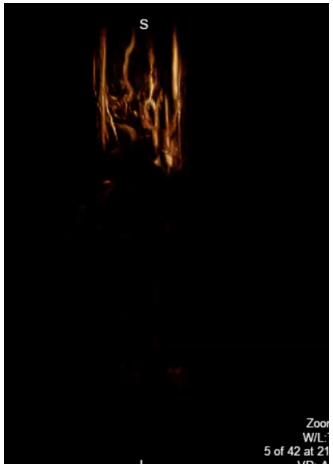

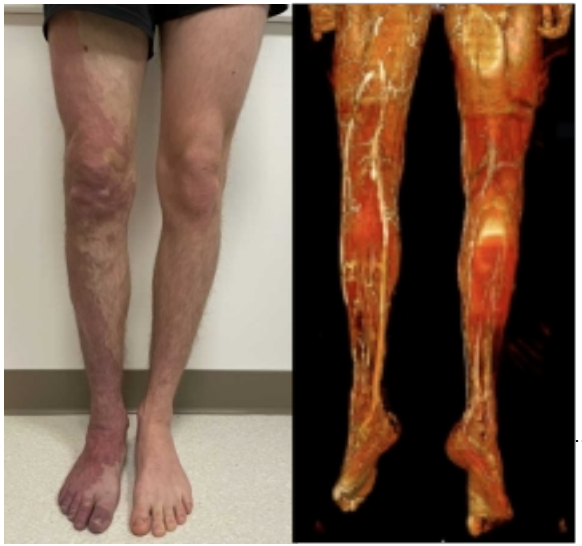

Ferumoxytol-enhanced Whole Body MRI for Characterization of Genetic, Syndromic and Diffuse Vascular Anomalies

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Disclosures

- Financial: None

- Will discuss off-label use of Ferumoxytol as a blood pool contrast agent for MR imaging

Spectrum of diffuse/genetic/syndromic VA

PTEN

BRBRS

SMAD4

HHT

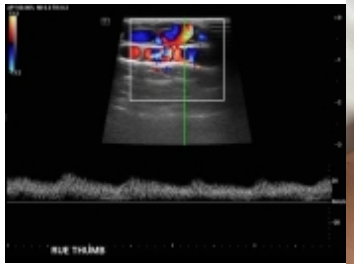
CM-AVM

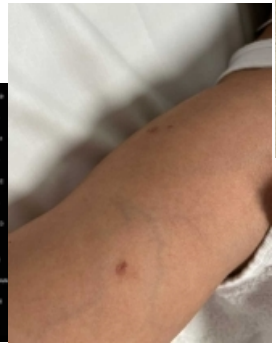
AVCRL

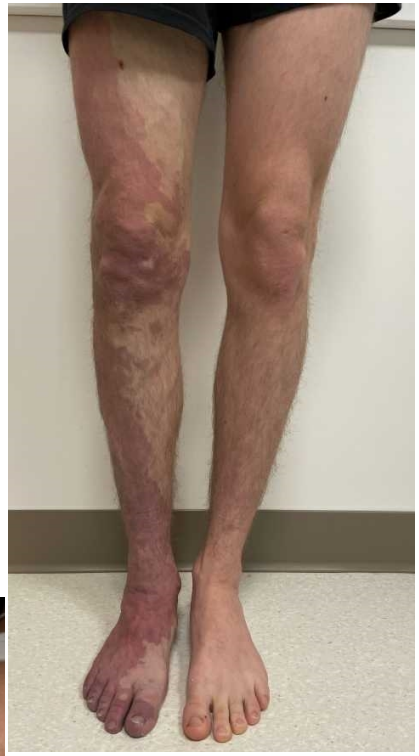
GLMN

RASA1

PWS





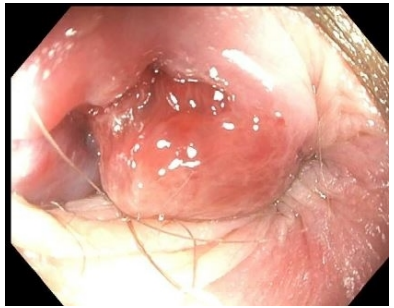


ILM

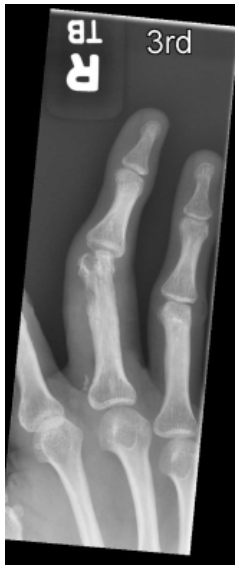
PIK3CA

KTS

HHML



FCD

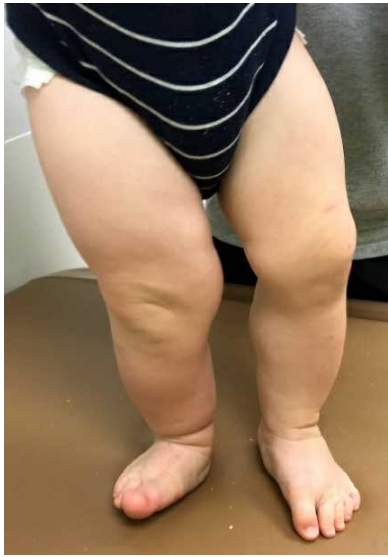


MCAP

FAO

FAVA

CLOVES



Diffuse Vascular Anomalies Pose Imaging Challenges

- Genetic syndromes, overgrowth, multi-organ involvement, multi-planar involvement, diffuse disease, combined slow-flow and fast-flow lesions
- Complications related to disease or treatment (thrombosis, hemorrhage, contractures, end-organ changes, non-target embolism)
- Misdiagnoses outside of specialist VAC settings common (>50%)
- VAC Specialist referrals: frequently underestimate extent and mischaracterize syndromic involvement:
- ***Imaging critical to Dx and Rx***
- Insufficiently characterized by conventional MR protocols which take too long, and are incapable of whole-body coverage

Objective

- Develop Whole Body / partial WB MRI protocol tailored for diffuse/syndromic/genetic vascular anomalies
- Short protocol
- Unsupervised performance in non-specialized centers
- Comprehensive assessment of vascular and non-vascular components

Referral Pathway for WB Diffuse Vascular Anomaly (DVA) Imaging protocol

- Patients seen by specialist vascular anomalies provider (radiology, derm, plastics, hem-onc) and presented at multi-disciplinary HVMC conference
- Clinical photos, physical exam and prior imaging reviewed
- Interventional Radiologist performs targeted US to identify approximate extent, and screen for high-flow lesions
- Provisional HVMC diagnosis assigned
- Patients with concern for overgrowth, syndromic or diffuse anomalies are referred for whole-body MR imaging protocol

Methods: Imaging Protocol

- Following IRB approval, clinical, imaging and management information from patients who underwent MR imaging using the DVA protocol reviewed.
- Siemens 3T Prisma or Skyra
- Exams performed after slow infusion of Ferumoxytol (**brand:** Feraheme IMAG Ph, **generic:** Sandoz Ph).
  - 3D RAVE (radial volumetric imaging) in small free-breathing patients OR BH VIBE (cartesian volumetric imaging) in cooperative patients
  - Axial SSFSE T2 without fat saturation
  - 3D T2-SPACE (TSE T2 with variable flip angles)
- Composite images for all sequences: ***Image stitching to provide single volume***
- *Suspicion of high-flow lesion: additional TWIST time-resolved MRA (1 sec temporal resolution) with extracellular Gd contrast focusing on region of concern*

Methods: Image Quality Assessment

- Technical image quality for each sequence (RAVE, VIBE, SSFSE T2, 3D T2 SPACE) graded by 2 expert readers with 20 years and 10 years of experience in pediatric vascular anomalies
- Consensus approach
- Standardized scale (1: non-diagnostic to 5: excellent).

Severe blurring/artifacts. Signal dropouts. Non-diagnostic.	1
Moderate to Severe blurring/artifacts. Loss of Diagnostic Accuracy.	2
Moderate blurring/artifacts. Does not interfere with diagnostic interpretation.	3
Minimal blurring/artifacts. Diagnostic	4
No evident blurring/artifacts. Diagnostic	5

Methods: 19 Reporting Elements for Diffuse Vascular Anomalies

- Arterial: Regional arterial anatomy, arteriovenous shunting/fistula
- Venous: Deep venous anatomy, superficial venous anatomy, deep intramuscular/visceral VM, superficial VM, anomalous veins
- Lymphatic: Macrocystic LM, microcyctic LM, Soft tissue edema
- Overgrowth, Limb size discrepancy, Limb length discrepancy, Limb shape
- Fatty hypertrophy, Soft tissue hamartomas/masses
- Visceral organ involvement, Spinal involvement, Bony involvement

Methods: Reporting Elements for Diffuse Vascular Anomalies

- Clinical grading of reporting elements for diffuse/syndromic vascular anomalies performed using standardized scale (1: non-diagnostic to 5: excellent)

Non-Diagnostic or Not Visible	1
Poor (Relevant anatomy visible but with significant blurring or artifacts, barely diagnostic)	2
Fair (Relevant anatomy visible, moderate blurring or artifacts, partially diagnostic)	3
Good (Good visualization of relevant anatomy, minimal blurring or artifacts)	4
Excellent (Excellent delineation of relevant anatomy, high quality diagnostic information, no artifacts)	5

Results: Patient characteristics, and contrast dosing

- A total of 31 patients (15 M: 16 F) underwent the diffuse vascular malformation protocol using Ferumoxytol contrast.
- Mean age at the time of the scan: 12.6 years (range: 0.1-52.3 yr).
- Mean weight 56.2 kg (range: 7.4-156.8 kg).
- Ferumoxytol contrast dosing range 1-3.5 mg/kg, (avg: 2.35 mg/kg).
- 17 /31 patients had prior MRIs performed at NCH or outside center
- 97% had prior vascular anomalies specialist review

Results: Technical Grading

- Sequences performed and average number of stations per sequence:

RAVE (2.75), VIBE (4.14) SSFSE (3.15) and 3D T2 SPACE (2.29)

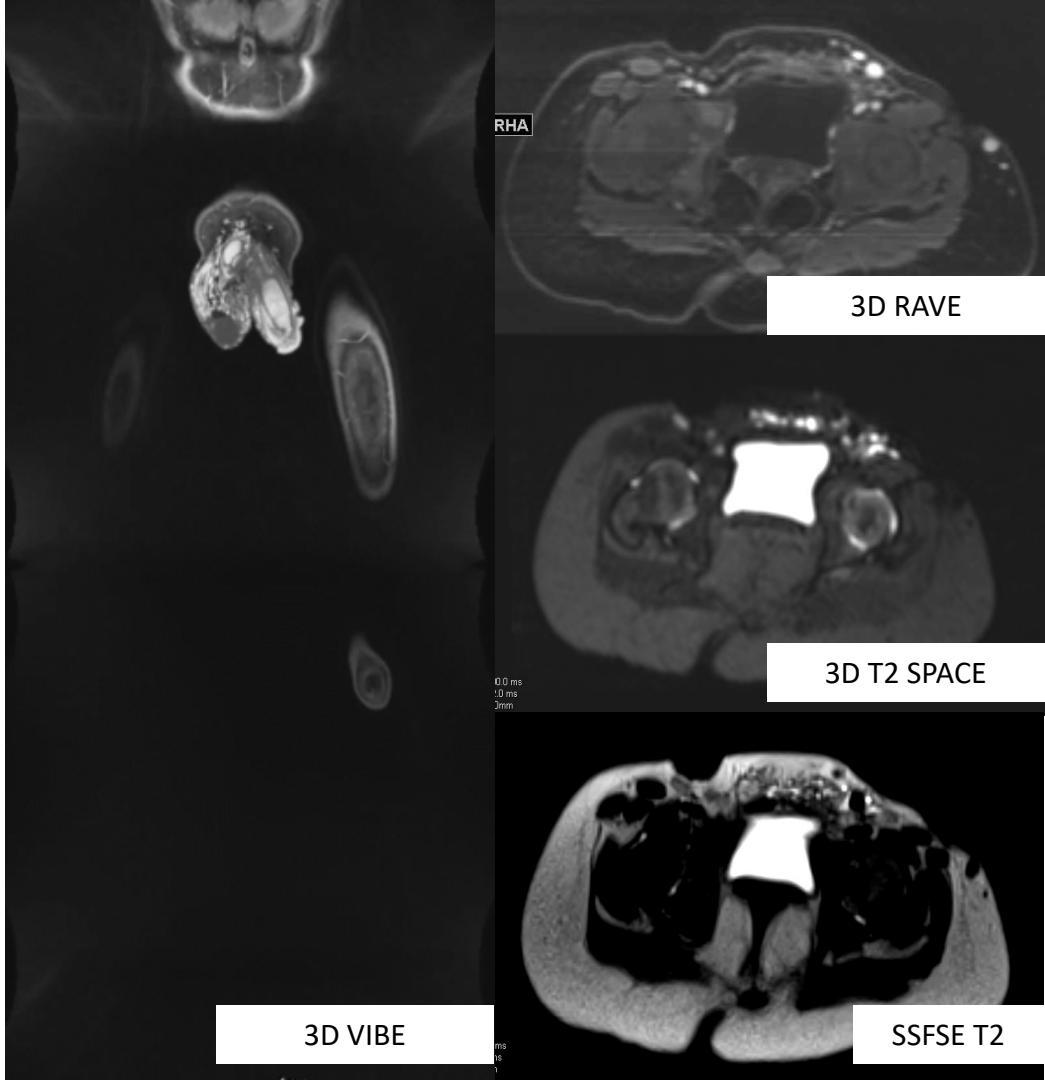
- Consensus technical image quality scores:

RAVE (4.5, range 2-5),

VIBE (4.21, range 3-5),

SSFSE T2 (4.81, range 4-5)

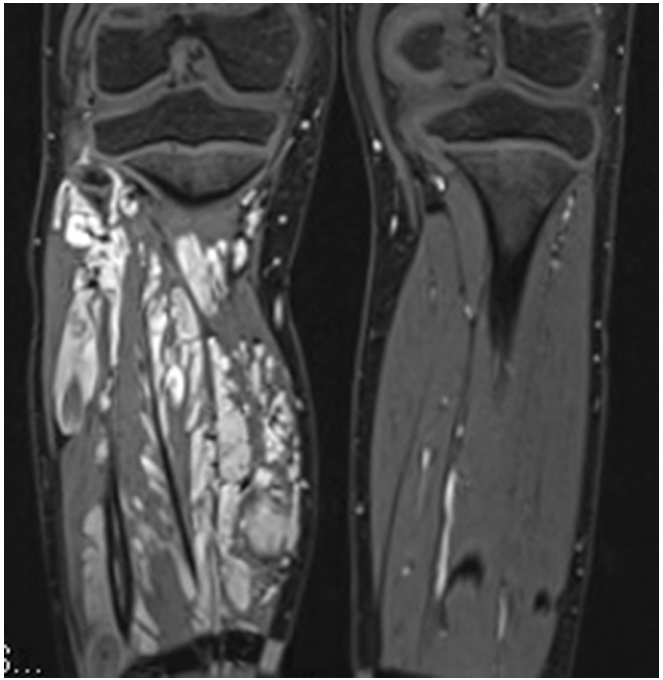
3D T2 SPACE (4.07, range 2-5)



Results: Clinical Grading of Arterial and Venous Component of DVA

Average clinical grades (and ranges) for delineation of reporting elements for arterial and venous components of diffuse vascular malformations:

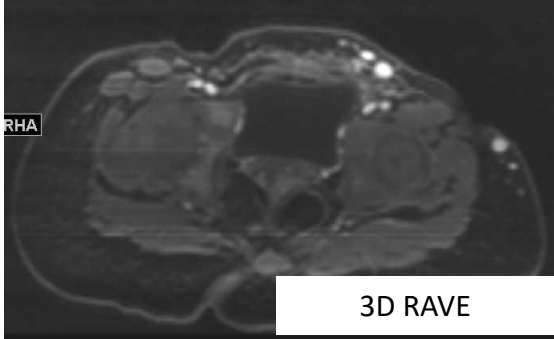
- Arteries (4.48, 3-5)
- Deep venous system (4.67, 3-5)
- Superficial venous system (4.70, 3-5)
- Anomalous veins (4.67, 3-5)
- Superficial venous malformation (VM) (4.70, 3-5)
- Deep/intramuscular VM (4.80, 4-5)

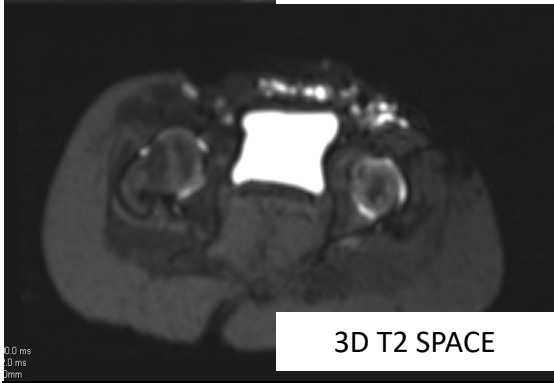


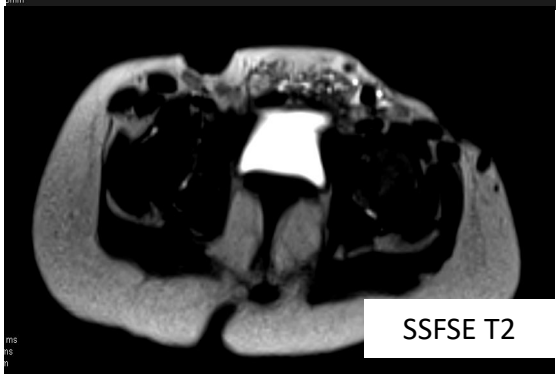
Results: Clinical Grading of Lymphatic Component

Average clinical grades (and ranges) for delineation of reporting elements for lymphatic component of diffuse vascular malformations:

- Macrocystic lymphatic malformation
  - SSFSE T2 (4.74, 4-5)
  - 3D T2 SPACE (4.5, 3-5)
- Microcystic lymphatic malformation
  - SSFSE T2 (4.67, 4-5)
  - 3D T2 SPACE (4.53, 3-5)
- Soft tissue edema
  - SSFSE (4.63, 4-5)
  - 3D T2 SPACE (4.38, 3-5)
- T2 imaging after ferumoxytol suppresses all vasculature, making assessment of lymphatic component or edema much easier
- SSFSE T2 and 3D T2 SPACE performed similarly in assessment of lymphatic component



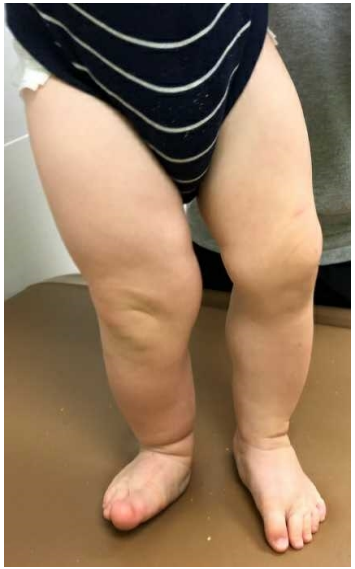


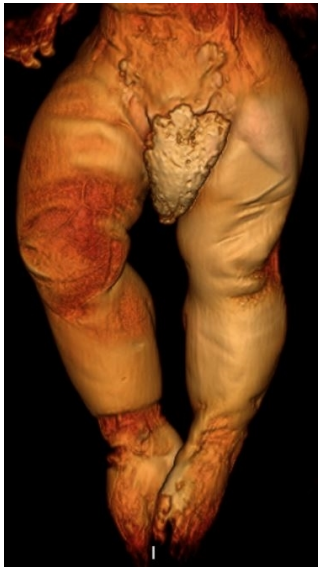


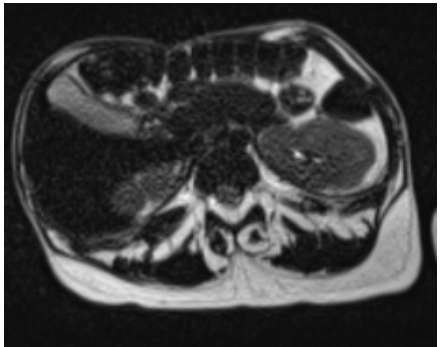
Results: Clinical Grading of Extravascular Involvement

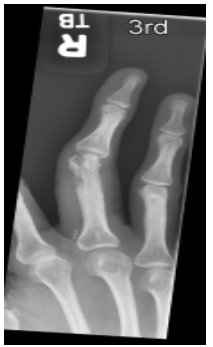
Average clinical grades (and ranges) for delineation of reporting elements for extravascular component of diffuse vascular malformations:

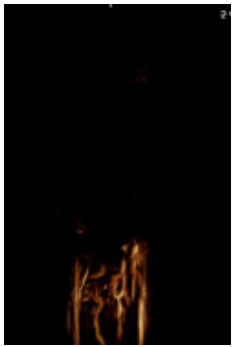
- Limb size discrepancy (4.72, 4-5)
- Visceral organ involvement (4.7, 4-5)
- Spine involvement (4.54, 3-5),
- Focal fatty hypertrophy (4.77, 3-5)
- Limb shape (4.75, 3-5)
- Bone involvement (4.76, 3-5)











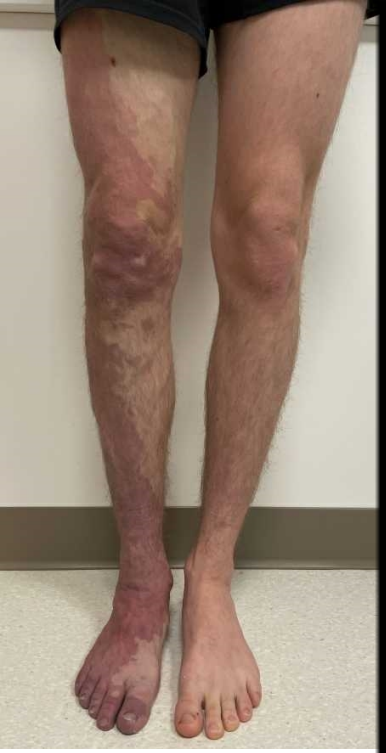
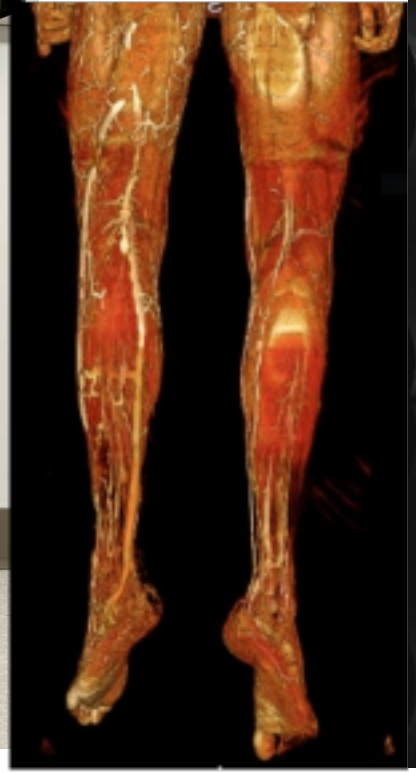
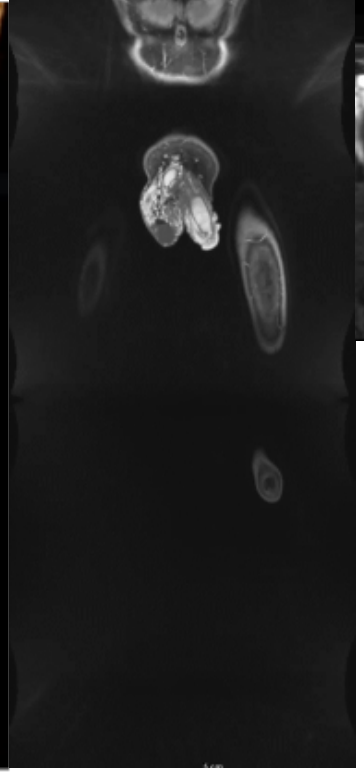
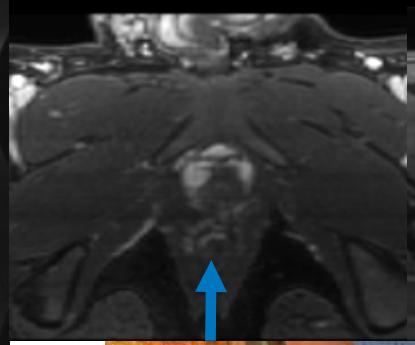
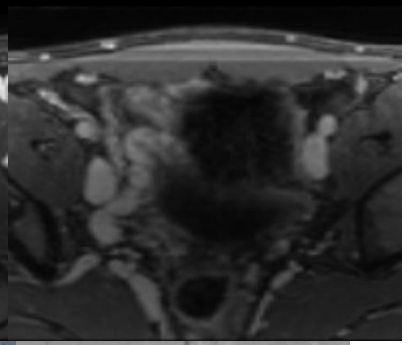
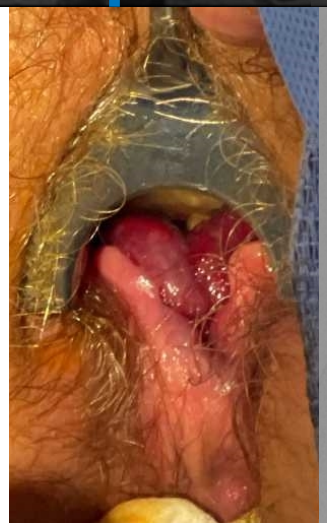
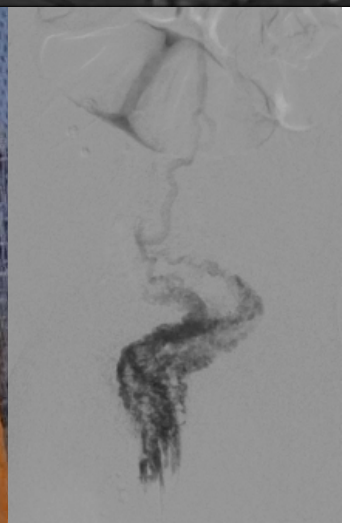
Results: Diagnosis

- Based on WB MRI, pre-procedure HVAC diagnosis modified in 67.7% of cases
  - *Genetic/syndromic diagnosis made, genetic/syndromic diagnosis modified, or region/extent of involvement changed*
- **Final Imaging Diagnoses:**
  - PIK3CA-related conditions (15): 5 CLOVES, 4 KTS, 6 not specified
  - Extensive/deep VM (6)
  - Superficial VM (3)
  - Other diagnoses:
    - unilateral lower extremity undergrowth in 2 patients, with 1 having tuberous sclerosis and PECOMA
    - isolated unilateral LE lymphedema (1)
    - extensive RUE AVM in RASA1 mutation (1)
    - hypervascular soft tissue neoplasm (1)
    - extensive cervicofacial LM (1)
    - isolated syndactyly (1)
  - 2 patients with suspected superficial VM had GSV Insufficiency proven with duplex US

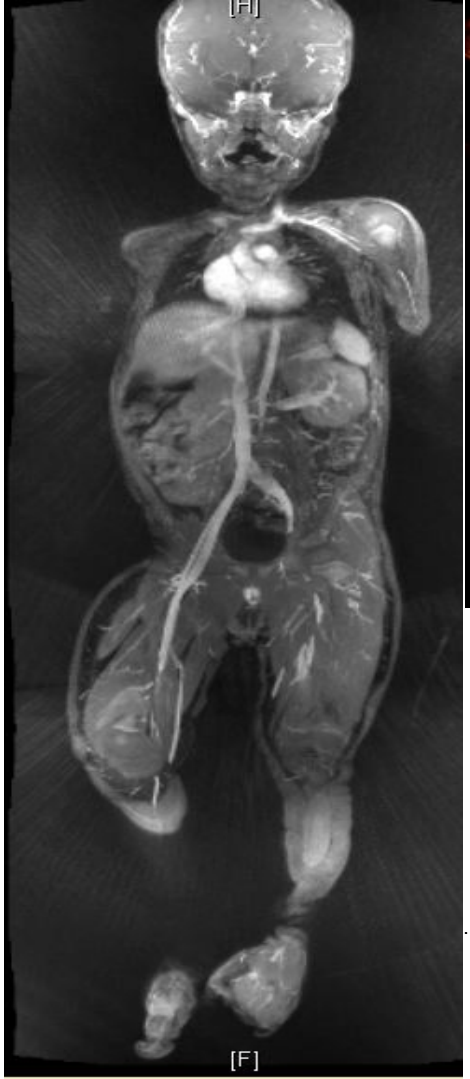
Results: Scan Duration and Suggested Protocol

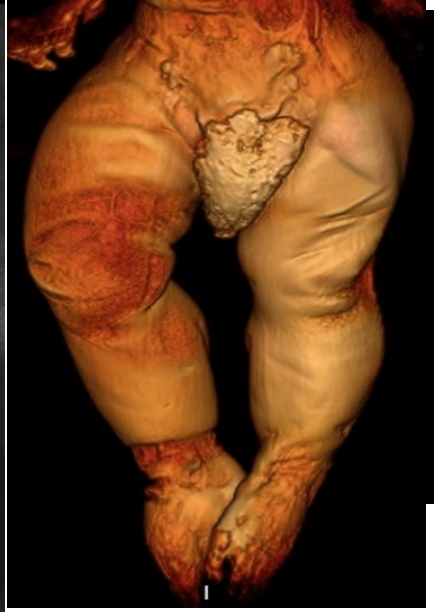
- Average time for completion of protocol: 61 minutes (range: 26 – 126 min)
- Duration of each sequence: 3D T2 SPACE > RAVE > VIBE > SSFSE T2
- Due to similar performance of 3D T2 and SSFSE T2 for edema, lymphatic component and soft tissue component, *we recommend removing 3D T2 SPACE from the protocol*
- **Final protocol:**
  - 3D RAVE in free-breathing/smaller patients or 3D VIBE in cooperative/breath-holding patients with composite stitching
  - Axial SSFSE T2 without fat saturation with composite stitching
  - *Suspicion of high-flow lesion: additional TWIST time-resolved MRA (1 sec temporal resolution) with Gd-contrast focusing on region of concern*

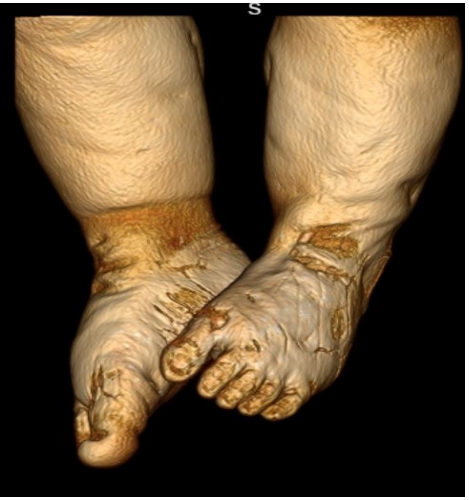
  Expected Duration of Protocol: 30-40 minutes depending on coverage

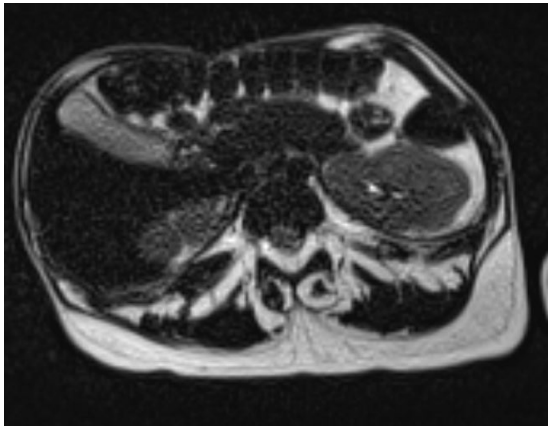








19yM, remote laser Rx for RLE port-wine stain, intermittent BRBPR, Hb 7
Pre-procedure Dx: KTS with rectal bleeding requiring blood transfusion
Post procedure Dx: PROS with pelvic/perirectal involvement and anomalous veins with several perforators to deep veins









14 mo male. Pre-procedure and post procedure Dx: CLOVES. RLE overgrowth, L sandal gap deformity, lipomatous overgrowth with fatty infiltration of paraspinal muscles on SSFSE. No anomalous venous or arterial vasculature

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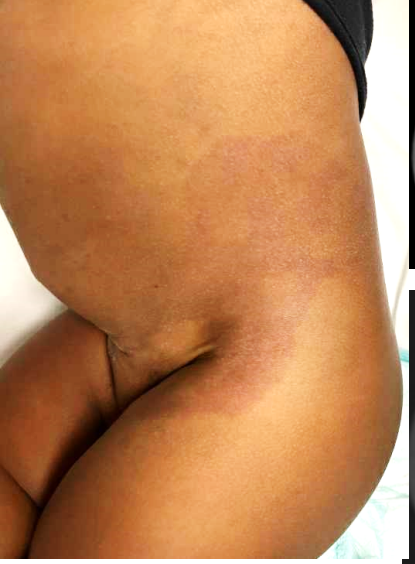
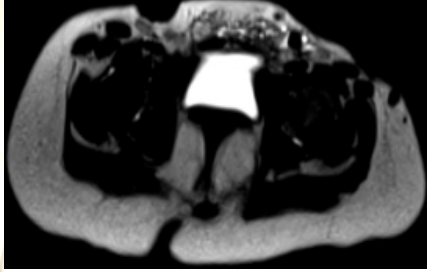
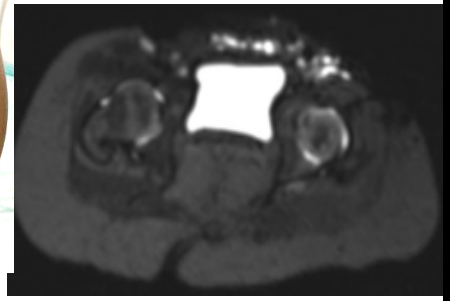
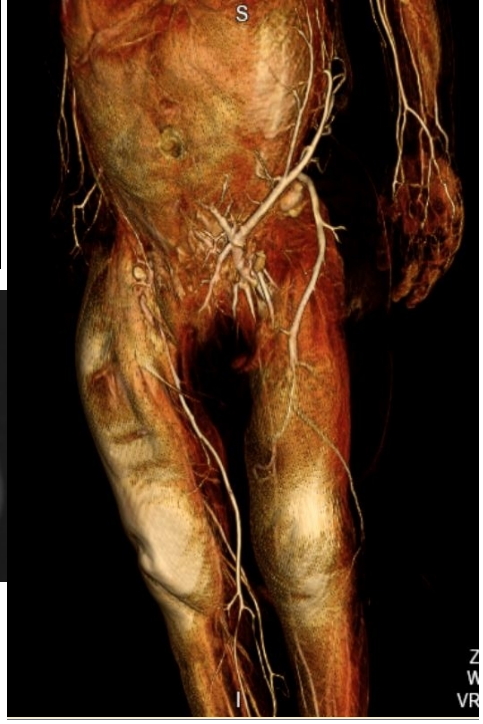
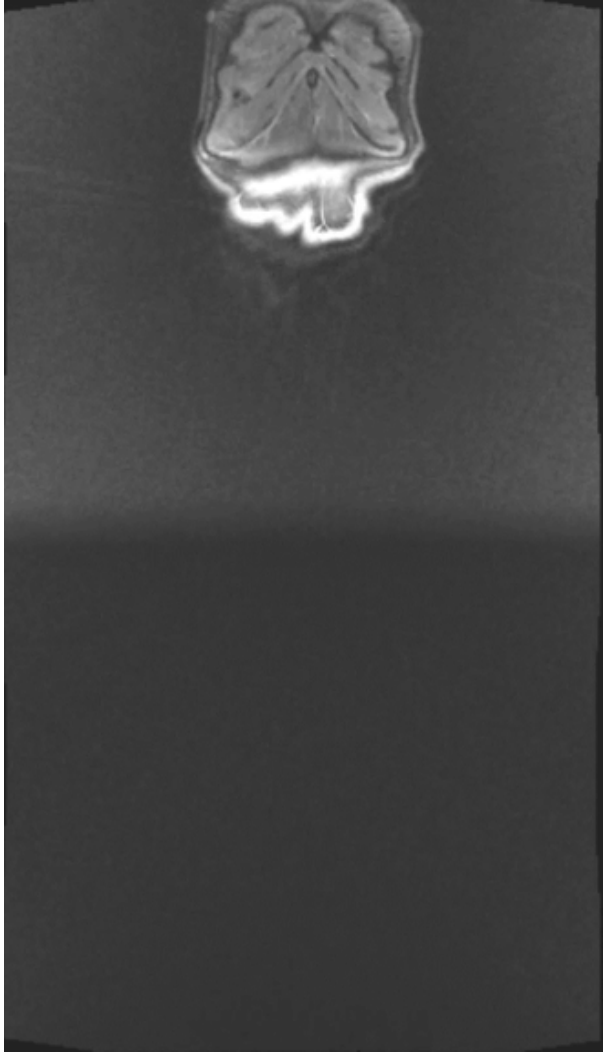




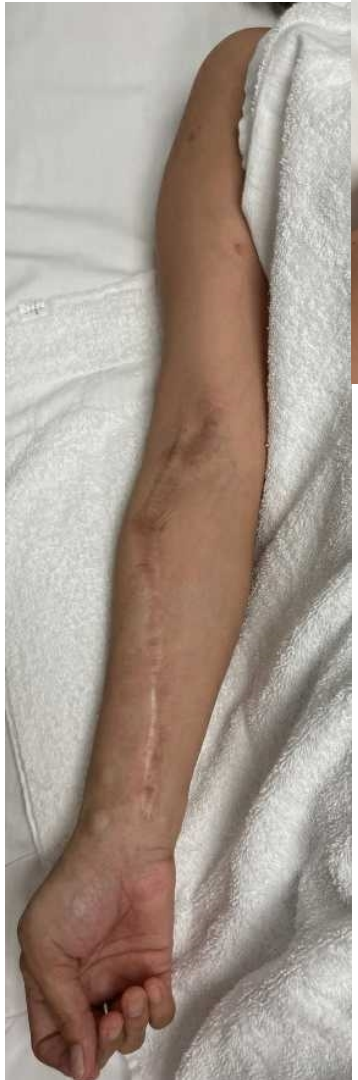


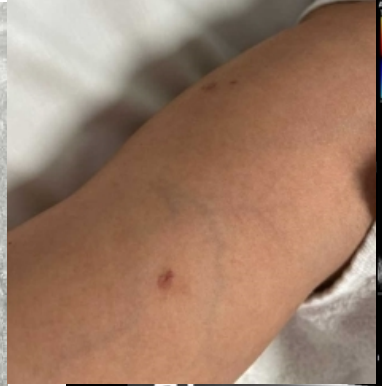


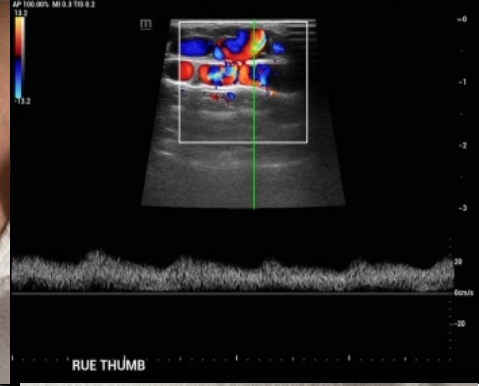


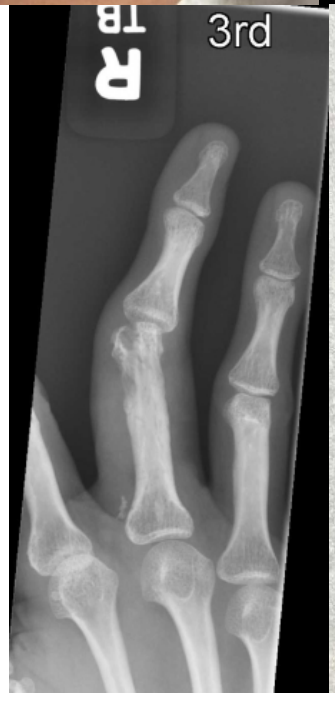
18 mo female. **Pre-procedure Dx:** Parkes Weber Syndrome and left inguinal VM
Post procedure Dx: PIK3CA related Overgrowth Syndrome
Truncal marginal vein communicating with the deep veins at the L saphenofemoral jn.
Adjacent hemorrhagic macrocystic LM, microcystic LM in the anterior pelvic subcutaneous tissues
Upper back lipomatous overgrowth, cutaneous CM over anomalous veins.

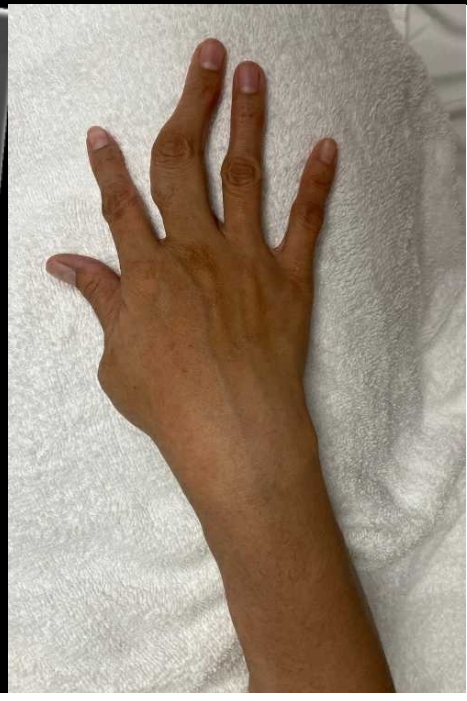
- 43yF, history of RUE AVM, prior partial resection in the forearm in the Philippines with saphenous vein graft to R radial artery in forearm
- Increasing angulation and pain in 3rd digit
- HVMC exam: Focal capillary malformation over upper arm and shoulder. Hypervascular lesion affecting forearm, thumb and 3rd digit with low resistance waveforms
- Erosive changes 3rd digit on radiograph











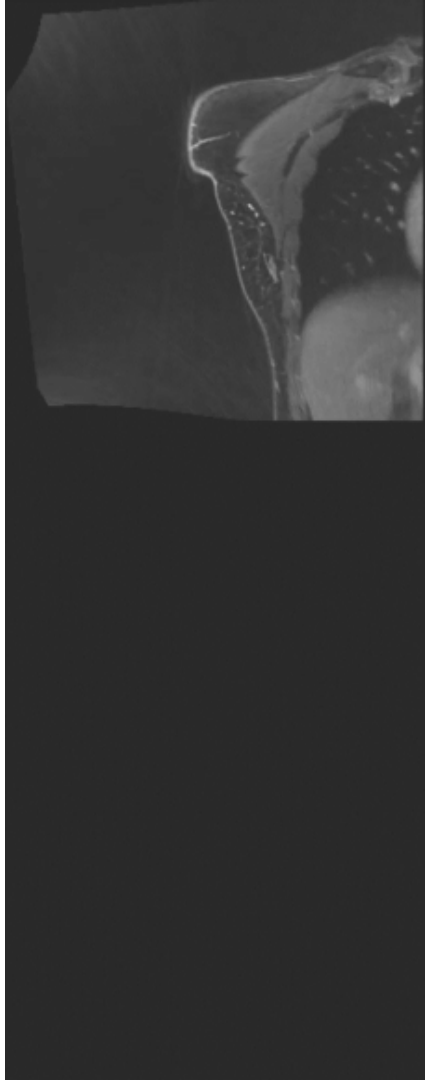
Arteriovenous Malformation: Dual contrast protocol

1-2 mg/kg Ferumoxytol
0.1 mmol/kg Gadavist

- Slow infusion of Ferumoxytol before study
- TWIST time resolved MRA with 1-2 second dynamics for 30 seconds after rapid bolus injection of Gd
- 3D RAVE/VIBE
- Ax SSFSE T2

Pre-procedure Dx: CM-AVM hand

Post procedure Dx: Multiple AVMs in,wrist, first digit & 3rd digit, aneurysmal changes saphenous venous graft
- likely RASA1 mutation



Limitations: WB MR Protocol for Diffuse/Syndromic Vascular Anomalies

- No reference standard, or formal comparison to conventional MR sequences
- Brain not covered
- Spinal involvement may be subtle on large FOV images, and missed without dedicated imaging
- No representation of PTEN (PHTS) spectrum in our series
- Difficulty ruling out high-flow component based on MR protocol alone: important to combine with specialist assessment and targeted ultrasound prior to MRI, so that additional time-resolved MRA may be performed as needed
- Central vascular structures in chest and abdomen may benefit from EKG gated and navigator respiratory gated IR-prepped 3D TFE, which performs better than RAVE/VIBE for angiography. RAVE/VIBE provides better soft tissue contrast.

Conclusions: WB MR Protocol for Diffuse/Syndromic Vascular Anomalies

- We demonstrate feasibility of an abbreviated, WB/partial WB MR protocol with Ferumoxytol for genetic, syndromic and diffuse vascular anomalies
- Suggest tailored 30 min protocol utilizing 3D RAVE in smaller children, 3D VIBE in larger patients, and composite axial SSFSE T2 without fat saturation +/- targeted TWIST: allows evaluation of fast and slow flow lesions and vascular/non-vascular/organ involvement with good technical and clinical performance
- Potential for unsupervised protocol in non-specialized centers
- High level of acceptance by specialized referral groups in our experience