puncture sclerotherapy for the treatment of perineal AVMs was performed. Clinical data and baseline demographics were extracted from the electronic medical record. SIR complication guidelines were used in the assessment of procedure safety. Details regarding the access technique, treatment medication and dose, and clinical follow up metrics including clinical assessment, abatement of symptoms, and as indicated imaging was performed and reviewed.

RESULTS: Symptom reduction was initially observed following sclerotherapy in 100% (3/3) of patients, but recurrence of symptoms such as swelling, pain, and bleeding was common and noted in 67% (2/3) of patients. Number of interventions required ranged from 2 to 8. All 3 patients were female, ranging in age from 5 to 75 years. The technique used for all procedures was ultrasound guided Sotradecol injection into affected anatomical locations. No complications were observed in any of the 14 interventions for 3 patients.

CONCLUSION: Direct puncture sotradecol sclerotherapy may be safe and partially effective in the treatment of AVMs in the perineal region. There were no complications during or after intervention. Sclerotherapy was effective in initial resolution of symptoms, however, recurrence requiring additional sclerotherapy was noted in two thirds of cases.

419 - Selective Lymphatic Embolization for Treatment of Primary Thoracic Lymphatic Conduction Disorders
Abhay Srinivasan (Children's Hospital of Philadelphia); Yoav Dori (Children's Hospital of Philadelphia); Christopher L. Smith (Children's Hospital of Philadelphia); Fernando Escobar (Children's Hospital of Philadelphia); Ganesh Krishnamurthy (Children's Hospital of Philadelphia)

PURPOSE: Primary thoracic lymphatic conduction disorders (LCD) and can produce severe morbidity. We present our experience with selective lymphatic embolization (SLE) for these disorders, performed with intent to preserve patency of the thoracic duct (TD), with focus on technical aspects and outcomes.

METHODS: Records of patients who underwent SLE for primary thoracic LCD, (i.e., chylothorax, plastic bronchitis, and/or chylopericardium not associated with palliation of single ventricle heart disease) from 2018-2021 were analyzed. Clinical and imaging data, including technical aspects of the procedure, complications, and outcomes, were collated.

RESULTS: Seven patients (3 females; median age 14.4 years, IQR 12.4 y, range 0.4-31.5y) were treated in a total of 10 procedures. Four patients had chylothorax, 4 had chylopericardium, and 1 had plastic bronchitis. Etiology of LCD included Turner syndrome, Noonan syndrome, Kaposiform lymphangiomatosis, and a MAP2K1 variant-associated overgrowth phenotype. The etiology was non-identified in 3 patients.

All procedures were performed after dynamic-contrast-enhanced MR lymphangiogram. Initial opacification of the lymphatic system was achieved with oily contrast via inguinal nodes in 7 procedures and water-soluble contrast via liver lymphatics in 3.

TD access was antegrade-plus-retrograde in 3 cases, antegrade in 1, and retrograde in 1. Selection of branches off the TD was achieved via microcatheter in 5 procedures, and an articulating microcatheter was used in 4. A dextrose-flood technique, requiring placement of 2 microcatheters, was used in these cases. All SLE was performed with glue. In 5 procedures, SLE was performed by direct-needle-puncture of target branches. The TD was confirmed to be patent in all cases.

Median follow-up was 521 days (IQR 441 d, range 203-1583d). Presenting symptoms resolved in 6 patients (86%) and were unchanged in 1 (14%).

CONCLUSION: SLE can be performed safely and may be useful in treatment of primary lymphatic conduction disorders. Importantly, selective techniques preserve the patency of the TD in these patients.

425 - Pigmentovascularis spilorosea due to a mosaic PTPN11 variant in a 7-year old girl: phenotypic and genotypic findings and review of the literature

Harper Price (Phoenix Children's Hospital); Supraja Prakash (Phoenix Children's Hospital); Theresa Grebe (Phoenix Children's Hospital)

RESULTS: A 3 month old baby girl presented with a port-wine stain and large café-au-lait (CAL) patch. The child continued yearly visits in clinic, developing an increasing number of brown macules. At age 6, neck pain resulted in the diagnosis of leg length discrepancy (LLD), requiring a shoe lift. Tissue biopsy was performed and negative for genetic analysis of overgrowth syndromes. Further testing for rasopathies revealed a mosaic PTPN11 mutation (24% VAF, p.A461T). Sanger sequencing from buccal swab showed the same variant in PTPN11 found in tissue, just above level of detection. Further work-up-echocardiogram, ECG, and laboratory studies were unremarkable. Our patient continues with yearly skin examinations and physical therapy. Her diagnosis is consistent with PPV spilorosea (PPV-SR) due to a PTPN11 mosaic variant.

CONCLUSION: PPV-SR is a rare multisystem disease. A single adult case of PPV-RS with PTPN11 mosaicism was documented in 2021. A recent series of mosaic variants in PTPN11 in eight individuals has been reported. Four pediatric patients had the PPV-SR phenotype with PTPN11 variant in affected skin biopsy in three. Our discovery, in addition to the four cases to date, illustrates the need for further deep pheno/genotyping of PPV. PTPN11 is a known driver of melanoma, and patients with PTPN11 variants may have increased risk for melanoma. PTPN11 is the cause of > 50% of cases of Noonan syndrome (NS), and allelic LEOPARD syndrome. PTPN11 somatic variants cause a spectrum of vascular

and pigmentary abnormalities of the skin, as well as ocular, neurologic and bony abnormalities. Also, mosaic PTPN11 variant carriers are theoretically at increased risk of having children with NS or lentigines. Future screening needs and work-up of affected individuals is unclear. We present this case for further input and to identify other potential cases, as well as promote awareness of these new genetic findings

429 - Clinical presentation and management of two consecutive cases of giant congenital hemangioma of the thigh.

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PURPOSE: Congenital hemangiomas are fully developed at birth. Postnatal involution defines patterns, named NICH, RICH or PICH. Larger volume lesions can be life threatening. Differential diagnosis with other vascular tumors, especially those related to hematological complications, must be performed. Two male patients, 2 and 8 months-old, with large complicated congenital hemangiomas are reported.

METHODS: Tumors were present at birth, with large-volume and curious similarities. More than 50% of the thigh circumference was compromised, without invading muscles. Thrombocytopenia was not detected, despite changes in coagulation tests. Images showed tumor lesions affecting the skin and subcutaneous tissue, respecting the fascial plane. MRI was similar showing a T1 isointense and T2 hyperintense mass. Pathological diagnosis was congenital hemangioma (GLUT-1 negative, CD-31 positive, D2-40 negative, Ki-67 low positivity). Large, ulcerated areas appeared early during evolution, posing a painful routine during dressing changes.

RESULTS: Sirolimus therapy was initiated just after diagnosis, with a significant reduction in the volume of the lesion. Surgical treatment was indicated due to large areas of necrosis and ulceration. Resection was radical in both cases, without significant bleeding. Closure was primary and the evolution was uneventful.

CONCLUSION: Interestingly, both cases presented the following similarities: location, dimensions, early massive necrosis with secondary infection. Sirolimus therapy was important and reduced the volume in few weeks, during surgical preparation, making the resection simpler and allowing primary closure.

Congenital hemangiomas are rare in these dimensions and clinically, the differential diagnosis with kaposiform hemangioendothelioma cannot be made, requiring anatomopathological study. Apparently, the use of sirolimus had positive response and if the absence of ulceration, single therapy and postponed surgery could be considered. On the other hand, surgery was definitive and curative, reducing the risk of adverse effects from the medication. The only question non answered was the differentiation between the evolutionary types of congenital hemangiomas, prevented by surgery.

430 - Sclerotherapy with Bleomycin of Head and neck venous malformations: impact of gelatin sponge, phlebographic type and extension of the Vm on the outcome.

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PURPOSE: To assess the effectiveness of bleomycin on head and neck venous malformations (Vm) according to the concomitant use of gelatin sponge, extension and phlebographic type (Puig-Dubois classification).

METHODS: Between 2016 and 2022 84 Patients > 0 years old with radiological and clinical diagnosis of venous head and neck malformations were treated with sclerotherapy with bleomycin +/- gelatin sponge. We analyzed extension and site of Vm, phlebography type of Vm (Puig-Dubois classification), use of gelatin sponge. 30% of patients answered to Ovama questionnaire pre and post treatment to assess aesthetic and clinical outcome. Volumetric reduction was assessed both by the patient (subjective evaluation) and by the physicians (objective evaluation)

RESULTS: We have preliminary results. Phlebographic types were I (56), II (26) e III (2). Patients reported a statistically significant improvement ($p<0.01$) of aesthetics, functionality and quality of life (relating to the Ovama items general symptoms scale and aesthetical appearance scale), showing satisfaction both for treatment and results. Subjective evaluation of volume reduction showed Vm completely disappeared in 14%, much smaller in 38%, smaller in 27% and slightly smaller in 14%. We found statistical correlation between objective volume reduction evaluation and improvement of both general symptoms scale ($p<0.03$) and aesthetical appearance scale ($p<0.05$). Considering phlebographic type of Vm and objective volume reduction, we found better response in type 2 treated with bleomycin and gelatin sponge compared to bleomycin alone; we did not found any difference in type 1 treated with bleomycin and gelatin sponge compared to bleomycin alone. We showed statistical correlation ($p<0.03$) between Vm extension and objective volume reduction.

CONCLUSION: We showed significative correlation between objective volume reduction of Vm and its extension but also with aesthetic and clinical improvement of the patient. Gelatin sponge influenced a better response to sclerotherapy for phlebographic type 2 Vm.

435 - The VASCERN-VASCA Diagnostic and Management Pathways for Kaposiform Hemangioendothelioma.

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PURPOSE: Kaposiform Hemangioendothelioma (KHE) is a rare locally aggressive vascular tumor. Its common association with the Kasabach-Merritt phenomenon makes it potentially lethal. The introduction of various therapeutic protocols and in particular the increased use of sirolimus have substantially improved outcomes in patients with KHE. In order to guide patients' families and physicians towards efficient diagnostics and management of patients with KHE, the working group VASCA within VASCERN (https://vascern.eu/) a European network for Rare Vascular Diseases has generated Diagnostic and Management Pathways for KHE.

METHODS: The Nominal Group Technique was used to establish the pathways. A center with specific clinical and research interest and experience in treatment of patients with KHE was choosen as the facilitator. The draft was subsequently discussed within the VASCERN-VASCA monthly virtual meetings and annual face-to-face meeting.
RESULTS: The pathway consists of three parts: (1) A summarized overview of the clinical, histological and genetic characteristics of KHE, followed by recommendations for diagnostics modalities; (2) a list of treatment options followed by a suggested treatment algorithm, modulated according to the clinical condition of the patient, which is objectively assessed by laboratory values and visible response on imaging; (3) Potential problems during the follow up, such as recurrence and sequelae are described. Color coded boxes are used in the pathway to differentiate a) clinical evaluations, b) investigations, c) treatments and d) associated genes.

CONCLUSION: The collaborative efforts of the VASCA working group of VASCERN, a network of the European Expert Centers, has led to a consensus or opinion statement Patient Pathways for KHE. These Pathways should help clinicians and patients outside VASCA, and it emphasizes the role of multidisciplinary expert centers in the management of KHE patients. This pathway will be available on the VASCERN website (http://vascern.eu/).

439 - Infantile Fibrosarcoma Mimicking a Vascular Tumor

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PURPOSE: To present a case in a female infant with a congenital mass on the right upper limb. The inicial presumptive diagnosis had been vascular tumor (RICH or Kaposiform Hemangioendothelioma). After performing imaging and histopatological studies, as well as molecular examination, the diagnosis of Infantil Fibrosarcoma was confirmed.

METHODS: A retrospective observational descriptive study.

RESULTS: A three-day-old female infant had an asymptomatic mass (diameter: 16cm) on her right upper limb. It was shiny red-violet and smooth-surfaced with overlying vascular paths.

The nuclear magnetic resonance (NMR) showed a mass of about 6.5 x 5.3 cm with well-defined borders on superficial planes in the medial forearm. It was T1-isointense with high signal on fluid-sensitive sequences along with marked and generalized enhancement after intravenous contrast injection. The NMR angiography revealed fast filling and findings consistent with dilated nutrient arteries and draining veins.

Lab test results were normal except for slightly elevated D-dimer. Propranolol was indicated (2mg/kg/day). Given that no improvement was reported and the mass was growing suddenly and rapidly, surgical biopsy was performed for histologic examination (87 B 2023) confirming the diagnosis of infantile fibrosarcoma.

For reducing tumor volume, chemotherapy was initiated according to EpSSG NRSTS 2005 and vincristine-actinomycin D was administered.

Molecular detection of ETV6 and NTKR3 rearrangement (FISH+) confirmed de diagnosis of infantile fibrosarcoma.

As partial response and difficulties in drug administration were observed, oral targeted therapy with larotrectinib, a specific TRK inhibitor, was started since a response rate higher than 90% has been demonstrated in patients with NTKR gen fusions.

Fast volume reduction of the tumor was achieved without any complications. Collaborative onco-dermatologic follow-up is ongoing.

CONCLUSION: If a highly vascularized mass is detected and imaging studies are not conclusive, diagnostic histologic examination should be performed. Infantile fibrosarcoma can frequently mimic other vascular tumors.

445 - Central conducting lymphatic anomaly caused by somatic activating KRAS variant in an adolescent girl with recalcitrant protein losing enteropathy unresponsive to trametinib – what is the next best step

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PURPOSE: Central conducting lymphatic anomaly (CCLA) is a rare disorder characterised by dilated and dysfunctional central conducting lymphatic channels, which can result in debilitating chylous effusions and protein losing enteropathy (PLE). Targeted therapy with MEK inhibitors have been reported to be effective in CCLA patients harbouring somatic pathogenic KRAS mutations.

We present a 12-year-old girl with CCLA caused by somatic activating KRAS variant which was unresponsive to trametinib (a MEK1/2 inhibitor) and transhepatic lymphatic embolization.

METHODS: The patient had history of linear sebaceous naevus syndrome with multi-system involvement, including left eye lid coloboma, diffuse aortopathy, microcystic right kidney, cervicothoracic spinal lipomata and right hemimegaencephaly.

She first presented with left chylothorax at age 12. Intranodal dynamic contrast-enhanced MR lymphangiogram showed dysplastic thoracic duct and retrograde lymphatic perfusion to left perihilar and pulmonary lymphatics. Needle disruption of cisterna chyli and pleurodesis resulted in temporary improvement of left chylothorax.

RESULTS: Her serum albumin is also markedly reduced (18g/L, normal range = 37-47g/L). Intrahepatic DCMRL demonstrated lymph leakage into the duodenum and retrograde lymphatic flow into mesentery and retroperitoneum. Biopsy of facial sebaceous naevus with DNA sequencing revealed a pathogenic variant in KRAS p.Gly12Asp (c.35G>A, NM 004985.4) at 11.4% variant allele fraction. A course of trametinib at 0.5mg daily was given for 6 months with no clinical improvement in PLE. Further embolization of hepatic lymphatic channels in attempt to arrest hepatic lymphorrhoea was also ineffective. The patient is currently on regular monthly intravenous albumin infusion with poor nutritional status.

CONCLUSION: For this challenging case of CCLA caused by activating KRAS mutation which is unresponsive to trametinib and embolisation of hepatic lymphatics, we would like to seek advice from other ISSVA members on the next best treatment strategy.

454 - Safety and Efficacy of Liposomal Bupivacaine Infiltration for Postoperative Pain Management in Patients with Vascular Anomalies

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PURPOSE: To assess the safety and effectiveness of liposomal bupivacaine (LB) infiltration for postoperative pain management in patients undergoing invasive procedures to treat vascular anomalies.

METHODS: A single-arm prospective pilot study was conducted, encompassing all invasive interventions for vascular anomalies in patients aged 6 years or older. DepoFoam-based 1.33% bupivacaine liposome injectable suspension (Exparel, Pacira, Miami, FL, US) was injected around the treated lesion and into access sites. Data collected encompassed patient demographics, underlying conditions, procedure types, weight-adjusted LB doses, pain levels, and pain medication use in the recovery unit. Follow-up phone calls were conducted on postoperative days 1, 2, 3, and 5 to assess side effects (e.g. decreased motor function, methemoglobinuria), pain level, as well as effects on mood, sleep, activity, and ambulation.

RESULTS: LB was utilized in 27 procedures in 24 patients with venous malformation (n=14), lymphatic malformation (n=3), arteriovenous malformation (n=3), capillary malformation (n=1), Klippel-Trenaunay Syndrome (n=1), Congenital Lipomatous Overgrowth with Vascular, Epidermal, and Skeletal anomalies CLOVES (n=1), and PTEN (n=1). The procedures included embolization, sclerotherapy, laser treatment, lymphangiography as well as removal and ligation of venous malformation. One patient was excluded due to a lack of follow-up data. The mean age was 17 years (range 6-33). The mean LB dose was 1.3 mg/kg (range 0.1-3.5). Twenty patients did not require any pain medication in the recovery unit. The mean pain level (1-10 scale) was 8, 2, 2, 2 on POD 1, 2, 3, and 5 respectively. No significant side effects were observed.

CONCLUSION: Liposomal bupivacaine (LB) proves to be a safe and effective local anesthetic agent, providing prolonged postoperative analgesia for patients undergoing painful treatments for vascular anomalies.

458 - Undergrowth is almost as common as overgrowth in large capillary malformations of the limbs
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Purpose: Diffuse capillary malformation with overgrowth (DCMO) has been well described, but there are only a few reports of capillary malformation with undergrowth. The purpose of this study was to characterize the clinical features of capillary malformations associated with over- or undergrowth in children.

Methods: After institutional approval, the records of all children with CMs treated in our tertiary institution between 2002-2019 were retrospectively reviewed. Both simple and combined CMs were included. Over- or undergrowth was defined as a difference over 1 cm in girth compared to the contralateral extremity. Statistical analyses were performed with SPSS Statistics and R. Fischer's t-test was used with significant P values of less than .05.

Conclusion: In our series, undergrowth was almost as common as overgrowth in patients with large CMs of the limbs. Undergrowth was seldom associated with a progressively worsening outcome, unlike overgrowth (p=NS, 0.051).

460 - The Benefits of Surgical Treatment of Intra-articular Vascular Malformations: A Retrospective analysis
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PURPOSE: Intra-articular vascular malformations (IAVM) are uncommon vascular anomalies typically observed in young individuals, predominantly found in the knee. The nomenclature for these lesions remains imprecise, frequently referred to in literature as synovial hemangiomas. Prompt identification poses a challenge, given their tendency to manifest with nonspecific clinical signs, contributing to delayed treatment.

METHODS: We conducted a retrospective analysis of 6 patients admitted to our centre, all of whom were diagnosed with IAVM – 5 with venous malformations (VM) and 1 with lymphovenous malformation (LVM). There were 3 female and 3 male patients with a mean age of 26.2 years (range: 10 to 53 years) at the time of the surgical treatment. Among these individuals, 5 presented with knee pain and swelling, while 1 exhibited recurrent hemarthrosis and restricted knee mobility.

RESULTS: All of the patients underwent surgical treatment, with 3 patients undergoing arthrotomies and 3 undergoing synovectomies. Immediate postoperative follow-up was uneventful in all patients. After a three-year follow-up, only one patient with LVM, who had previously undergone synovectomy, required additional surgical intervention due to a recurrence of knee pain. This led to the performance of an arthrotomy. After a mean follow-up of 1.5 years, all patients were free of symptoms, including the patient with previous hemarthrosis and restricted knee mobility.

CONCLUSION: Resection of knee IAVM by open surgery is considered the treatment of choice, as it can lead to long-term improvement of pain and joint mobility. We emphasize the significance of early surgical treatment in individuals with intra-articular VM and LVM to avert potential joint damage. Lesions treated by synovectomy diminish the risk of hemarthroses and, therefore, protect the cartilage from further erosion. Achieving complete resection through arthrotomy ensures conclusive recovery without the return of symptoms.

462 - Epilepsy with faint capillary malformation or reticulated telangiectasia associated with mosaic AKT3 mutations
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PURPOSE: Capillary Malformations (CM) are the most common type of vascular anomalies, affecting around 0.3% of newborns. They are usually caused by somatic pathogenic variants in GNAQ or GNA11. PIK3CA and PIK3R1, that regulate the PI3K-AKT-mTOR pathway, are mutated in fainter CMs such as diffuse capillary malformation with overgrowth (DCMO) and megalencephaly-capillary malformation (M-CM).

RESULTS: In this study, we present two young patients with a CM-like phenotype, associated with cerebral anomalies and severe epilepsy. Pathogenic variants in PIK3CA and PIK3R1, as well as GNAQ and GNA11 were absent in affected cutaneous tissue biopsies. Instead, we identified two somatic pathogenic variants in the AKT3 gene. Subsequent analysis of the DNA obtained from surgically resected brain tissue of one of the two patients confirmed the presence of the AKT3 variant. Focal cortical dysplasia was also detected in this patient. Genetic analysis thus facilitated work-up to reach a precise diagnosis for these patients, associating the vascular anomaly with the neurological symptoms.

CONCLUSION: This study underscores the importance to search for additional signs and symptoms to guide the diagnostic workup, especially in cases with atypical vascular malformations. Additionally, it strongly emphasizes the significance of genotype-phenotype correlation studies in guiding clinicians' informed decision-making regarding patient care.

463 - Navigating the Pulmonary Arteriovenous Malformations (PAVMs) Treatment Landscape: Unveiling Reported Common Data Elements and Core Outcome Measures

Marisabel Linares Bolsegui (Johns Hopkins Hospital); Abby Liu (The Johns Hopkins University); Thalia Liu (The Johns Hopkins University); Clifford R. Weiss (The Johns Hopkins Hospital)

PURPOSE: Over the past two decades, the literature on therapeutic interventions for pulmonary arteriovenous malformations (PAVMs) has considerably increased. While various treatments, including percutaneous transcatheter embolization (TCE) and surgical procedures, have been explored, there exists significant heterogeneity in the elements and outcomes evaluated in the management strategies. This scoping review aims to map the literature on treatment modalities for PAVMs and describe common data elements and core outcome measures in these studies.

METHODS: Using the Nested Knowledge (NK) AutoLit living platform, we analyzed retrospective studies in English that evaluated management or comparison of interventional strategies for PAVMs. Searches across three bibliographic databases (PubMed, Embase and Scopus), yielded 749 studies. After screening and eliminating of duplicates, thirty-two studies met eligibility criteria. Articles were tagged with relevant outcomes of interest, categorized by objectives, interventions, sample sizes, and outcomes.

RESULTS: TCE was the predominant focus in 30/32 records (93.7%), the most frequently evaluated outcomes included effectiveness (10/32, 34.3%), safety and complications (9/32 studies, 28.1%), and PAVMs persistence (8/32, 25%). A comparative analysis between surgical modalities and TCE was addressed in two studies. Standard post-embolization follow-up intervals were at 1, 6, 12 months, and subsequently every 6 months. Embolotherapy, using devices such as detachable balloons and coils, consistently demonstrated success rates ranging from 83% to 100%, resulting in long-term PAVMs resolution. There were no major complications, and recurrent PAVMs were effectively managed. However, there was notable variability in procedural techniques, persistence patterns, and indications for Microvascular plug systems, Amplatzer vascular plug, and coils.

CONCLUSION: Although TCE demonstrates a high rate of success, minimal complications and favorable long-term outcomes for the treatment of PAVMs, comparison of results across studies remains challenging given the heterogeneity in outcomes measures. Further development of more standardized protocols is needed for a better assessment of minimally invasive techniques for the treatment of PAVMs.

465 - A Positive Result You Don't Want – Tuberculosis and the Use of Sirolimus in Vascular Anomalies
Autumn Atkinson (UTHealth); Madison Mau (UTHealth); Alyson Galanga (UTHealth); Matthew Greives (McGovern Medical School at the University of Texas Health Sciences Center in Houston and Children's Memorial Hermann Hospital); Adelaide Hebert (UTHealth); Neethu Menon (UTHealth)

PURPOSE: While the number of cases of tuberculosis (TB) has decreased over 30 years, cases are increasing in the USA over the last two years. Several states are above the national rate and experiencing significantly increasing numbers (9.9% growth in Texas 2021-2022). Many institutions screen for TB prior to initiating immunosuppressant drugs, such as sirolimus. This presentation highlights two cases of TB in vascular anomalies (VA) patients who utilize sirolimus, reviews literature of TB screening, and proposes a decision-making tree to aid vascular anomalists in screening and treating patients for TB.

METHODS: Case 1: 16-year-old female with KTS presented with worsening of symptoms (pain and lymphatic drainage) requiring initiation of sirolimus. As part of protocol, T-SPOT was obtained and returned positive. Further work up confirmed latent TB. Initiation of sirolimus treatment was held until cleared by TB experts.
Case 2: 30-year-old female with GLA, well-controlled on sirolimus, presented to acute care facility with active extrapulmonary TB. Sirolimus was held during the acute phase of her disease and restarted after cleared by TB experts.

RESULTS: Treatment of VA during TB infections has many variables, including urgency of initiating treatment with sirolimus and status of the TB disease (latent (LTBI) versus active). In cases where sirolimus can be delayed/held, it is recommended that treatment is delayed one month for LTBI, or in active disease held until the TB symptoms start to improve. In VA that require concomitant TB treatment with sirolimus, the patient should be monitored closely when initiating LTBI treatment.

CONCLUSION: While working with immunosuppressive drugs, it is important for vascular anomalists to understand the screening processes for TB and the treatment goals while on these agents. Through these case examples and literature review, a clearer pathway for future cases is outlined and will expedite more efficient and improved care for this rare disease population.

468 - Complete cessation of massive vaginal bleedings in a patient treated with sirolimus for kaposiform lymphangiomatosis with consumptive coagulopathy.
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PURPOSE: Kaposiform lymphangiomatosis (KLA) is a rare, aggressive subtype of generalized lymphatic anomaly (GLA), typically complicated with consumptive coagulopathy. The prognosis of patients with KLA before sirolimus era was dismal, with up to 50% 5-year mortality. Sirolimus efficacy in KLA has been observed, however, data regarding the long-term prognosis, quality of life and treatment complications in patients with KLA treated with sirolimus is lacking.

METHODS: Clinical data of a 26-year-old female with KLA, treated with sirolimus for almost 9 years, have been retrieved from hospital records. Consent for publication has been obtained.

RESULTS: At the age of 7, the patient was diagnosed with GLA involving soft tissues of the neck, mediastinum, abdomen, pelvis and multiple bones. Due to gradual progression and occurrence of consumptive coagulopathy, she received interferon-alpha-2b and low molecular weight heparin, with only temporary improvement. Since the age of 16, she experienced recurrent massive bleedings from vaginal vascular malformations, requiring numerous blood transfusions. Progression of the bones' involvement led to chronic pain and compressive fracture of the Th12 vertebra. At the age of 17, labiaplasty was required due to extensive involvement of the vulvar area. Histopathological examination revealed a diagnosis of KLA, following first reports on this new entity. Sirolimus therapy was started which produced immediate cessation of vaginal hemorrhages and improvement of coagulation parameters.

Almost nine years later, the patient remains clinically and hematologically stable, with normal platelet values and coagulation profile (except for elevated D-dimer). Imaging examinations reveal consistent decrease in vascular malformations' volume. Treatment complications comprised mild hypertension, iron-deficiency anemia and recurring ovarian cysts (one requiring surgical intervention). One episode of life-threatening erysipelas complicated with streptococcal sepsis occurred in the first year of sirolimus therapy.

CONCLUSION: Sirolimus treatment may provide long-term control of severe clinical symptoms and coagulopathy in patients with initially life-threatening KLA, with manageable side effects profile.

471 - Impact of contraception and pregnancies on adult women living with complex VA.

Sandra Ondrejchak (CHU Ste-Justine); Jérôme Coulombe (University of Montreal); Josée Dubois (University of Montreal); Powell Julie (University of Montreal); Catherine McCuaig (University of Montreal); Catherine Farrell (University of Montreal); Catherine Taillefer (University of Montreal); Elizabeth Rousseau (University of Montreal)

PURPOSE: Literature is scarce regarding contraceptive and reproductive health in women with complex vascular anomalies (VA).

METHODS: Female adult patients of childbearing age from the VA clinic of a single tertiary care center in Canada have been recruited by retrospective chart review, and administered phone interviews.

RESULTS: Of the 16 patients recruited (mean age 32,8 years old), 14 used oral contraceptive pills (OCP) and intrauterine devices (IUD), with three patients experiencing worsening of their VA under OCP. Fifteen women had children, with 12 experiencing variable worsening of their VA that returned to baseline after delivery or nursing cessation. Three women had severe complications. Degree of complications was variable in each subsequent pregnancy.

CONCLUSION: Contraception and pregnancy management in women should be individualized and coordinated with a VA referral center.

472 - Fern baby Fern!

Jérôme Coulombe (CHU Ste-Justine); Josee Dubois (CHU Ste-Justine, Université de Montréal); Julie Powell (CHU Sainte-Justine, U of Montreal)

PURPOSE: A day old female term infant, with normal prenatal ultrasounds, and delivered by C-section for a breech presentation, was seen at the neonatalogy unit for a voluminous violaceous mass on her left bicep and several pinpoint purple papules on her body. Ultrasound-Doppler imaging of the mass demonstrated a heterogeneous slow flow vascular lesion measuring 5.0 x 4.5 x 3.9 cm with areas of thromboses, calcifications, and large venular ectasias compatible with a venous malformation (VM). The VM was covered with peculiar branching venules constituting the fern-patch sign of blue rubber bleb nevus syndrome (BRNBS). BRNBS is a rare sporadic genodermatosis associated with TIE2/TEK gene mutation, and characterized by progressive formation of multiple small venous malformations affecting mainly the skin and the gastrointestinal (GI) tract. When a voluminous VM associated with BRNBS is present on the skin it bears the unique fern-patch sign. At any age, some BRNBS patients may present with GI bleeding. Treatment is multimodal including watchful waiting, supportive care, blood transfusions, oral sirolimus, intestinal laser therapy, sclerotherapy, and surgery.

In our patient coagulation studies and complete blood cell count (CBC) were normal. TIE2/TEK mutation screening in the blood was negative. Genetic studies on a skin biopsy revealed a new pathogenic complex frameshift mutation of TIE2/TEK. Now one year old our patient is still asymptomatic and her VM is treated with serial sclerotherapy with doxycycline. Her work-up consists of clinical follow-up and annual CBC. Capsule and GI endoscopy were not elected due to the young age of the patient and her asymptomatic status. If she remains symptoms free a screening endoscopy will be performed around puberty; a period known for hormonal activation of VM. In conclusion, the presence of the fern-patch sign on a VM should alert physicians to the possibility of BRBNS, expediting treatment and surveillance for complications.

473 - Lymphatic malformations of the external genitalia in boys: isolated and combined with lower extremities lymphostasis

Iryna Benzar (Pediatric Surgeon); Rashad Mamedov (Pediatric Urologist, National Children Hospital OKHMATDYT); Anatolii Levytskyi (Head of Pediatric Surgery Department Boomlets National Medical University)

PURPOSE: To determine the peculiarities of the clinical course and manifestations, treatment options in boys with lymphatic malformations (LMs) of the external genitalia, isolated and combined with lymphedema of the lower extremities

METHODS: The study included 8 patients aged 9 to 16 years, three had isolated LMs of the scrotum and penis, and 5 were combined with lymphedema of the lower extremities. All patients underwent general clinical investigations, determination of protein fractions, ultrasound and MRI.

RESULTS: The clinical symptoms had their own features. Swelling of the scrotum and some hypertrophy of the foreskin were noticed by the parents from birth, a significant progression of swelling was noted at 7-10 years of age. Lymphostasis also existed from birth. Patients with isolated genitalia LMs had a significant lymphorrhea in adolescence, the volume of lymph oozing reached 1-2 liters per day. Bleomycin injections and systemic sirolimus therapy had a short-term effect. Patients with lymphostasis did not have lymphorrhea, but moderate hypoproteinemia and hypoalbuminemia were noted. All patients underwent surgical intervention in the scope of debulking, circumcision, reconstruction of the skin of the scrotum and penis. The age of patients at the time of surgical treatment was 13-16 years. Treatment of lymphostasis of the lower extremities was carried out conservatively. Both according to

the results of the preoperative MRI and intraoperatively, significant fibro-indurative changes in the subcutaneous tissue and tunica dartos against the background of lymphatic oedema drew attention.The result of the treatment is regarded as good (τ=7) and satisfactory (τ=1).

CONCLUSION: The manifestation of isolated LM of the external genitalia was severe lymphorrhea, which appeared in adolescence. Conservative treatment had an unstable result, surgical treatment was performed in all patients in the postpubertal period.

475 - **Unlocking Quality of Life: Navigating Vascular Anomalies in Lower Limbs with OVAMA Insights**
Verónica Carolina Morillo Jiménez (Vascular Surgery, Hospital Universitario La Paz); Clara Plaza Pelayo (Vascular Surgery, Hospital Universitario La Paz); Ana Mayor Di-az (Vascular Surgery, Hospital Universitario La Paz); Covadonga Mendieta Azcona (Vascular Surgery, Hospital Universitario La Paz); Álvaro Fernández Heredero (Head of Department Vascular Surgery, Hospital Universitario La Paz); Juan Carlos López Gutiérrez (Head of department Pediatrics Surgery, Hospital Universitario La Paz); Elena Marin Manzano (Vascular Surgery, Hospital Universitario La Paz)

PURPOSE: Vascular malformations (VM) are a chronic condition, sometimes limiting, due to the pain and dysfunction they entail, leading to a consequent decrease in the quality of life (QoL) for patients. Therefore, their treatment should be multidisciplinary and personalized, given the complexity involved.

In 2021, the Lokhorst group developed the OVAMA questionnaire (questionnaire for measuring symptoms and appearances in VM) with the aim of standardizing and uniformly recording the effects and impact of different types of VM from an individual perspective.

Our goal is to verify the applicability of this questionnaire in patients with low-flow vascular malformations in the lower limbs (LL).

METHODS: Out of the 369 patients in our vascular anomalies clinic, 27 patients with diffuse low- flow vascular malformations located in the LL, and without prior interventions, have been selected.

RESULTS: We collected 21 questionnaires, with an average time of 7 minutes per questionnaire, resulting in an average score of 139.75 points in the ''General Symptoms'' section (40- 300) and 43.78 points in the ''Appearance'' section (20-100).

CONCLUSION: By standarizing patients through tools that are quick, efficient, reproducible, and simple, we aim to objectively assess how different types of VM impact the QoL of our patients. This helps us provide holistic treatments. Currently there are no QoL questionnaires for complex patients with VM in the lower limbs.

In our series, all patients had low scores on the OVAMA questionnaire, indicating minimal impact on their QoL. This is consistent with the fact that this specific group of patients has not received any treatment for their condition.

Validating tools that can quickly and simply help discern which specific group of patients with VM will experience greater impact on their QoL would be beneficial. It could enable a more proactive approach in the treatments offered.

478 - Surgical resection as definitive treatment for a large symptomatic high flow arteriovenous malformation after multiple failed endovascular and medical therapies.
Jennifer Culig (St Paul's Hospital); Jodi Spelay (St pauls Hospital)

479 - Mandibular Arteriovenous Malformation (AVM) Diagnosis and Curative Treatment
Wayne Yakes (Vascular Malformation Center)

PURPOSE: To determine optimal management strategies for the treatment of intraosseous mandibular AVM.

METHODS: 12 patients (9 females, 3 males), age 9 -14; mean age 10, underwent endovascular therapy to treat their mandibular AVMs. 9 patients had distinct intraosseous AVMs. 3 had additional multiple facial and intra-maxillary AVMs requiring treatment. Outside institutions recommended massive hemi-facial resections in these patients. 4 patients had prior PVA and gel foam embolization, 1 patient had a lip graft, 1 had prior mandible surgery, all that had failed.

RESULTS: All 12 patients have demonstrated MR and angiographic cure of their AVMs. 1 patient's therapy is not completed and is on-going. The patients mandibular AVMs cured, a third AVM in this patient in the infratemporal fossa is still undergoing treatment. The follow-up range is 11 months – 41 months, with a mean follow-up of 29 months. No complications noted in treatment of mandibular AVMS. 1 patient required a minor gingival surgery after treatment of an additional intramaxillary AVM with inferior extension.

CONCLUSION: Endovascular approaches to manage mandibular AVM can be curative. Mandibular intraosseous variety is largely a fistula between artery and vein within the bone and the bulk are Yakes Type IIIa/IIIb AVMs. All can be cured by endovascular ethanol therapy alone. Surgery was not required in any patient. Surprisingly no complications were encountered in this patient series. Long-term cures are noted in this patient series with endovascular approaches alone. No massive surgical resections in any patient, even in patients with multiple AVMs of the soft tissues, mandible and maxilla, was required to effect cure. In patients who suffered hemorrhages from floating teeth, bone formed and stabilized the teeth and no further hemorrhages occurred. Ethanol sclerotherapy proved curative in mandibular intraosseous AVMs in patients who had additional facial soft-tissue and intramaxillary AVMs that were cured as well at long-term follow-up.

484 - Efficacy of a Modern AVM Classification System that Directs Curative Endovascular Therapies Accurately

Wayne Yakes (Vascular Malformation Center)

PURPOSE: To determine AVM angioarchitecture characteristics that can be predictive and direct specific curative endovascular procedures accurately and consistently to cure high-flow malformations in all anatomic locations.

METHODS: Type I: Direct arterial/arteriolar to vein/venule connection; e.g., as commonly seen in pulmonary AVF, congenital renal AVF, etc.
Type II: Arterial/arteriolar connections to a ""nidus"" that have several out-flow veins with no intervening capillary beds in any of the vascular interconnections.
Type IIIa: Arterial/arteriolar connections to an aneurysmal vein (""nidus"" is the vein wall) that drains into a dominant out-flow vein with no intervening capillary bed in these connections.
Type IIIb: Same angioarchitecture as Type IIIa, except there are more than one out-flow veins.
Type IV: ""Infiltrative"" form of AVM whereby innumerable micro-arteriolar branches fistulize through a tissue (e.g., ear AVMs) totally infiltrating it, shunting into multiple out-flow veins. Capillary beds also exist in the tissue and are admixed with the innumerable AVFs. Without the capillaries the tissue could not be viable, therefore must be present.

RESULTS: Type I: Effectively treated with mechanical devices; e.g., coils, Amplatzer Plugs, etc.
Type II: Effectively treated with ethanol embolization; trans-cath and direct puncture.
Type IIIa: Effectively treated by transcatheter ethanol, retrograde vein catheter access or direct puncture access of the aneurysmal vein and treatment with ethanol and coils, or even by coils alone.
Type IIIb: Effectively treated as above, but can be more challenging by the vein route as more veins (not a single out-flow vein) require closure.

Type IV: Effectively treated by transcatheter or direct puncture of the innumerable microfistulous AVFs by embolization with 50% -50% ethanol non-ionic contrast mixture.

CONCLUSION: This newly reported AVM Classification system has a direct impact on the curative endovascular and direct puncture embolizations and also determines embolic agents that will successfully treat and cure complex AVMS in all anatomies.

488 - Difficult Yakes Type IIa, IIIb, and IV AVMs infiltrating the Right buttock, pelvis and posterior thigh causing tissue necrosis and hemorrhages and a high output cardiac state
Wayne Yakes (Vascular Malformation Center)

Patient History
• Diagnosis: 51 yo female with massive multiple Yakes Type IIa, IIIb, and IV AVMs infiltrating the Right buttock, pelvis and posterior thigh causing tissue necrosis and hemorrhages and a high output cardiac state (CO exceeding 10 lit/min)
• 1992 - Patient noticed discoloration in her right buttock. Then developed enlarging buttock/posterior thigh ulcerations with intermittent life-threatening hemorrhages.
• 2012 - Patient presented to YVMC for initial consultation and embolization. Underwent 3 embolizations and was lost to follow-up.
• 2019 – 2020 - Patient seen and was offered no further treatments in Philadelphia, New Jersey, NY and Baltimore. Later Pt suffered a significant ulcer hemorrhage and was emergently admitted in Camden, NJ and offered right hemipelvectomy. Patient declined and was then air-evacuated to the Yakes Vascular Malformation Center in Denver, CO. - Patient had 2 emergent surgical suture ligations performed during embolization procedures on 10-06-19 & 02-12-20 - Patient had port placed on 10-30-19 - Underwent 6 wound debridements and protruding coil removal surgeries from 10-06-19 to 12-14-20 - 82 Endovascular Embolizations from 10-06-19 to 05-11-20, at times treating the patient 3-5 times weekly - Total Ethanol Utilized: 3141mL - Total Coils Utilized: 101 Nester Coils • F/up angiograms on 9-14-20 and on 12-14-20 demonstrated angio cures of the massive Rt buttock/pelvis/posterior thigh AVM, total primary healing and closure of the large ulcerations without surgical reconstructions and skin grafting, and normalization of her CO, CI, and SVR.

489 - Difficult Yakes Type IIIa/IIIb AVMs in the Right face, scalp, and neck area, massive aneurysmal outflow veins, with gross tissue enlargement of the Rt face and neck areas.
Wayne Yakes (Vascular Malformation Center)

Patient History
• Diagnosis: Massive Yakes Type IIIa/IIIb AVMs in the Right face, scalp, and neck area, massive aneurysmal outflow veins, with gross tissue enlargement of the Rt face and neck areas.
• 2018 - Patient noted rapid growth of the right neck. Patient was referred to head and neck specialist who performed a CT which revealed AVMs. Patient was then referred to YVMC.
• 2019 - 2020 - 9 Endovascular Embolizations from 09-16-19 to 10-16-20. - Total Ethanol Utilized: 57ml - Total Coils Utilized: 128
• F/up angio on 02-12-21 demonstrated cures of the massive Yakes Type IIIa/IIIb AVMs in the Right face, scalp, and neck area; and loss of the masses in the Rt face and neck area with normalization of the tissues.
• Pt underwent his final curative endovascular procedure on 10/16/20 and suffered blindness in the Rt eye spontaneously on 10/30/20. F/up angio 02/12/21 documented persistent AVM cure.
1. 39 yo male with multiple massive AVMs of the Rt face and neck & prior ligation of his Rt Ext Carotid artery. This is an extremely complex lesion in that the vascular supply was derived from both Internal Carotid arteries intracranial supply, all branches of the Lt Ext carotid, and the intracranial & extracranial supply from the Rt & Lt Vertebral arteries. Pt underwent 9 endovascular ethanol and coil procedures that ultimately cured his multiple massive Yakes Type IIIa/IIIb AVMs.

2. 14 days after his final endovascular procedure, the patient spontaneously developed blindness in his Rt eye. It is thought to be related to the final spontaneous thrombosis of his AVM causing retrograde vascular thrombosis in the Rt eye orbital arteries and veins contributing to the supply to the Rt face and neck AVMs.
3. This case shows that in complex head and neck multiple AVMs with numerous arterial supplies from intracranial and extracranial arterial sources can be cured by not addressing the in-flow arteries, but by permanently ablating the nidal elements alone, then the collaterals to the AVMs will atrese and only supply normal tissues. In this process other tissues can be affected, such as the much delayed 14 day post-procedure Rt blindness in this case. Of note, on the Ophthalmologic exam 4 months later, normal bilateral eye vascularity was documented on fundascopic exam.

490 - Unmasking the Mimic: The Tale of a Chest Lesion with a Hidden Identity

Marisabel Linares Bolsegui (Johns Hopkins Hospital); Clifford R. Weiss (The Johns Hopkins Hospital); Roy Ruttiman (The Johns Hopkins Hospital)

PURPOSE: A 44-year-old male presented with a history of chest mass, which initially appeared as a discolored birthmark, that later evolved into a fluctuating mass suspected to be a lipoma. Attempted surgical excision resulted in severe bleeding, swelling, hypersensitivity, tightness, and scarring. Ultrasound (US) indicated a low-flow AVM. MRI and MR angiography suggested a vascular tumor. Biopsy reported vascular anomaly without signs of malignancy. Subsequent US revealed a highly vascular mass (5.2 x 1.8 x 5.2 cm) with tortuous vessels. Physical examination identified a hypersensitive soft mass near the xiphoid measuring with overlying incisional keloid. Initial admission was considered as a ""high-flow vascular anomaly"" with a differential diagnosis of partially involuting congenital hemangioma (PICH). Due to risk of re- bleeding, angiogram and endovascular embolization were planned.

METHODS: Vascular access was obtained through right common femoral access.Angiogram revealed tortuous arterial vasculature, from bilateral internal mammary arteries. Mild tumor perfusion corresponded with the chest mass, without immediate shunt. PICH diagnosis was confirmed.A 5 French JB1 and a double marker microcatheter aided feeding artery sub-selection. Embolization with Embosphere® microspheres in 10 cc of 50/50 saline/Omnipaque 350 per cc of beads occurred at four sites(bilateral superior and inferior mass margins)on the right side. On the left side,1 cc of 300-500 plus 1 cc of 500-700 beads were used in sites 1 and 2. Embolization continued until 5 beats of stasis were achieved.

RESULTS: Post-procedure angiography showed no arterial enhancement, with residual static contrast.US demonstrated decreased size(1.8 x 3.6 cm)and vascular enhancement.The patient experienced significant symptomatic relief.

CONCLUSION: This case underscores the complexity of vascular anomalies, emphasizing the need for a thorough diagnostic journey and a multidisciplinary approach. The successful endovascular embolization highlights the crucial role of interventional radiology in managing intricate vascular lesions and the importance of considering a wide range of differential diagnoses in atypical clinical presentations

491 - TUFTED ANGIOMA: ANALYTICAL DESCRIPTION OF 13 CASES IN THE DERMATOLOGY SERVICE, UNIVERSITY HOSPITAL

Jessuangela M. Moreno (Universidad Central de Venezuela); Arianny K. Silva (Universidad central de Venezuela); María G González (Universidad Central de Venezuela); María D Esteves (Universidad Central de Venezuela); Elizabeth Ball (Universidad Central de Venezuela); Ana M Sáenz (Universidad Central de Venezuela)

PURPOSE: Characterize patients with histological diagnosis of tufted angioma from the Dermatology consultation between January 1, 2000 and December 31, 2022. Analyze the demographic characteristics

according to sex and age group, clinical presentation, average time of diagnosis, indicated treatment and evolution.

METHODS: Retrospective, observational and descriptive study, where a review was made of all patients who had a diagnosis of AT from January 1, 2000 to December 31, 2022, from the Dermatology Service of the University Hospital.

RESULTS: A total of 13 histopathologically confirmed TA cases were included in the study. The female sex predominated.61.54% were documented cases in pediatric ages and 5 patients in adults. The female sex predominated with 61.53% (8 patients). The age of onset of the lesions was: at birth 30.77% (4 patients), followed by 15.38% (2 patients) in the breastfeeding period and 2 patients in the preschool and school period with 7. 69%, while 38.46% developed the lesions in adulthood. The predominant clinical morphology was tumors (38.46%), followed by plaques, papules and nodules of variable location.Regarding associated symptoms, only 30.77% reported pain and 61.54% did not present any concomitant symptoms. A pediatric patient suffered from the Kasabach Merrit Phenomenon. Therapeutic management was documented in 10 patients; Surgical removal was performed in 4 adult patients (30.76%). In the pediatric group, the documented management was systemic corticosteroids in 2 patients due to associated pain; Tumor regression was evident in 3 pediatric patients.

CONCLUSION: TA presents various clinical and pathological characteristics. It is important to consider it as a differential diagnosis for any congenital and acquired vascular tumor, and a histological study is necessary for the diagnosis.

492 - Percutaneous sclerotherapy of a supraglottic venous malformation under endoscopic visualization

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PURPOSE: Vascular anomalies of the head and neck have the potential to cause life threatening upper airway obstruction. There are scattered case reports describing the management of upper airway vascular anomalies. However, there are no previous reports of a supraglottic vascular anomaly that was managed simultaneously via a percutaneous ultrasound-guided and endoscopic (laryngoscopic) approach.

METHODS: We herein describe a 12 year old male patient with a diagnosis of multifocal venous malformation who presented with near-complete supraglottic airway obstruction. The patient was placed in suspension laryngoscopy and a large, obstructive supraglottic mass was visualized. The mass was visually consistent with a venous malformation of the upper airway. The patient was carefully intubated with a small endotracheal tube around the mass.

With the mass under endoscopic airway visualization by the otolaryngology team, the mass was percutaneously accessed under ultrasound guidance by the interventional radiologist and bleomycin foam injected under a combination of endoscopic and ultrasound visualization. The patient was extubated immediately post-procedure, monitored overnight and discharged the next day.

RESULTS: Simultaneous visualization of the vascular anomaly by the otolaryngology team allowed for precise and targeted filling of the anomaly with the appropriate volume of sclerosing agent. Extensive endoscopic photo-documentation and video recording of the mass filling with sclerosing agent was

performed for future presentation. At a 6 week clinic nasolaryngoscopy the patient had a patent airway with complete resolution of the supraglottic mass.

CONCLUSION: Supraglottic venous malformations can lead to life threatening upper airway obstruction. Percutaneous ultrasound-guided bleomycin sclerotherapy under simultaneous endoscopic visualization is an effective treatment option. This combined approach may allow for more precise and targeted sclerotherapy. Despite near-complete glottic obstruction in this case, the patient recovered fully without any need for prolonged intubation or further intervention.

493 - TREATMENT WITH DIRECT ORAL ANTICOAGULANTS, APIXABAN, IN LOW FLOW VASCULAR MALFORMATIONS.

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PURPOSE: Patients with diffuse low-flow vascular malformations present chronic limiting pain that is poorly controlled despite third step analgesia, antithrombotic treatment and other interventions such as surgery, endovascular procedures, or intralesional laser.

Direct oral anticoagulants, specifically, apixaban, seem to control chronic pain and the consumption coagulopathy in patients with low flow malformations.

Our purpose is to analyze whether a significant improvement in the characteristics under study is observed in our patients treated with apixaban.

METHODS: A retrospective longitudinal study is developed with patients with low flow malformations who present uncontrolled pain and consumption coagulopathy with elevated D-dimer levels in treatment with Apixaban in our hospital.

Monitoring and comparison of D-Dimer levels and symptoms are carried out before starting treatment with apixaban and afterwards, adherence to treatment and occurrence of complications.

RESULTS: We included 12 patients from our cohort of 369 patients with slow-flow malformations. We had 3 losses due to lack of monitoring. All patients had a previous increase in D-dimer levels (median 2830 ng/dl and range 842 and 23940 ng/dl). All patients experience a reduction in D-dimer levels.

We observed a statistically significant reduction in D-dimer levels post-treatment (P=0.015),the median reduction is 1386 ng/ml with a reduction range between 280 and 4860 ng/ml. The median reduction time was 5.23 months, this reduction is maintained with a median of 25.4 months in 8 of the 9 patients. In addition, a subjective improvement of symptoms is observed.

All patients had complete adherence to treatment, without the appearance of adverse effects.

CONCLUSION: In conclusion, treatment with apixaban offers a safe therapeutic alternative in the treatment of low-flow MVD, with better pain control and control consumption coagulopathy demonstrated by a reduction in D-dimer levels.""Patients with diffuse low-flow vascular malformations present chronic limiting pain that is poorly controlled despite third step analgesia, antithrombotic treatment and other interventions such as surgery, endovascular procedures, or intralesional laser.

Direct oral anticoagulants, specifically, apixaban, seem to control chronic pain and the consumption coagulopathy in patients with low flow malformations.

Our purpose is to analyze whether a significant improvement in the characteristics under study is observed in our patients treated with apixaban.

495 - Customized ‘cookie-cutter' technique in the management of a scalp AVM in a pediatric patient: a multidisciplinary approach

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PURPOSE: We present the case of a 13-year-old male patient with a progressively enlarging symptomatic arteriovenous malformation (AVM) located in the medial frontal scalp region near the bregma. Following multidisciplinary evaluation, the AVM nidus was precisely characterized by angiography, with dimensions of approximately 4.5 x 3.5 cm, and 1.5 cm thick. Afferent arteries included bilateral frontal and parietal branches of superficial temporal arteries (STAs), and the right ophthalmic artery. AVM drainage was through subcutaneous veins: left frontal vein directed toward the facial vein and bilateral parietal veins.

The treatment plan involved the placement and inflation of a skin expander and, three months later, nidus embolization the day before AVM excision.

METHODS: To preserve scalp arterial vascularization and prevent embolic fluid leakage into subcutaneous veins, a ""cookie-cutter technique"" (CCT) was considered. However, due to the presence of the tissue expander, the conventional cylindrical container approach as per CCT was unsuitable for peripheral compression of nidus, because of the irregular surface. This challenge was overcome by obtaining 3D photographs of the patient's head, enabling the design of a custom 3D printed PET tube section with one side exactly following the patient's head shape around the AVM.

RESULTS: A nearly complete nidus embolization was achieved injecting 11 ml of PHIL® liquid embolic agent and 7 ml of 40% diluted Glubran2® glue through direct percutaneous punctures, while reducing AVM flow with temporary balloon occlusion of STAs, systemic blood pressure reduction and compression on the custom "cookie cutter".

The following day, AVM excision and scalp reconstruction were performed with negligible blood loss.

The patient experienced an excellent recovery with no complications, except for two small occipital pressure sore skin lesions related to the headrest of the angiographic table.

CONCLUSION: This case shows the useful application of custom 3D-printed CCT for the treatment of superficial AVMs located on irregular surfaces.

498 - Dermoscopic findings in targetoid hemosiderotic hemangioma

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PURPOSE: Targetoid hemosiderotic hemangioma (THH) is a benign vascular lesion. Its dermoscopic findings have been reported in a few studies. Our purpose is to further describe them.

METHODS: A retrospective observational study was carried out in a tertiary hospital. A search was undertaken in the Pathology records of the last fifteen years using the key words: targetoid hemosiderotic hemangioma, and ""hobnail"" hemangioma. Clinical and dermoscopic photos, if available, were reviewed.

RESULTS: There were 26 patients with a histological diagnosis of HHT, 12 of them women. The median age was 34 years, and the most frequent location were lower extremities (9 patients) and the back (5 patients). Five patients presented symptoms, such as bleeding or pain. Dermoscopic images were available in 10 cases. The most frequent findings were a homogeneous pink background (9 cases), clods (5 cases) and fine peripheral pigment network (5 cases). Less frequently, dots, ecchymotic halo, chrysalis, scales, and perifollicular plugs were observed.

CONCLUSION: Dermoscopy is a useful tool during physical examination, which allows a more accurate diagnosis of THH.

503 - Alpelisib outcomes in cervicofacial lymphatic malformations: early observations
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PURPOSE: Cervicofacial lymphatic malformations (CFLM) are congenital vascular anomalies associated with somatic activating mutations in PIK3CA. Individuals with CFLM have unique functional and aesthetic complications including airway obstruction, dysphagia, and oral bleeding that are difficult to manage with surgery and sclerotherapy. Alpelisib, a PI3K inhibitor, is an emerging therapy available for treatment PIK3CA-related disease. Our objective is to describe the initial outcomes and side effects of alpelisib utilization in a cohort of individuals with CFLM.

METHODS: Individuals with CFLM currently treated with alpelisib through a multidisciplinary vascular anomalies clinic at a tertiary children's hospital were included in the study. Clinical characteristics including prior treatments, malformation complications, medication dosage, side effects, and subjective clinical outcomes were collected.

RESULTS: Ten individuals with CFLM were treated with alpelisib. The median age at alpelisib initiation was 12.8 years (range: 7.5-45.8). Prior treatments including debulking surgery (N=6), sclerotherapy (N=5), sirolimus (N=9), and miransertib (N=1). PIK3CA mutations were identified in seven individuals. Median length of therapy at last evaluation was 6.4 months (range: 1.6-14.0). Starting dose was 125 mg for adults and 50 mg for children. Dose reductions were performed in all adults (N=2) for side effects, while dose increase was performed in five children (N=8) with no dose reductions. Side effects included headache (N=5), hair loss (N=3), weight loss (N=3), increased thirst (N=2), eczema/rash (N=2), and decreased appetite (N=2). Nine individuals (90%) had subjective improvement at last follow up. Subjective improvements included decreased oral bleeding (N=4) and decreased size/fullness of CFLM (N=7). All individuals elected to continue therapy at last follow up.

CONCLUSION: Alpelisib was well-tolerated in our cohort of individuals with CFLM with limited side effects. Subjective improvement in CFLM size and/or symptoms were found in 90% of individuals despite limited length of therapy to date, supporting the ongoing use of alpelisib in CFLM.

504 - Radiological-pathological agreement in reporting venous malformations. Comparison between Magnetic Resonance Imaging (MRI) and histopathological findings
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PURPOSE: The pathological patterns of venous malformations (VMs) vary in severity and are generally characterized by large, dilated vessels and low flow blood that over time can organize into phleboliths. Sometimes small capillary and/or lymphatic vessels can also be present, along with micro and/or macro-shunts alone or in different combinations. Furthermore adipose tissue can be interposed between the malformed vessels. Magnetic resonance imaging (MRI) is a crucial examination in diagnosis of these lesions since it can accurately identify different typical features of VMs.

The aim of our study was to compare MRI and histopathological findings in VMs of children to assess MRI possibilities and limitations.

METHODS: In a retrospective study two observers independently evaluated contrast-enhanced MRI of 26 patients affected by VMs. Several radiological parameters were evaluated and compared with histopathological findings. The agreement between the inter-observer radiological evaluation and between the histopathological and the radiological diagnosis was verified using Cohen's Kappa.

RESULTS: MRI inter-observer agreement was optimal for microshunts and excellent for the remaining findings. The radiological-pathological agreement was perfect for the presence/absence of phleboliths and of macroshunt; almost perfect for the presence of intralesional adipose tissue, lymphatic component and microshunts.

CONCLUSION: Even considering the inter-observer variability, MRI in VMs can detect the presence of phleboliths, adipose tissue and lymphatic component with an excellent accuracy. MRA can detect AV microshunts in simple VMs and also in combined VMs with a substantial agreement with histopathological findings.

505 - Generalized lymphatic anomaly with pleomorphic bizarre cells

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PURPOSE: Complex lymphatic anomalies are a group of disorders characterized by diffuse or multifocal lymphatic malformations. Three different conditions are usually distinguished under this term: Generalized lymphatic anomaly (GLA), kaposiform lymphangiomatosis (KLA) and Gorham-Stout disease (GSD). All of them are characterized by the presence of irregular vascular channels lined by bland endothelial cells. The presence of highly atypical endothelial cells has not been described in these lesions.

METHODS: We present the case of a 6 month-old male who developed bilateral chylothorax.

RESULTS: Imaging studies revealed the presence of multiple lesions involving the right pectoral region, the spleen and bone. A biopsy of the pectoral lesion revealed irregular thin-walled vessels in a dissecting pattern, lined by large, pleomorphic cells with smudgy chromatin, some of them forming clusters floating inside the lumen. It was diagnosed as a lymphatic malformation with degenerative atypia based on the clinical presentation, the appearance of the nuclei and the lack of mitoses.

CONCLUSION: The cytological features were similar to those observed in other lesions with degenerative atypia, such as ancient schwannoma or symplastic hemangioma. It represents a potential pitfall, which should not lead to the diagnosis of angiosarcoma, when all clinical and histopathological information is taken into account.

506 - Primary Lymphedema: the gene matters

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PURPOSE: Primary lymphedema (PLE) is a rare genetic disorder characterized by chronic tissue swelling due to developmental defects of the lymphatic system.It can occur in an isolated form or as part of a genetic syndrome. The genetic background is heterogeneous, more than 30 different genetic and clinical entities are reported and associated.

METHODS: We aimed to characterize a cohort of patients treated at our interdisciplinary PLE clinic.All individuals underwent a careful clinical evaluation and physical examination.Genomic technologies such as SNP array,whole exome Trio-sequencing as well as karyotyping were applied.

RESULTS: Twenty-eight patients were included,in 15 patients genetic testing was performed (53%). In 10 (35%), possible underlying genetic etiologies were identified:3 patients with a syndromic form of PLE: 45,X karyotype (Turner syndrome, n=2)) and biallelic pathogenic variants in GATA-2 (n=1). In one patient with a late-onset PLE a heterozygous variant in PIEZO1 (n=1) was detected.In three patients with congenital PLE, a pathogenic variant in VEGFC (n=3) was found.A heterozygous variant in MAP3K3 (n=1) was found in one patient with a Lymphedema of all extremities and the face. In two patients variants with uncertain significance were detected: in one patient with generalized lymphatic anomaly (GLA) and PLE a variant in MET (n=1) was identified,in another patient with congenital PLE a variant in APPL2 (n=1) was found.

CONCLUSION: In this cohort of 28 patients with PLE, a genetic abnormality was identified in 10 patients (35%), which is in concordance with the literature.

Molecular analysis greatly impacts clinical management. Pathogenetic variants in GATA2 (Emberger Syndrome) are associated with many extracutaneous abnormalities such as immunodeficiency,deafness and malignancy.PIEZO1 pathogenetic variants may lead to deafness and learning disabilities whereas PLE in Turner syndrome has a good prognosis with possible spontaneous regression.

For the first time, a heterozygous germline variant in MAP3K3, a gene involved in multiple other vascular anomalies, was found in PLE.

508 - Effective treatment of a unifocal venous malformation expressing an activating PIK3CA mutation with topical sirolimus

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PURPOSE: A 2-year-old female presented with a history of a of red-purple nodule on the right lateral nasal bridge present since the first year of age. There was no overgrowth or asymmetry noted. Over the subsequent year, the nodule enlarged, with development of superficial surface ulceration. There was one episode of mild bleeding after trauma, but it was otherwise asymptomatic. MRI demonstrated thickening of the soft tissues, no extension into adjacent bone, asymmetric prominence of the right facial artery but no abnormal vessels within the lesion. Skin biopsy revealed small thin vascular channels within the reticular dermis negative for GLUT-1, in keeping with a venous malformation (VM). Genetic testing was performed on DNA extracted from affected tissue revealing a pathogenic mutation in PIK3CA (NM_006218.2:c.3140A>G, p.His1047Arg; allele fraction 2%, consistent with somatic mutational event). Topical sirolimus 0.2% in petrolatum was recommended twice daily. After 6 weeks of treatment, the lesion had faded and flattened, and after 5 months, it was barely visible. At the last follow up, 19 months after starting topical sirolimus, the treatment had been continued and benefit maintained.

Topical sirolimus is used increasingly in the management of a variety of superficial vascular anomalies, most commonly capillary-venous-lymphatic malformations (CLVM) and lymphatic malformations (LM), but less is known about the response of VM to this modality1-4.

This case demonstrates the potential dramatic improvement in overall cosmetic appearance and symptoms in a patient with PIK3CA-associated venous malformation treated with topical sirolimus. The favorable response may be related to the underlying genetic mutation, as well as the localization of the lesion on the nasal bridge where the skin is thinner (and therefore a topical preparation is more readily absorbed). This may prove a non-invasive and effective treatment options in this subset of lesions.

510 - Differences in phenotypes and response to Sirolimus between venous malformations harbouring TEK vs PIK3CA mutations

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PURPOSE: Venous malformations (VMs) are caused by somatic gain-of-function mutations in TEK/PIK3CA, which, through the PIK3CA-AKT-mTOR pathway, lead to excessive and abnormal angiogenesis. mTOR inhibitors, like sirolimus, can block this pathway. Our research question was - do VMs caused by TEK mutations present differently and respond differently to sirolimus vs those with PIK3CA mutations.

METHODS: We present nine children with VMs in whom we have identified somatic mutations in TEK (n=7)/PIK3CA (n=2). Charts were reviewed for demographic features, baseline characteristics and symptoms, localized intravascular coagulation (LIC) profiles, previous/adjunct therapies, and sirolimus use. We assessed side effects as well as clinical and LIC (d dimer, fibrinogen, platelet count) response to sirolimus.

RESULTS: 7/9 children were started on sirolimus at ages 6-17. This included the 4 patients with a ""Bockenheimer"" TEK mutation (Leu914Phe). Variant Allele Fraction (VAF) ranged from 1.60 - 14.0%. All patients had unifocal VMs except one with multifocal sporadic venous malformation (MSVM). 6/7 patients with TEK mutations had very elevated (median of 17.7 ug/ml) D-dimers (DD) and reduced fibrinogen pre-sirolimus. 6/7 patients with TEK mutations were commenced on sirolimus although one prematurely stopped it after 1 month due to side effects. The 5 remaining patients on sirolimus all showed significant improvement in LIC markers: a median decrease in DD of 69% and normalization of fibrinogen.

1/2 patients with PIK3CA mutations showed a slightly elevated DD with normal fibrinogen whilst the other showed no features of LIC. Patients were on sirolimus from 1 mo-3 years (targeting levels of 5.0-15.0 ug/L) and most reported improvement in symptoms, and LIC markers. Generally, it was well tolerated although most reported oral ulcers.

CONCLUSION: VM caused by TEK mutations were more extensive and debilitating and exhibited much more features of LIC than those with PIK3CA mutations. Generally, sirolimus improved symptoms and significantly improved LIC profiles.

516 - Anticoagulation Effects on Quality of Life in Patients with Slow-Flow Vascular Malformations

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PURPOSE: Pain from slow-flow vascular malformations (SFVM) is common and may due to slow-flow, swelling, and localized intravascular coagulopathy (LIC) with frequent impact on quality of life (QOL). The objective of this study was to determine if anticoagulation in SFVM would improve QOL, decrease pain and/or improve laboratory markers of LIC.

METHODS: This multi-institutional prospective nonrandomized observational study included subjects with SFVM and prescribed anticoagulation by their treating physician. Subjects were excluded if anticoagulation was initiated only for peri-procedural interventions or if they were on sirolimus for less than 3 months.

Patient assessments (Peds QL survey, demographic and laboratory data) occurred at study entry, 2 weeks and 4 weeks after starting anticoagulation.

RESULTS: Data were available on 35 patients with SFVM. Median age was 20 (range 7-59) years. Patients were predominately female (65.7%) and Caucasian (65.7%). All were started on a direct oral anticoagulant - rivaroxaban (n=33) or apixaban (n=2). Six (17%) patients were stable on sirolimus prior to starting anticoagulation. Four patients were stable on aspirin (81mg-325mg daily). 12 patients experienced minor adverse bleeding events, including heavy menstrual bleeding, rectal bleeding, bruising and epistaxis. 1 patient experienced major bleeding with hematuria requiring cessation of anticoagulation.

D-dimer and pain scores decreased and QOL increased significantly by 2 weeks (Table 1).

CONCLUSION: Patients with SFVM and pain benefit from short-term anticoagulation which is supported by improved QOL, decreased pain and improvement of coagulation parameters. This improvement will need to be carefully balanced with bleeding risks.

519 - Extensive Venous Anomalies in a patient with TEK gene mutation

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PURPOSE: A three-year-old female with bluish/purple vascular discoloration on hands, feet, chest, and back presented to a vascular anomaly clinic at three months of age. The discoloration, present since birth, gradually increased in size and intermittently caused pain, swelling, and hard nodules, with no excessive bruising or bleeding. This case aims to discuss a patient with extensive TEK-associated venous malformation, emphasizing the diagnostic role of MRI, venography, and genetic testing.

METHODS: The diagnostic workup included whole-body MRI with/without contrast, MRA angiography from pelvis to toes, and digitally subtracted venography using 21-gauge micropuncture needles of intramuscular venous malformations of the right and left popliteal fossa. Ultrasound-guided percutaneous core biopsy of the malformation and skin punch biopsy of lower extremity soft tissue were sent for deep next-generation sequencing of a panel of genes associated with vascular malformations.

RESULTS: MRI findings indicated extensive edema and abnormal T2 hyperintensity in bilateral lower extremities, right upper extremity, and back and pelvis muscles without osseous involvement, consistent with extensive venous malformation. Venogram demonstrated lower extremity venous malformation without discernible deep infra-popliteal veins and hypoplastic popliteal and femoral veins. Genetic testing showed a somatic TEK:c.2740C>T (p.Leu914Phe) pathogenic variant at 4.4% variant allele fraction.

CONCLUSION: Patients with extensive venous malformations, especially without functional deep venous drainage require multimodal treatment from an interdisciplinary team to address symptoms like swelling and pain, and to manage complications of bleeding and intravascular coagulation. Treatment with sclerotherapy or surgical debulking may be indicated. Clinicians need to be familiar with the common genetic mutations and signaling pathways underlying vascular anomalies as genetic testing results directly affect treatment options. Targeted drug therapies, such as mTOR inhibitor sirolimus and PI3K inhibitor alpelisib, have proven effective in improving outcomes and quality of life for TEK-associated venous malformation patients.

520 - Prenatal Sirolimus for Congenital Lymphatic Malformations - ethical dilemmas, review of literature, case reports, and discussion

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PURPOSE: The use of prenatal medications for fetal treatment of vascular anomalies (VA) is rising and currently under study. Presently, there are very few case reports and available data on the prenatal use of sirolimus for congenital lymphatic malformations (LM). Conversely, there is literature present in the fields of transplant medicine and tuberous sclerosis (TSC) that describes maternal and fetal effects while on sirolimus.

METHODS: This presentation includes literature review of sirolimus use in VA, transplant medicine, and TSC for congenital rhabdomyomas, followed by case presentations. By reviewing the successes and challenges of these cases, the presentation will dive into the ethical considerations, barriers to care, and needs for future application.

Regarding ethical concerns, questions/concerns to be addressed include:

1) What is the acceptable maternal risk for fetal benefit?

2) Who is the appropriate person to determine what risks are acceptable?

3) When expert opinion conflicts with patient goal, what is the ethically permissible option?

4) How to respect for patient autonomy while simultaneously protecting/promoting safe practice?

RESULTS: Two patient cases are highlighted where sirolimus was introduced at 26-30 weeks gestation and continued to delivery. Maternal drug levels and fetal growth curves, along with fetal MRI imaging will be shown. Prenatal complications were limited and unrelated to sirolimus. After delivery, case 1 showed clinical effects of sirolimus, but later developed localized infection of the LM that later required surgical interventions. Case 2 is set to be delivered at the time of this abstract submission.

CONCLUSION: The objectives include to review/analyze the medical indications and ethical dilemmas in prenatal/maternal use of sirolimus; and demonstrate successful use of prenatal sirolimus through case presentation and discussion. Furthermore, it is imperative to share this experience to prompt further studies and collaboration to grow this sector in the VA field to improve morbidity and mortality of our youngest patients.

521 - Mouse model of GNAQ-related vascular anomalies and coagulopathy

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PURPOSE: Activating somatic mutations in the guanine nucleotide-binding protein G(q) subunit alpha (GNAQ) gene family have been identified in childhood vascular tumors. Patients experience extensive disfigurement, chronic pain and severe complications including a potentially lethal coagulopathy termed Kasabach-Merritt phenomenon. Animal models for this class of vascular tumors do not exist. This has severely hindered the discovery of the molecular consequences of GNAQ mutations in the vasculature and, in turn, the preclinical development of effective targeted therapies.

METHODS: We generated the first mouse model for GNAQ-related vascular anomalies, using an inducible Cre/lox system to drive EC-specific expression of mutant p.Q209L GNAQ in postnatal and adult mice. The vasculature in different model tissues such as the subcutaneous and intestinal tissue was analyzed histologically and by 3D confocal microscopy. Furthermore, hematological analysis was performed to validate the occurrence of coagulopathy. RNA sequencing was conducted to reveal targetable pathways.

RESULTS: Analysis of mutant mice revealed abnormal vascular morphogenesis, widespread vascular tufts and increased vascular permeability. These mice also developed thrombocytopenia and coagulopathy. RNA sequencing of EC expressing GNAQ p.Q209L highlighted the MAPK/ERK pathway as one of the most highly upregulated compared to GNAQ WT cells. This mechanistic finding was confirmed in vitro, in the murine model and in patient-derived tissue. In a preventative study we demonstrated that inhibition of the MAPK/ERK pathway with a MEK inhibitor prevented the formation of vascular lesions by reducing EC proliferation, vascular permeability, and normalized thrombocytopenia and coagulopathy. In a therapeutic study, MEK inhibition significantly improved the survival of mice, suggesting it may be a promising therapy for patients.

CONCLUSION: The murine model presented in this work will be instrumental to decipher the cellular and molecular mechanism driving vascular tumors and associated coagulopathies.

523 - Resolution of refractory coagulopathy in two cases of complex lymphatic anomaly following partial splenic embolisation

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PURPOSE: Complex lymphatic anomaly (CLA) is a rare disorder characterised by diffuse, multicentric proliferation of lymphatic vessels, leading to disruption of normal tissue architecture and organ dysfunction and in some cases a severe refractory coagulopathy. Recurrent somatic activating mutations in the genes PI3KCA and NRAS have been described in CLA, which has enabled successful use of targeted therapies to reduce disease progression and reverse coagulopathy in severe cases. We present two patients with CLA with severe chronic thrombocytopaenia refractory to medical therapy who had complete resolution of thrombocytopaenia following partial splenic embolisation.

Case 1 - A 19-year-old boy was known to our team with complex lymphatic anomaly affecting the left leg, retroperitoneum, spleen, left kidney and vertebral bodies. He was wild-type for known genetic causes of CLA following high-depth Next Generation Sequencing. He had an ongoing consumptive coagulopathy with chronic thrombocytopenia refractory to medical treatment with alpha-interferon, vincristine, propranolol, thalidomide and steroids. He underwent partial splenic embolisation at the age of 4 years, which removed 80% of his spleen and lead to resolution of his thrombocytopaenia.

Case 2 - A 17-year-old boy known to our team with NRAS p.Q61R complex lymphatic anomaly involving the left thigh, pelvis, abdomen and retroperitoneum, spleen, thoracic cavity and right lung. He had an ongoing consumptive coagulopathy with chronic thrombocytopaenia and platelet numbers in single figures. He had a transient platelet increase following prednisolone which was not sustained and trialled sirolimus which was stopped to a significant adverse reaction. He then underwent splenic embolisation at the age of 16 years which normalised his platelet count. We present two cases of severe thrombocytopenia resolved by partial splenic embolisation. Clinicians should be aware of this as a possible simple effective intervention to treat consumptive coagulopathy in CLA with splenic involvement and which may obviate the need for life-long medical therapy.

524 - Epidural Venous Malformation with Unseen Connection to the Azygos Vein

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PURPOSE: Despite being congenital, spinal vascular malformations can have various clinical presentations, often enlarging in response to stimulation such as trauma or infection. We present the first case report of a superficial venous malformation (VM) and an unrecognized epidural plexus VM that were anatomically separate aside from a connecting draining vein. Treatment with transarterial coil embolization resulted in immediate improvement in bilateral lower extremity weakness and dystonia.

CONCLUSION: Our case is unique in that the epidural VM was not initially visible with MR imaging, and symptoms presented suddenly after ethanol sclerotherapy of the peripheral VM. Although unknown at the time, it is likely that ethanol refluxed via the draining vein into the unrecognized VM, potentially stimulating it and resulting in partial thrombosis or an increase in size. This highlights the need to monitor draining veins closely on MR when embolizing peripheral lesions to avoid damaging other lesions poorly visualized on imaging. Due to the progressive nature of VMs, it is also important to monitor epidural draining plexuses if visualized. This is especially difficult to do when patients have VNS implants. Albeit rare, epidural plexus VMs should be embolized, as venous interventions can lead to an improvement in neurological symptoms.

526 - Recurrent orbital epithelioid hemangioma with bony metastases: a difficult case

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PURPOSE: We present this difficult case to obtain the opinion from colleagues on management

METHODS: retrospective case review

RESULTS: A 15 year old male patient was previously healthy until November 2021, when he noted a mass near the lateral canthus. Thereafter he developed blurry vision, thus prompting evaluation.

Biopsy of this mass showed a vascular proliferation with + CD31, + ERG, + FLI1, scattered + CD34, scattered + TLE1, KI67 5%. Stains were negative for FOSB, EMA, SMA, Desmin, Myogenin, S100, NSE, and STAT6. Histopathology favored epithelioid hemangioma (EH), and the mass was resected. Repeat imaging showed regrowth of the tumor, prompting a second resection. He developed daily continuous bleeding from the right lower conjunctiva after resection, and most recent repeat MRI showed a focal 10 mm region of enhancement in the right periorbital soft tissues.

Additionally, he developed new lower back pain, prompting MRI of the spine. This showed multiple enhancing lesions measuring up to 12 mm involving the L2, L5, S1 vertebral bodies as well as within the inferior left sacral ala, sacrum, and right iliac bone.

The differential diagnosis currently includes metastatic epithelioid hemangioendothelioma (EHE) vs metastatic epithelioid hemangioma. FISH and molecular analysis are pending to clarify diagnosis as EH and EHE are each typified by specific gene rearrangements.

CONCLUSION: Both EH and EHE are extremely rare vascular tumors, and even more rare in pediatric patients. EH is more likely to occur in young adults, however distant bony metastases are not typical, and most cases in the literature are treated with resection. No evidence-based treatment recommendations exist for EH with multifocal bony lesions. EHE may present with distant metastases, and various modalities have been studied retrospectively on small numbers of patients, however there are limited cases in the literature to guide therapy in pediatric patients. Therefore, we seek to discuss best course of treatment.

527 - Bleomycin-induced hyperpigmentation following treatment of vascular malformations.
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PURPOSE: To report and characterize cutaneous hyperpigmentation following bleomycin injections for the treatment of vascular malformations.

METHODS: We conducted a retrospective analysis of patients who developed hyperpigmentation following injection of bleomycin for the treatment of vascular malformations. Data extracted included age, gender, weight, skin type, diagnosis and location of the treated lesion, dose of bleomycin dose and other agents, location and potential causes of the hyperpigmentation as well as the evolution of pigmentation over time.

RESULTS: Eighteen patients (11 males) developed hyperpigmentation following 20 procedures during which bleomycin injection was used for the treatment lymphatic (n=12), venous (n=3) and other vascular malformations (n=3). The mean age was 6.6 years (range 0.1-28.4 years) with a mean weight of 27.3 kg (3.3-86.6 kg). Malformations were located in the head and neck region (n=8) followed by the lower extremities (n=4) and upper extremities (n=3). Fitzpatrick skin type 2 was the most common (n=6), followed by types 4 (n=3) and 5 (n=3), 2 patients were unable to be determined. The mean bleomycin dose per procedure was 5.7 units (range: 0.8-15.0 units) with a mean dose per weight of 0.21 units/kg. The mean cumulative dose was 7.8 units (range: 2.0-16.0 units) or 0.28 units/kg. The average follow-up period was 1.0 year (range: 0.1-7.9 years). Hyperpigmentation most frequently occurred at the sites of adhesive tape application (n=8), sites of bleomycin injection (n=5), pressure (n=2), scratching (n=2) and unclear (n=1). None of these hyperpigmentations fully resolved.

CONCLUSION: Permanent bleomycin-induced hyperpigmentation is frequent and caused primarily by small traumas to the skin by adhesive tape, needle puncture, pressure and scratching.

530 - Clinical, histological and radiological characterisation of a cohort of PHOST
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PURPOSE: PTEN hamartoma syndrome (PTEN-HS) is a cancer predisposition syndrome caused by heterozygous germline mutations in the tumor suppressor gene PTEN. Patients have an increased risk of benign and malignant tumours and require lifelong tumour surveillance. PTEN-HS is associated with with vascular anomalies, typically intramuscular fast-flow vascular anomalies termed PTEN hamartoma of

soft tissue (PHOST) 10. PHOST can be difficult to differentiate clinically and histologically from sporadic vascular anomalies e.g. FAVA, AVM. The aim of this study was to characterise a cohort of PHOST with respect to their clinical, histologic, and radiological findings to determine key differentiating features from sporadic vascular anomalies.

METHODS: We conducted a retrospective review of cases of PHOST presenting to tertiary vascular anomaly centre. Clinical features, location, imaging, histology and treatment were reviewed.

RESULTS: 12 patients were identified (3 males, 8 females). Median age at presentation was 8.7 years (0-20) and median length of follow up was 9.5 years (1.5-39). The most common location was lower limb (n=8) followed by upper limb (n=2) and face (n=1). Neurodevelopmental delay was observed in 5 patients. 6/6 with available data had macrocephaly. Management included analgesia (n=4), oral anticoagulation (n=1), oral sirolimus(n=1), embolization (n=3), sclerotherapy (n=4) cryoablation (n=2) or surgery (n=6). Rapid recurrence post radiological/surgical intervention was common (n=9). Pain was a predominant feature in 8 patients. In 5/12 patients PTEN-HS was not suspected/confirmed at time of presentation.

CONCLUSION: We describe a cohort of PHOST and suggest clues to diagnosis include aggressive growth, recurrence post intervention, and significant pain. A significant proportion of our cohort were diagnosed only after presenting with a vascular anomaly. This highlights the needs for a full systems examination including head circumference in all children presenting with vascular anomalies as early identification of syndromes such as PTEN-HS will enable appropriate developmental support, tumour surveillance and genetic counselling/screening of family members.

531 - Mediastinal slow-flow vascular malformation manifesting with acute embolic stroke

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PURPOSE: To report the first case of a mediastinal slow-flow vascular malformation (VM) presenting as an embolic stroke managed via endovascular closure of the draining connection to the pulmonary venous system.

METHODS: A 24-year-old, previously healthy male presented with acute, right-sided hemiparesis, hypoesthesia, and dysarthria. Magnetic resonance imaging (MRI) of the brain revealed a focus of diffusion restriction in the left posterior frontal lobe and bilateral remote cerebellar infarcts. Comprehensive evaluation, including for inherited and acquired thrombophilias, and imaging of the head, neck, chest, abdomen, and pelvis were performed.

RESULTS: No congenital or acquired prothrombotic conditions were identified in laboratory testing. Chest computed tomography (CT) revealed a poorly-defined, posterior mediastinal mass encompassing the esophagus and abutting the anterior aspect of the descending thoracic aorta. Imaging findings were suggestive of VM. Cardiac catheterization was performed, and retrograde venography demonstrated significant dilated venous collaterals communicating with the paraspinal system coalescing to a single egress entering the right upper pulmonary vein (RUPV). Endovascular device embolization of the pulmonary-venous communication was performed without complication. No further therapy was pursued on upstream venous segments. The mediastinal slow-flow VM with a single egress to the right pulmonary vein is clinically analogous to levoatriocardinal vein patency. We hypothesized that maneuvers which alter intrathoracic pressure, such as Valsalva, could result in flow disturbance in the VM and subsequent embolic cerebrovascular events. At 7 months post-treatment, the patient is clinically asymptomatic with no further events concerning for stroke.

CONCLUSION: This case underscores the importance of a multidisciplinary approach to the evaluation and management of mediastinal VMs. These VMs are uncommon and may present as systemic thromboembolic events independent of other thrombotic factors. This case outlines a transcatheter management strategy for mediastinal VMs with a singular connection to the pulmonary venous system.

532 - Effect of alpelisib therapy in a patient with superimposed mosaicism of PTEN hamartoma tumor syndrome and recurrent hypoglycemia

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PURPOSE: To add evidence for the role of PI3K-inhibition by alpelisib in the context of PTEN tumor hamartoma syndrome patients.

METHODS: Case report.

RESULTS: A 12-year-old girl was born with lipomatous masses on her trunk, intra-abdominal lipomatosis and an extensive capillary malformation in a segmental distribution. A heterozygous germline PTEN variant (c.1027-1G>C) was found and loss of heterozygosity in affected tissue with overgrowth. At the age of 4 years she became paraplegic due to expansion of intraspinal tumors. She started treatment with sirolimus (trough levels of 5 to 11 ug/L). At the age of 10 years she underwent orthopedic spine surgery due to scoliosis which resulted in wound infections and progressive growth of hamartomatous tissue on her back (slide 1). She experienced daily symptomatic hypoglycemia requiring nasogastric tube feeding and continuous nursing care at home. Following international expert discussion we initiated alpelisib therapy and stopped sirolimus. After only the first 50mg tablet of alpelisib her blood sugar reached hyperglycemic levels. By adapting her feeding and continued alpelisib therapy (dose of 125mg/day) she retained normal blood sugar values thereafter (slide 2). She also showed reduction of her abdominal circumference, weight and hamartomatous tissue (slide 3). Seven months after the initiation of alpelisib therapy she experienced urosepsis which resulted in an uncontrolled infection and the patient's death.

CONCLUSION: PI3K is the key isoform involved in insulin signaling. PTEN heterozygous null mice show lower fasting glucose levels and remained much lower glucose levels after insulin injection. There are only few patients with PTEN germline variants and hypoglycemia reported to date, however some with a similar phenotype to our patient. This case expands the phenotype of patients with PTEN hamartoma tumor syndrome and highlights the risk of hypoglycemia. We show that PI3K-inhibiting treatment with alpelisib lead to resolution of hypoglycemia and shrinking of abdominal lipomatosis and hamartomatous tissue.

533 - A Model for Shared Multi-Disciplinary Care of Patients with Vascular Anomalies Living in Underserved Regions

Nadav L. Kastle (Maine Medical Center); Melisa Ruiz-Gutierrez (Boston Children's Hospital); Erin Spera (Boston Children's Hospital)

Due to the complex diagnostic dilemmas and treatment decisions involved in caring for patients with vascular anomalies, multidisciplinary team management has become the standard of care. Unfortunately, multidisciplinary clinics are difficult to access consistently for patients that live far from a quaternary care center. We have created a partnership between the multidisciplinary Vascular Anomalies Clinic of a large pediatric quaternary care center and providers at a geographically distant, smaller pediatric program with the aims of facilitating diagnosis, quickly establishing a treatment plan

and prioritizing interventions that takes advantage of the strengths of each institution. This proposed model can be applied to other regions experiencing similar barriers to care. Our model includes multiple points of contact for smooth transitions and seamless patient care, including a multidisciplinary, multiregional tumor board run out of the smaller center with providers at both institutions as well as multiple other smaller regional hospitals, bimonthly patient review meetings, local site visits to promote a collaborative approach, and easy access to real-time multidisciplinary case reviews. We currently share about 20 patients with complex vascular anomalies that receive care at both institutes and are continuing to expand. We intend to measure success with the use of a questionnaire to assess patient satisfaction and provide feedback to the model. This model benefits the medical team by aligning goals of care and utilizes each site to its fullest potential, improving communication, increasing access to clinical trials and research protocols, and avoiding redundant medical procedures such as imaging. This ultimately saves healthcare dollars and we believe that it improves patient satisfaction as well.

534 - **Tracheotomy avoidance and decannulation in head and neck lymphatic malformation using targeted therapy and genotype**

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PURPOSE: Purpose: Grade 2 head and neck lymphatic malformation (HNLM) patients have tenuous airways. HNLM invasive therapy during infancy and early childhood can lead to tracheotomy. Early genotype diagnosis and lesion extent aids treatment selection. Tracheotomy avoidance and decannulation are important in treatment of large function-threatening malformations. Cell-free DNA(cfDNA) from HNLM cyst aspiration is being used to determine malformation genotype and justify targeted medical therapy; with a goal of tracheotomy avoidance, or decannulation. Experience with this novel strategy for Grade 2 HNLM is reported.

METHODS: Methods: Pediatric patients with large HNLM presenting in-utero were enrolled in a prospective IRB-approved study. All patients had NICU care. A staging malformation MRI and airway endoscopy were performed. Malformation fluid aspirated for cfDNA and cyst decompression. Older patients with HNLM and tracheotomy were similarly assessed. Data collected included primary treatment, genotype, airway management, tracheotomy presence, treatments rendered and decannulation.

RESULTS: Results: Twelve patients were enrolled, 9 in infancy and 3 long-term tracheotomy patients (median age 15 years, 12-24). All infants had LM cyst fluid aspiration. PIK3CA genotype was determined in 6 aspirates. Primary medical therapy with sirolimus was begun in 8 infants, one infant used aspirin and then had malformation resection after 6 months of age. No tracheotomies were performed and patient's breathing and eating are normal. The tracheotomized patients had multiple prior invasive therapies and sirolimus therapy. Tissue based PIK3CA genotype was determined and alpelisib initiated. After one year on alpelisb all patients had improved exercise tolerance, normalized capped sleep studies. Decannulation was possible in 2/3 patients.

CONCLUSION: Conclusion: New primary targeted medical therapies and genotype determination from cyst fluid cfDNA in infant Grade 2 HNLM patients can result in tracheotomy avoidance. Grade 2 HNLM patients with lifelong tracheotomy and known genotype can be decannulated using targeted medical therapy. In both situations this is a management change.

535 - KTS with repeated episodes of cellulitis

Marilia Emi Sato Ito (University of Sao Paulo); Rebecca Rossener (University of São Paulo, Brazil); Dov Charles Goldenberg (University of Sao Paulo)

PURPOSE: Discussion of the management of KTS with multiple episodes of cellulitis and thrombophlebitis, that had already gone through an amputation of the lower limb (one of 8 surgical procedures) and did not present results pharmacological treatment with sirolimus.

METHODS: JPV, 15yo male, no comorbidities, is an outpatient of our institution since 2008 (when he was 2 months old). KTS of the left lower limb was a presumed diagnosis at the beginning of the clinical follow-up (we do not dispose of genetic panel for vascular anomalies in our country). In 2010 and 2011, it was performed 3 partial debulkings of the lesion on the left foot, with immunohistochemical results: CD34+, CD40+, CD31+, D240+. During follow-up, the main concern of our team was the multiple episodes of cellulitis, which motivated a few hospitalizations. Due to infectious episodes, it evolved to chronical osteomyelitis of the left leg. In 2018, it was decided to perform amputation of the left lower limb (knee disarticulation). Despite this procedure, the number of infection episodes did not decrease. In 2022 and 2023, it was performed a debulking with liposuction, with a remission of infection for 2 months after the surgeries.

RESULTS: To date, patient was admitted in the emergency room 60 times (14 times only in 2023 – mostly infection and some episodes of thrombophlebitis. Currently taking only heparin due to recent episode of thrombophlebitis.

CONCLUSION: The main issues to be addresses are:

1) Are there any other radiological interventions to be performed in this case?

2) Should lymph nodes transplantation and/or lymph-venous anastomosis be considered?

3) Is debulking a good idea, considering the episodes of infection?

4) Are there any other pharmacological treatments that should be considered?

5) Are there any radiological interventions to be considered?

537 - **Clinicopathologic Characterization of Hepatic Lesions in Pediatric and Young Adult Patients with Congenital Portosystemic Shunt**

Ian Gelarden (Lurie Children's Hospital); Aida Richardson (Lurie Children's Hospital); Riccardo Superina (Lurie Children's Hospital); Anita Gupta (Lurie Children's Hospital)

PURPOSE: Congenital portosystemic shunt (CPSS) is a vascular malformation where portal venous blood bypasses the liver. A subset of patients with CPSS develop liver lesions such as regenerative nodules (RN), focal nodular hyperplasia (FNH), hepatocellular adenoma (HCA), or hepatocellular carcinoma (HCC). The characteristics of hepatic lesions in CPSS are not well characterized. This study describes the clinicopathologic findings in pediatric/young adult patients with hepatic lesions in the setting of CPSS at a stand-alone children's hospital.

METHODS: A retrospective search was performed between 2010 to 2023 for children and young adults with CPSS with hepatic lesions. Inclusion criteria included tissue sampling of one or more lesions for each patient with pathologic review. Select patient demographics, clinical information, imaging findings, histologic findings, and findings of ancillary studies (e.g. immunohistochemistry or molecular studies) were reviewed. The study was approved by our institutional review board.

RESULTS: Eighty-four patients were evaluated for CPSS. Thirty-two patients had hepatic lesions, twenty of which were biopsied (Table 1). Fourteen patients had one lesion, 2 had 2 lesions, 3 had 3 lesions, and

1 had 4 lesions. Ages ranged 2 to 26 years (median 12 years). There were 11 female patients and 9 males (female to male ratio 1.2:1). Lesion sizes ranged from 1.1 to 13.4 cm (median 2.2 cm). FNH was the most common diagnosis, followed by HCA. Six lesions were B-Catenin activated, with molecular analysis performed on 4 (table 2).

CONCLUSION: This is the largest description of hepatic lesions arising in CPSS. The molecular data shows mutations in CTNNB1 exon 7/8 and exon 3 S45, rather than other encountered molecular alterations. The prevalence of FNH and HCA, along with the occurrence of HCC, underscores the complexity of hepatic pathology in the context of CPSS, necessitating further investigation and clinical management strategies tailored to the unique characteristics of this patient population.

541 - Case report: Worsening of arteriovenous malformation during pregnancy
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PURPOSE: Arteriovenous malformations can affect skin, muscle, bone, spine, and central nervous system and may lead to life-threatening complications such as bleeding, chronic pain and heart failure. Pregnancy may lead to the development of these complications.

We report a case of a woman who presented worsening of her AVM during pregnancy.

METHODS: We discuss a 38 year old female patient with a history of a congenital, arteriovenous malformation on her right forearm. Previous treatment was not necessary since she remained asymptomatic during her childhood and youth.

Throughout pregnancy the patient experienced dyspnea, serious pain, sudden swelling and augmented temperature of the forearm along with cold hands.

Clinical examination showed a small capillary vascular malformation on the forearm on the right arm.

Embolization was considered in this patient but unfortunately, routine fetal scan revealed severe polyhydramnios followed by premature rupture of membranes at 21 weeks of gestational age which led to spontaneous abortion. After abortion the symptoms disappeared.

RESULTS: Imaging and laboratory testing were performed. MRI and computed tomography angiography revealed a capillary vascular malformation with muscle, bone and skin involvement with fistulas and without presence of nidus.

Blood samples were collected for genetic testing. The patient was both RASA1 and EPHB4 negative. Fetal necropsy was performed as well , the fetus had no vascular anomalies.

Fertility assessment was delivered to decrease risks in future pregnancies.

CONCLUSION: Further studies are needed to evaluate the relationship between elevated hormone levels and the worsening of arteriovenous malformations in order to determine possible risk factors of maternal and fetal morbidity.

Although genetic testing was negative for RASA 1 and EPBH 4 we consider CM- AVM as the diagnosis.

We bring the case to discussion in order to decide the best approach in a future pregnancy.

542 - Beware the port wine stain that transforms into an arteriovenous malformation
Kristina Derrick (SUNY Downstate Health Sciences University); Sharon Glick (SUNY Downstate Health Sciences University, Maimonides Medical Center); Soodeh Kabir (SUNY Downstate Health Sciences University)

RESULTS: A 14-year-old boy with a right facial capillary malformation (CM) including nose, eyebrow, temple, lateral cheek, upper lip, presented with 2 months of increased erythema and nodularity on his nose. He denied trauma or other inciting event. Eight years prior, a direct injury to the nose was followed by several months of increased swelling and darkness of the lesion until it returned to being indistinguishable from the rest of the vascular malformation. He never received laser treatment. No family history of vascular malformation.

On physical examination, the right nose had a 3.5 cm x 3 cm protuberant violaceous irregular plaque with warmth and pulsation. The right eyebrow, temple, lateral cheek, and upper lip had a homogeneous pink patch, without warmth or pulsation. Doppler ultrasound of the nose showed prominent abnormal clustered veins and arteries, indicating arteriovenous malformation (AVM). Cerebral angiogram localized the AVM from right ophthalmic artery to dilated vein in right nasal bridge. Multiple facial vessels bilaterally were dilated and draining into the same dilated nasal vein, reflecting angiogenesis. MRI brain was normal. He underwent embolization of right ophthalmic artery and right nasal venous fistula. Five months later, the nasal AVM was smaller and less red, without residual warmth or pulsation.

CONCLUSION: This case highlights the challenge of differentiating unilateral segmental CM from quiescent AVM. We suggest the entire lesion is a quiescent AVM activated focally by trauma, puberty, or natural course of lesion. However, there could be two separate lesions: CM on the right face and AVM on the nose. Risks of inability to distinguish quiescent AVM from CM include misdiagnosis, poor outcomes from laser therapy, and complications of AVM including heart failure, hemorrhage, and seizures. More research is needed to differentiate vascular lesions by non-invasive imaging and genetic testing, predict long-term outcomes, and treat and prevent AVMs.

544 - Giant Congenital Hepatic Hemangioma

Alejandro Celis Jimenez (IMSS); Gerardo Martinez (Hospital General de Mexico)

Clinical Case: This is a male newborn weighing 2,800g. At birth with significant hepatomegaly, presence of venous engorgement in the liver, respiratory difficulty and cardiorespiratory stress when breastfeeding. Laboratories with the presence of elevated d-dimer, thrombocytopenia and grade I anemia. CT angiography with the presence of a hypervascularized image in the liver, so the decision was made to admit him to the ICU. Liver function tests and tumor markers (alpha pheto protein and carcinoembryonic antigen) were negative and malignancy was ruled out, however, the Pediatric Oncosurgery service with suspicion of hepatoblastoma vs hemangioma proposed subtotal hepatectomy as initial treatment. Assessment by Vascular Surgery: in the presence of a single, large and vascularized lesion on AngioCT and absence of malignancy, a high probability of HHC is concluded. Expectant management and low molecular weight heparin at a prophylactic dose were initiated. After 3 weeks, the patient showed clinical improvement, being able to tolerate feeding, without supplemental oxygen support, and a decrease in D-dimer, so it was decided to discharge him. Ten months after birth, the patient remains asymptomatic and has normal laboratories.

Conclusion: • Although the majority of HHC are asymptomatic, some cases can be fatal, so early and accurate diagnosis is important. Screening with abdominal USG is recommended in newborns with hepatomegaly and heart failure. HHC shares the same evolution process as a congenital cutaneous hemangioma, characterized by an involution phase of variable time or non-involution, reserving invasive procedures only in cases of liver failure, heart failure, severe respiratory failure or inability to feed the patient.
• Periodic monitoring of the patient is a valid therapeutic measure avoiding unnecessary treatments. Given the lack of guidelines for the diagnosis of HHC, it is a challenge for doctors unfamiliar with vascular anomalies to provide correct treatment.

546 - Surgical treatment for a benign lymphangioendothelioma after two incomplete excisions

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PURPOSE: Benign lymphangioendothelioma (BL) is a rare, poorly identified, slow-growing benign vascular lesion characterized by asymptomatic, solitary, well-demarcated macules, or by mildly infiltrated plaque.

RESULTS: We report a case of an atypical BL that arose as a tender, protuberant, flesh-colored mass with cyanotic vesicles, and then progressed to a persistent exudative wound after two incomplete excisions.

The patient was also diagnosed with thoracic duct narrowing. Although the stenosis was removed by surgery, the right lower extremity ulceration and exudation did not improve. Thus, we performed a thorough excision and split-thickness skin graft transplant following vacuum sealing drainage, and eventually the patient had a favorable functional and cosmetic outcome. A biopsy revealed irregular, dilated vascular spaces lined with a single layer of flat endothelial cells extending from the superficial dermis to the subcutis that did not reach the striated muscles.

CONCLUSION: Clinicopathological correlation, imaging examination, and pathological examination are essential for diagnosing BL and excluding lymphangiomatosis, Kaposi's sarcoma, and angiosarcoma. This case also demonstrates that complete excision and split-thickness skin graft transplant following vacuum-seal drainage is an effective course of treatment for recurrent BL.

549 - Hemifacial AVM with intra-auricular bleeding

Marilia Emi Sato Ito (University of Sao Paulo); Rebecca Rossener (University of São Paulo, Brazil); Dov Charles Goldenberg (University of Sao Paulo)

PURPOSE: Discussion of the management of an extensive hemifacial AVM, that mainly presents bleeding from the external ear canal. Two previous radiological interventions were performed this year. Despite the procedures, patient was admitted in the ER with 9 episodes of bleeding.

METHODS: RSC, 36yo, male, only comorbidity was arterial systemic hypertension. He is an outpatient of our institution since 2020, and with the Vascular Anomalies Team since 2021. In his first appointment, it was introduced propranolol (for heartbeat rate control) and gabapentin (for pain control). During his follow-up, patient did not have any bleeding episodes until 2023. First major intra-auricular bleeding occurred on May 2023, when it was treated with endovascular procedure (embolization of the distal stump of the external carotid artery (arteriovenous fistula), with 5 platin microsprings, Histoacryl and lipiodol). After this episode, patient needed another endovascular treatment on July 2023 (Embolization of the posterior auricular artery with Histoacryl and lipiodol). To date, there was a total of 9 bleeding episodes and 3 other ER admissions due to pain.

RESULTS: Considering the anatomical aspect of the lesion, the head and neck surgery team, along with the plastic surgery team were not favorable of surgical removal. Patient is taking tranexamic acid and propranolol to prevent other bleeding episodes.

CONCLUSION: The issued to be addressed in this case are: Are there any additional radiointerventional procedure to be considered in this case? Is there any pharmacological treatment to be considered? Should surgery be considered in this case? If so, what is the best surgical strategy?

552 - Impact of race and primary language on care for a large population of patients with lymphatic malformations

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PURPOSE: The management of patients with lymphatic malformations (LM) can be highly complex, frequently requiring multidisciplinary care. The impact of social and structural determinants of health in these patients is incompletely described. We used data informatics to elucidate the impact of social determinants on disease comorbidity and access to targeted therapies.

METHODS: The study includes patients presenting with LM at a single academic institution from June 2012-June 2022. Data collected included sex, self-reported ethnicity and race, primary language, insurance status, comorbidities, age at presentation and therapeutic interventions.

RESULTS: 605 patients were identified using diagnosis codes. Mean age at presentation was 17.5 years (median 11.8 years). 39.0% were White, 12.2% Asian, 4.0% African American and 32.2% Other--primarily Hispanic. 85.0% spoke primarily English. 54.9% had commercial insurance. 8.3 % were treated with sirolimus.

Higher rates of chronic pain were observed in African American patients (20.0%), compared to other racial groups (12.9% White, 7.2% Asian and 13.4% Other, p=0.018 for Pearson's Chi Square test). In addition, no African American patient (0/24) was treated with sirolimus compared to 9.2% White (20/216), 13.8% Asian (9/65) and 12.1% Other (p-value=0.017). On multivariable regression, non-English speaking patients had significantly reduced odds of sirolimus use (Odds ratio:0.63, 95% confidence interval:0.10-0.88, p=0.04). This association remained true in patients <18 years old (OR:0.28, CI:0.07-0.86, p=0.04).

CONCLUSION: Complex care for patients with LM is resource-intensive, especially when using molecular therapeutics like sirolimus. On univariate analysis, African American patients were more likely to be diagnosed with chronic pain and less likely to receive sirolimus compared to other racial groups. After controlling for other demographic factors, English-speakers were more likely to receive sirolimus. As treatment becomes more complex and targeted therapies increasingly common, we must work to understand the health impact of social determinants and ensure equity in access, especially as this relates to patient counseling.

553 - Successful Management of Intestinal and Cutaneous Hemangiomas in a Pediatric Patient with PHACES Syndrome

Khoa Nguyen (Kaiser Permanente); Valentina Sosa (Kaiser Permanente Los Angeles)

PURPOSE: PHACES syndrome is a common neurocutaneous disorder. Diagnostic criteria include posterior fossa malformations, segmental hemangioma, arterial anomalies, cardiac defects, eye abnormalities, and sternal clefting. Hemangiomas of the gastrointestinal (GI) tract can lead to life-threatening bleeding. We present the successful management of a challenging case of intestinal and cutaneous hemangiomas in a patient with PHACES syndrome.

METHODS: Our patient is a 35-day-old female who presented for melena. The patient was diagnosed with PHACES syndrome due to segmental hemangiomas of the right face, left torso, and left arm, right anterior cerebral artery hypoplasia, and cerebellar hypoplasia. The patient's GI bleed was significant, with hemoglobin dropping to 5.5 requiring red blood cell transfusions. Exploratory laparotomy was

performed and identified serosal hemangiomas involving the entire jejunum. Small bowel resection and anastomosis stabilized the GI bleed. The patient's cutaneous hemangiomas were treated with topical timolol, however they grew and ulcerated. Treatments discussed included oral propranolol, systemic corticosteroids, and vincristine. Systemic steroids increased the risk of bowel anastomosis dehiscence. Vincristine increased the risk of paralytic ileus. There was hesitancy in starting propranolol given the risk of an ischemic stroke. However, imaging identified collateral vasculature present, and the risk of stroke with oral propranolol was deemed low.

RESULTS: Patient started propranolol at 0.5mg/kg/day and increased up to 2.2mg/kg/day with no neurologic deficits identified. At five months old, the patient's cutaneous hemangiomas remain stable in size and no return of GI bleed.

CONCLUSION: Intestinal hemangiomas are seen in up to 58% of patients with PHACES who have extracutaneous involvement.1 Although mortality rates are near 25% for patients with PHACES syndrome who have intestinal hemangiomas, there is a critical knowledge gap regarding first-line management for these difficult cases.2 We recommend clinicians consider resection of significant intestinal hemangiomas in conjunction with oral propranolol in patients with symptomatic intestinal and cutaneous hemangiomas.

557 - Weekly Sirolimus Therapy for the Treatment of Venous and Lymphatic Malformations

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PURPOSE: Sirolimus, an mTOR inhibitor, is efficacious in providing symptomatic and size improvement in venous (VM) and lymphatic (LM) malformations. Standard dosing is once or twice daily; however, potential adverse effects (AEs) including hypertriglyceridemia, oral ulceration, and neutropenia may limit its use. Thus, treatment is typically reserved for moderate to severe cases.

METHODS: A single-site, open-label, proof-of-concept study was initiated to evaluate the efficacy of weekly-dosed oral sirolimus (WOS), which is sub-immunosuppressant dosing, for VM and LM not meeting physician-determined criteria for daily dosing.

RESULTS: We present a case series of three patients treated with WOS (1.5-2 mg/m2) for venolymphatic malformations. Patient 1 is an 8-year-old female with a right posterior thigh VM associated with exertional pain, maintained on WOS. She achieved improvement in pain on sirolimus, and Pediatric Quality of Life Inventory (PedsQL) improved from 81.7 to 85 and 96.7 at 1 month and 10 months, respectively. Her last MRI showed stable to minimally-increased malformation size, and no AEs or lab abnormalities were noted. Patient 2 is a 16-year-old female with a distal right forearm VM associated with exertional pain, treated with WOS. She reported improvement in pain during follow-ups, and PedsQL improved from 83.3 at baseline to 95 at 7 months. CBC and CMP were stable, though triglycerides slightly increased from baseline, however did not warrant dose adjustment. Patient 3 is a 3-year-old male with a nonpainful right upper arm VM status post one round of sclerotherapy, started on WOS. PedsQL was relatively-unchanged at 8 months; labs were stable over his treatment course.

CONCLUSION: Pain and PedsQL improved for Patients 1 and 2 on WOS without significant lab abnormalities or AEs. This dosing regimen may be an option for patients with focal malformations, either as maintenance therapy or a bridge to further intervention, though more research is needed.

559 - Efficacy of Minimally Invasive Sclerotherapy in Pediatric Abdominal Lymphatic Malformations: A Retrospective Study

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PURPOSE: Abdominal lymphatic malformations (ALMs) are rare, congenital lymphatic anomalies within the peritoneal cavity. Predominantly occurring in the cervicofacial region, abdominal manifestations (mesentery, omentum, retroperitoneum) are uncommon in children (<5% of cases). This study reviews our centers' last 15 years of experience in minimally invasive sclerotherapy for ALMs, highlighting technique specifics and outcomes.

METHODS: We retrospectively analyzed 26 patients with ALMs treated at our center (2010-2023), out of whom 7 had primary resection and 19 were qualified for microinvasive approach. Data of microinvasive group were analyzed using descriptive statistics, focusing on demographics, clinical presentation, diagnostic methods, and post-treatment outcomes. The sclerotherapy protocol involved doxycycline with vitamin C injected into cysts either once or 3-4 times during consecutive days.

RESULTS: The cohort underwent 26 minimally invasive procedures (10 percutaneous and 16 laparoscopically assisted punctures); only one patient eventually required open surgery. Four patients underwent multiple interventions (2-4), and 7 await further sclerotherapy. The interventions achieved mean reduction in malformation size of 50.7% ($p<0.05$). Most patients experienced symptomatic relief; 7 had complete or almost complete resolution after only one procedure, 7 showed partial improvement, and 5 saw no significant change. 4 cases were lost to follow-up. The average hospital stay was four days, with a three-day doxycycline regimen.

CONCLUSION: Sclerotherapy, as a minimally invasive approach for pediatric intraabdominal lymphatic malformations, demonstrates promising efficacy and safety. Most patients achieved significant size reduction and symptomatic relief, with a few requiring additional interventions. These preliminary findings support sclerotherapy's potential as a primary treatment modality, warranting further comparative research to solidify its role against other therapeutic options.

560 - Dual Targeted Therapy in PTEN-Related Vascular Anomalies

Ramrada Lekwuttikarn (Stanford University); Michael Jeng (Stanford University); Joyce Teng (Stanford University)

PURPOSE: PTEN Hamartoma Tumor Syndrome (PHTS) is a rare genetic disorder predispose patients to multi-system tissue overgrowth and malignancy, due to pathogenic germline variants in the tumor suppressor gene Phosphatase and Tensin homolog (PTEN). Aside from risks of benign and malignant tumors of different organ systems, vascular anomalies are also common among those with PHTS. PTEN, a tumor suppressor protein, downregulates pro-proliferating AKT/mTOR pathway. Dysfunctional PTEN will result in activation of AKT as well as downstream RAF/MARK/ERK signaling pathway. Thus, therapeutic management of severe clinical manifestation in PTEN patients may require synergistic targeting of both mTOR and MARK/ERK pathways.

METHODS: Retrospective review of 3 cases of complex vascular anomalies in patients with PTEN.

RESULTS: Two of the patients were born with extensive AVM, one involving the right shoulder and arm; and the other with involvement of the entire left leg. The third patient has a large painful PTEN hamartoma involving the forearm with Fastflow vasculature note on MR as well. All three patients received sirolimus at optimal therapeutic dose for 3-5 years with considerable disease progression including pain, congested heart failure and arrythmia. Following the addition of MEK inhibitor trametinib, both AVM progression and CHF were stabilized. In addition, the pain and ulceration have

also improved. Unfortunately, one of the two patients had to stop trametinib due to asymptomatic pericardial effusion. Despite that, his AVM remains well-controlled using mTOR inhibitor. Other side effect was acne in all three patients. The third patient had significant pain relief and improved hand function on dual therapy. Two of the patients have been on dual therapy for over three years.

CONCLUSION: Our case series highlighted possible benefit of using combination therapy for patients complex vascular anomaly and PHTS. Future larger-scale randomized study will be essential to evaluate the safety and effectiveness of combination therapy.

563 - Successful Management of Complex Lymphatic Malformation with Combination Therapy
Ramrada Lekwuttikarn (Stanford University); Michael Jeng (Stanford University); Mai Thy Troung (Stanford University); Avnesh Thakor (Stanford University); David Hovsepian (Stanford University); Karen Griggs (Stanford University); Joyce Teng (Stanford University)

PURPOSE: Targeted therapy, especially mTOR inhibitor has become the first line treatment for lymphatic malformation over the past decade. Here we present 9 cases of complex lymphatic anomalies with less optimal response to targeted therapy alone and required additional medical treatments to optimize therapeutic outcomes.

METHODS: Retrospective review of 9 case series.

RESULTS: Our cases comprised eight children and one adult diagnosed with LM since birth. The LM involved orbit (3), face and neck (4), chest wall (1), or being more generalized (1). Sirolimus treatment was initially attempted but was not able to control these patients' disease manifestations i.e. pain, recurrent hemorrhage, and respiratory distress. Therefore, trametinib (MEK inhibitor), sildenafil (phosphodiesterase five inhibitors (PDE5i)), and/or propranolol (nonselective anti-angiogenic agent) were added in addition to optimize the therapeutic outcome. Four patients were treated with sirolimus, sildenafil, and propranolol; two received sirolimus and propranolol, two received sirolimus and sildenafil, one received sirolimus, sildenafil, and trametinib. All patients had better responses to combination therapy with decreased frequency of swelling, pain and hospitalization. MRI following one year of combination therapy showed decrease in the size of the LM in 6 cases, and stable in three. No disease progression was reported while on combined therapy. The treatment was well-tolerated, and all subjects remained on this regime to date. There was no additional laboratory or clinical abnormalities noted in comparison to those on sirolimus alone.

CONCLUSION: Our case series suggests that personalized approach in managing complex lymphatic anomalies is important. Incorporating medications with alternative mechanism of action other than mTOR pathway inhibition may have synergistic effects therefore improve clinical outcome and prevent life-threatening events. Larger scale study in the future will be important to delineate the safety and efficacy of these therapeutic strategies.

565 - Single Center Real World Experience using Alpelisib for PROS.
Ramrada Lekwuttikarn (Stanford University); Jordan Bui (Stanford University); Karen Griggs (Stanford University); Ann Louise Marqueling (Stanford University); Joyce Teng (Stanford University)

PURPOSE: PIK3CA-related overgrowth spectrum disorders (PROS) encompass a group of disorders with diverse clinical phenotypes. Alpelisib has received provisional approval from FDA as targeted therapy for PROS. Here we report our single-center real-world experience using alpelisib in the management of PROS patients.

METHODS: Retrospective review of 16 case series

RESULTS: We reviewed clinical records of 16 patients (9 children and 7 adults) who carried clinical or genetically confirmed diagnosis of PROS and were treated with alpelisib for at least 6 months between

January 2021 to October 2023. The ages when medical therapy began range from two to forty years old. Two of these patients carry mosaic germline PI3KCA mutations. Clinical improvements documented including reduced pain, swelling, improved range of motion and the stability or reduction of overgrowth features demonstrated by MRI in all patients. Remarkable behavior changes were also noted in the adult with germline mosaicism and developmental delay. We noted transient dose-dependent hyperglycemia events and complaints of hair loss reported in adult patients, which improved with dose reduction. We also observed weight loss side effects during the first six months of therapy in four adults and two children, whose weight eventually stabilized and was age-appropriate. Other side effects noted in our patients include nausea, diarrhea, and headaches, which were mostly reported by adults. Overall, the medication is well-tolerated, and all of our patients are continued with close monitoring.

CONCLUSION: Our case series showed that alpelisib is well-tolerated, safe and efficacious. The most interesting observation we have had is the improvement behavior changes. Ongoing clinical trials will provide us with more efficacy and safety data.

566 - A tale of two vascular anomalies in one small patient - just a coincidence?

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History: • Prenatal U/S: multiple congenital abnormalities (enlarged kidneys, macrocephaly, hypertelorism, polyhydramnios, polydactyly) • Fetal MRI revealed polymicrogyria • Amniocentesis for genetic testing resulted with pathogenic variant in PIK3CA (c.1093G>A, p.Glu365Lys) • Born at 35w2d, CM noted on face; diagnosed with PROS, specifically megalencephaly-capillary malformation-polymicrogyria syndrome (MCAP) • At birth, also noted a large (3 cm x 4 cm) vascular lesion on his posterior medial right thigh that appeared most consistent with congenital hemangioma vs kaposiform hemangioendothelioma • No coagulopathy other than a mildly elevated D-dimer • Angiopoietin-2 slightly elevated • Started to ulcerate and decrease in size around 2 weeks of age • Lesion was biopsied – pathology consistent with congenital hemangioma (GLUT-1 negative, no significant D2-40 or PROX-1 staining)

Issues to be addressed: • Two seemingly unrelated vascular anomalies in one patient • How common is this? • Is the PIK3CA mutation associated with the congenital hemangioma at all? • Have others seen congenital hemangiomas with MCAP? • One MCAP patient with NICH reported in 2021 Garde et al paper in Clinical Genetics

567 - Interim Analysis of Phase II Clinical Trial of MEK Inhibitor Trametinib for Extracranial Arteriovenous Malformations

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PURPOSE: MEK inhibitors (MEKi) like trametinib is approved in US for the treatment of metastatic melanoma and non-small cell lung cancer. Our study, MEKi is repurposed for the management of extracranial arteriovenous malformations (AVM) primarily due to genetic variants in the RAS/MAPK pathway. This trial aims to test the safety and efficacy of trametinib used off-label in patients with extracranial AVMs.

METHODS: Interim analysis of phase II clinical trial

RESULTS: Fourteen patients aged 13-49 years old have been enrolled to date; patients with germline mutations were excluded. Due to the risk of documented side effects in oncology patients, patients received baseline evaluation including ophthalmology exam, echocardiogram, pulmonary function test,

and radioimaging which are repeated every three months while on treatment. All patients in our cohort experienced acneiform cutaneous toxicity, requiried management with topical therapies (14), systemic antibiotics (3), or spironolactone (1). Treatment discontinuation (3) and treatment interruption (3) were also due to cutaneous toxicity and dose reduction was requested by one patient. Three patients experienced non-clinically significant echo changes such as slightly increased tricuspid, aortic or mitral regurgitation. One patient demonstrated mild obstruction on PFTs at 11 months of therapy that deem to be clinically nonsignificant as well. Other toxicities noted such as headaches or xerosis were all mild. More than half of the patients reported significant reduction of pain and improvement of function. MR imaging following 6- or 12-months treatment also demonstrated marked reduction of blood flow to AVMs.

CONCLUSION: Our study demonstrates lower rates of systemic adverse effects, suggesting that extensive monitoring as recommended for oncology patients may not be necessary among this relatively healthy cohort. Further study with a larger multicenter collaboration is needed to validate our results to determine optimal monitoring guidelines for vascular anomaly patients being treated with trametinib. Proactive management of cutaneous toxicity will minimize therapy interruption.

569 - Pancreatic Kaposiform Hemangioendothelioma with Poor Response to Medical Therapy Complicated by Multiorgan Dysfunction and Death

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PURPOSE: Kaposiform hemangioendothelioma (KHE) is a rare, locally aggressive vascular tumor occurring in infants and young children. KHE most commonly occurs in skin or subcutaneous tissue, but can occur extracutaneously, including in the retroperitoneum. Improvements in medical therapy and supportive care have improved outcomes in this life-threatening condition, but complications can be severe.

METHODS: A 5-month-old term female presented with vomiting. Labs showed anemia (not hemolytic), neutropenia, severe thrombocytopenia (<10K). The latter didn't improve with transfusion, IVIG, steroids. She was diagnosed (labs, MRCP) with necrotizing pancreatitis with associated ascites and bowel inflammation. Despite conservative management, labs remained abnormal, including new low fibrinogen. She developed obstructive jaundice, portal vein thrombosis, hematochezia. Repeat MRCP showed a soft tissue mass associated with the pancreas, infiltrating liver and bowel. Biopsy was consistent with KHE, and labs with Kasabach-Merritt phenomenon.

RESULTS: Medical therapies were initiated: methylprednisolone (x9 weeks, 6 weeks at 2mg/kg/day), vincristine (5 doses; 0.01mg/kg x 4 due to liver dysfunction; 0.05mg/kg x 1), sirolimus (x12 weeks). Sirolimus therapy was complicated by liver dysfunction and likely poor absorption from bowel inflammation; many trough levels were either well above or below goal (8-10ng/mL). Despite various treatments for KHE and complications, clinical status declined. She was listed for multivisceral transplant, but this option was removed after development of severe peritonitis (multiple drug-resistant organisms) not able to be cleared with antimicrobials. The patient died after a 4-month hospitalization (mostly ICU) despite efforts by multiple teams.

CONCLUSION: Diagnosing an uncommon presentation of a rare disease is difficult. Treatment with medical therapies is complicated in critically ill patients, and the risks and benefits of each agent must be considered continuously. Our patient did not have a good response to medical therapy and ultimately died from complications of her KHE, highlighting the severity of this vascular tumor and the need for

multidisciplinary care." Kaposiform hemangioendothelioma (KHE) is a rare, locally aggressive vascular tumor occurring in infants and young children. KHE most commonly occurs in skin or subcutaneous tissue, but can occur extracutaneously, including in the retroperitoneum. Improvements in medical therapy and supportive care have improved outcomes in this life-threatening condition, but complications can be severe.

571 - Systemic Propranolol reduces the epistaxis frequency in Hereditary Hemorrhagic Telangiectasia (HHT)

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PURPOSE: HHT is an autosomal vascular dysplasia that affects 1/5000 individuals worldwide. It causes mucocutaneous telangiectasias and vascular malformations in various organs such as the brain, lungs, gastrointestinal tract and liver. Epistaxis is a symptom that affects most patients with HHT and can affect quality of life, cause anaemia or be life-threatening. Propranolol is a known anti-angiogenic agent. It has been proven in few preclinical and clinical studies to reduce epistaxis in HHT, mainly in intranasal application and in different formulations, including topical timolol.

METHODS: We carried out a large retrospective observational study of 151 patients with HHT treated with oral propranolol for 6 months. Over 151 patients, 44 received oral propranolol. Frequency and intensity of epistaxis were measured in a combined and stratified manner using the Sadick scale. We adjust by other treatments and confounders as well as prescription bias using the propensity score.

RESULTS: Treated patients had higher severity indices of anemia, vascular malformations and age at baseline. No difference was found in improvement as defined by the combined outcome (frequency and intensity) OR (95% CI) 2.2 (0.9-5.6) p=0.079; 2.8 (0.9-8.6) p= 0.083 However, a significant difference was observed in the stratified analysis in the reduction of bleeding frequency OR (95% CI 1.3-11.2) 3.8 p=0.016. No treated patients required an increase in other treatments such as antifibrinolytics . No serious adverse effects were reported.

CONCLUSION: Propranolol may help treat the epistaxis in patients with HHT to reduce its frequency. May be an attractive alternative alone or in combination with other pharmacologycal or interventional treatments .

572 - The Use of IV Bevacizumab in a Child with Severe and Aggressive Hereditary Hemorrhagic Telangiectasia

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PURPOSE: We present a four-year-old male who presented with refractory anemia, epistaxis, and gastrointestinal bleeding on nasal and gastrointestinal endoscopy diagnosed with hereditary hemorrhagic telangiectasia (HHT) . Local control attempts only provided transient improvement. Intravenous bevacizumab was used which showed promising results. HHT rarely presents this aggressively in a young child which highlights the need for heightened awareness for all physicians. Further studies are needed to investigate the use of intravenous bevacizumab in pediatric HHT patients.

METHODS: A four-year-old African American male child presented to his local emergency department with acute onset of emesis, fatigue, and severe anemia (hemoglobin of 2.0 gm/dL). Due to persistent anemia and worsening epistaxis, he was referred to ENT for nasal endoscopy which revealed telangiectasias throughout, consistent with HHT. Genetic testing demonstrated a heterozygous frameshift mutation in the ENG gene. Endoscopies of the small and large intestines showed scattered AVMs throughout. Attempts to control epistaxis locally with intranasal injections of bevacizumab

(Avastin) and oral aminocaproic acid (Amicar) along with supportive packed red blood cell (pRBC) transfusions and iron supplementation were not successful. The patient was placed on a trial of propranolol, 1.5 mg/kg twice a day -symptoms did not improve.

He was then treated with intravenous bevacizumab (1 mg/kg/dose) given every 2 weeks for 3 doses.

RESULTS: Repeat endoscopy showed a normal esophagus, stomach, duodenum, and jejunum. ENT nasal endoscopy revealed decreased number of telangiectasias.

CONCLUSION: HHT often goes unrecognized or under diagnosed. It should be considered when confronted with a suspicious family history and/or refractory symptoms of mucosal bleeding with anemia with or without telangiectasias. Improved treatment options for aggressive pediatric HHT disease prompt consideration of intravenous bevacizumab. Treatment options for pediatric HHT require much needed continued investigation.

576 - A Novel Case of Parkes Weber Syndrome Caused by a Novel Somatic MAP2K1 Mutation
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Introduction: Parkes Weber Syndrome (PWS) is a rare vascular overgrowth disorder featuring capillary malformations, arteriovenous malformations (AVMs), and arteriovenous fistulas in a single extremity, leading to severe limb overgrowth. 1 Somatic RASA1 and EPH4B variants are classically implicated with this disorder. 1 Literature suggests that additional germline and somatic activating variants in the ras/mitogen-activated protein kinase signaling pathway have been associated with PWS. 2 Pathogenic variants in MAP2K1 have been associated with various cancers and extracranial AVMs, but it is not a known locus of PWS.3
Case: We present a case of a 7-year-old male referred to the vascular anomalies clinic for evaluation of left lower extremity hemihypertrophy with cutaneous capillary malformations and multifocal, high-flow AVMs from the left hip to knee with hemi-scrotal involvement confirmed on MRI. Further workup with left pelvic and left lower extremity arteriography confirmed multiple highflow AVMs in the left hemiscrotum, left pelvis, and proximal left lower leg. CT head and MRI/MRA brain were negative for intracranial AVMs. Echocardiography was unremarkable. The patient underwent three embolizations for scrotal ulceration and continued to have progressive limb overgrowth requiring femur epiphysiodesis. An incisional biopsy was performed, and tissue was sent for somatic overgrowth mutation analysis panel, which revealed a somatic variant of MAP2K1. This specific variant (c.306_311del;p.Ile103_Lys104del) has not been commonly reported in association with vascular malformations. The variant is likely pathogenic based on ACMG/AMP guidelines and the ClinGen Criteria Specification Registry.
Discussion: Current literature describes only one other case of PWS with a MAP2K1 mutation. 1 The MAP2K1 gene codes for the MEK1 protein, a component of the RAS/MAPK signaling pathway. 3 MEK1 inhibitors play a role in helping endothelial cells differentiate into capillary beds and could serve as a potential therapeutic option. 1 This further reinforces the importance of genetic testing in patients with suspected PWS, as new variants are discovered.

578 - "Multidisciplinary Management and Ethylene Vinyl Alcohol Embolization of Neonatal Congenital Hemangioma: Resolving Heart Failure in a Complex Head and Neck Lesion"

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PURPOSE: This clinical case report aims to document the presentation, diagnostic evaluation, and management of a 2-day-old baby girl with a complex arteriovenous fistula-induced congenital hemangioma associated with heart failure and pulmonary hypertension.

METHODS: The patient, born prematurely via programmed cesarean section, exhibited signs of heart failure and pulmonary hypertension shortly after birth. Diagnostic assessments included echocardiogram, chest X-ray, and MRI revealing a vascularized lesion with arteriovenous fistulas in the temporo-parieto-occipital and cervical area. Histopathological analysis confirmed the diagnosis of congenital hemangioma. Cerebral angiography identified arteriovenous fistulas in branches of the external carotid artery, subsequently treated with Ethylene Vinyl Alcohol Copolymer selective embolization.

RESULTS: Clinical intervention, including corticosteroids, sirolimus, and propranolol, was initiated and discontinued two weeks post-embolization due to significant clinical improvement and confirmation of the histopathological diagnosis. Cardiac function improved immediately following the embolization procedure. Long-term management involved furosemide and spironolactone for one year due to cardiac dilation, with subsequent discontinuation as the patient exhibited normal cardiac function. The skin lesion continued to involute

CONCLUSION: Early diagnosis and a multidisciplinary approach involving medical and interventional therapies, including Ethylene Vinyl Alcohol embolization, contributed to the successful management of the congenital hemangioma with associated arteriovenous fistulas. This case highlights the importance of tailored therapeutic strategies in addressing complex vascular anomalies in neonates, resulting in improved cardiac function and sustained resolution of the cutaneous lesion

581 - Fibro-Adipose Vascular Anomaly (FAVA): A Comprehensive Exploration of Clinical, Imaging, and Histopathological Features for Enhanced Diagnosis and Treatment Dilemmas in two third world medical centers

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PURPOSE: This retrospective, descriptive study aims to characterize the clinical, imaging, and histopathological features of Fibro-Adipose Vascular Anomaly (FAVA). The primary objective is to contribute to a comprehensive understanding of FAVA and highlight the challenges associated with its diagnosis and treatment.

METHODS: A total of 27 patients diagnosed with FAVA were included in this study, with a mean age of 12 years (range: 1 to 41 years) and a majority being female (74%). The most common symptom reported was activity-related pain. The analysis involved a retrospective review of patient medical records, excluding cases with incomplete data. All patients underwent surgical excision due to the lack of access to cryoablation. Microscopic examination, including Hematoxylin and Eosin (HE) staining, Masson's Trichrome staining, and immunohistochemistry (lyve1 and D240 markers), was performed to elucidate the histopathological characteristics.

RESULTS: Microscopic examination revealed distinctive features of FAVA, including alternating skeletal muscle and mature adipose tissue, irregular and dilated vessels immersed in fibroconnective tissue, and thickened vessels with concentric fibrosis. Immunohistochemical analysis confirmed positive markers for lymphatic tissues (lyve1 and D240). Pain resolved in all cases after surgery.

CONCLUSION: FAVA poses a treatment dilemma due to challenges in histological confirmation, despite its distinct clinical and imaging characteristics. The study underscores the importance of a thorough correlation between clinical presentation, imaging findings, and histopathology for an accurate diagnosis. This comprehensive approach is essential for navigating the complexities associated with FAVA diagnosis and subsequent treatment decisions.

583 - A Complicated Lymphatic Anomaly Conundrum

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We present the case of a five year old female with persistent, diffuse left upper extremity swelling noted at birth. Ultrasound confirmed no abnormalities other than edema. MRI demonstrated enlargement of the left arm and lateral chest without proximal obstruction. Nuclear lymphoscintigraphy showed enhancement at the dorsal hand injection site without further enhancement. Newborn screening was notable for T-cell immunodeficiency. She had a normal ECHO, EKG, urinalysis and CMP. EGD and colonoscopy with biopsy demonstrated hypoalbuminemia and intestinal lymphangiectasia. Genetics panel from affected tissue showed absence of pathogenic variants. Chromosomal microarray analysis was normal. There was short term improvement following liposuction of the left hand performed by plastic surgery with symptom recurrence within three weeks. Other management included propranolol, compression and massage with minimal improvement.

While the diagnosis is not entirely clear, the clinical workup thus far leans towards a primary, centralized lymphatic pathology. Complicated lymphatic anomalies (CLA) is an umbrella term that refers to high-risk lymphatic phenotypes with overlapping patterns of clinical features, anatomic locations, imaging findings, hematologic abnormalities, and complications. CLA includes generalized lymphatic anomaly (GLA), Gorham-Stout disease (GSD), central conducting lymphatic anomaly (CCLA), and Kaposiform lymphangiomatosis (KLA). Given the variable and wide clinical spectrum, patients with CLA are often misdiagnosed given the absence of established guidelines. A comprehensive examination of the patient is required as CLA often spans multiple systems requiring care by numerous medical and surgical specialties. Recognition of a multifocal lymphatic malformation can aid in evaluation of potential complications including chronic pain, respiratory failure, ascites, immune failure, sepsis, malnutrition, and coagulopathy. The initiation of preemptive treatment may lead to unexpected therapy-related complications and poor prognosis. This case aims to highlight the diagnosis, management and treatment of suspected CLA given lack of standardized consensus for evaluation of a remarkable clinical phenotype.

584 - Successful treatment of problematic chronic GI bleeding in a patient with Turner syndrome and GI angiodysplasia with IV Bevacizumab

Jorie E. Gatts (Cincinnati Children's Hospital Medical Center); Kelly Blache (Cincinnati Children's Hospital); Belinda Dickie (Boston Children's Hospital); Philip E. Putnam (Cincinnati Children's Hospital Medical Center); Kiersten Ricci (Cincinnati Children's Hospital Medical Center)

History: • Now 23 y.o. female with Turner syndrome, bicuspid aortic valve, celiac disease and gluten sensitivity, and GI angiodysplasias involving the small intestine and proximal large intestine complicated by persistent, chronic GI bleeding. These GI hemorrhages worsened in adolescence, have been life-threatening, and resulted in dependency on frequent pRBC transfusions and IV iron infusions. - Prior/Failed Treatments: sirolimus, exogenous estrogen, lenalidomide, desmopressin, antifibrinolytics, Humate-P (Antihemophilic Factor VIII/Von Willebrand Factor Complex), Vonvendi (recombinant von Willebrand factor) (still receives given acquired deficiency), multiple GI scopes & surgical procedures
• Based on international, multicenter study of IV bevacizumab for bleeding in HHT: the InHIBIT-Bleed study, started her on IV bevacizumab (every 2 weeks for 6 cycles for induction then every 4 weeks for maintenance)

Issues to be addressed • Bevacizumab has led to significant improvement in patient's symptoms: - Spaced pRBC transfusions from every 1-2 weeks to 6-8 weeks - Spaced IV iron infusions from every 3 months to 5 months - Requiring fewer doses of VonVendi, FVIII level has increased -Patient reports quality of life is much improved, able to go on first solo trip with friends ever
• Bevacizumab is an effective treatment option to consider for patients with angiodysplasia refractory to medical and surgical treatments

586 - Vascular Anomalies and Multidisciplinary Pain Management
Anjali Koka (Boston Children's Hospital); Mary Landrigan-Ossar (Boston Children's Hospital); Elizabeth Eastburn (Boston Children's Hospital)

PURPOSE: Patients with complex vascular anomalies have significant morbidity from pain. Both slow-flow (CLOVES, KT, and FAVA) and high-flow (arteriovenous) lesions cause pain by direct mass involvement, intralesional bleeding, chronic venous insufficiency, cellulitis, superficial thrombophlebitis, deep vein thrombosis, calcification, intraosseous vascular malformation, arthritis, neuropathic pain and musculoskeletal disarray.

Evaluation and management of these patients in the interdisciplinary pediatric pain clinic aims to:

- Assess patient and family goals for pain control.
- Optimize chronic pain management.
- Minimize sleep disturbances.
- Maximize opioid sparing analgesics and neuromodulation with
  – Medications (NSAIDS, antiepileptics, antidepressants, local anesthetics (regional analgesia))
  – Nerve cryoablation
  – Peripheral nerve stimulation
- Provide psychoeducation from psychologist.
- Address fear of pain, anxiety, and catastrophizing.
- Provide comprehensive pain planning with communication to all team members.
- Offer follow-up care for continuity in Pain Clinic 1 week after discharge.

METHODS: Since 2000, 200+ patients with vascular anomalies were seen in Pain Clinic. A retrospective, descriptive study focused on patients who underwent IR procedures from 01/2017 to 05/2019 and received regional analgesia.

RESULTS: Of the 13 patients identified (2 CLOVES, 9 FAVA, 2 KTS), 6 were followed in Pain Clinic. The mean age was 19.3 years; 8 were female (61%). All patients reported pain, 69% swelling, 46% contracture or limited ROM, 15% skin hyperesthesia, 7.5% muscle atrophy. 5 patients (38.5%) had anxiety/depression; 4 of these patients had chronic pain on regular opioids. All patients with KTS and CLOVES had thrombotic events. All patients received general and regional anesthesia before the incision. One patient received a continuous epidural, 3 received a single shot peripheral nerve block

(PNB), and 9 a continuous PNB. 11 patients (84.6%) reported adequate postoperative pain control prior hospital discharge.

CONCLUSION: An interdisciplinary approach to maximize pain control in patients with vascular anomalies and chronic and perioperative pain utilizes pain psychology, regional analgesia, perioperative medication management and inter-team communication.

587 - Segmental (Verrucous) Venous Malformation (VVM) in Neonate with Positive SSA
Darren Kempton (UNM Dermatology); Nikifor Konstantinov (University of New Mexico); Shelly Stepenaskie (University of New Mexico); Aimee Smidt (University of New Mexico)

Clinical History: A 2-day old term girl presented from an outside hospital with concern for aplasia cutis congenita. Sepsis evaluation had been initiated due to concern for chorioamnionitis in setting of premature rupture of membranes. Maternal history was significant for celiac disease and Sjogren's syndrome previously treated with hydroxychloroquine, discontinued 3 months prior to pregnancy; prenatal care had otherwise been routine. Family history was positive for father and aunt with "hemangiomas."
Physical Exam: 4x2cm ulcerated purpuric-appearing stellate irregular plaque on the right foot with 4 small purple papules tracking up leg. Father with bluish-purple focal thickened plaque overlying right foot.
Labs/Imaging: • SSA: > 8.0 • Anti-smith, anti-scleroderma, anti-Jo, Anti-RNP: All negative • HSV/VZV PCR: Negative • Right lower extremity venous/arterial duplex with no abnormalities. • Abdominal and cranial US with no abnormalities
Biopsy (4mm): Preliminary read concerning for thrombotic process with presence of fibrin thrombi; final showed increased dilated vessels with GLUT-1 expression in the papillary dermis.
Discussion: After transfer to our institution, more in-depth history revealed paternal grandfather with known cerebral cavernous malformation (CCM); patient's father had not had genetic testing but was presumed to have disease. Patient found to be heterozygous for KRIT1 gene mutation; diagnosis of VVM in association with CCM made. This case highlights a few interesting points. First, maternal history of Sjogren's and positive SS-A with preliminary biopsy concerning for thrombosis served as distractors resulting in diagnostic delay/ added testing. Second, ulcerated appearance at birth was a source of confusion and potential misdiagnosis. Finally, it demonstrates the necessity of performing a multi-generational family history. Of significance, there is an increased prevalence of CCM in northern New Mexico, likely due to founder effect.

589 - Unusual course of a large venolymphatic malformation of the abdomen treated with Vijoyce
Joseph Gemmete (University of Michigan Hospitals)

PURPOSE: A 13-year-old male with no significant medical history was admitted due to fever, vomiting, and the discovery of an abdominal mass. His fever spiked at 102°F, accompanied by abdominal pain, decreased appetite, nausea, vomiting, and diarrhea. Notably, he had a previous abdominal issue linked to a probiotic. Initial tests showed a low Absolute Lymphocyte Count, elevated CRP, LDH, and hematuria. A CT scan revealed an abdominal mass, possibly a venolymphatic malformation. Severe dehydration led to a 3-liter fluid bolus, and concerns of sepsis prompted Ceftriaxone and Vancomycin treatment.

METHODS: Recovery was challenging, with a 3-month hospitalization, 4 days in the pediatric ICU, high-flow nasal cannula support, intravenous fluids, and antibiotics. Prolonged hospitalization resulted from oral intake difficulties and uncontrolled abdominal pain. An MRI confirmed veno-lymphatic malformation. Complications included C. difficile gastroenteritis requiring temporary Total Parenteral Nutrition (TPN) support and an upper extremity deep vein thrombosis (DVT). Sirolimus therapy for over 60 days didn't significantly impact the abdominal lesion, which displayed potential necrotic areas on a PET scan.

RESULTS: Genetic testing identified a PIK3CA gene somatic pathogenic variant, making him eligible for Vijoyce treatment. Initiated 2 ½ months post-admission, Vijoyce therapy marked a turning point, and he was discharged with daily Vijoyce dosing (50 mg) and monthly CBC/CMP follow-ups.Two months after starting Vijoyce, follow-up imaging showed promising venolymphatic malformation regression. However, a new concern arose with erythema on the abdominal wall and fluid drainage, emphasizing the ongoing complexity of his medical journey.

CONCLUSION: Questions:

1. Does Sirolimus have a role in treatment without genetic testing?

2. Does Vijoyce cause regression of a large venolymphatic malformation – time course?

3. What is the cause of the erythema and drainage of the anterior abdominal wall wound? Is this related to the treatment with Vijoyce from necrosis of the lesion?

590 - Arteriovenous malformation of the hand: Long-term course according to the spread of the lesion
Tadashi Nomura (Department of Plastic Surgery, Kobe University Graduate School of Medicine); Reiko Takeda (Department of Plastic Surgery, Kobe University Graduate School of Medicine); Kousuke Masaoka (Department of Plastic Surgery, Kobe University Graduate School of Medicine); Misato Ueda (Department of Plastic Surgery, Kobe University Graduate School of Medicine); Daichi Aoki (Department of Plastic Surgery, Kobe University Graduate School of Medicine); Takeo Osaki (Department of Plastic Surgery, Hyogo Cancer Center); Shunsuke Sakakibara (Department of Plastic Surgery, Kobe University Graduate School of Medicine); Hiroto Terashi (Department of Plastic Surgery, Kobe University Graduate School of Medicine)

PURPOSE: Arteriovenous malformations (AVM) of the hand are generally difficult to treat, and in many cases digital amputation occurs when symptoms of ulcers or bleeding develop. Endovascular therapy always has the potential for finger necrosis, and surgical resection usually requires soft tissue reconstruction. There are currently no standard treatments or strategies. The objective of this study was to investigate the long-term outcome of patients with AVM of the fingers experienced in our department and to investigate the optimization of treatment methods.

METHODS: We examined the extent of disease, treatment, and course of hand AVM cases that we have seen in our department over the past 10 years. Spread of the lesion was classified three groups; group 1: fingers only, group 2: fingers to palms, and group 3: greater than wrist joints.

RESULTS: Sixteen patients with 7 cases at Schoebinger stage 2 and 9 cases at stage 3. were enrolled. There were 7 cases in Group 1, 4 cases in Group 2, and 5 cases in Group 3. There were 10 cases in which some type of surgical treatment was performed, of which 2 cases in Group 1 underwent wrap-around flap and 2 with venous flap. Four cases (80%) in Group 3 involved amputation. Endovascular treatment was performed in 4 cases, of which 3 cases later underwent some type of amputation. There was one case in Stage 3 and Group 2 in which the hand was saved with sclerotherapy alone.

CONCLUSION: Based on the results of this study, we found that by surgical resection disease could be controlled well in Group 1. Ensuring that the lesion is removed surgically and reconstructed with fresh and vascular-rich soft tissue is effective. On the other hand, Group 3 cases required finger amputation at a high rate.

591 - A comparison of scientific articles, institutional press releases, and health news reports on alpelisib treatment in patients with PIK3CA-related overgrowth spectrum (PROS).
Pierre Vabres (Université de Bourgogne)

PURPOSE: Many health news stories inaccurately represent research results, by overstating the efficacy or safety of a treatment, an issue known as ""spin"" or ""hype"". We sought to determine whether news reports on the use of alpelisib in patients with PIK3CA-related overgrowth spectrum (PROS) in mainstream media were accurate.

METHODS: We studied articles published in peer-reviewed journals on the use of alpelisib in PROS, to determine the Oxford Centre for Evidence-Based Medicine (OCEBM) level of evidence and grade of recommendation supporting this treatment approach. We collected press releases from the authors' institutions, newspaper and magazine articles, and radio or television interviews in the French media pertaining to this topic between 2018 and 2023, and we compared their content with the actual evidence.

RESULTS: Almost all published articles were case reports or case series. We found only one published retrospective non-controlled observational study (NCT04285723) where the primary outcome measure was reported, with a modest response achieved only in a minority of patients. Based on these results, the OCEBM level of evidence (4) and grade of recommendation (C) for alpelisib in PROS were low. In contrast, multiple enthusiastic news stories appeared in major French media during a five-year period, claiming that a ""miracle cure"" allowed ""the rebirth of ""Cloves children"" suffering from the ""Elephant Man syndrome""""". Such overly enthusiastic tone was also present in the initial press release from the authors' research institute, which stated ""results beyond expectations"", a ""dramatic impact on all symptoms"", and a ""major benefit of this therapeutic approach"" that ""would radically change the future of patients"".

CONCLUSION: A major discrepancy was found between actual evidence and health news stories on PROS treatment with alpelisib. As previously reported, exaggeration in news was associated with exaggeration in press releases. This may cause major disappointment in PROS patient whose expectations are not met.

592 - Successful Trans-arterial Embolization of Challenging Arteriovenous Fistula Involving Orbital and Paranasal Sinus : A Case Report

Heltara Ramandika (RSCM); Jacub Pandelaki (Interventional Radiologist)

PURPOSE: To present a challenging case of arteriovenous fistulas (AVF) involving the orbital and paranasal sinus.

METHODS: We report on a 50-year-old male presenting with proptosis, redness of the left eye, decreased visual acuity (6/15), increased intra-orbital pressure, episcleral injection, conjunctival injection, and ciliary injection. The symptoms manifested since childhood, with three prior unsuccessful surgeries and recurrences. Orbital and sinus MR examination revealed tortuous vascular structures in the left orbital, left maxillary, and ethmoidal sinus, mixed with lymphatic components and sinus mucosal thickening. Digital Subtraction Angiography confirmed a high-flow vascular malformation without presence of nidus, consistent with Arteriovenous Fistula (AVF). DSA and embolization were performed. There were three feeding arteries detected: superficial temporal artery, middle meningeal artery, and internal maxillary artery. All of them are significantly tortuous and long. The embolization was performed using Coils and NBCA (N-butyl cyanoacrylate) in those arteries. Due to challenging feeding arteries, the procedure required two separate sessions, in which the three feeding arteries were successfully embolized.

RESULTS: Clinical follow-up demonstrated a significant improvement and satisfactory results, with the complete disappearance of clinical symptoms such as proptosis and redness within three months.

CONCLUSION: Arteriovenous Fistula (AVF) involving both the orbital and paranasal sinus is rare. Despite the challenges posed by multiple, tortuous, and lengthy feeding arteries, super-selective embolization

using Coils and NBCA in separate sessions proved to be satisfactory for this case. This case report aims to contribute valuable insights to the management of vascular anomalies in patients with similar conditions.

593 - Kaposiform Lymphangiomatosis (KLA) harboring NRAS mutation are highly responsive to low dose trametinib

Niina Kleiber (CHU Sainte-Justine, Université de Montréal); Josee Dubois (CHU Ste-Justine, Université de Montréal); Michèle David (CHU Sainte-Justine); Antoine Gourmel (CHU Sainte-Justine); Julie Powell (CHU Sainte-Justine, U of Montreal); sandra ondrejchak (CHU Ste-Justine); Yves Théoêt (CHU Sainte-Justine); Thai Tran (CHU Sainte-Justine)

PURPOSE: The high morbidity and mortality of KLA have declined with sirolimus use but disease control is often partial with residual symptoms and poor radiological response. Trametinib was reported effective in a single case report of KLA harboring NRAS mutation. Data on dosing, effective blood level, and treatment response according to disease activity remain limited.

METHODS: All consecutively admitted patients with NRAS-mutated KLA with partial response to sirolimus were switched to trametinib. Starting dose was half of the age-based recommended phase 2 dose of trametinib in cancers (0.0125mg/kg daily oral dose) and dosing escalation was planned based on response. To monitor toxicity, echocardiography, ophthalmologic exam and extensive blood work up were regularly performed. Trough trametinib blood concentration was obtained. Radiological response was assessed with MRI after 6 months of treatment.

RESULTS: Three patients with NRAS-mutated KLA were treated during the active phase of disease (Patient 1), during chronic symptomatic (Patient 2) and asymptomatic phase (Patient 3). Response was good regardless of disease activity. All patients responded to low dose trametinib (trough blood level 3-6ng/ml). Patient 1 (extensive cervical and mediastinal involvement) had resolution of coagulopathy, pleural effusions and ascites. Patient 2 (extensive cervical, thoracic, and digestive involvement) could be weaned from home oxygen, gastrostomy feeding, blood transfusion and pleural effusions disappeared. Patient 3 was asymptomatic. Excellent radiological response was documented in all patients with resolution of effusions (Patient 1: pleural effusions, ascites; Patient 2: pleural effusion) and marked decrease in the size of the lesions (all three patients). Trametinib was very well tolerated in all patients. Adverse effects due to previous treatment (sirolimus, steroids, vincristine) completely resolved.

CONCLUSION: Low dose trametinib are effective and well tolerated in KLA with partial response to sirolimus regardless of disase activity. Remaining symptoms and effusions disappeared and rapid radiological decrease in the size of the lesions was observed.

603 - An Extremely Premature Infant with a Massive Cervicofacial Lymphatic Malformation with Poor Response to Sirolimus and Sclerotherapy

Rachael Schulte (Riley Children's Hospital, Indiana University School of Medicine); Diane Chen (Riley Children's Hospital, Indiana University School of Medicine); Lauren Sowa (Riley Children's Hospital, Indiana University School of Medicine); Christopher Sinsabaugh (Riley Children's Hospital, Indiana University School of Medicine); Sean Pfaff (Riley Children's Hospital, Indiana University School of Medicine); Francis Marshalleck (Riley Children's Hospital, Indiana University School of Medicine); Anita Haggstrom (Indiana University)

PURPOSE: Prenatal cervicofacial lymphatic malformations can cause severe postnatal complications and require a multidisciplinary treatment approach.

METHODS: A male infant born at 26 weeks EGA (placenta previa, bleeding) had a prenatally diagnosed large cystic neck mass, likely lymphatic malformation (LM). He was intubated at birth, extubated day of life 1-12, then reintubated and required high ventilator settings; also diagnosed with bronchopulmonary

dysplasia. He underwent drainage and sclerotherapy to dominant cysts, with post-procedure swelling/hemorrhage complicating his respiratory status at times. Unfortunately, fluid reaccumulated after each procedure, and the mass continued to grow. MRI showed encasement/deviation of numerous structures/vessels, including airway deviation. Sirolimus was started at 6wk old, with dosing complicated by extreme prematurity. After two weeks, troughs remained in/close to goal range (10-13 ng/mL) for 5 weeks, dosed at approximately 0.3-0.4mg/m2 (estimated BSA). MRI at 8wk old showed increased size of LM, worsened airway deviation. Sclerotherapy was performed intermittently when felt to be appropriate. Despite therapies, the mass continued to grow. At 8 weeks old, he developed severe bilateral swelling of face and scalp, ultimately felt to represent lymphatic obstruction with no procedural intervention available. His respiratory status continued to worsen, likely a combination of his lung disease of prematurity and the LM. Excisional biopsy was performed at 12wk old to rule out cystic teratoma; pathology consistent with LM, and somatic genetic testing revealed a PIK3CA mutation. After multidisciplinary discussion, debulking surgery was planned. One week pre-surgery, sclerotherapy was abandoned when purulent fluid was aspirated. Antibiotics and IVIG were given.

RESULTS: Upon further discussions on the high risk of surgery in setting of infection, family elected comfort care / compassionate extubation and the patient died at age 15wk.

CONCLUSION: This patient did not respond well to sclerotherapy or sirolimus, highlighting the need for ongoing research in this population, including investigation of alpelisib in certain cases.

604 - Use targeted therapy in two spindle cell hemangioma patients with IDH1 or IDH2 mutations.
Melisa Ruiz-Gutierrez (Boston Children's Hospital); Amir Taghinia (Boston Children's Hospital); Whitney Eng (Boston Children's Hospital/Dana Farber Cancer Institute)

PURPOSE: Spindle cell hemangiomas (SCH) are caused by IDH1/2 mutations. Current management is focused on surgical resection, but recurrence of disease is common. Treatment with sirolimus has not been effective. We treated patients with IDH1/2 inhibitors on a compassionate basis with the aim improving symptoms.

METHODS: A 30 yr old patient with recurrent and progressive SCH of the left foot s/p multiple resections presented with significant pain, difficulty ambulating and fitting shoes. Targeted somatic NGS panel revealed IDH1 mutation c.394C>T p.R132C with VAF 21%. A 14 yr old patient with recurrent SCH of the left hand s/p multiple surgical excision presented with significant pain and impaired function of the hand. Targeted somatic NGS panel revealed IDH2 mutation c.515G>T p.R172T with VAF 19%. The histopathology for both patients was consistent with SCH. The mutations in IDH1/2 were known to be pathogenic activating mutations. Neither patient had evidence of enchondromas on skeletal survey. Dosing for both patients based on AML literature for Enasidenib 50-100mg PO daily and Ivosidenib 500mg PO daily.

RESULTS: Patient with IDH1 mutation remains on treatment with Ivosidenib, current duration of treatment is 14 months. Patient experienced mild GI upset and headaches in the first 3 months of treatment, these have resolved. Patient has experienced significant decrease in pain, now able to stand and wear shoes. Patient with IDH2 remains on treatment with Enasidenib, current duration of treatment is 21 months. Patient has not experienced side effects or toxicities. Neither patient has experienced new lesions or growth in existing lesions.

CONCLUSION: Currently the potential risks and benefits of IDH1/2 inhibitors in SCH are unknown. The SCHs responded to treatment with decreased size of lesions, no new lesions, decreased pain, and increased function of extremities. The IDH1/2 inhibitors were well tolerated at the therapeutic dosing with no adverse side effects.

Social Programs (in-person only)

Welcome Reception

We invite all in-person attendees to the Welcome Reception, which will occur in the IFEMA Main Congress Hallway on Tuesday, 7 May from 18:30 - 20:00. There will be light appetizers and drinks available, as well as the opportunity to network with colleagues and visit the Exhibition Hall. This reception is included with your in-person registration.

Tuesday, 7 May • 18:30 - 20:00
Location: IFEMA Main Congress Hallway

Congress Social Event

Join colleagues for an evening of celebrating the ISSVA World Congress 2024 and the city of Madrid. Tapas, drinks, a flamenco demonstration, and music will allow you to mingle with colleagues while enjoying the incredible venue, the Casino de Madrid. **You will need to get to the venue on your own.**

The Congress Dinner requires a ticket to attend. If available, extra tickets will be available at the Registration Desk onsite (there are a limited number of tickets).

Thursday, 9 May • 20:00 - 23:00
Location: Casino de Madrid **Address:** C. de Alcalá, 15, Centro, 28014 Madrid, Spain
Dress Code: **Jacket and tie required**

Running Club

The ISSVA Running Club will be meeting on the morning of Friday 10 May for a casual run\walk through El Retiro Park. There will be running group and a walking group. To join the Running Club, we request a donation to the ISSVA Education Fund.

10 May • 6:30-7:15am
Meet at: Puerta de la Reina Mercedes del Retiro (Entrance Gate), Av. de Menéndez Pelayo, Retiro, 28009 Madrid, Spain

Farewell Reception

At the conclusion of the scientific sessions on Friday, 10 May, there will be a brief Farewell Reception consisting of appetizers and drinks. This reception is included with your in-person registration.

Friday, 10 May • 16:00 - 17:00
Location: IFEMA Main Congress Hallway

Non-CME Symposia & Affiliate Meetings (In-Person)

Non-CME Symposia

IGEA Lunch Symposium
13:45 - 14:45 on 8 May 2024 (Room N106)
"Bleomycin Electrosclerotherapy"
Moderator: Prof. Juan Carlos López Gutiérrez
Speakers: Prof. Lluis Mir, Prof. Walter A. Wohlgemuth, and Prof. Giacomo Colletti

Pierre Fabre Lunch Symposium (Gold Sponsor)
13:30-14:30 on 9 May 2024 (Room N105)
"Management of Infantile Hemangiomas. 2014-2024: What have we learned?"
Moderator: Prof. Juan Carlos López Gutiérrez
Speakers : Christine Léauté-Labrèze and Alain Delarue

Novartis Lunch Symposium (Platinum Sponsor)
12:50-13:50 on 10 May 2024 (N106)
"Look to the root of the overgrowth to understand PROS (PIK3CA-Related Overgrowth Spectrum)"
Speaker: Jochen Rössler, MD

Affiliate Meetings (In-person)

International Patient Advocacy Group Meeting
A meeting for patient advocacy groups that are interested in the opportunity to meet and coordinate efforts will take place on Tuesday, 7 May 2024 from 19:30-20:30 in room N109.

Vascular Anomalies Coordinator Meeting
Texas Children's Hospital and CHOP will be hosting a meeting for vascular anomaly coordinators on Wednesday, 8 May 2022 from 14:00-16:00 in room N111. All coordinators are welcome to join the discussion!

Vascular Anomalies Canada
Vascular Anomalies Canada is a patient advocacy group located in Canada and they will be hosting a meeting for their in-person membership, 10 May 2022 from 12:50-13:50 in room N111.

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