VASCULAR ANOMALIES
(TUMORS AND MALFORMATIONS)

Soheil S Dadras MD-PhD

A TRIBUTE LECTURE

- Board-certified in Dermatology, Pathology and Dermatopathology
- Student of Drs. Wallace Clark and Thomas Fitzpatrick
- Founded Harvard Dermatopathology Training Program
- Unassuming international expert in melanoma (subtyping, AJCC, MITF), vascular lesions (GLUT-1)
- My mentor in dermatopathology, friend
- Established vascular anomaly clinic at MGH
  - MGH Pediatrics
- NIH Training grant at MGH CBRC (lymphatic endothelial cell biology, Dadras and Detmar)
- Introduced me to Dr. Paula E. North

Kupper T, Piris A, Kroshinsky D, Kaya G. In Memoriam-Martin C. Mihm, Jr. Dermatopathology (Basel). 2022 Sep 8;9(3):304-306.
Murphy GF. A Festschrift for Martin C. Mihm, Jr. J Cutan Pathol. 2010 Apr;37

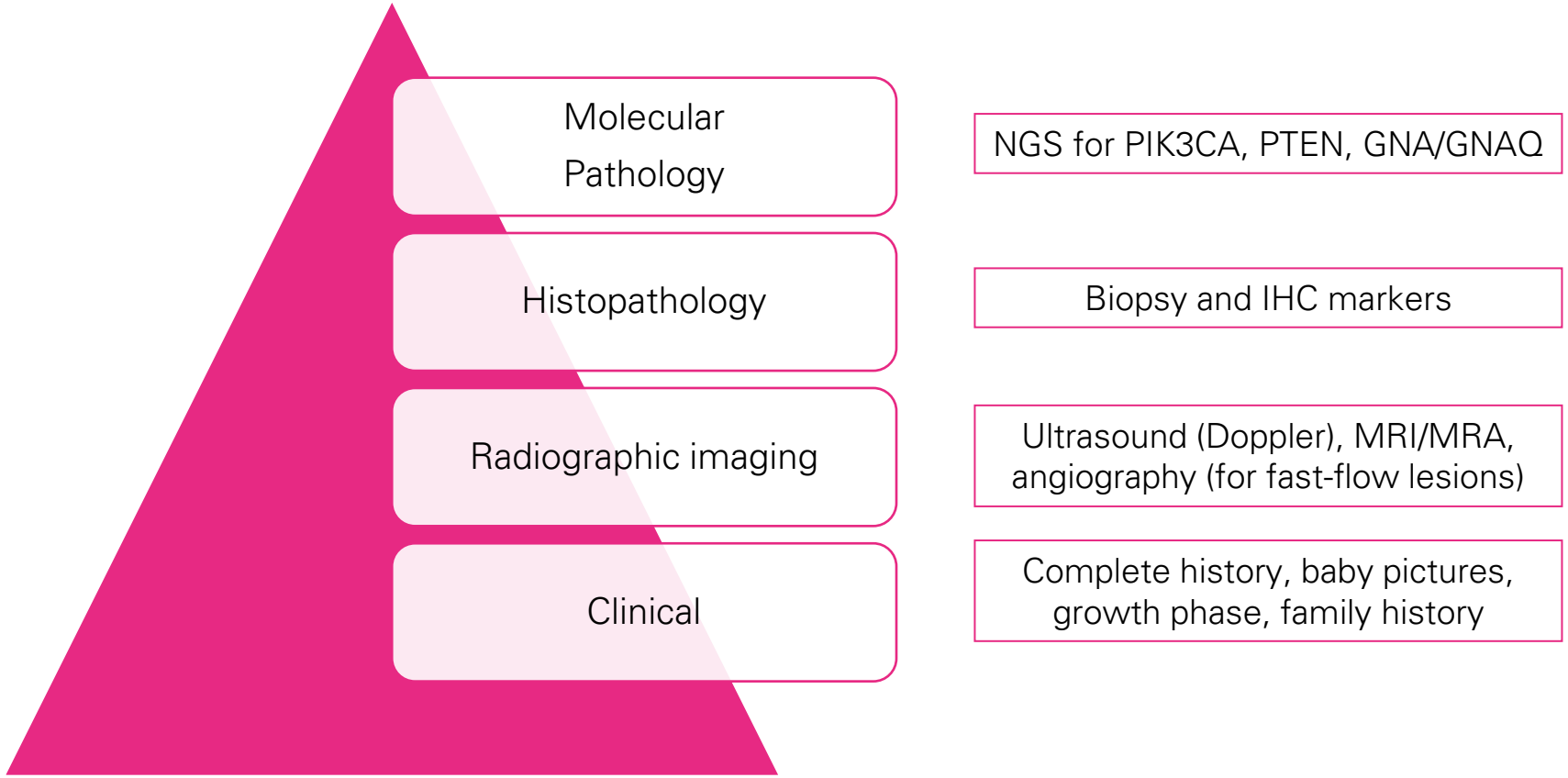
Martin C. Mihm Jr., MD

March 15, 1934 - July 19, 2022

INTRODUCTION: LEARNING TIPS

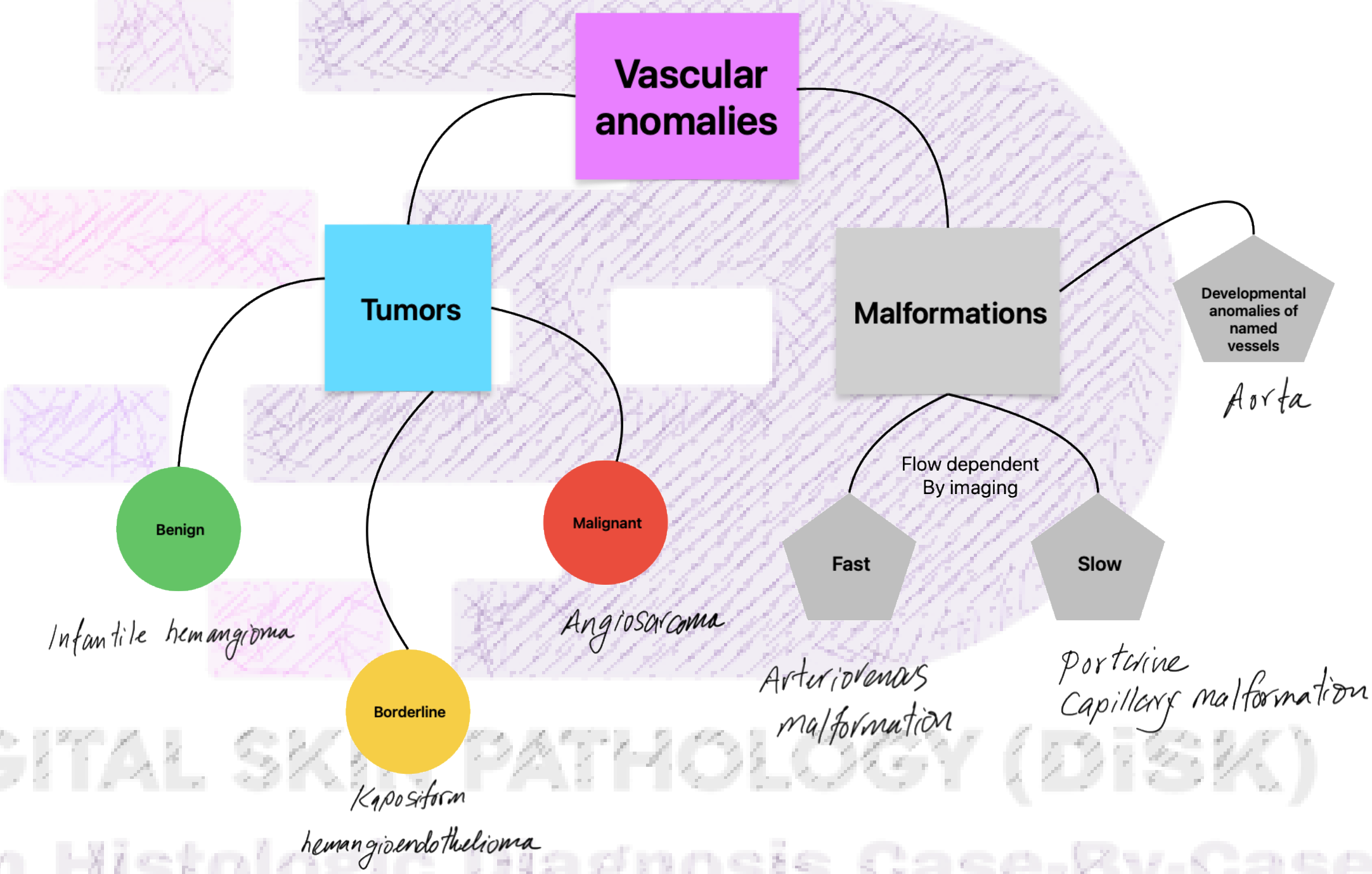
- Learn the clinical (biologic) behavior, histopathology, immunohistochemistry, and molecular genetic data (somatic and germline)
- Don't be confused by hemangioma vs. malformation strict classification
  - Some show overlapping features
  - Use it as a biologic framework
- Use classification framework endorsed by the International Society for the Study of vascular Anomalies (ISSVA), www.issva.org (scroll to the end of this file)
- Many textbooks lump unrelated entities into unnatural categories "Capillary hemangioma" most confusing
- Don't call anything with blood vessels, "hemangioma" or "angioma"
- Attend an established multidisciplinary vascular anomaly clinic or start one (Lucile-Packard Children's Hospital VAC, Bruckner, Lane and Dadras)
- Need tissue diagnosis to guide management (not biopsy for NGS)

Diagnosis of Complex Vascular Anomalies (multispecialty vascular anomaly clinic)



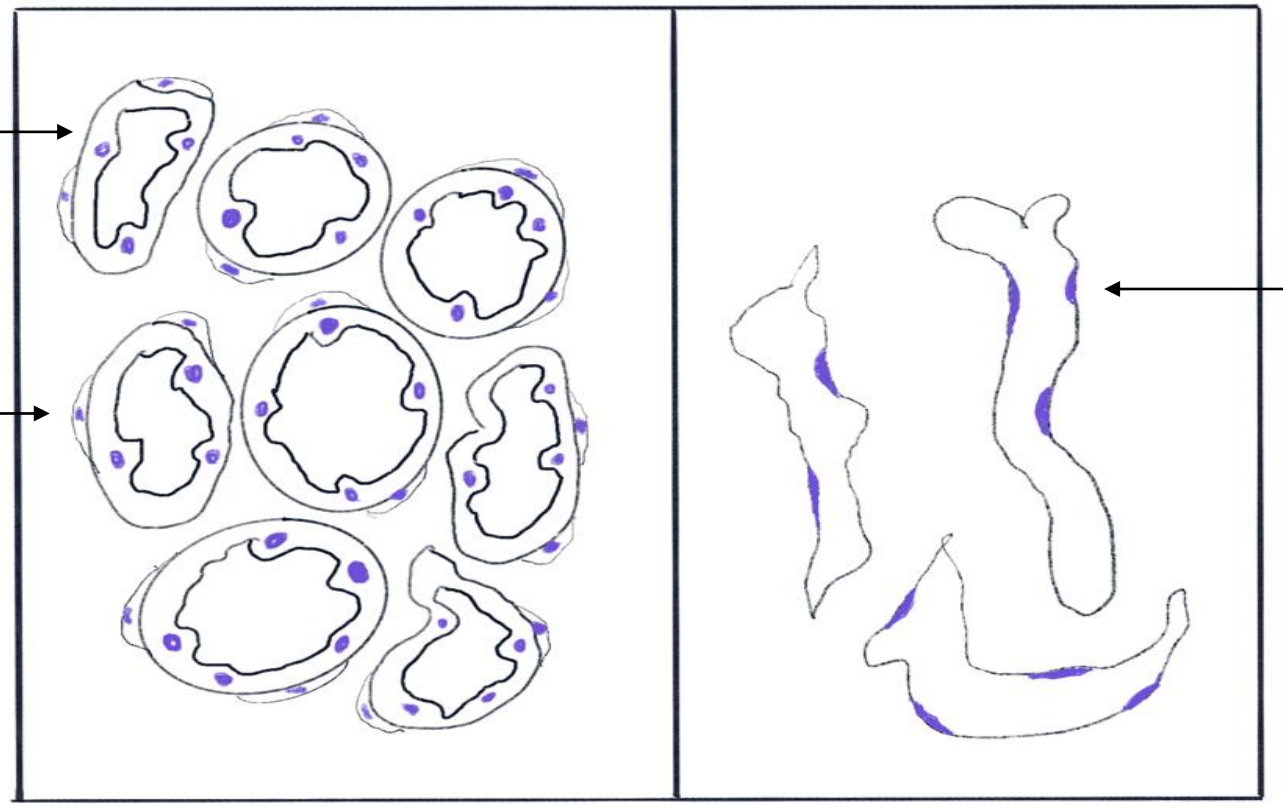
Molecular Pathology	NGS for PIK3CA, PTEN, GNA/GNAQ
Histopathology	Biopsy and IHC markers
Radiographic imaging	Ultrasound (Doppler), MRI/MRA, angiography (for fast-flow lesions)
Clinical	Complete history, baby pictures, growth phase, family history

Vascular Anomalies Simplified



BASIS OF CALSSIFICATION

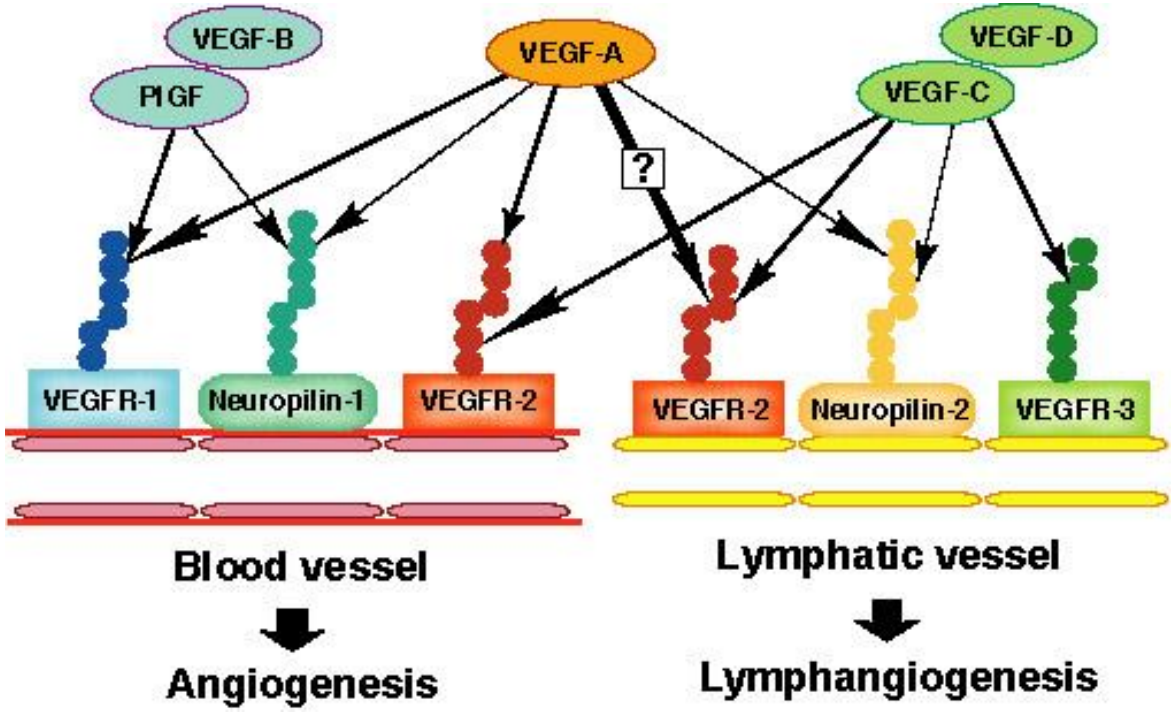
Tumor	Malformation
Benign cellular proliferation	Error in vascular morphogenesis
Packed lobular capillary	Irregular anastomosing
Mitotically active	Mitotically inactive
Congenital or acquired	Usually evident at birth
e.g., Infantile hemangioma	e.g., Arteriovenous malformation

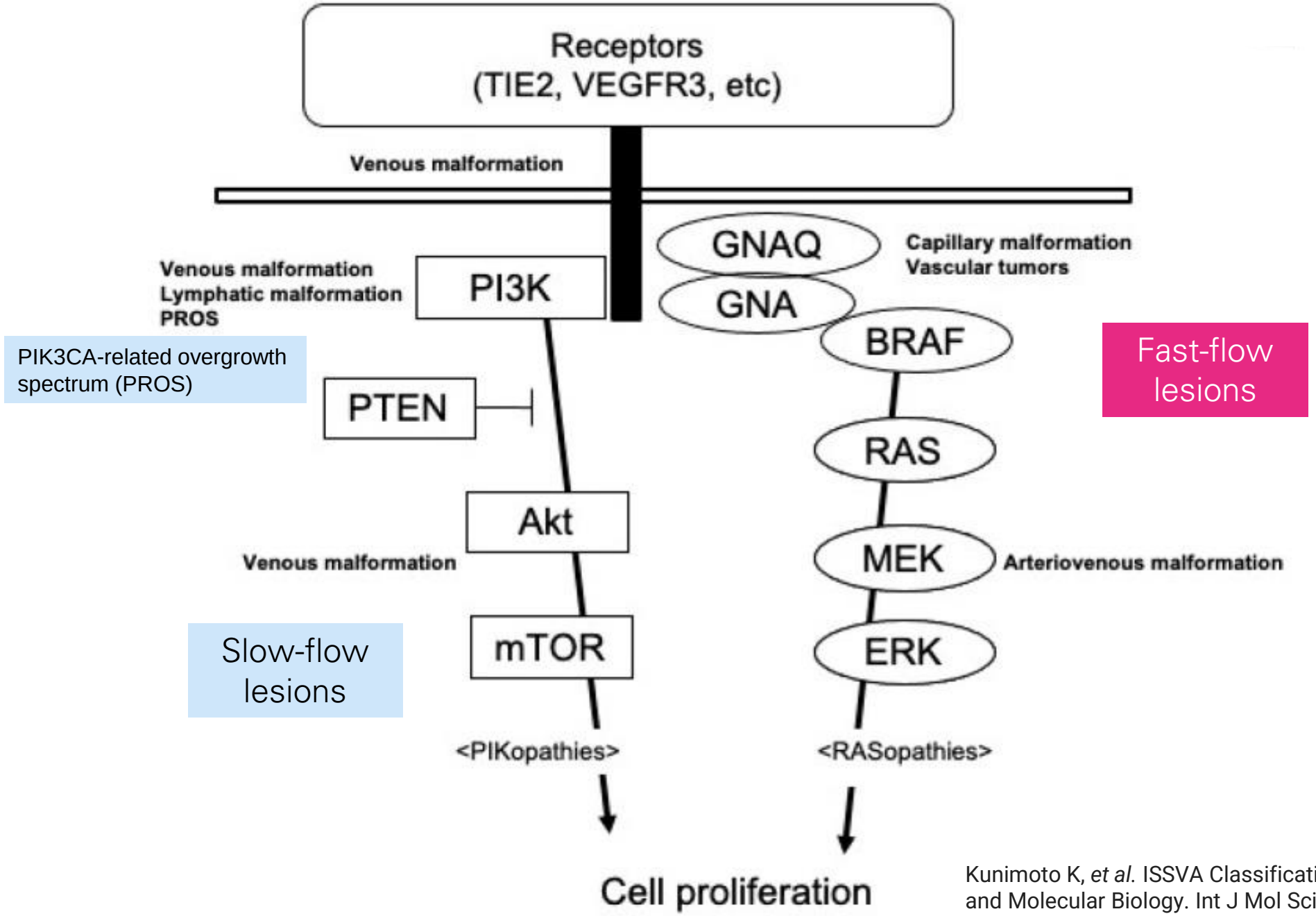


Illustrated by DADARAS

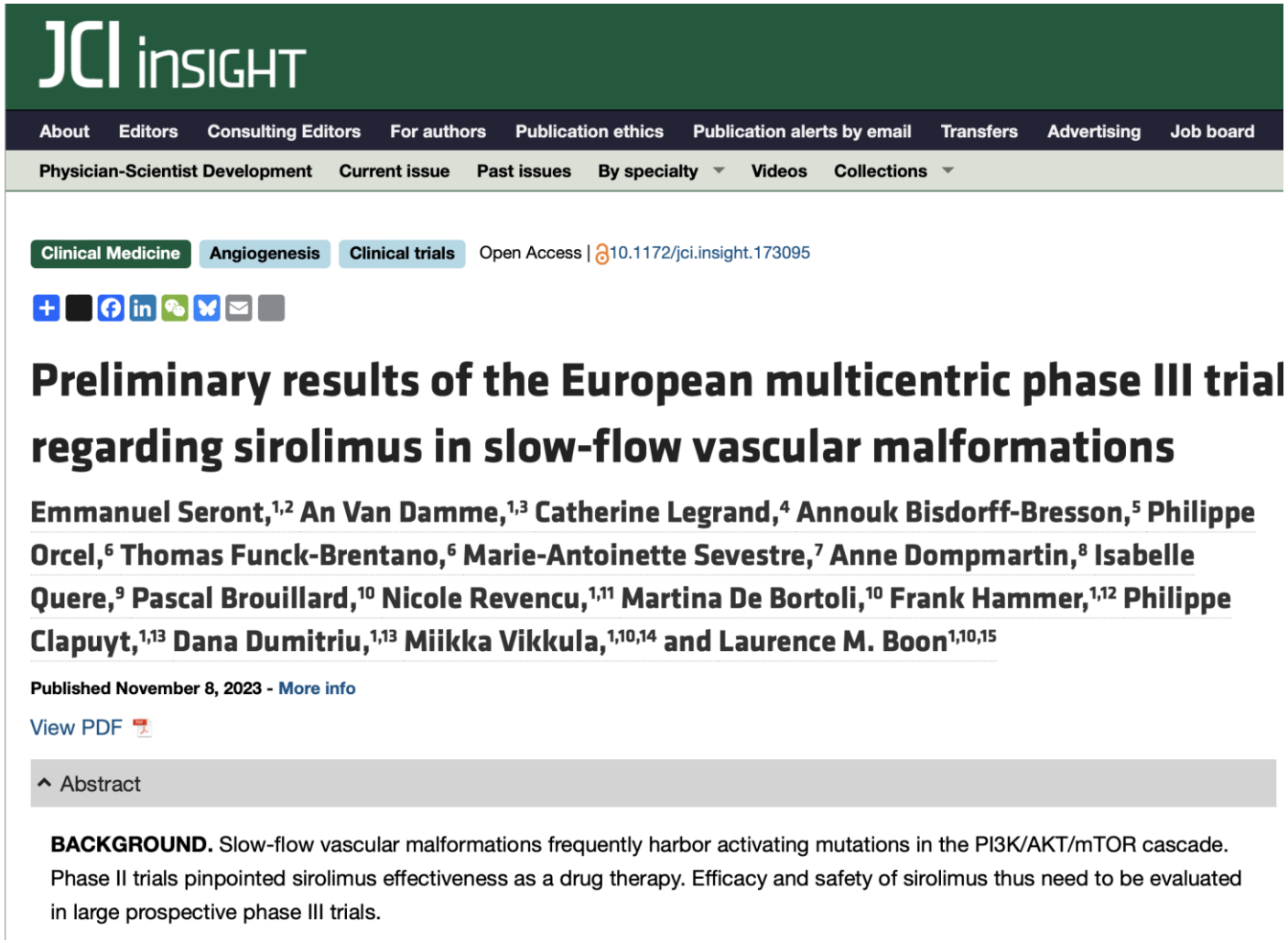
VGFRs (Vascular Endothelial Growth Factor Receptors)

- Family of receptor tyrosine kinases
- Play role in
  - **Angiogenesis** (formation of new blood vessels)
  - **Lymphangiogenesis** (formation of lymphatic vessels)
- Bind to **VEGF** (Vascular Endothelial Growth Factor) ligands
- Regulate blood vessel growth, vascular permeability, and cell survival





Kunimoto K, *et al.* ISSVA Classification of Vascular Anomalies and Molecular Biology. Int J Mol Sci. 2022 Feb 21;23(4):2358.



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Preliminary results of the European multicentric phase III trial regarding sirolimus in slow-flow vascular malformations

Emmanuel Seront,[1,2] An Van Damme,[1,3] Catherine Legrand,[4] Annouk Bisdorff-Bresson,[5] Philippe Orcel,[6] Thomas Funck-Brentano,[6] Marie-Antoinette Sevestre,[7] Anne Dompmartin,[8] Isabelle Quere,[9] Pascal Brouillard,[10] Nicole Revencu,[1,11] Martina De Bortoli,[10] Frank Hammer,[1,12] Philippe Clapuyt,[1,13] Dana Dumitriu,[1,13] Miikka Vikkula,[1,10,14] and Laurence M. Boon[1,10,15]

Published November 8, 2023 - More info

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Abstract

BACKGROUND. Slow-flow vascular malformations frequently harbor activating mutations in the PI3K/AKT/mTOR cascade. Phase II trials pinpointed sirolimus effectiveness as a drug therapy. Efficacy and safety of sirolimus thus need to be evaluated in large prospective phase III trials.

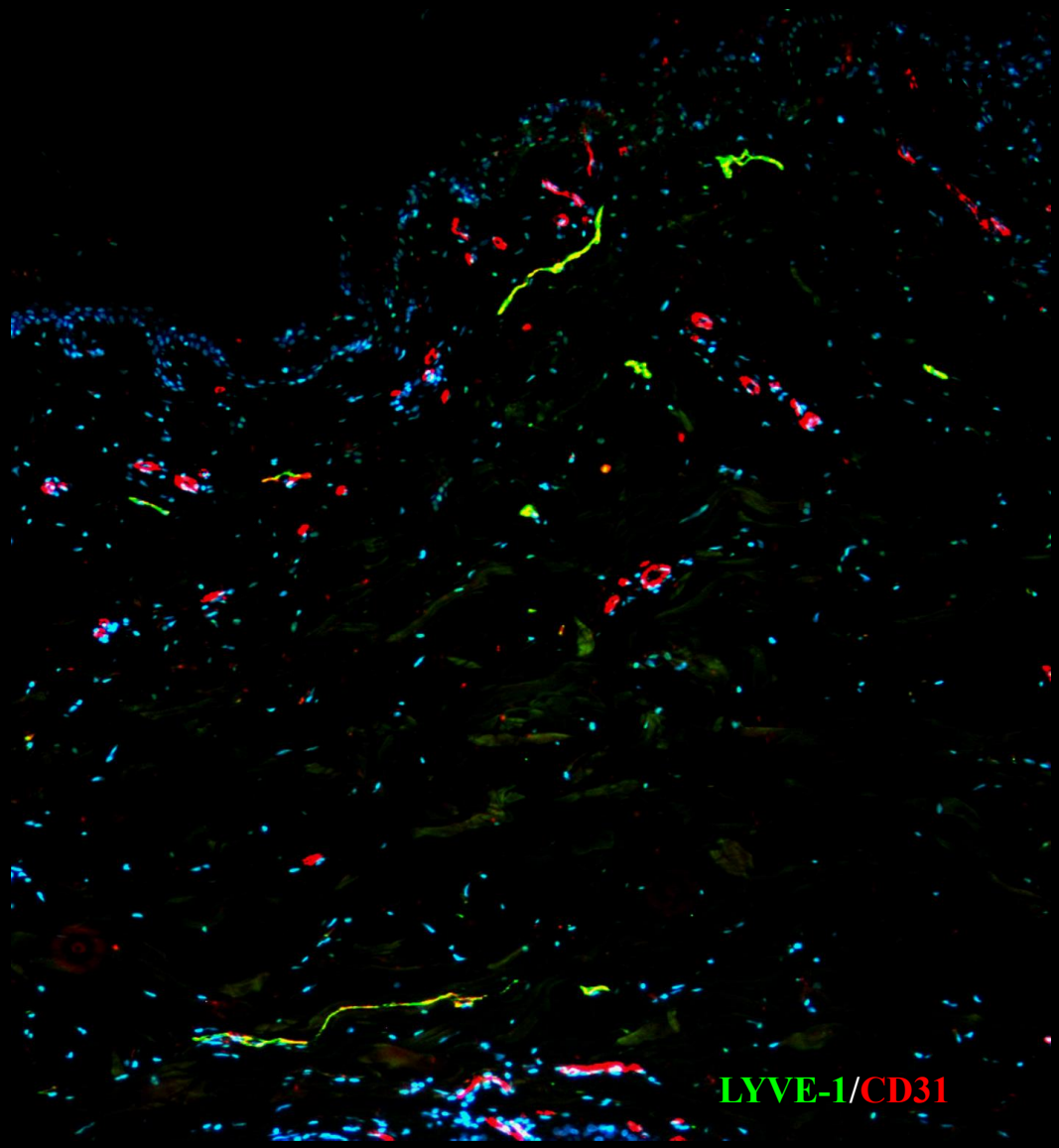
Efficacy of Sirolimus in the treatment of vascular malformations

- Harbor activating mutations in the PI3K/AKT/mTOR
- mTOR inhibitor
- Patients enrolled
  - Pediatrics, 31
  - Adults, 101
- Initiated in 2016
- Clinical improvement in 85% of patients

IMMUNOHISTOCHEMICAL MARKERS: BLOOD VS. LYMPHATIC

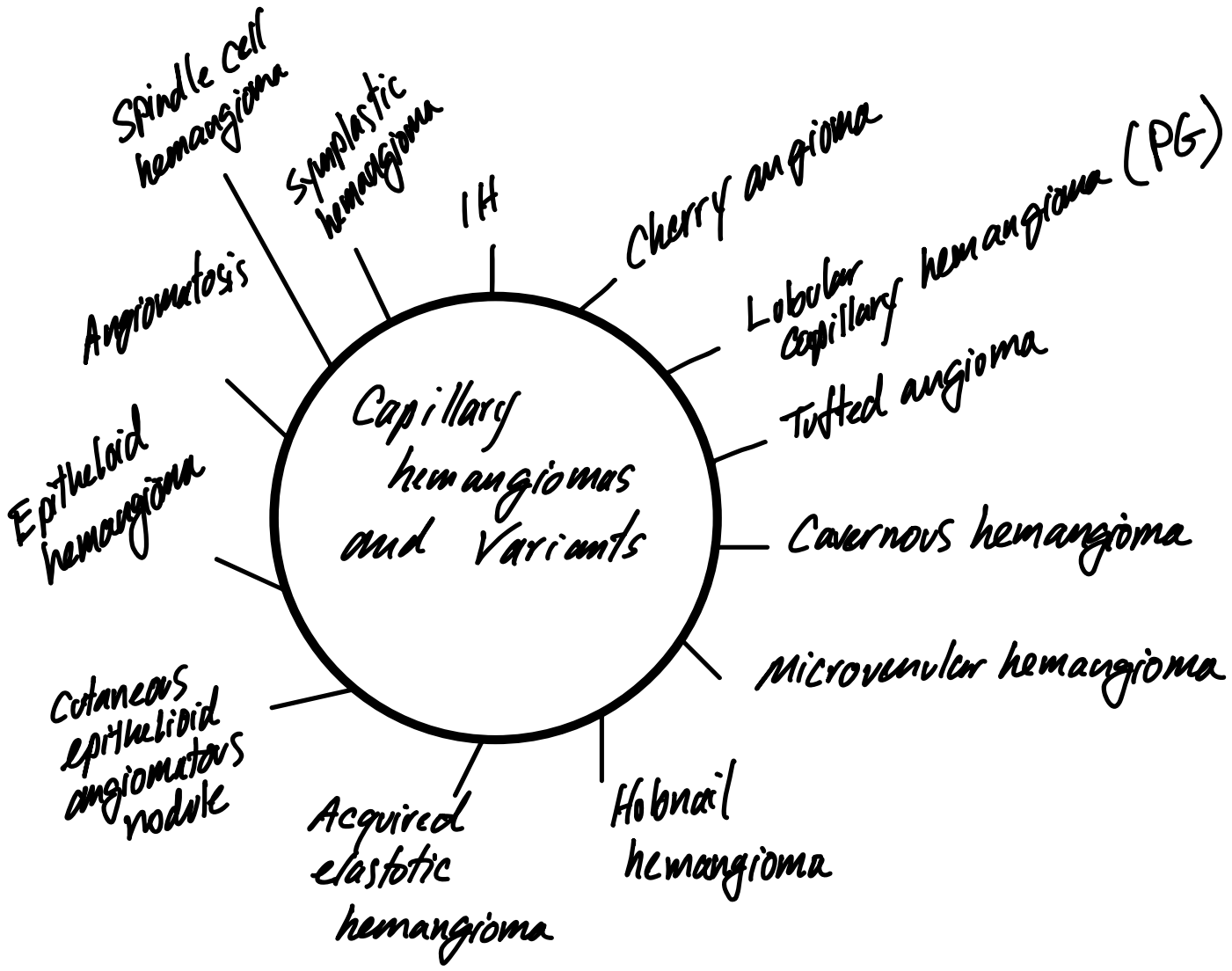
Marker	Lymphatic Vessels	Blood Vessels
Blood Vascular Specific		
CD34	-	+
CD44	-	+
PAL-E	-	+
Collagen type IV	-/(+)	+
Collagen type XVIII	-/(+)	+
Laminin	-/(+)	++
Neuropilin-1	-	+
Lymphatic Specific		
VEGFR-3	+	-
Podoplanin	+	-
SLC/CCL21	+	-
LYVE-1	+	-
Prox1	+	-
Panvascular		
CD31 (PECAM-1)	+	++
VEGFR-2	+	+
Factor VIII-related antigen	+	++

Dadras and Detmar, *Hem. Onc. of North Ame.* 2004



‘CAPILLARY HEMANGIOMAS’

- Avoid diagnostic term ‘hemangioma’
- Confusing
- Non-specific
- Provides no prognostic information



Vascular tumors

Benign

- Infantile hemangioma
- Congenital hemangioma
- Tufted angioma
- Masson tumor
- Spindle cell hemangioma
- Lobular capillary hemangioma
- Microvenular hemangioma

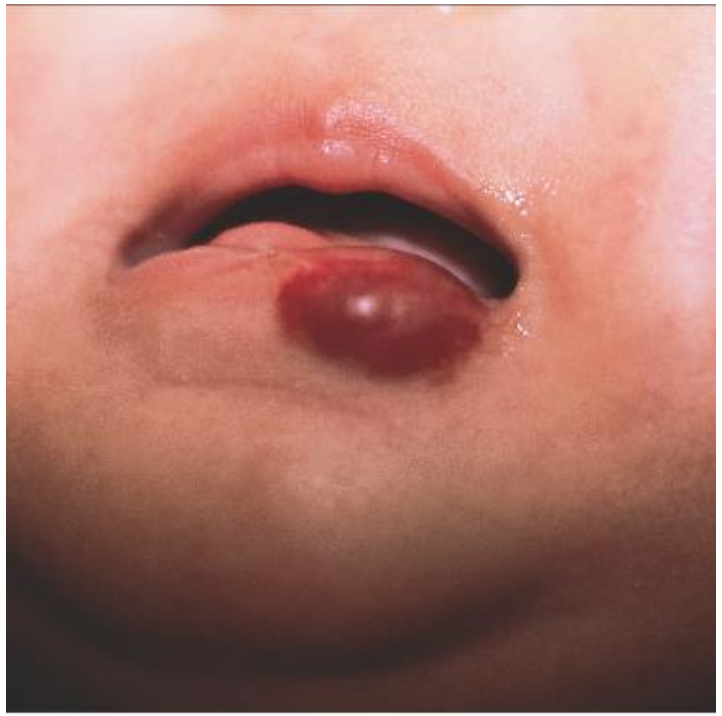
Borderline

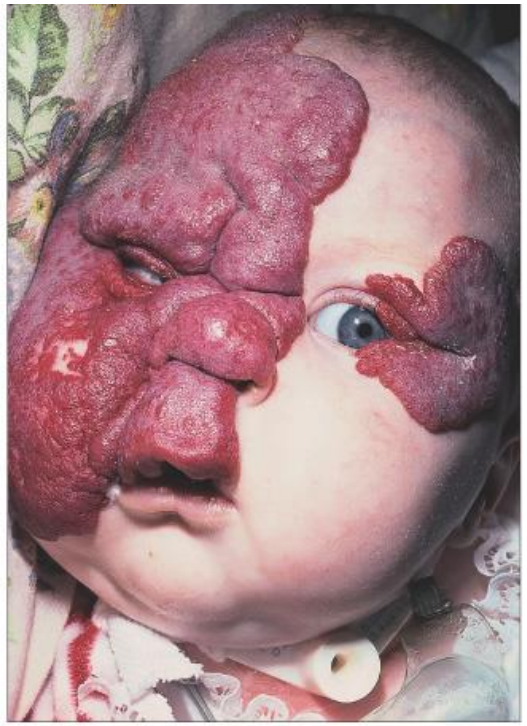
- Kaposi's sarcoma
- Kaposiform hemangioendothelioma

Malignant

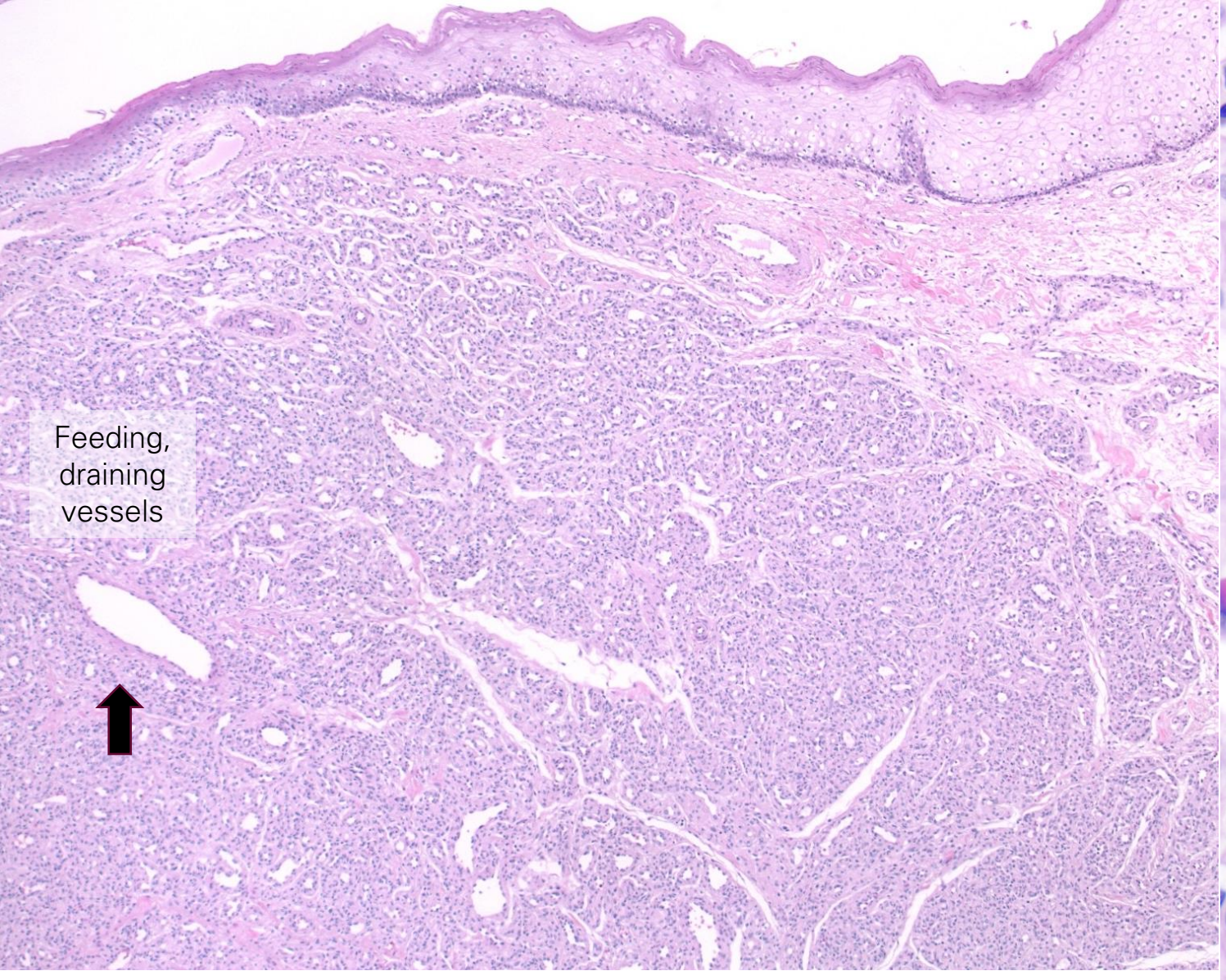
- Angiosarcoma

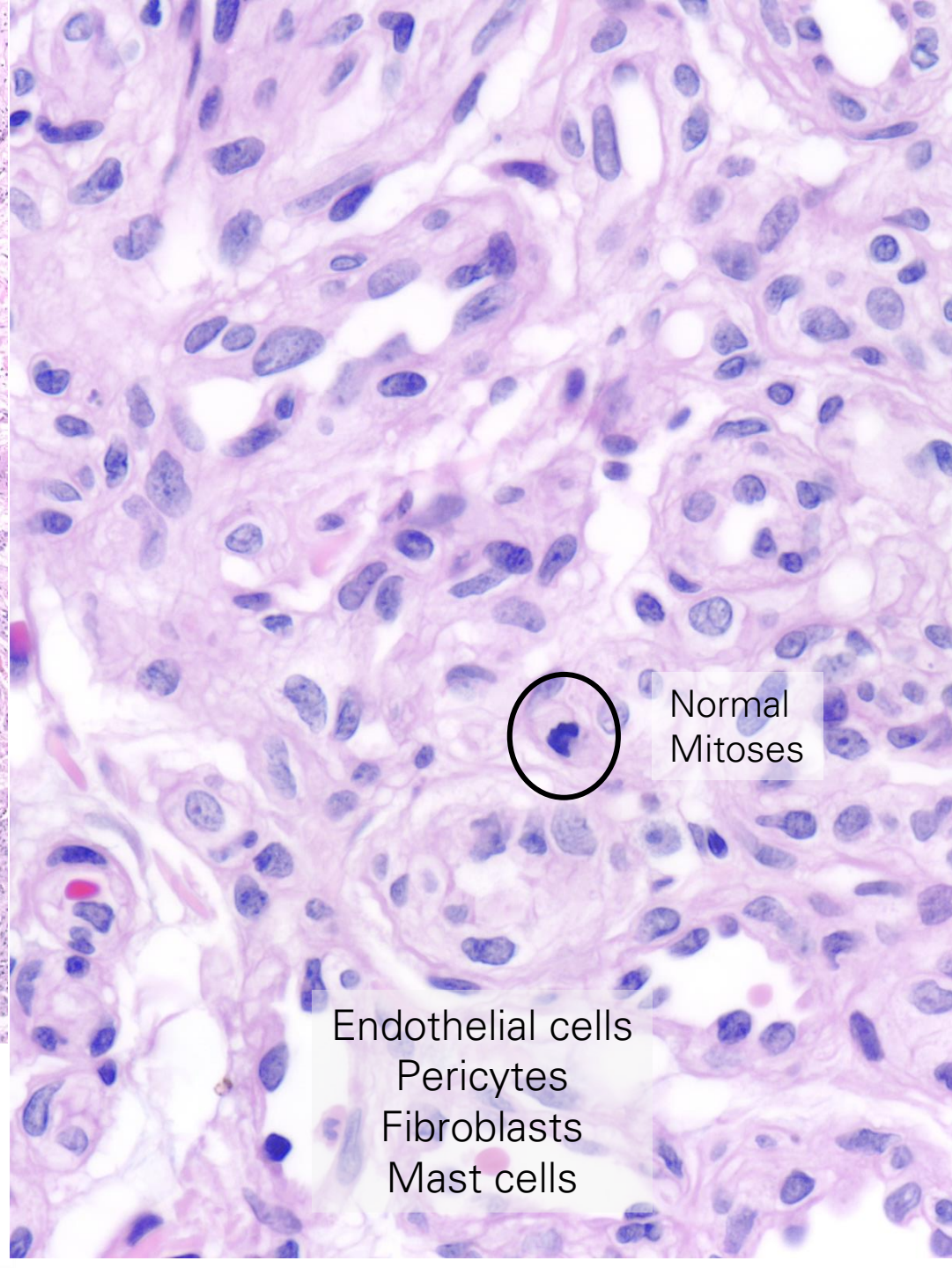
INFANTILE HEMANGIOMA





- Most common tumor of infancy and vascular tumor of childhood
- Absent at birth, develop within few weeks of life
- Females, head and neck
- Solitary, plaque, or multiple
- Growth pattern: proliferating, involuting and involuted
- DDX: congenital hemangiomas, LCH, congenital intramuscular hemangioma
- IHC: GLUT-1+, LYVE-1+ (proliferating phase), LeY+, WT-1+, Prox-1-
- Heterogenous tumor: endothelial cells, fibroblasts and pericytes

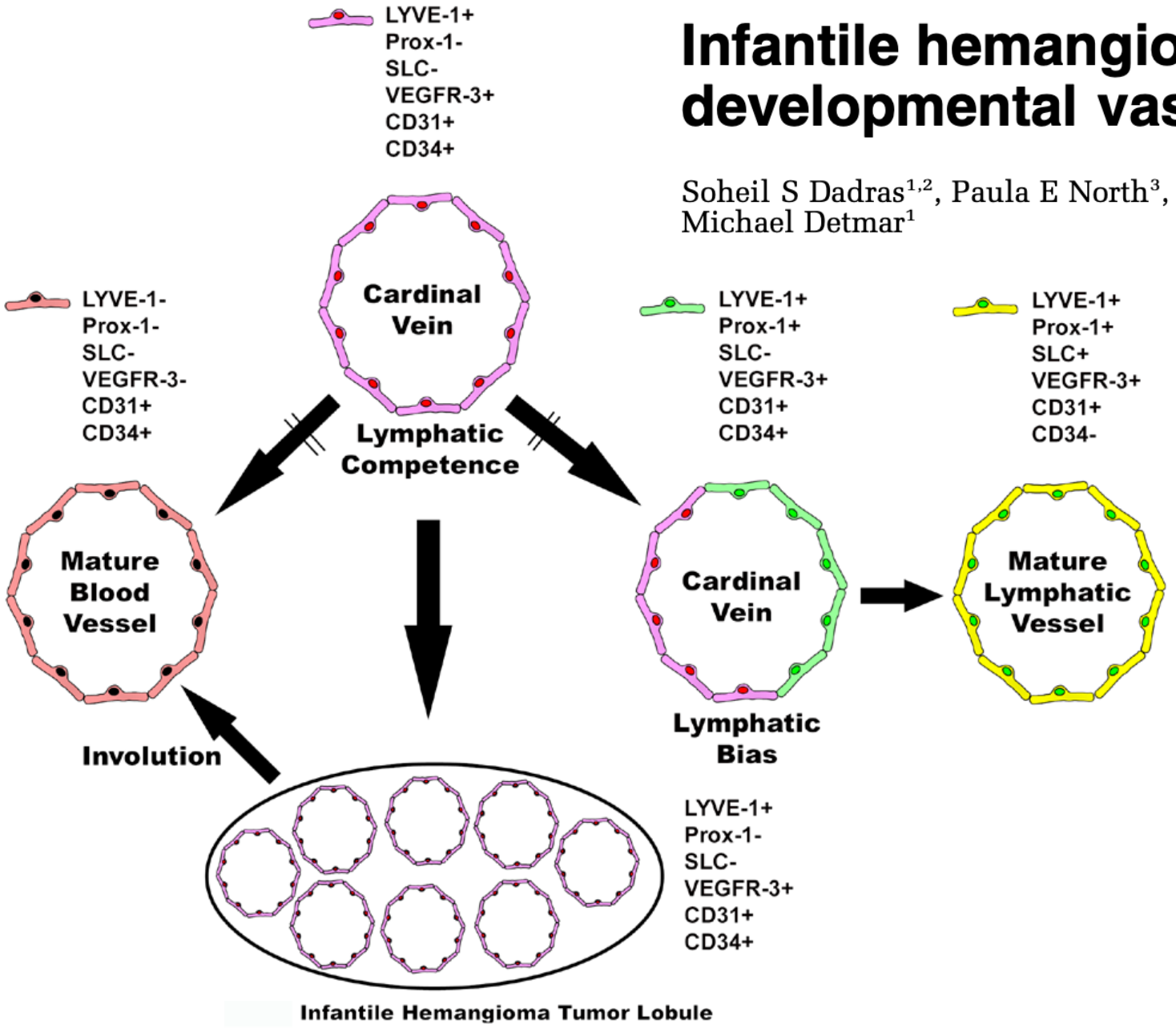




Intradermal or <u>submucosal</u>
Multinodular proliferation
Lobular configuration
Numerous, tightly packed capillary-sized blood vessels

Infantile hemangiomas are arrested in an early developmental vascular differentiation state

Soheil S Dadras[1,2], Paula E North[3], Jennifer Bertoncini[1], Martin C Mihm[2] and Michael Detmar[1]

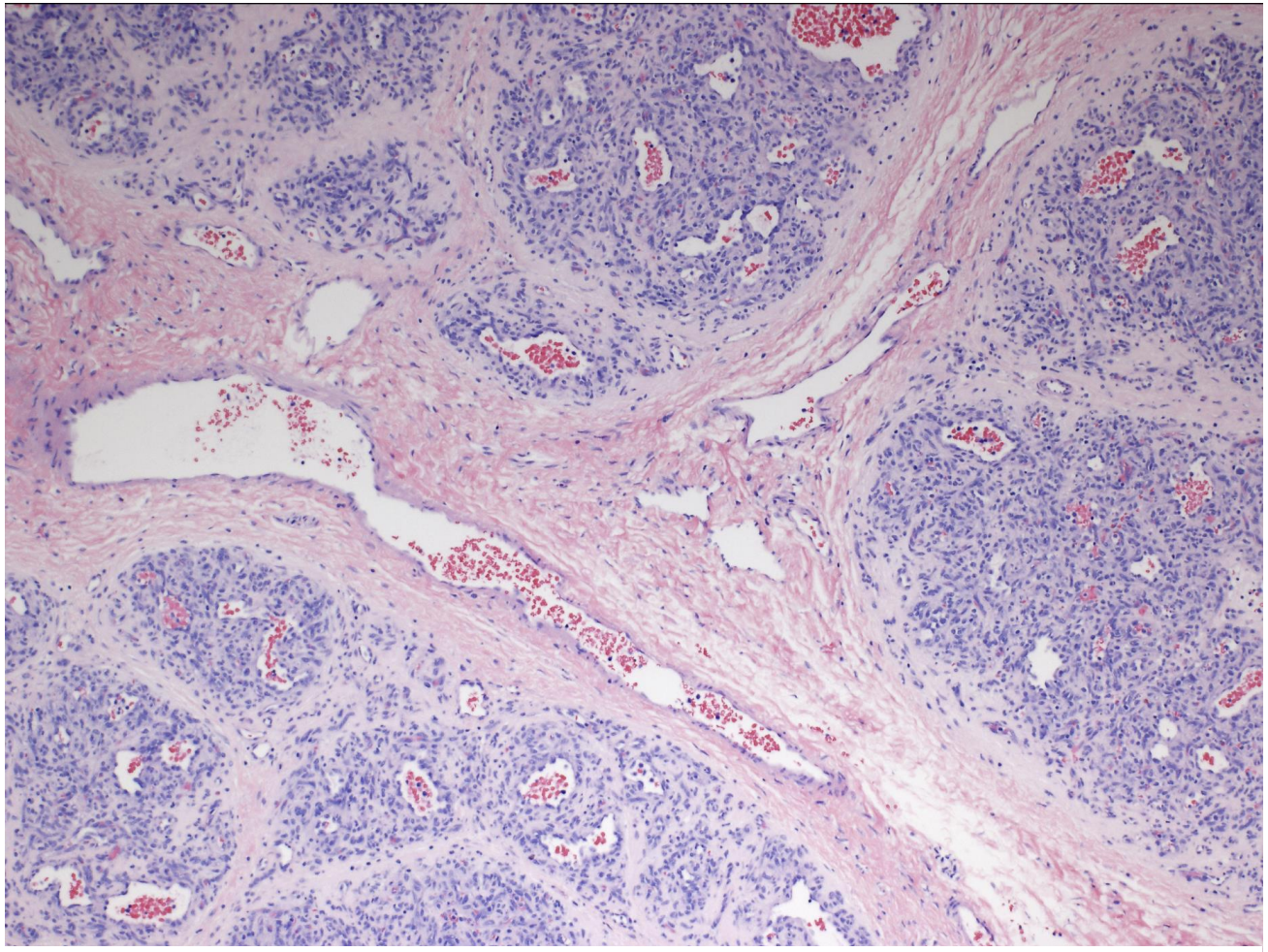


Arrested Vascular Development Hypothesis

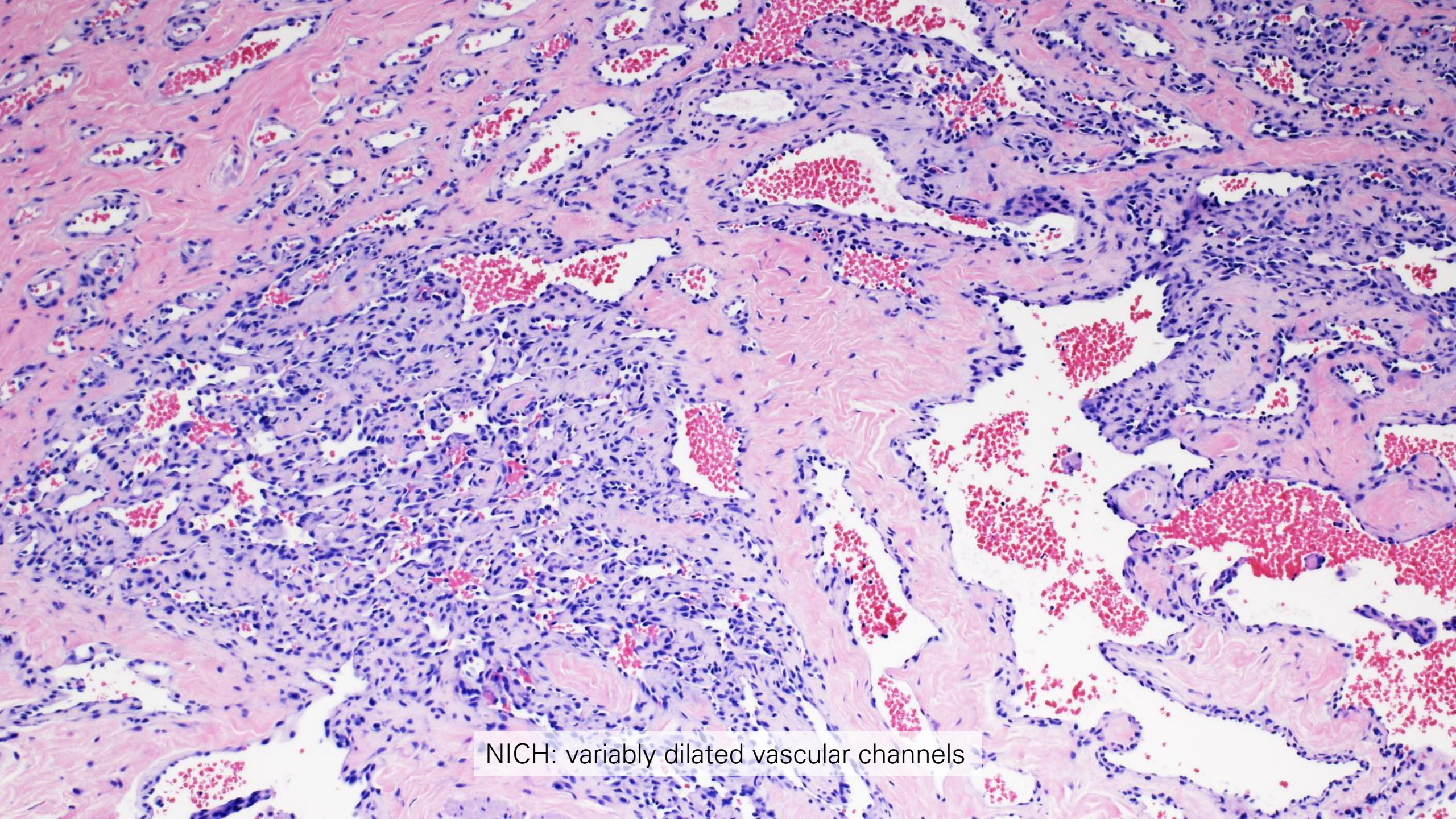
Dadras et al., *Mod. Path.* 2004

CONGENITAL HEMANGIOMAS

- Develop in-utero, fully developed at birth
- M=F incidence
- Clinical behavior:
  - Rapidly involuting (RICH)
  - Non-involuting (NICH)
  - Partially involuting (PICH)
- *GNAQ* and *GNA11* mutations
- DDX: infantile hemangioma, congenital intramuscular hemangioma
- IHC: GLUT-1-, LYVE-1-



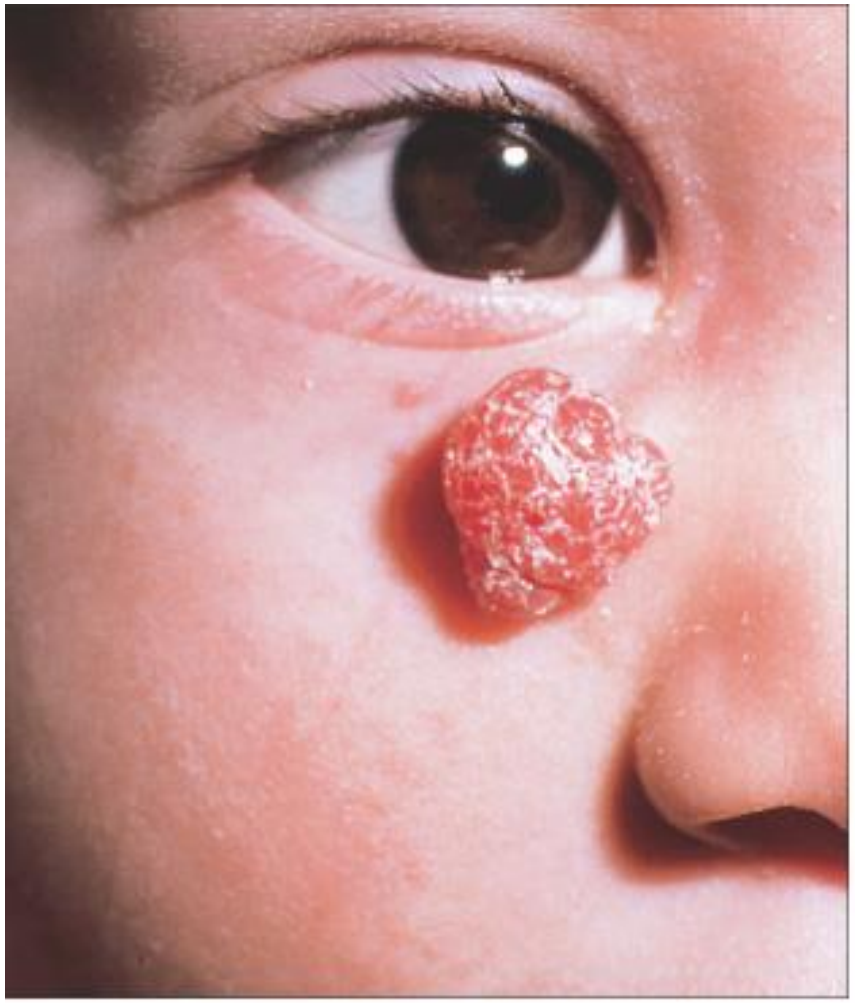
RICH: Multinodular proliferation
Lobular configuration
Numerous, tightly packed capillary-sized blood vessels



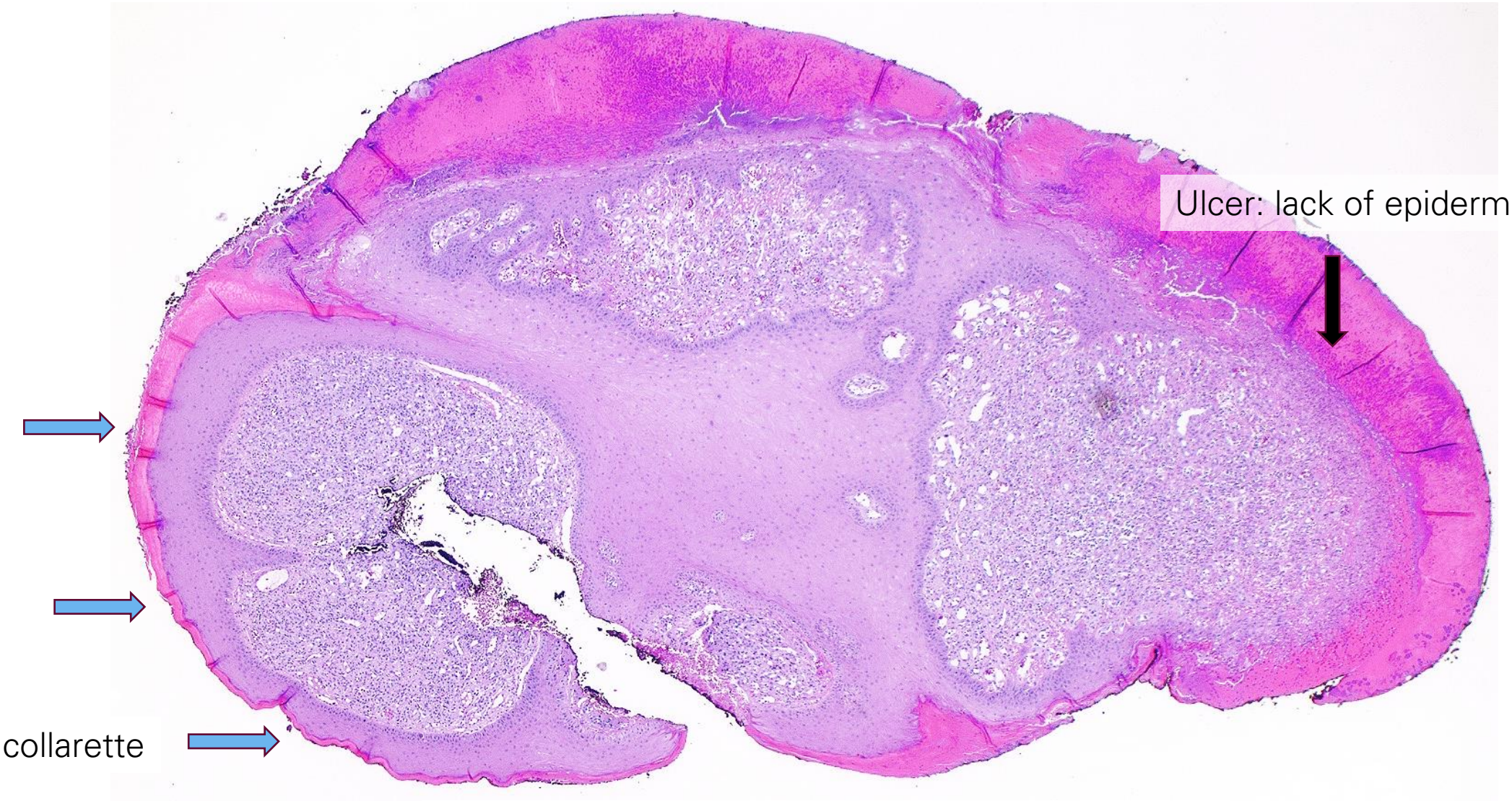
NICH: variably dilated vascular channels

LOBULAR CAPILLARY HEMANGIOMA (PYOGENIC GRANULOMA)

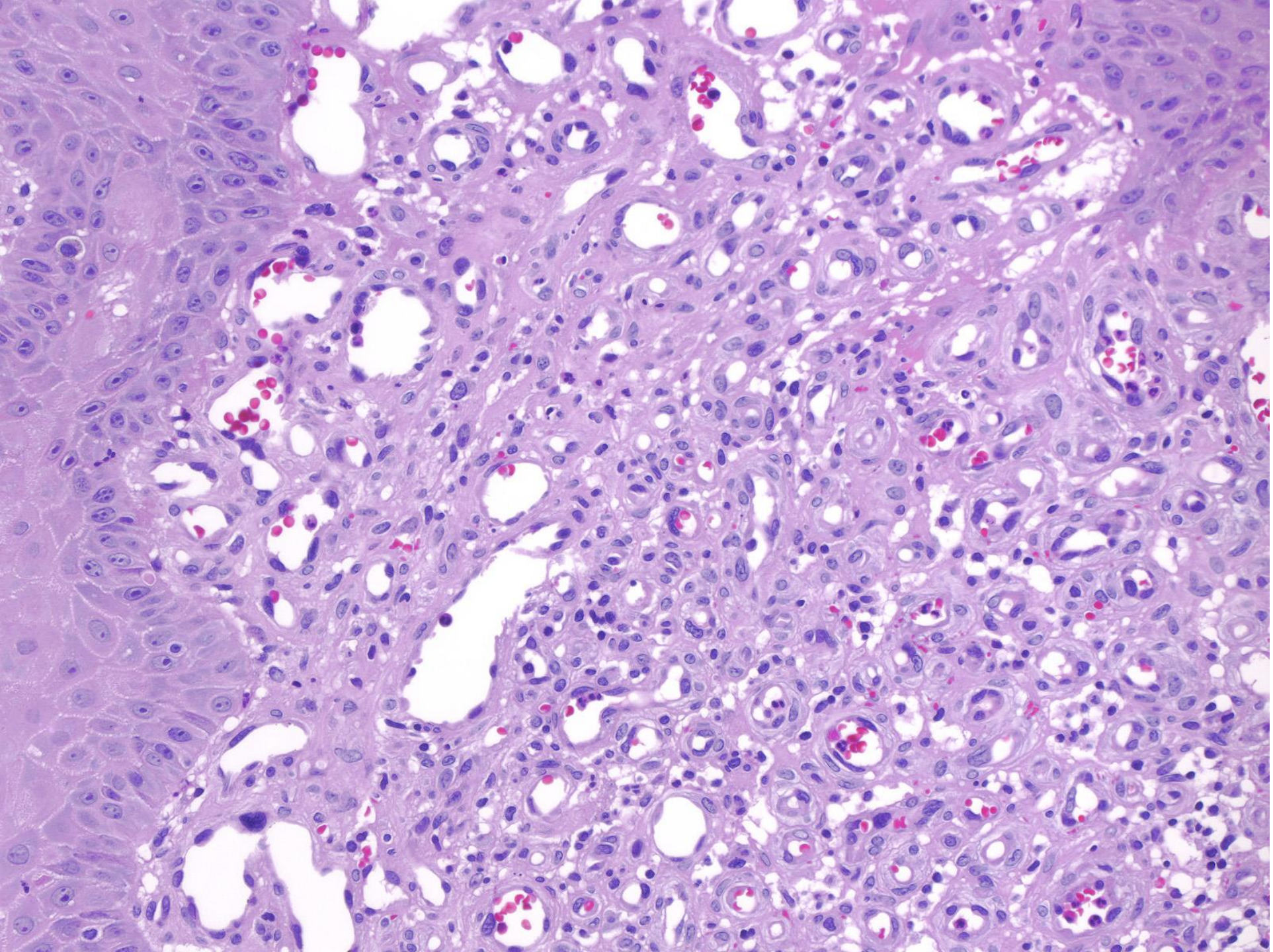
- Common, benign neoplasm
- Any age, M=F, head and neck >> limbs
- Local recurrence with multiple satellite lesions
- Pregnancy
- Variants:
  - Subcutaneous/deep (upper limbs) Intravascular (neck, upper extremities)
- DDX: infantile hemangioma, bacillary angiomatosis
- *RAS* and *BRAF* V600E mutations



ier - Bolognia, Jorizzo and Rapini: Dermatology - www.dermtext.com



Exophytic lobulated dermal nodule
Ulcerated, well-formed collarette
Numerous capillaries
Edematous stroma with secondary inflammation

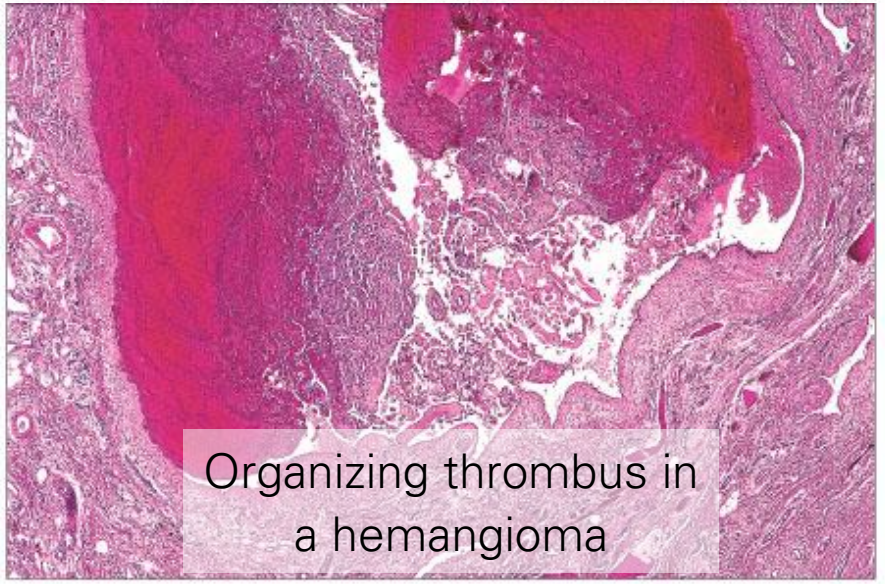


Capillaries form lobules
Mitoses
Minimal cytologic atypia

INTRAVASCULAR PAPILLARY ENDOTHELLIAL HYPERPLASIA (MASSON TUMOR)

- Benign, common, slow growing cystic nodule
- Organizing thrombus
- Presents
  - Primary: head and neck or extremities of young females
  - Secondary (incidental): in other vascular tumors (spindle cell hemangioma)
- DDX: Angiosarcoma

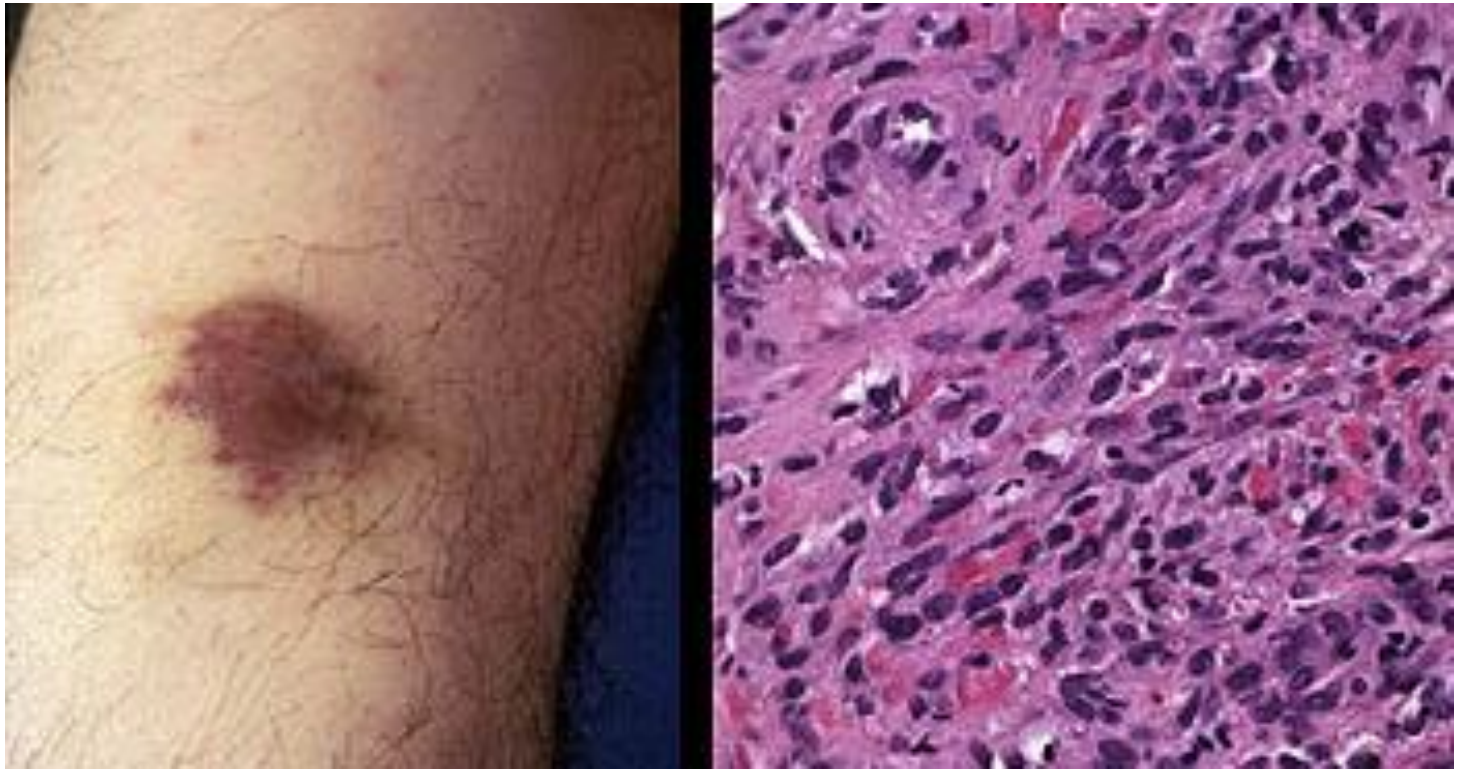
Numerous papillae in the lumen



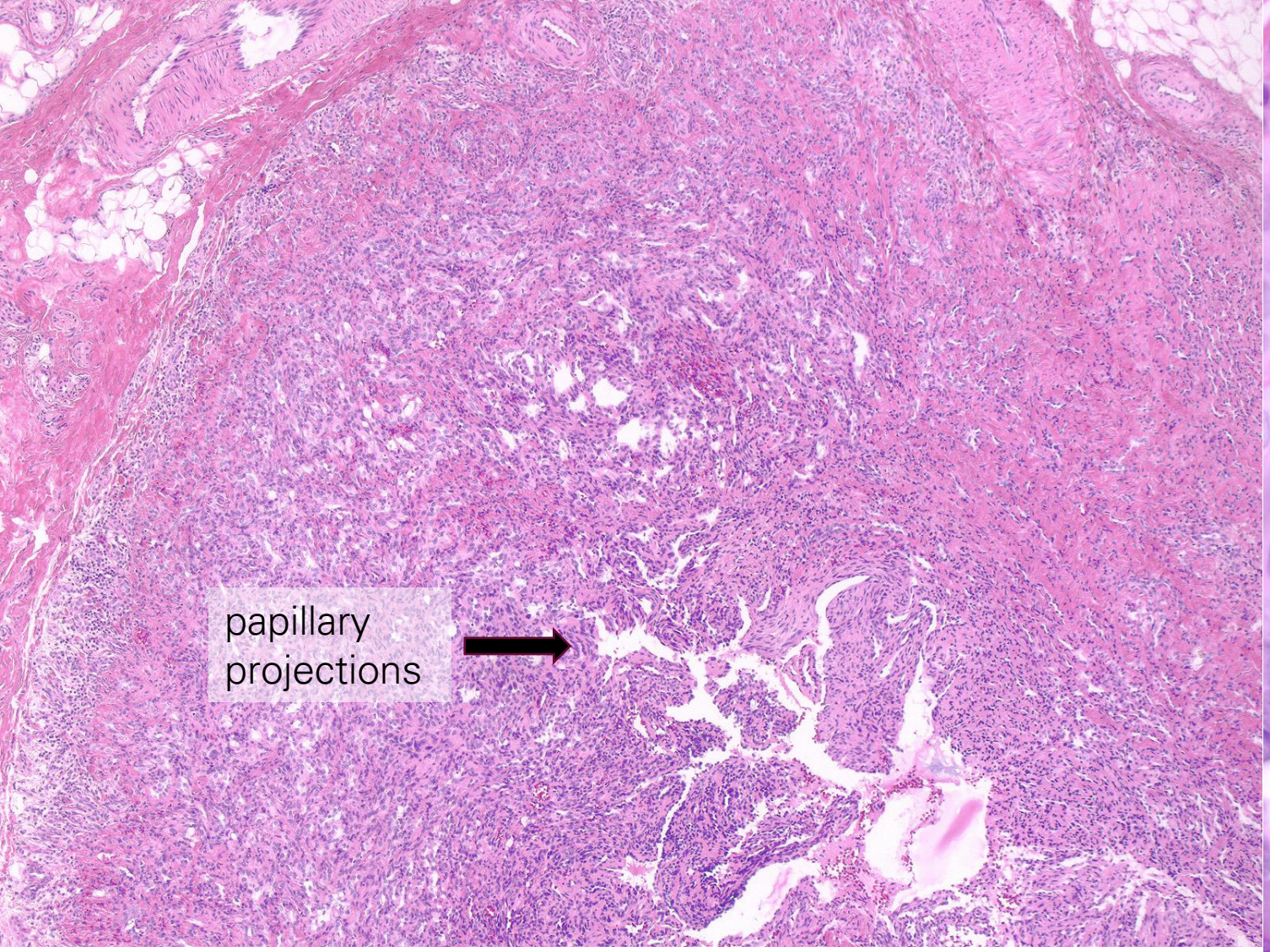
Organizing thrombus in a hemangioma

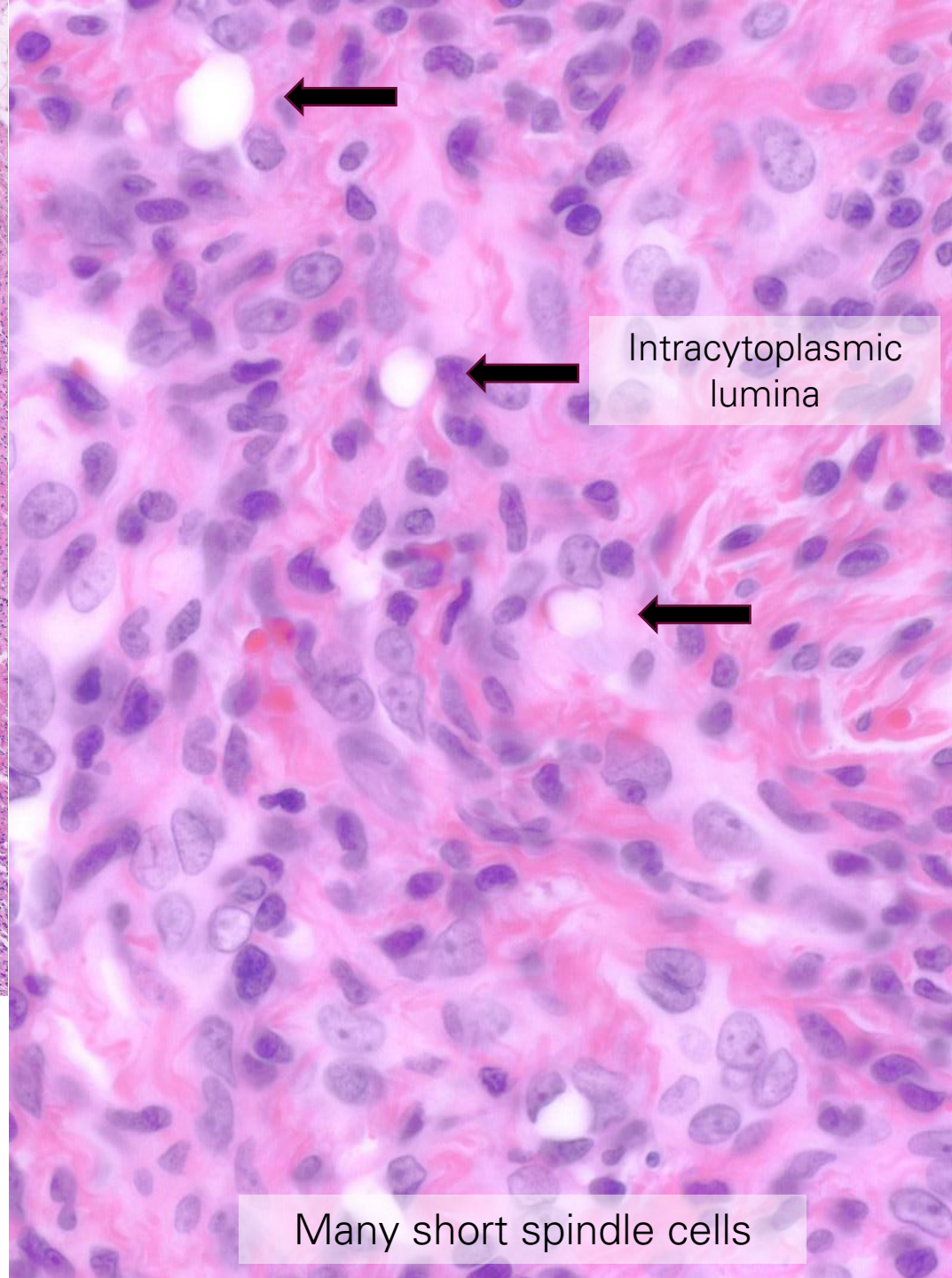
Eosinophilic hyaline material covered by a single layer of endothelia

SPINDLE CELL HEMANGIOMA



- 1st three decades of life
- Distal extremities, red-blue painful nodule
- Associated (rare): Maffucci or Klippel-Trenaunay syndrome
- *IDH* R132C mutation
- DDX: Kaposi sarcoma, epithelioid hemangioendothelioma, (low-grade angiosarcoma)
- IHC: CD31+, CD34+, ERG+
- Reticulin: shows vasoformative architecture

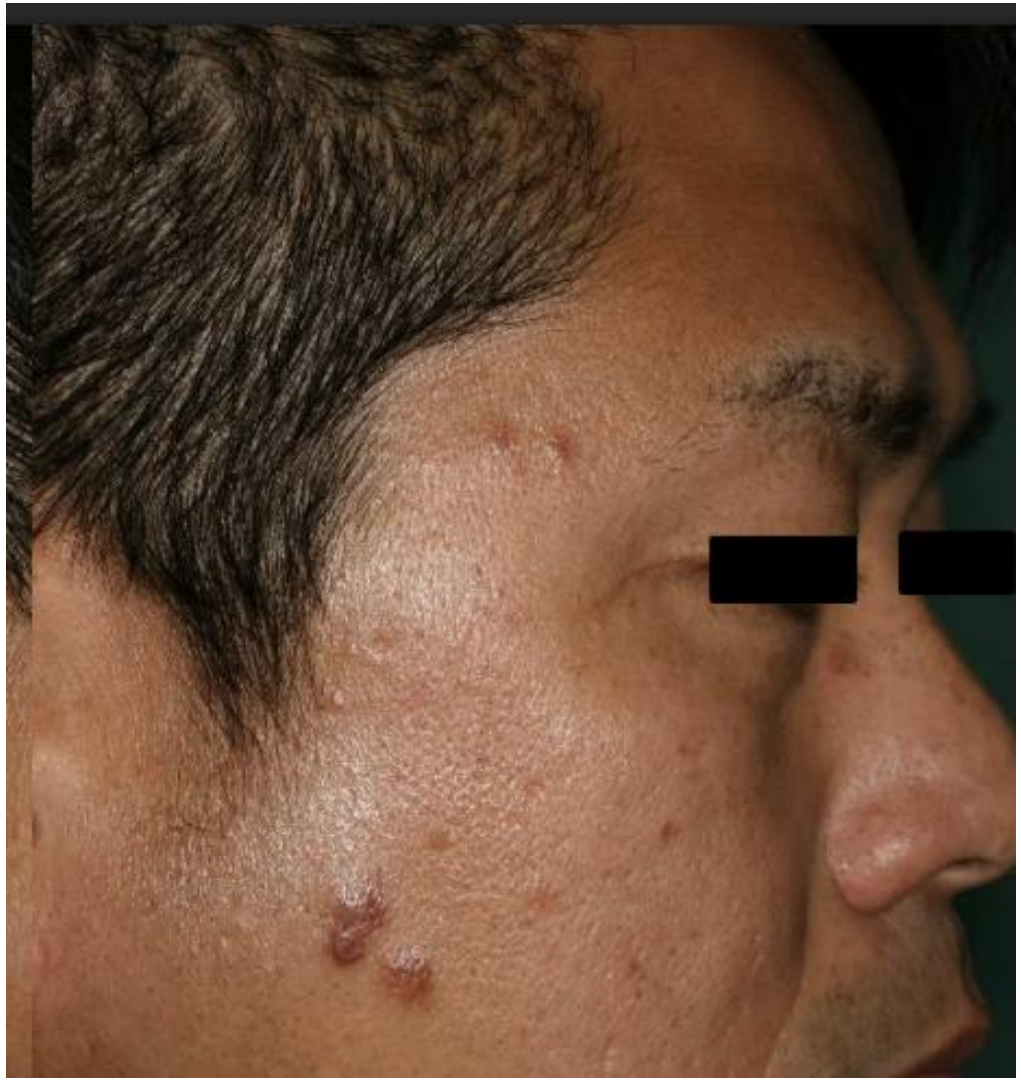




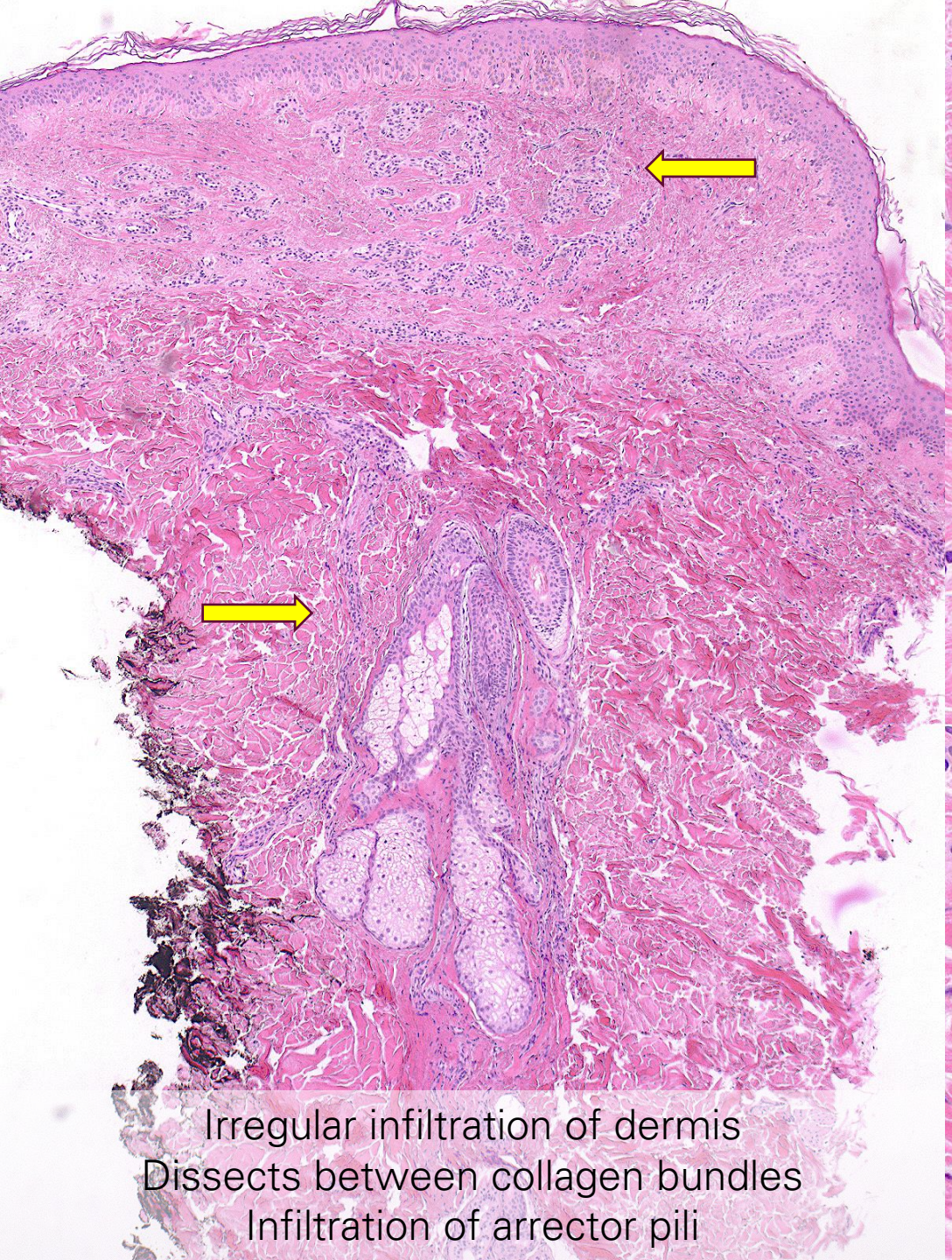
Subcutaneous mass
Dilated, irregular, cavernous vascular channels (~malformation)
Bundles of smooth muscle around blood vessels
Thrombosis and papillary projections

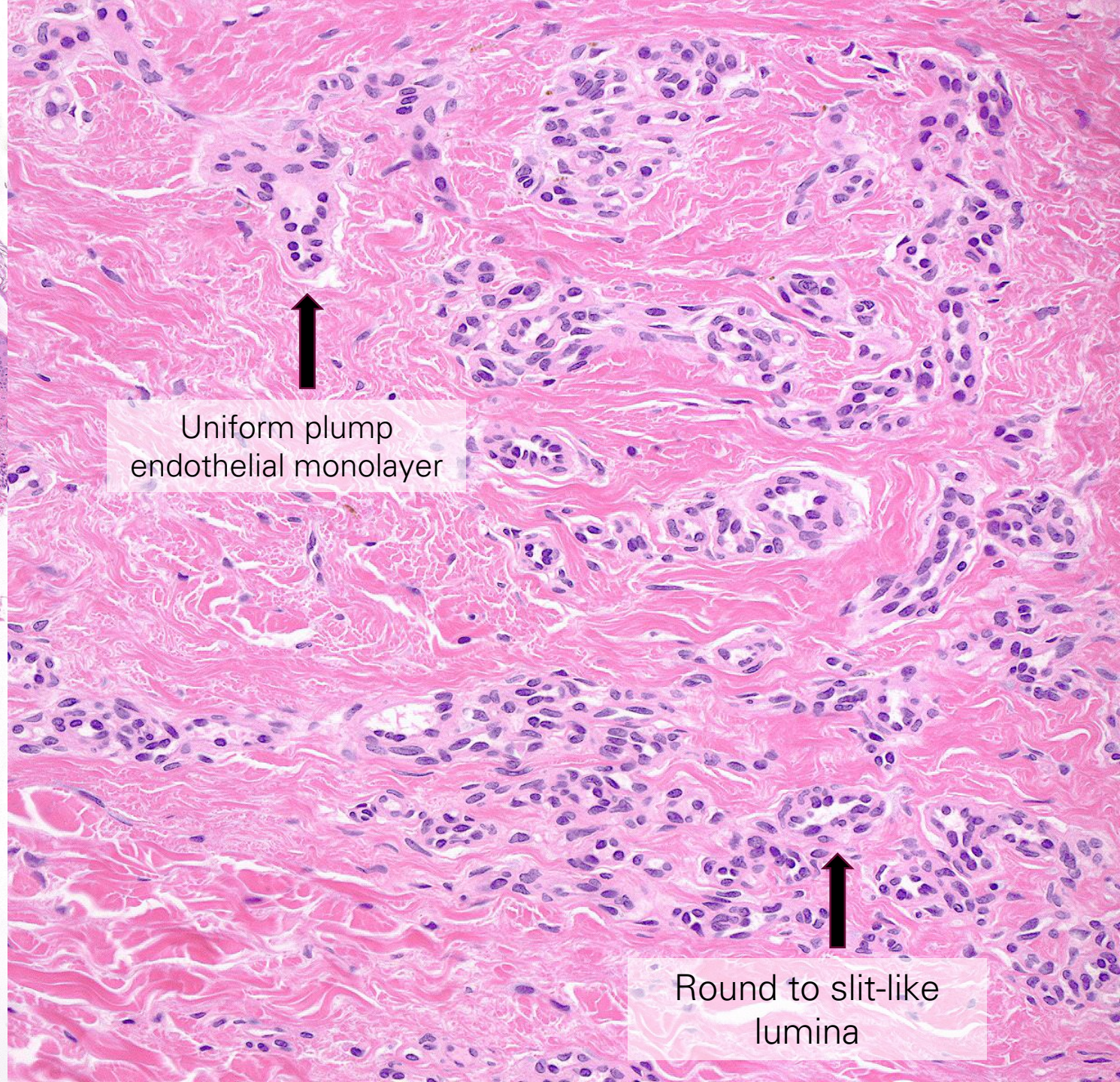
MICROVENULAR HEMANGIOMA

- Limbs of young adults
- Red-bluish papule, nodule, or plaque
- Benign, recurrence is rare
- IHC: CD31+, CD34+, ERG+, WT1+
  - GLUT-1-, Podoplanin-
  - SMA+ pericytes surround vascular channels
- DDX: Kaposi sarcoma, (angiosarcoma)



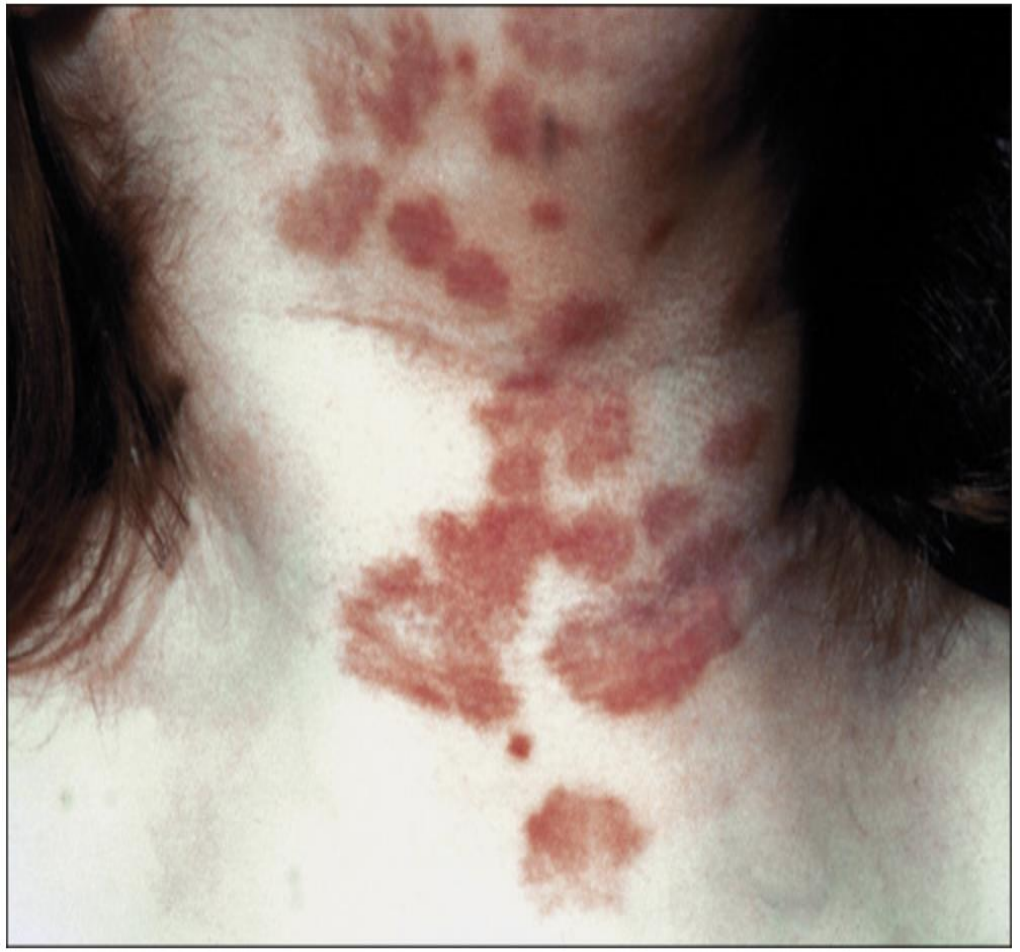
Yuko EHARA *et al.* Multiple microvenular hemangioma eruptively concentrated on an adult https://images.app.goo.gl/pyERbNfgqSXio1rP7

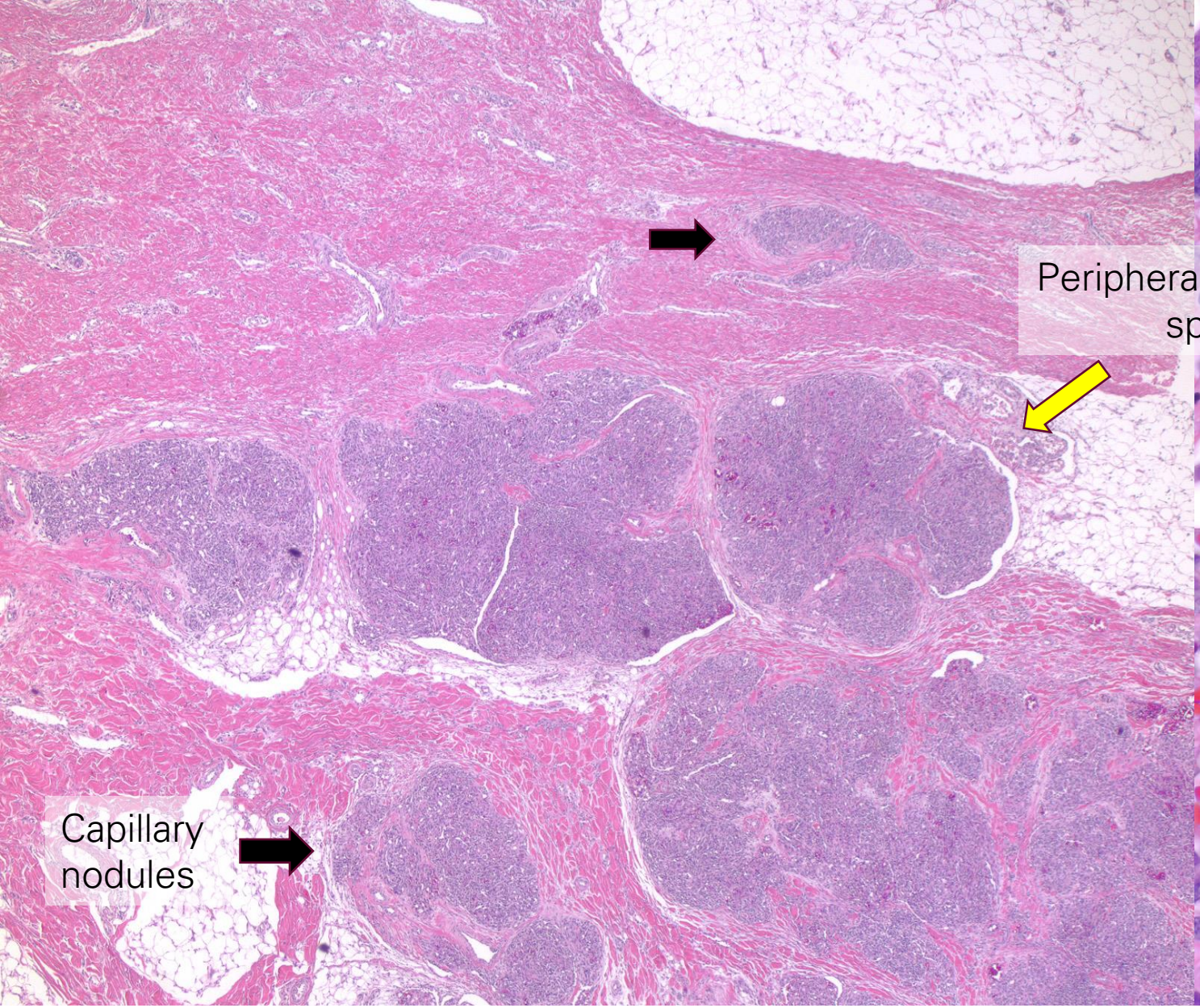

Irregular infiltration of dermis
Dissects between collagen bundles
Infiltration of arrector pili


Uniform plump
endothelial monolayer
Round to slit-like
lumina

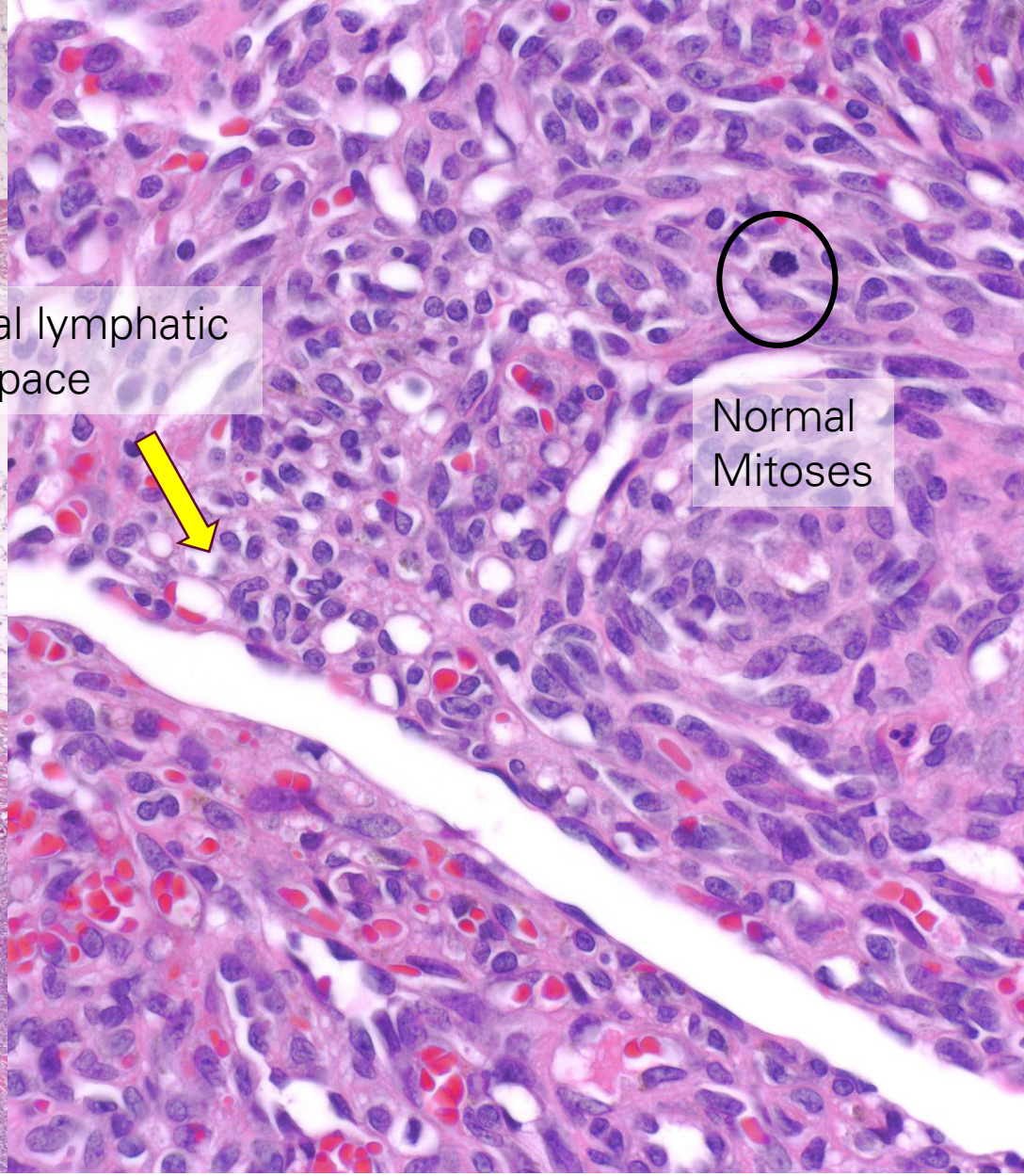
TUFTED ANGIOMA

- Any age, M=F, head and neck >> limbs
- First year of life, congenital (25%)
- Macules and plaque, red-purple
- Usually benign, can be complicated by
  - Consumptive coagulopathy (Kasabach-Merritt syndrome)
- DDX: LCH (deep), Kaposi sarcoma (rare in children)
- IHC: Prox-1+, Podoplanin+

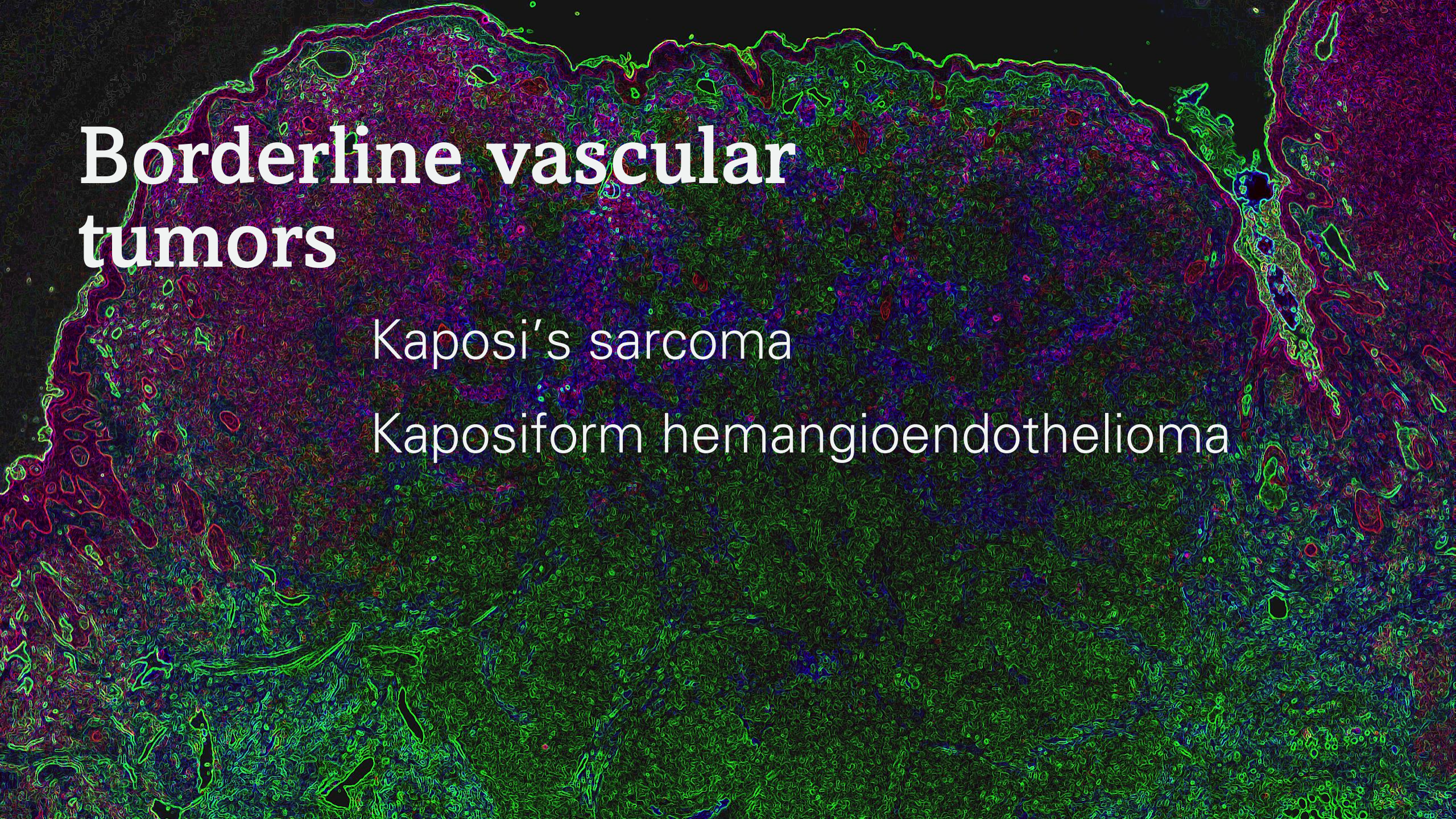




Tightly knit capillaries form subcutaneous tumor nodules
Tiny holes suggest capillaries
Peripheral crescent shaped lymphatic space



Peripheral lymphatic space, lined by attenuated endothelium
Microthrombi (consumptive coagulopathy)



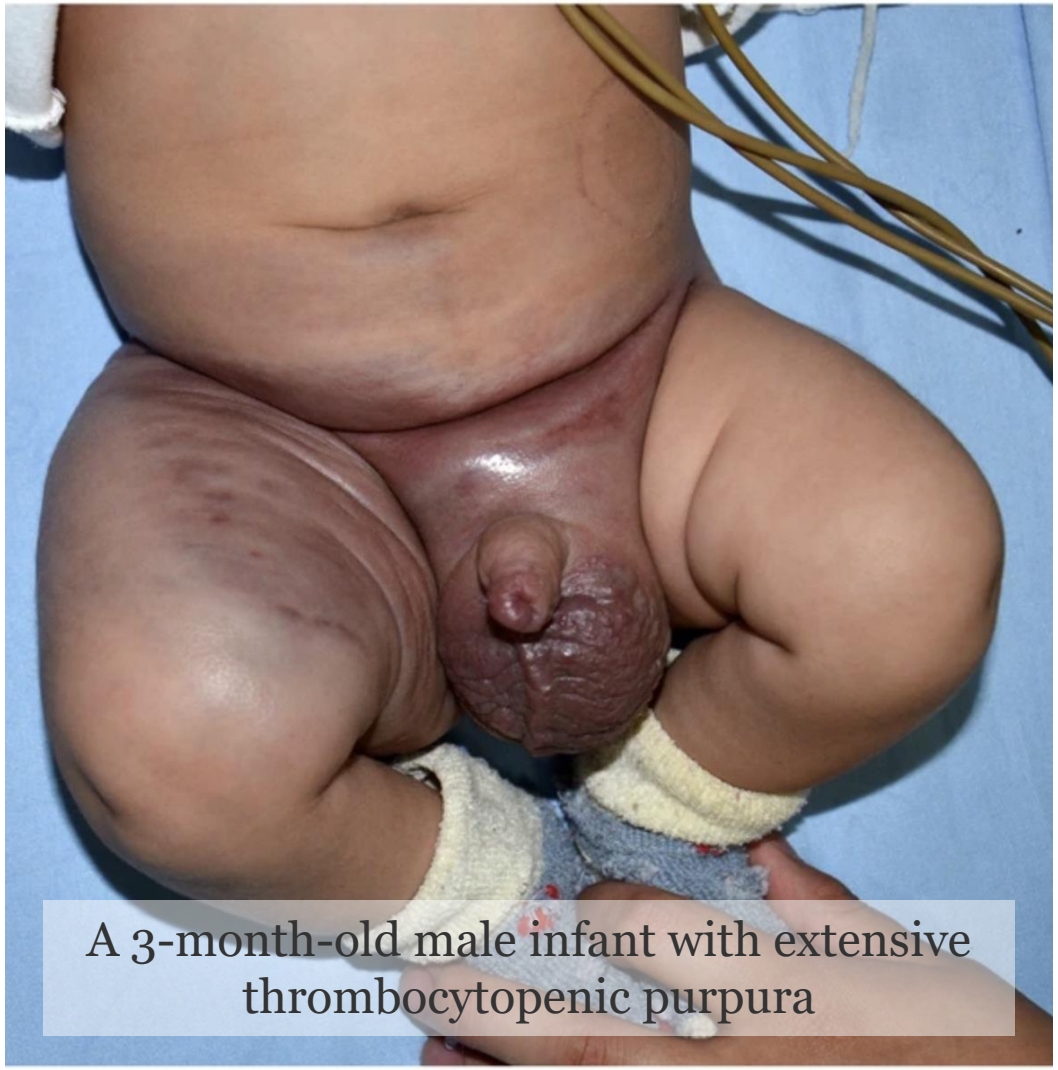
Borderline vascular tumors

Kaposi's sarcoma

Kaposiform hemangioendothelioma

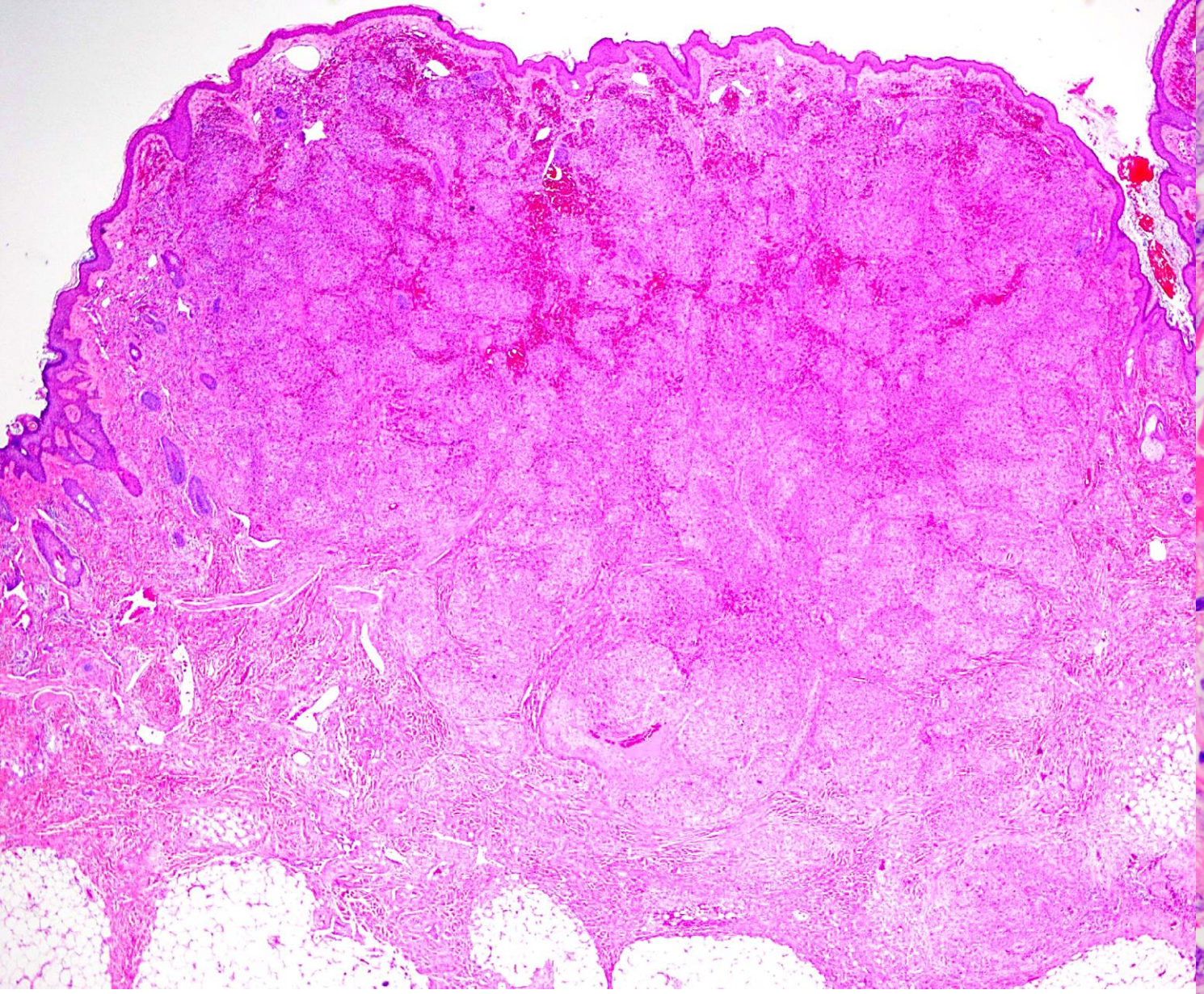
KAPOSIFORM HEMANGIOENDOTHELIOMA

- Infants (<1 year), may occur in older children/adults.
- Solitary, ill-defined, violaceous (purplish) mass or plaque.
- Painful, firm, and infiltrative (unlike infantile hemangioma).
- Kasabach-Merritt phenomenon (KMP) in ~50% of cases:
  - Severe thrombocytopenia (platelet trapping)
  - Hypofibrinogenemia, elevated D-dimer (DIC-like coagulopathy)

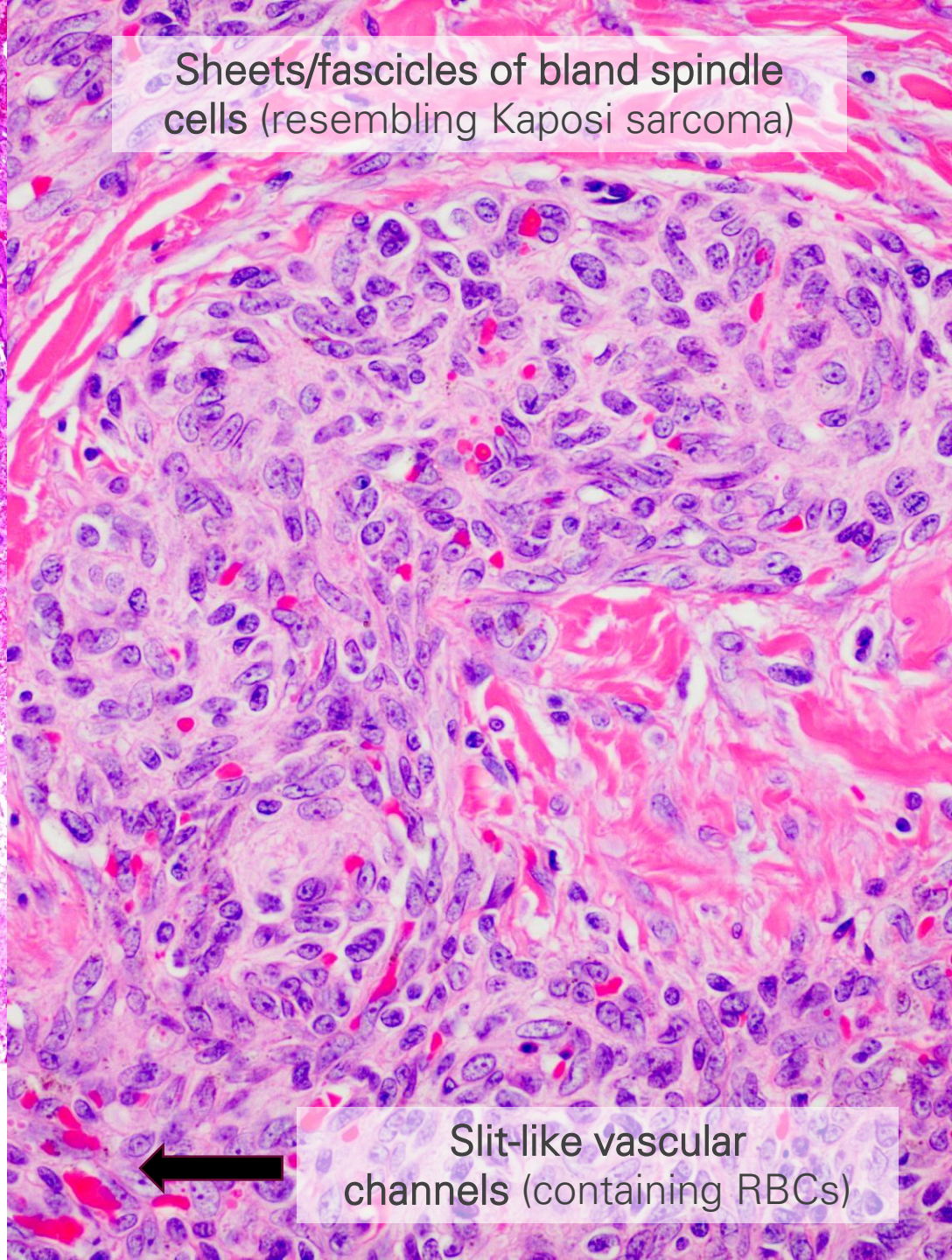


A 3-month-old male infant with extensive thrombocytopenic purpura

Ji, Y., *et al.* Kaposiform hemangioendothelioma: current knowledge and future perspectives. *Orphanet J Rare Dis* **15**, 39 (2020).



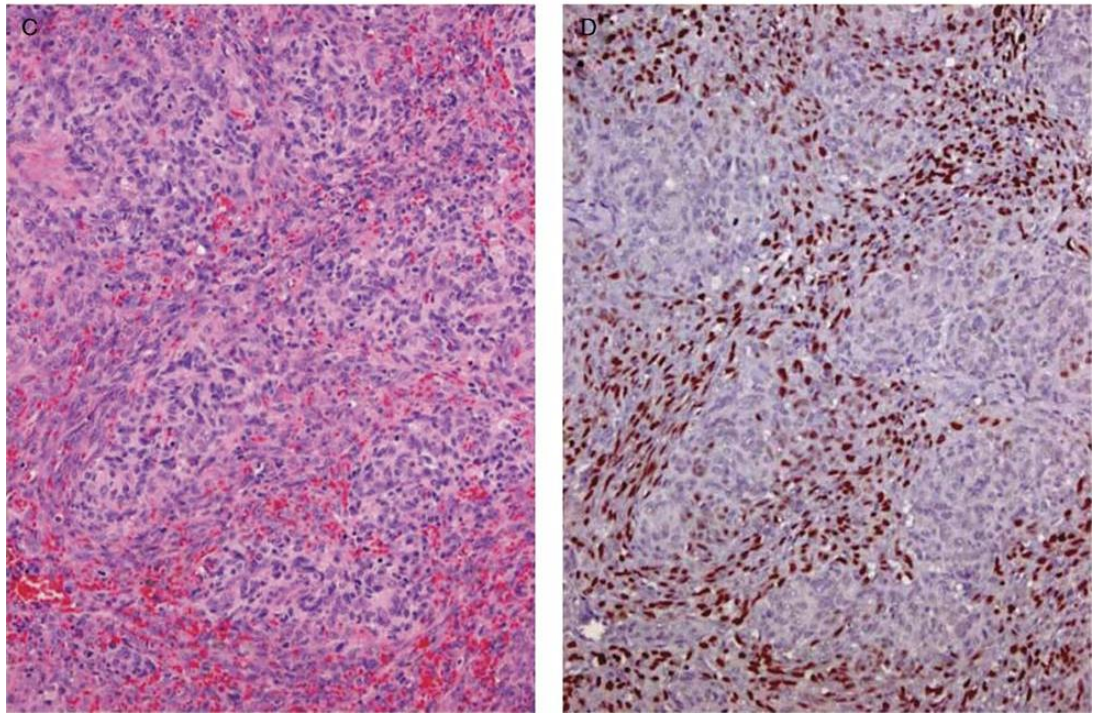
Deep dermal and subcutaneous tumor nodules
Hemorrhage, hemosiderosis



- Mouse model: ectopic *Prox-1* expression
  - Local aggressive growth:
  - Dadras *et al*. (Detmar) *JID* 2008.
- KHE, TA, IH, PG and GT (n= 75)
- KHE and TA are closely related
- Shared an identical endothelial immunophenotype:
  - Glomeruloid cells negative: Prox-1, Podoplanin (D2-40) and LYVE-1
  - Spindle cells positive: Prox-1, Podoplanin (D2-40), LYVE-1, CD31 and CD34
- IHC DDX: IH, LCH negative for Prox-1 and Podoplanin (D2-40)

Expression of Prox1, Lymphatic Endothelial Nuclear Transcription Factor, in Kaposiform Hemangioendothelioma and Tufted Angioma

Aude Rimella Le Huu, MD,† ‡ Chris H. Jokinen, MD,§ Brian P. Ruben, MD, PhD,§ Martin C. Mihm, MD,‖ Sharon W. Weiss, MD,¶ Paula E. North, MD, PhD,# and Soheil S. Dadras, MD, PhD*†*



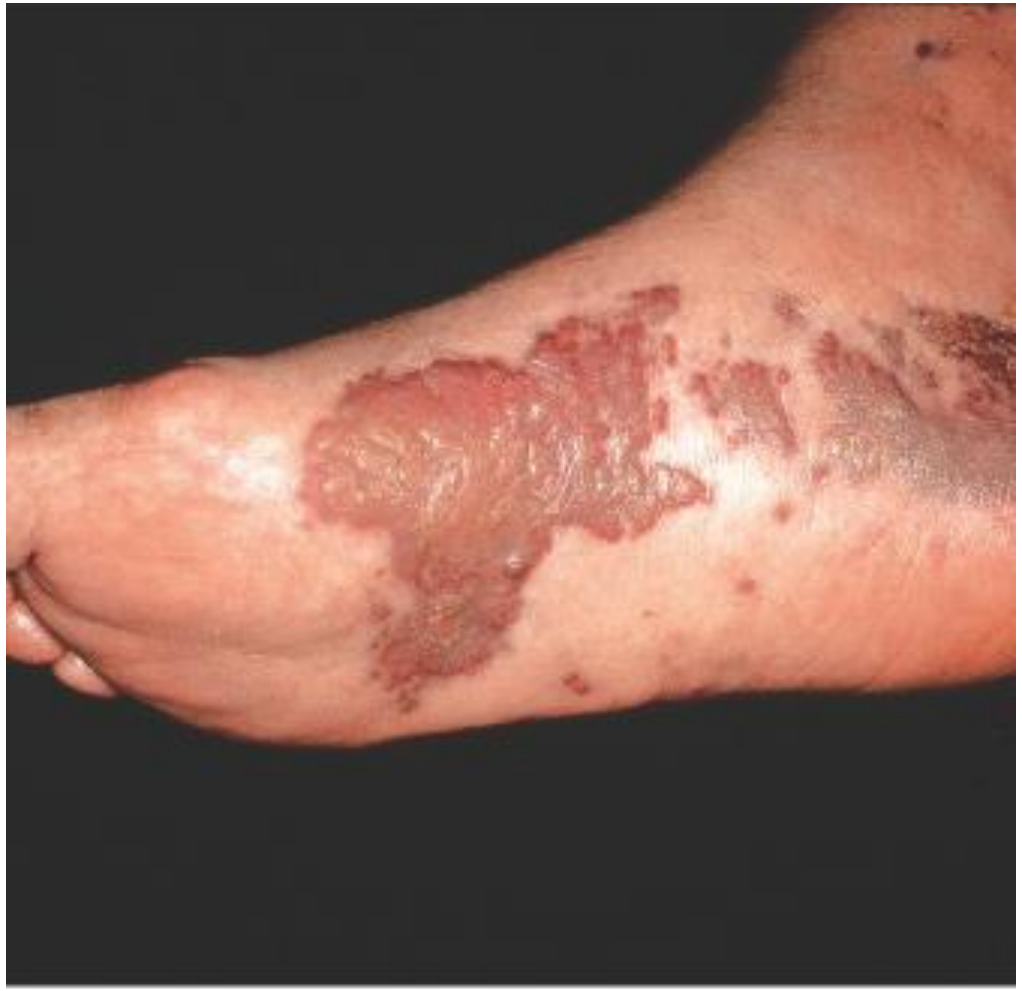
Glomerloid foci (central) : PROX-1- Podoplanin-

Spindle cells (peripheral): PROX-1+ Podoplanin+

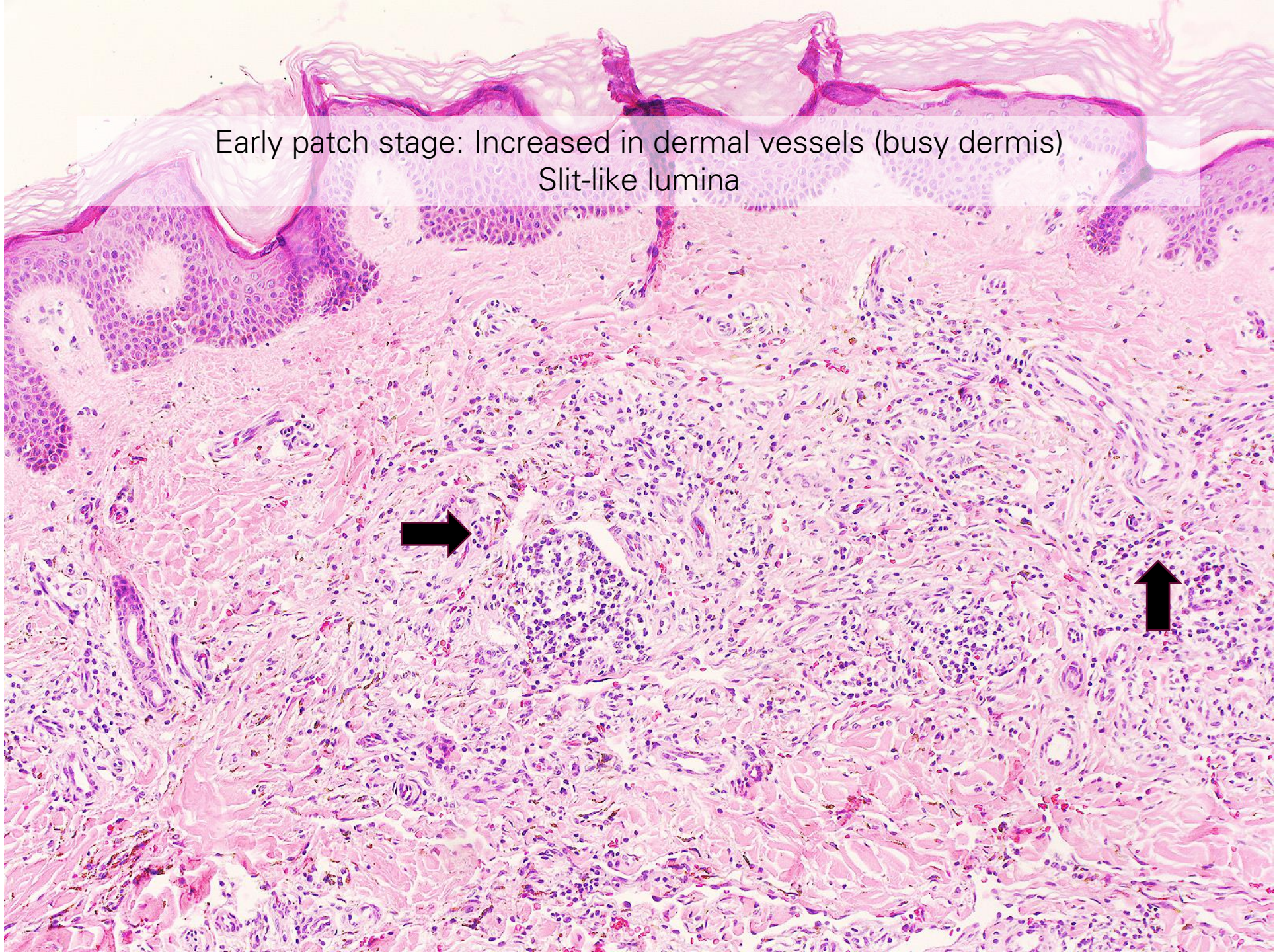
Am. J. Surg. Pathol. 2010

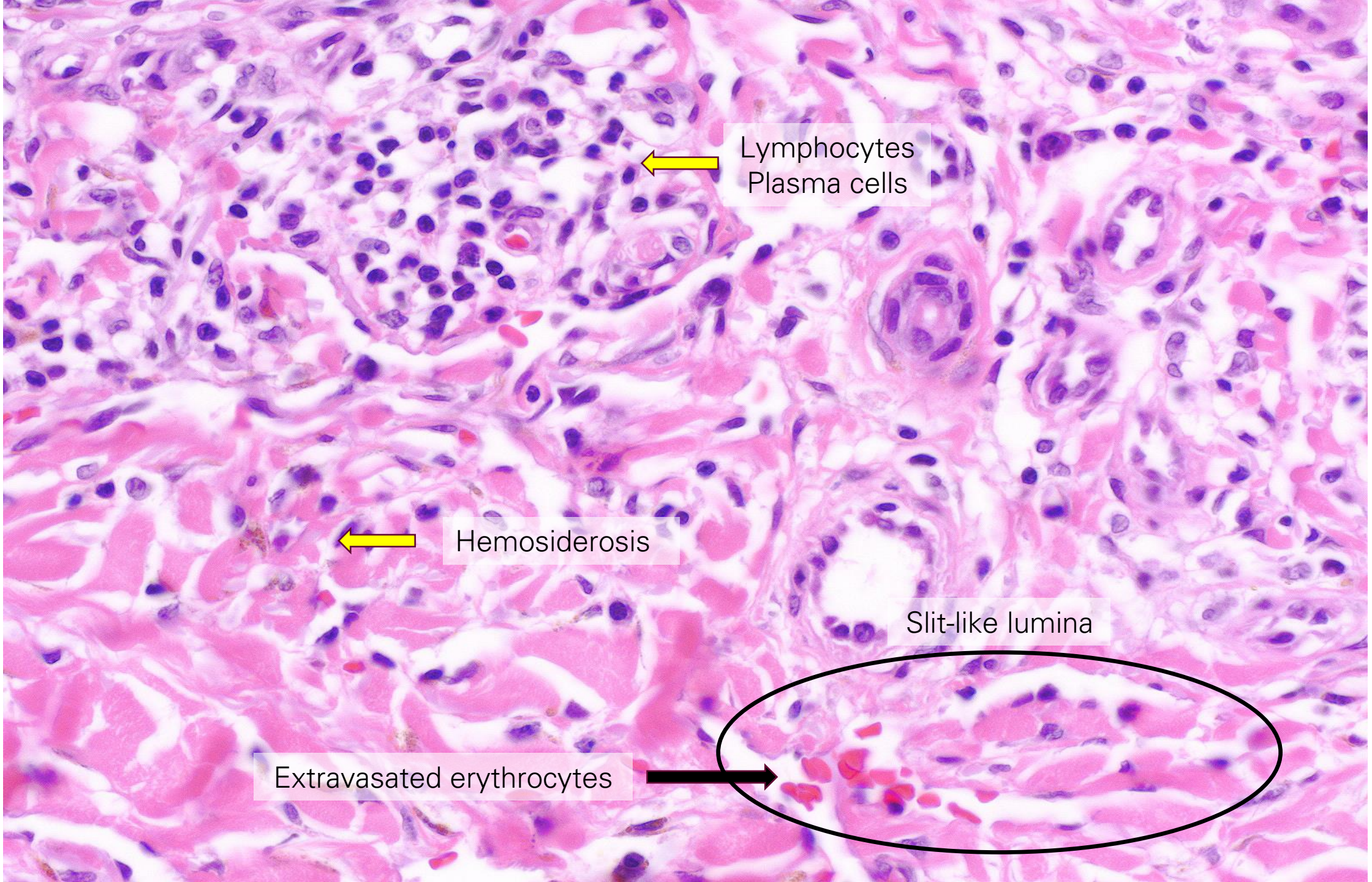
KAPOSI SARCOMA

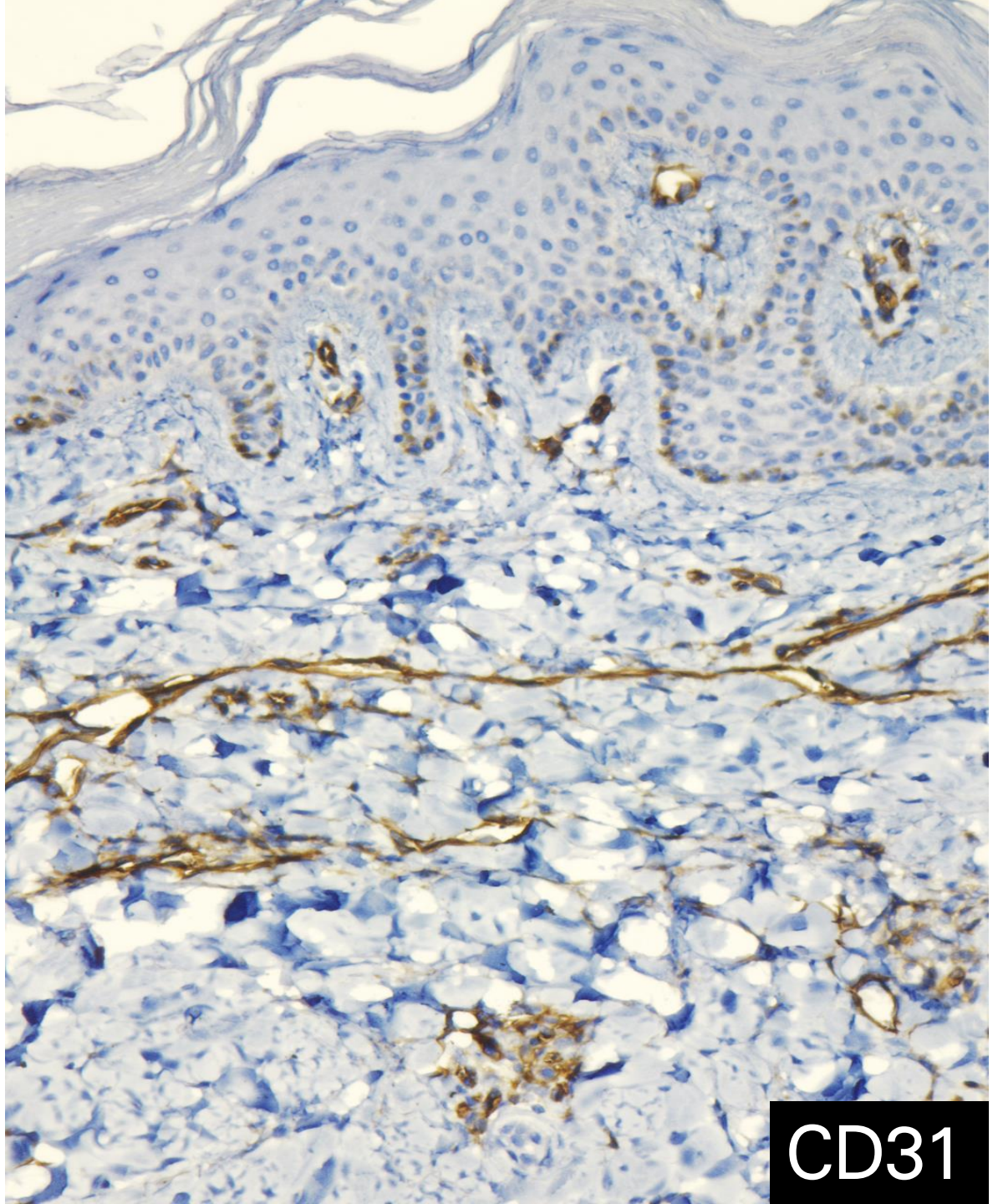
- Human herpesvirus (HHV-8, KS-associated herpesvirus)
- Clinical groups:
  - Classic: elderly male
  - AIDS-related: young adult males
  - Immune-associated: rare, kidney transplantation
  - African, sub-Saharan Central Africa
- Reddish-blue patch, nodule
- DDX: progressive lymphangioma, angiosarcoma, tufted angioma, KHE
- IHC: HHV8+, CD31+, CD34+, D2-40+

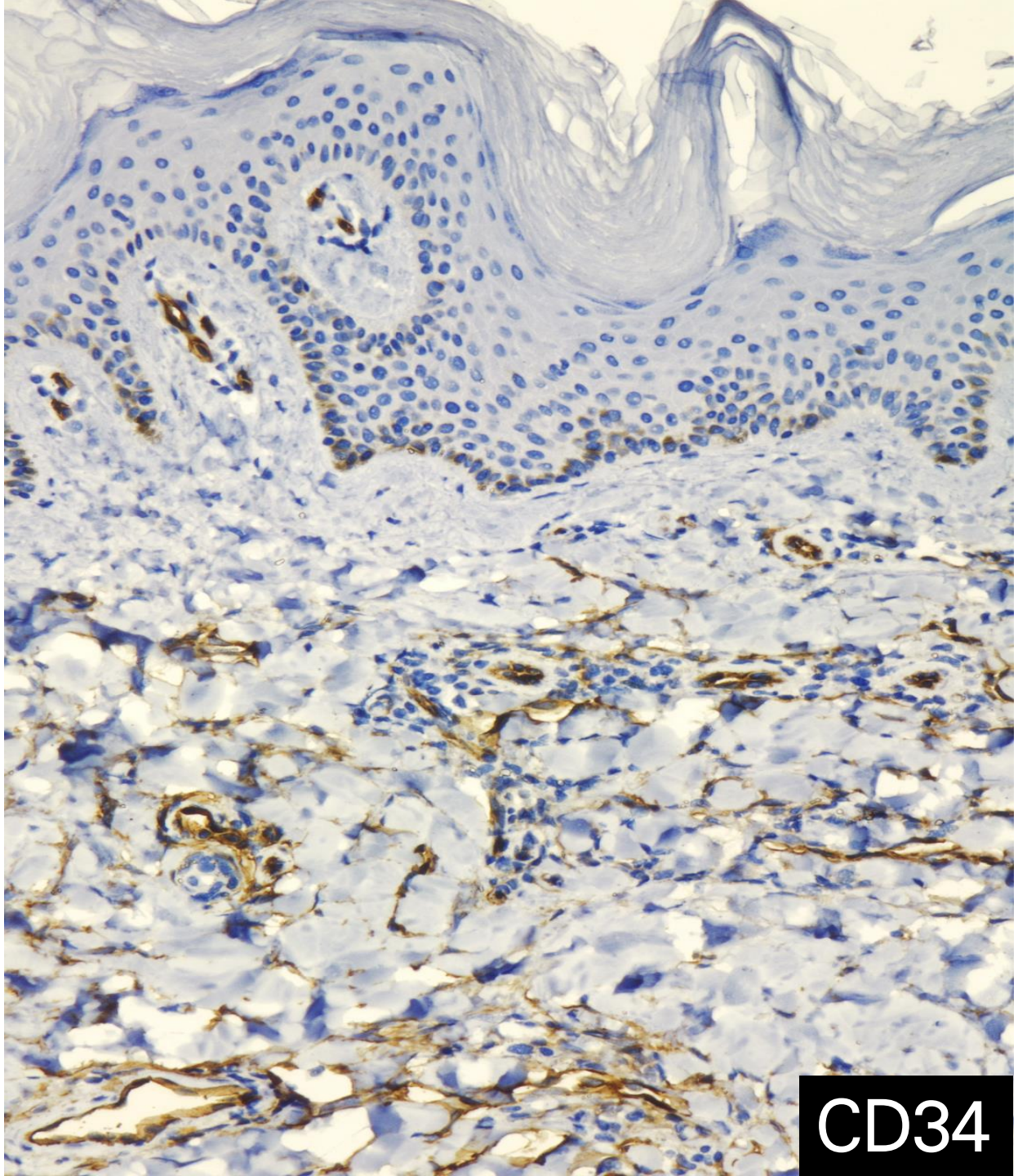


Isevier - Bolognia, Jorizzo and Rapini: Dermatology - www.der


Early patch stage: Increased in dermal vessels (busy dermis)
Slit-like lumina

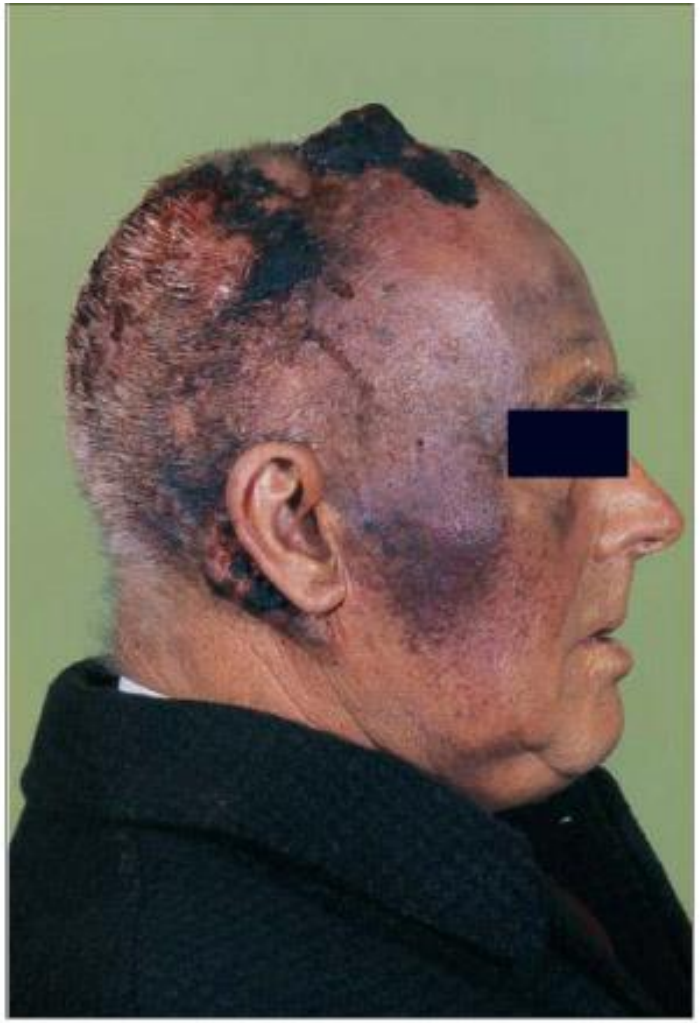

Lymphocytes
Plasma cells
Hemosiderosis
Slit-like lumina
Extravasated erythrocytes

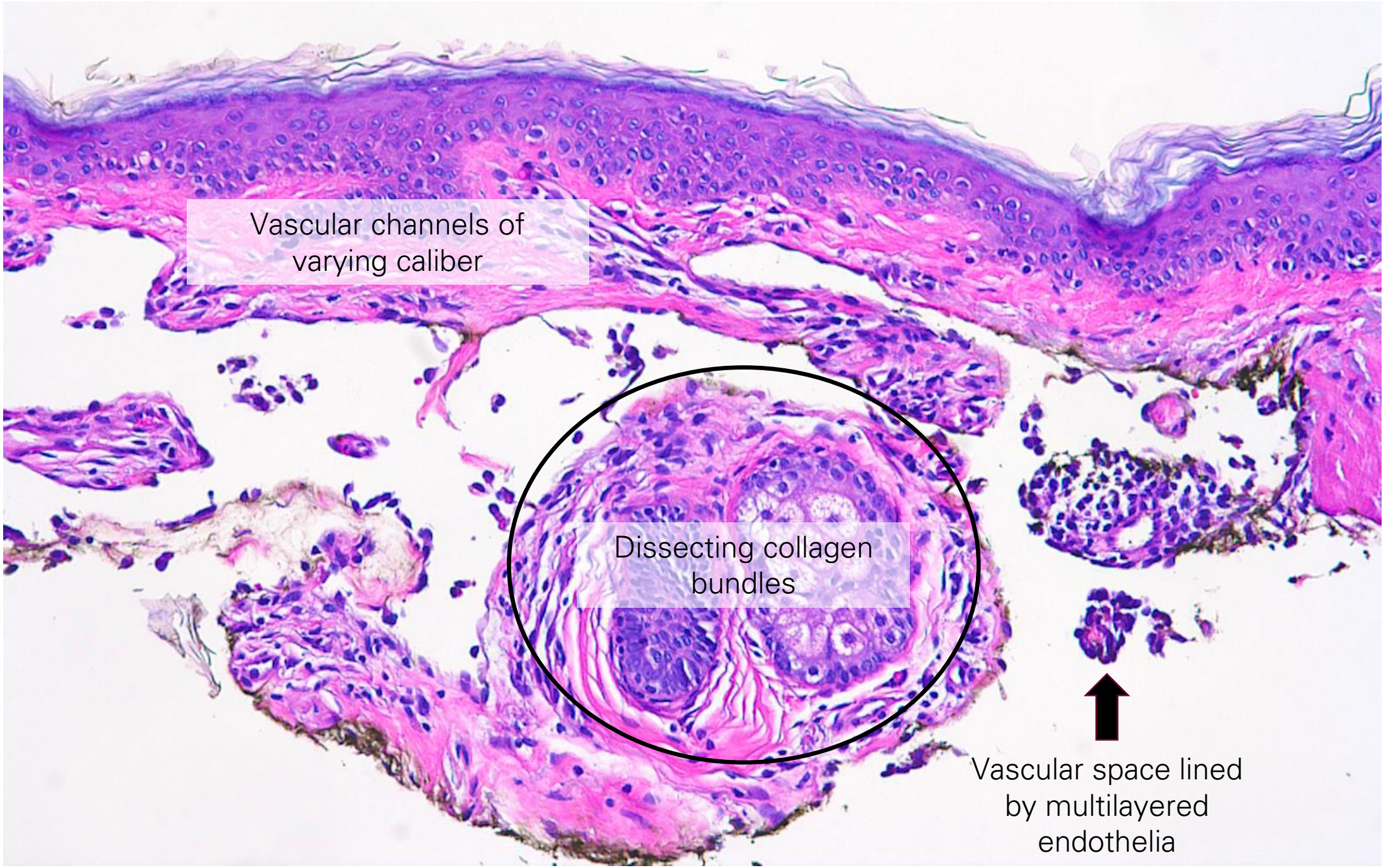

CD31


CD34

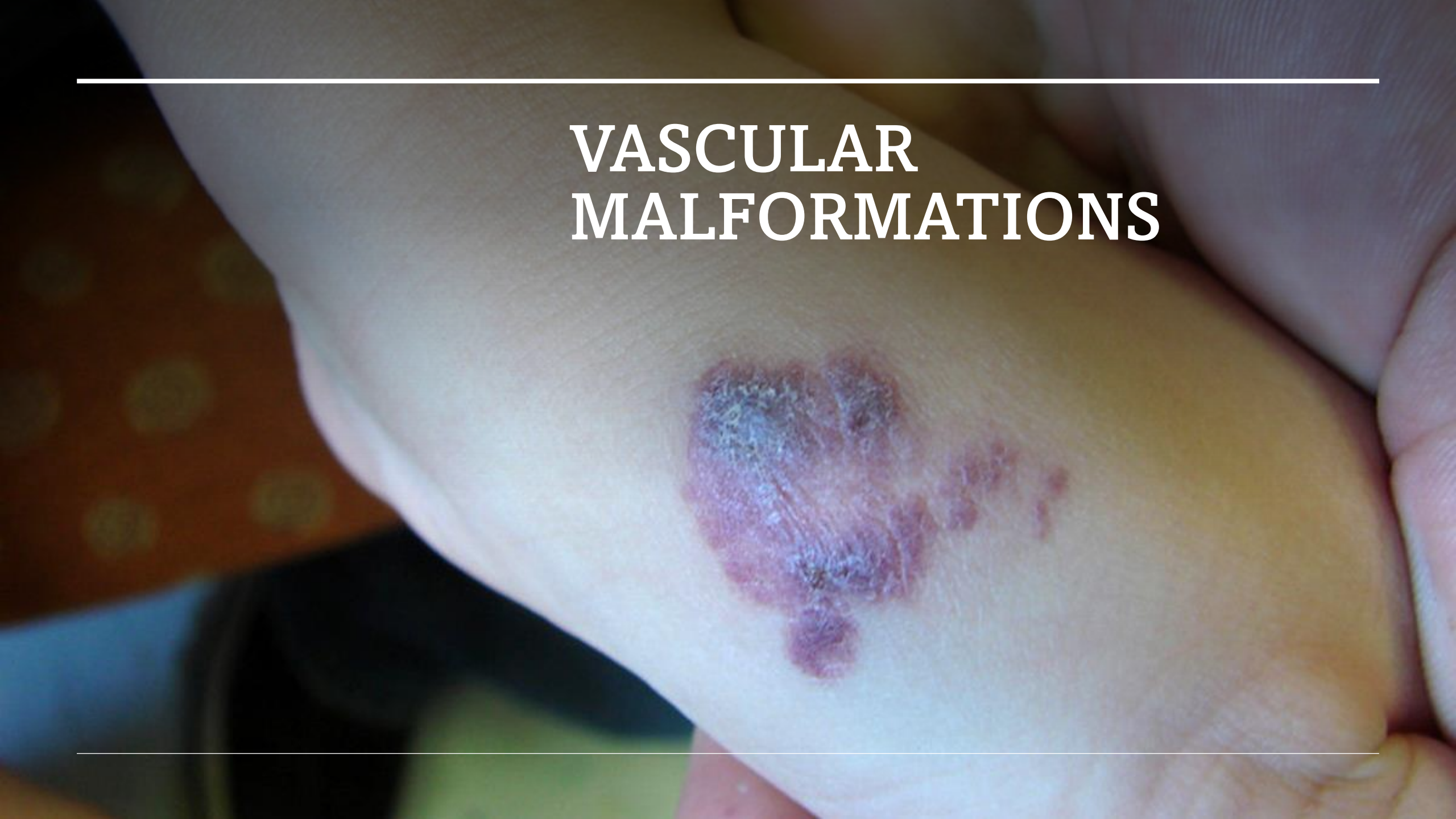
ANGIOSARCOMA

- Clinical settings
  - Idiopathic, head and neck, older adults
  - Lymphedema-associated, any age, limbs
  - Post-irradiation
- Bruise-like patches and plaques, hemorrhagic
- Many gene mutations (melanoma), ERK/MAPK pathway
- DDX: Kaposi sarcoma
- IHC: CD31+, CD34+, FLI1+, ERG+, HHV8-




Vascular channels of varying caliber
Dissecting collagen bundles
Vascular space lined by multilayered endothelia

VASCULAR MALFORMATIONS



VASCULAR MALFORMATIONS

SLOW-FLOW VASCULAR MALFORMATIONS

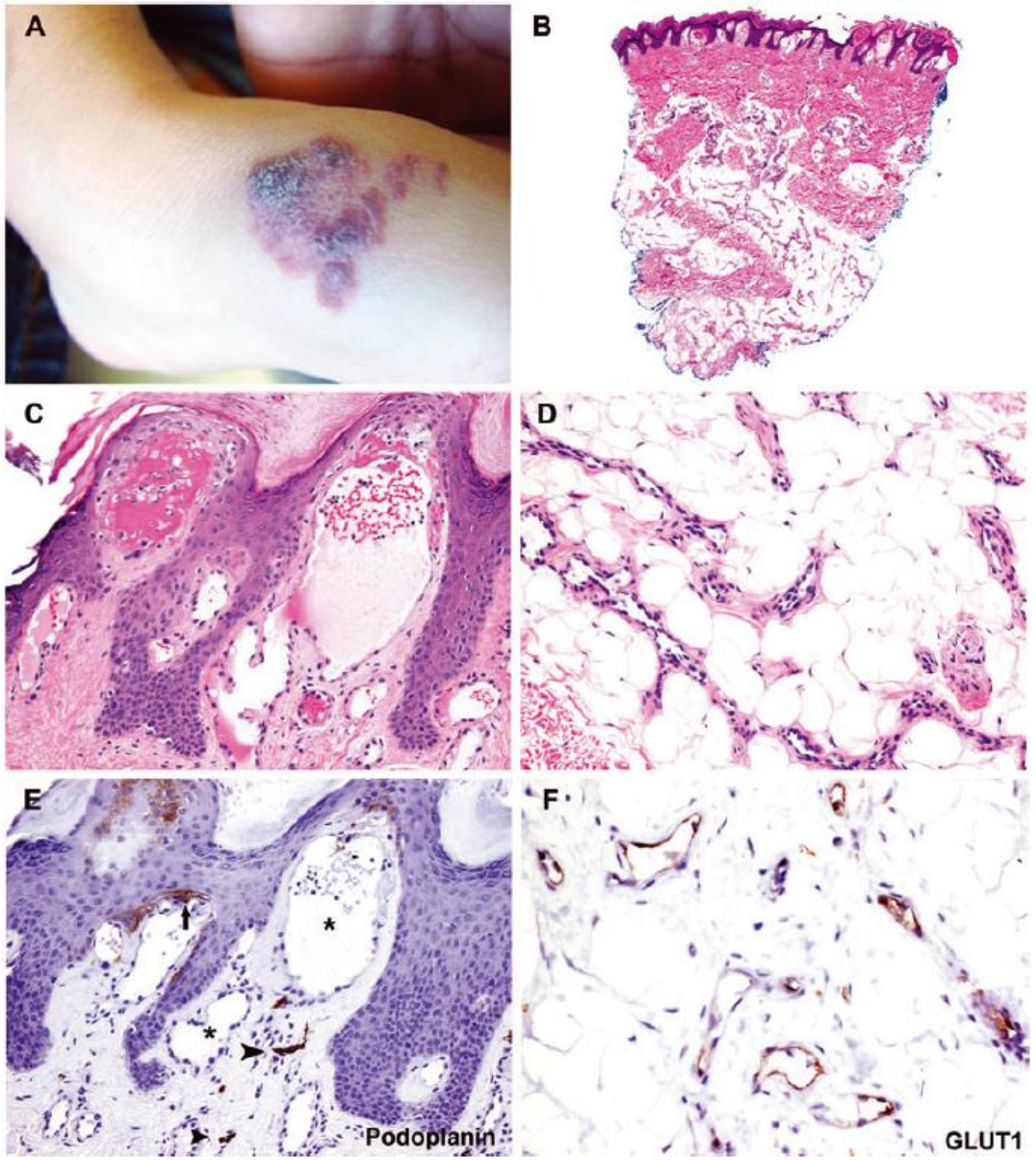
- Blood flow is sluggish or low-pressure
- Types:
  - Venous malformations (VMs)
  - Lymphatic malformations (LMs)
  - Capillary malformations (CMs)
- **Symptoms:** Pain, swelling, localized mass, sometimes bleeding or clotting (in venous malformations)

FAST-FLOW VASCULAR MALFORMATIONS

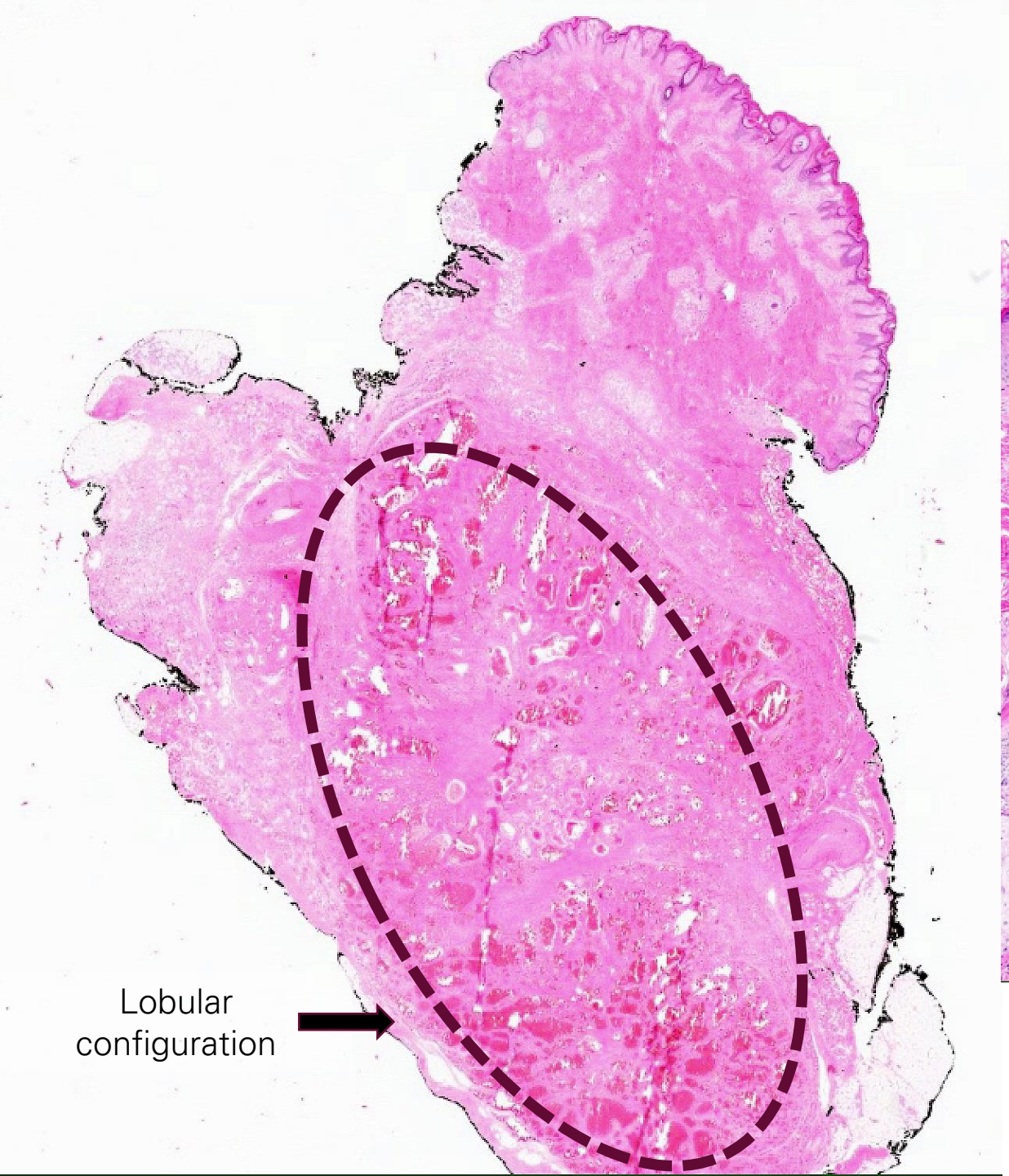
- Blood flow is rapid, high-pressure, often with arterial involvement
- Types:
  - Arteriovenous malformations (AVMs)
  - Arteriovenous fistulas (AVFs)
- **Symptoms:** Pulsations, pain, ischemia (due to "steal" phenomenon), bleeding, or cosmetic deformity

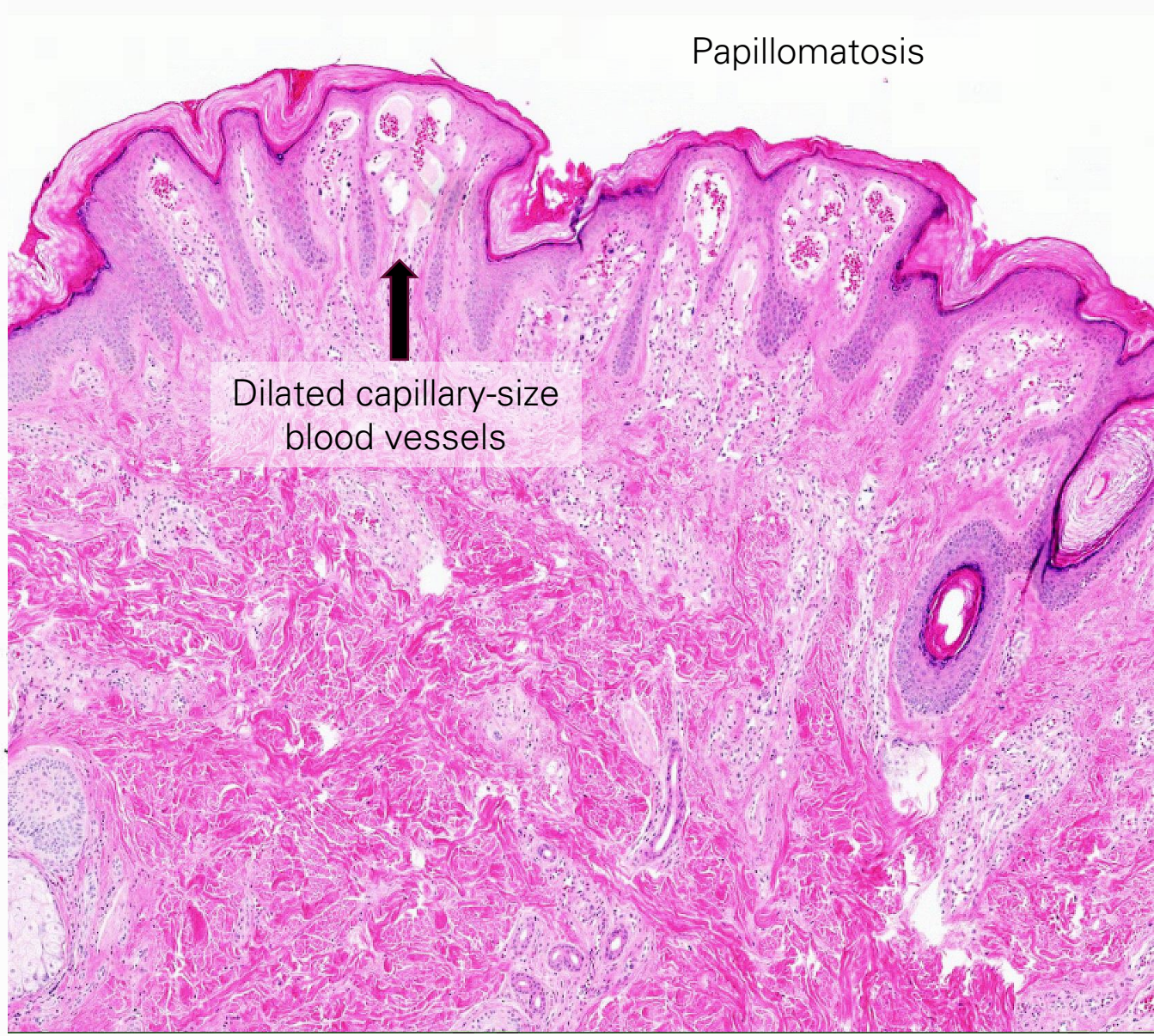
VERRUCOUS VENOUS MALFORMATION (VERRUCOUS HEMANGIOMA)

- *MAP3K3* missense somatic mutation
- Resembles angiokeratoma (superficially)
  - Dilated, congested capillaries push up into dermis
  - Papillomatosis, acanthosis, hyperkeratosis (verrucous)
  - Subcutaneous component numerous capillaries
- DDX: angiokeratoma, infantile hemangioma (GLUT1+)
- IHC: GLUT1- (focal+), WT1±

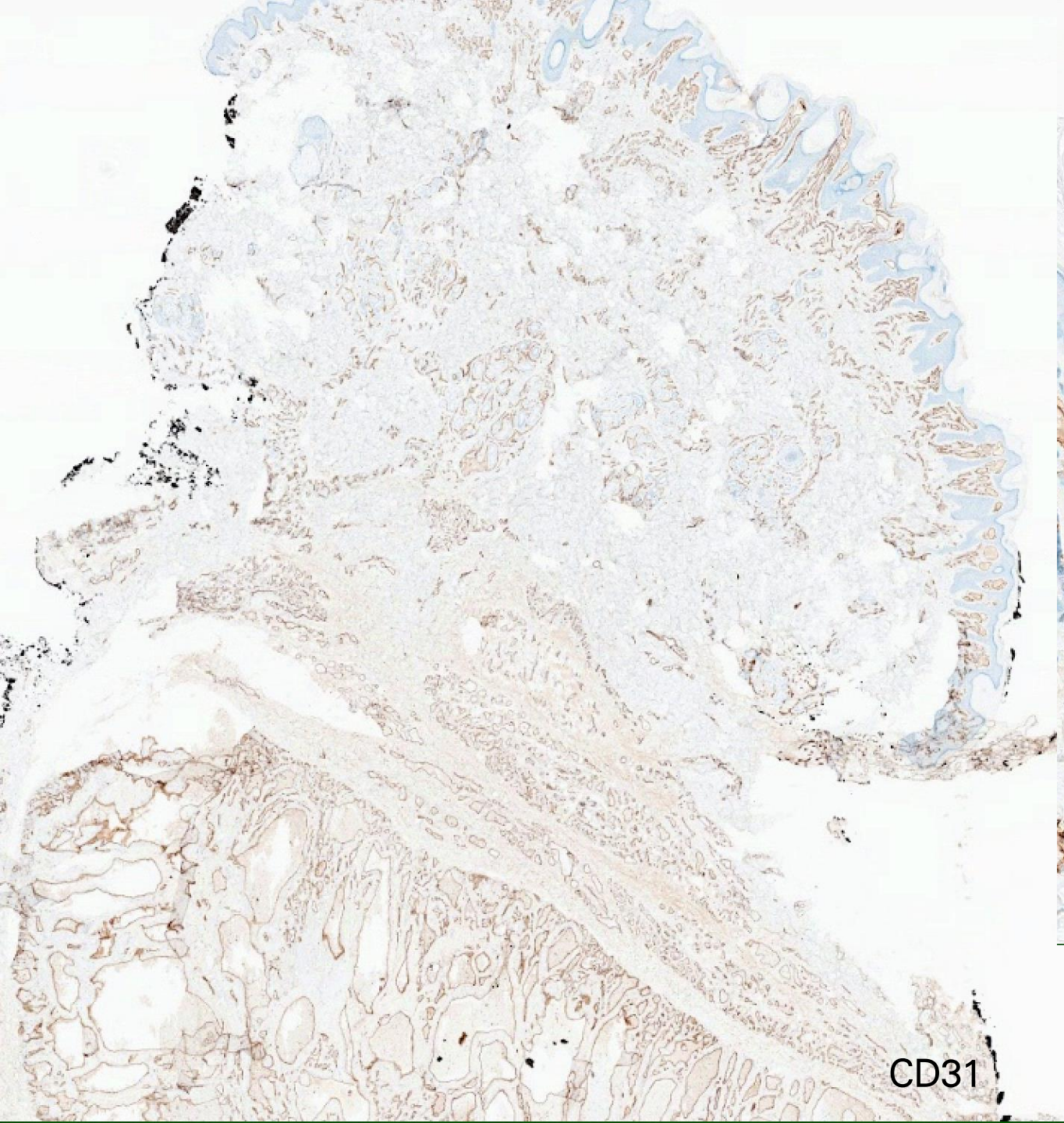


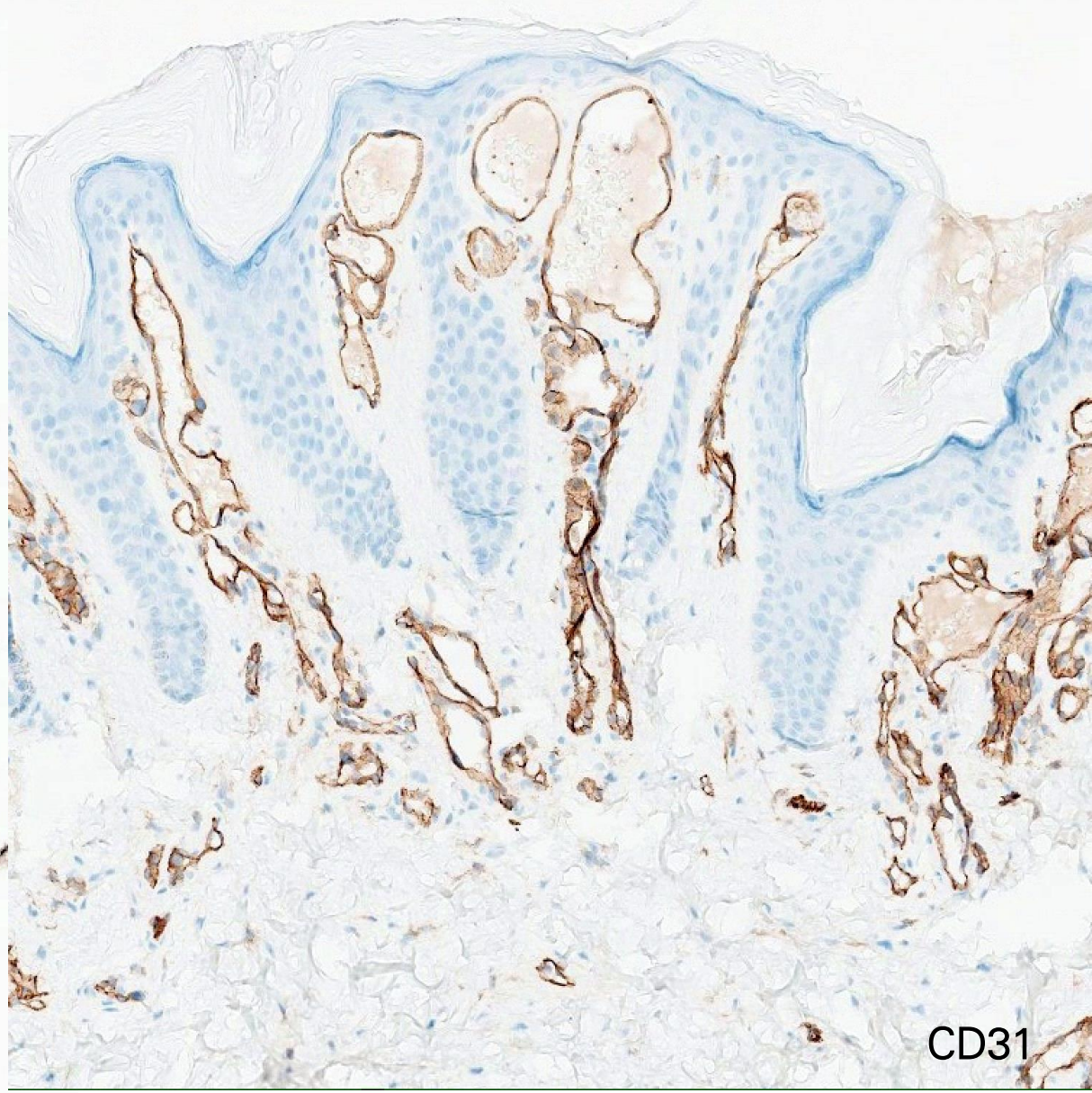
Verrucous hemangioma. Clairwood, Bruckner & Dadras. *JCP* 2011
Lucile-Packard Vascular Anomaly Clinic



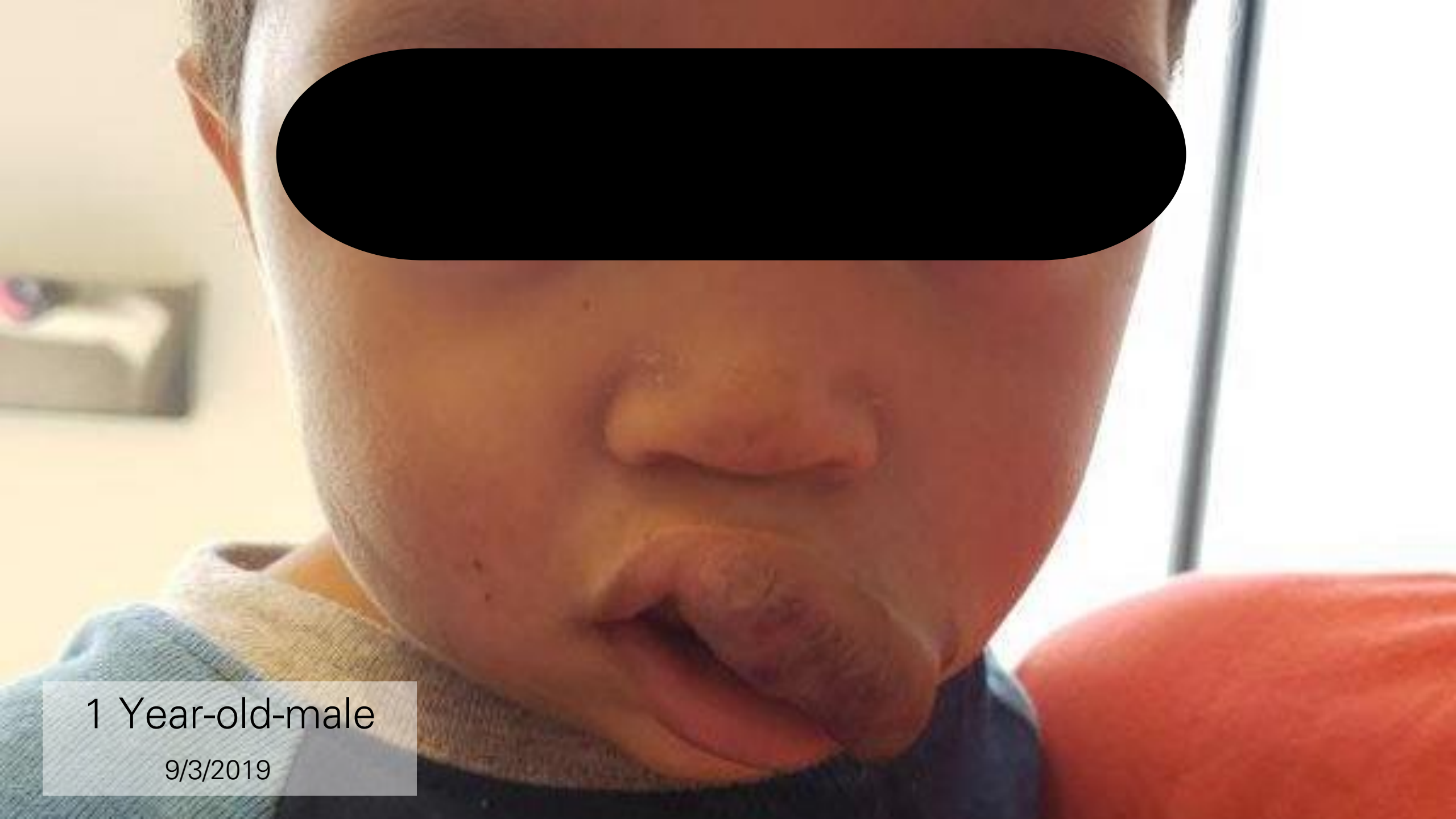


15-year-old male, Right Wrist
Ganglion cyst



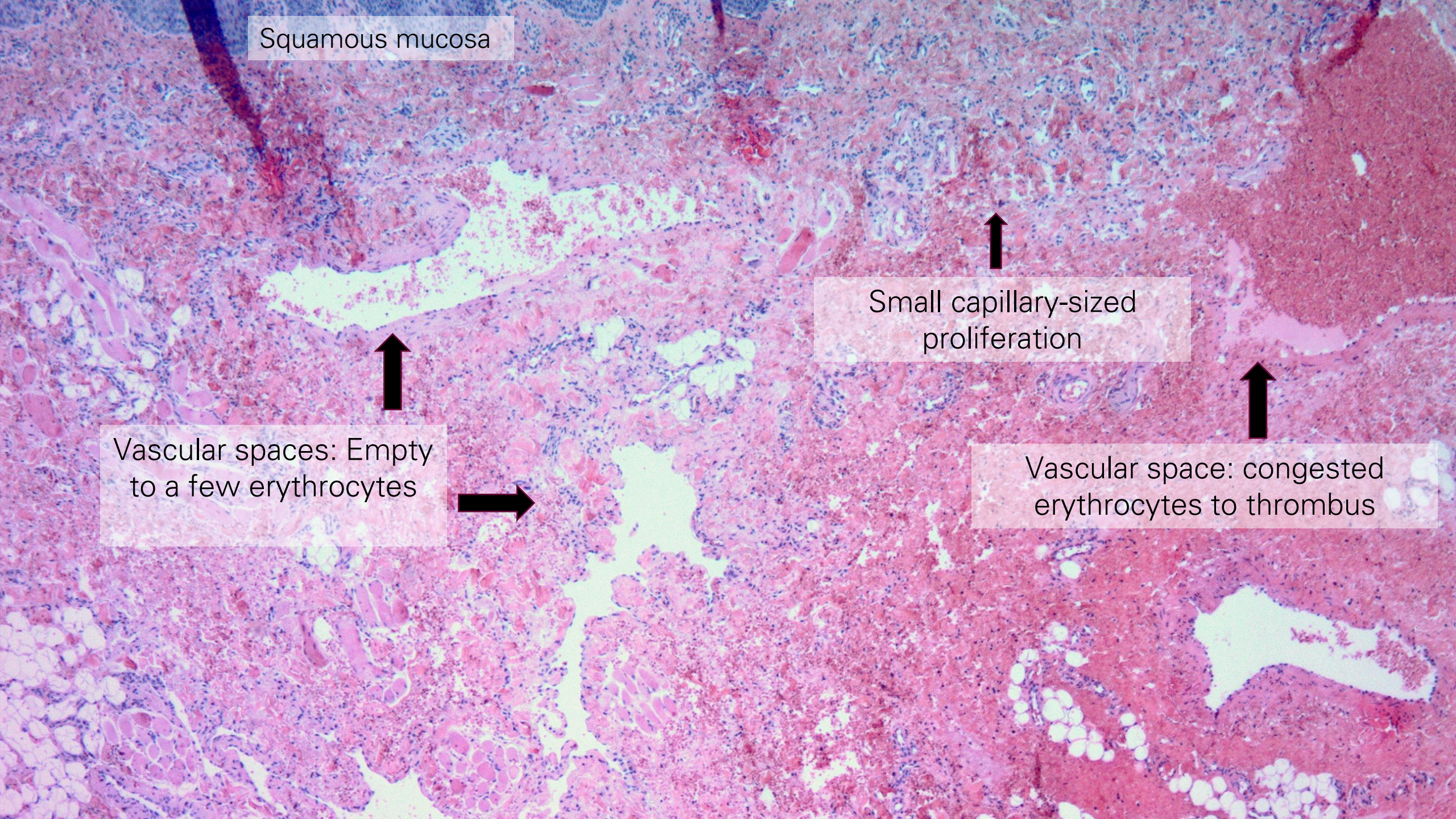


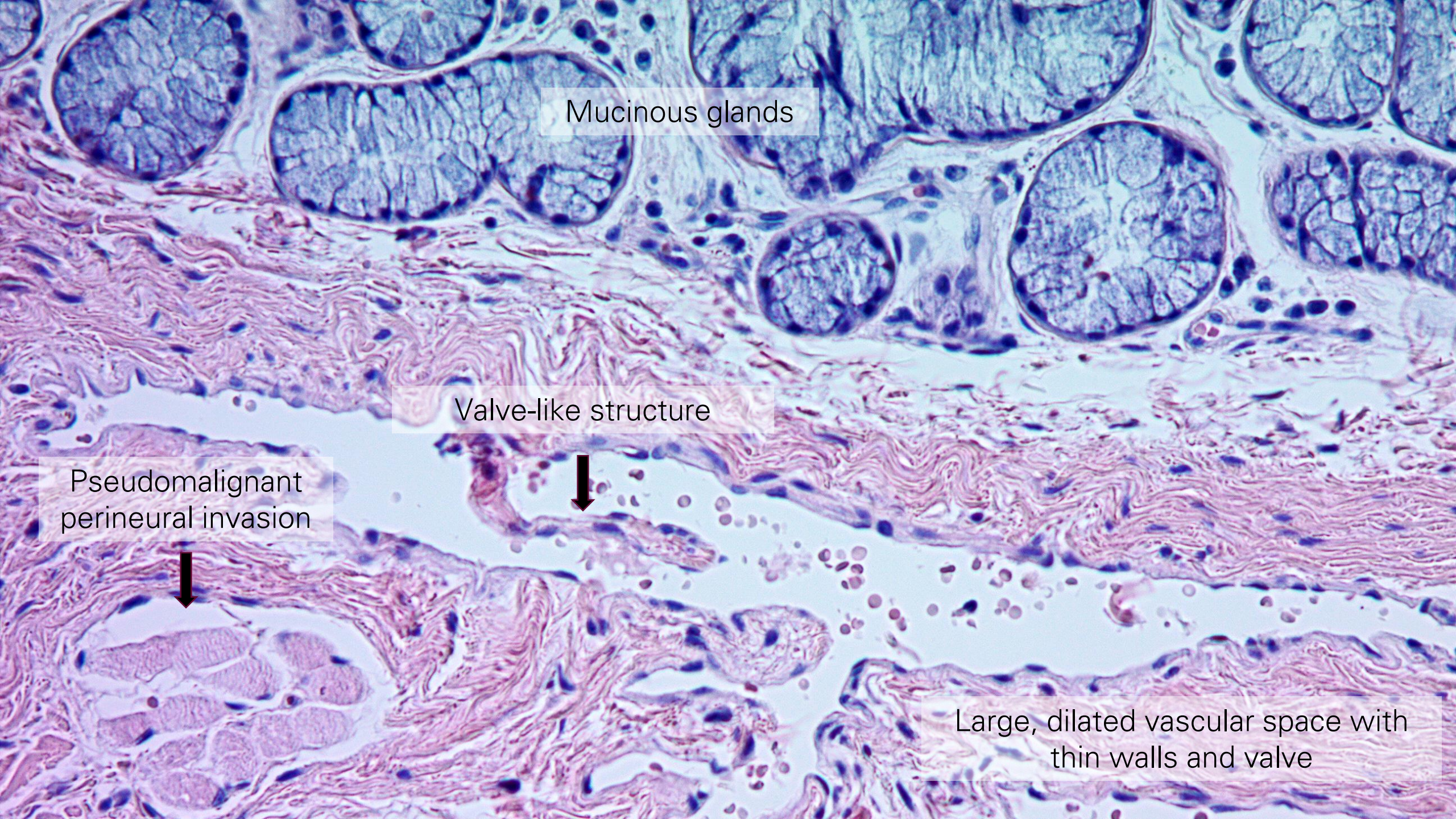
CD31+; ERG+; GLUT1-

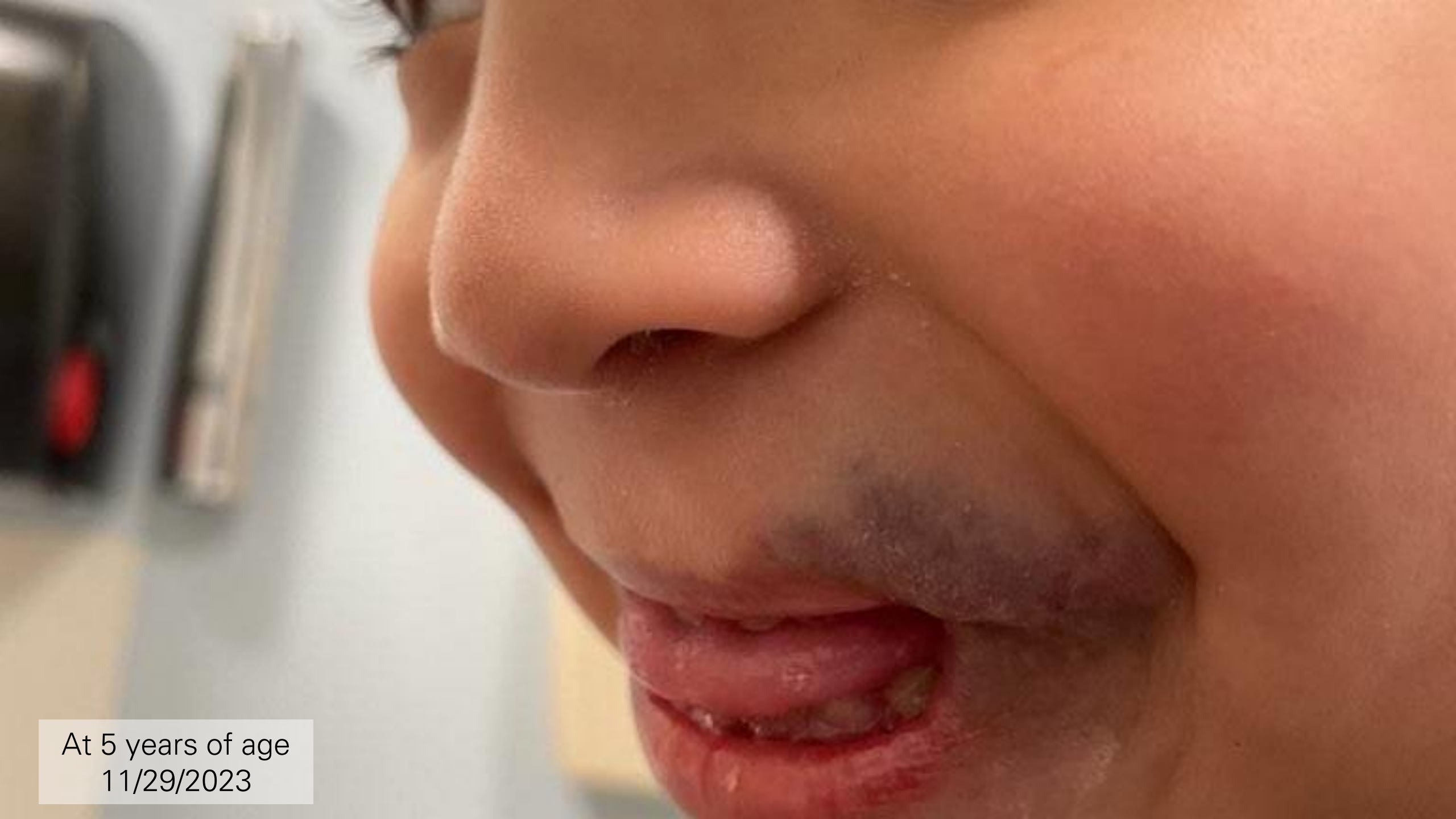


1 Year-old-male

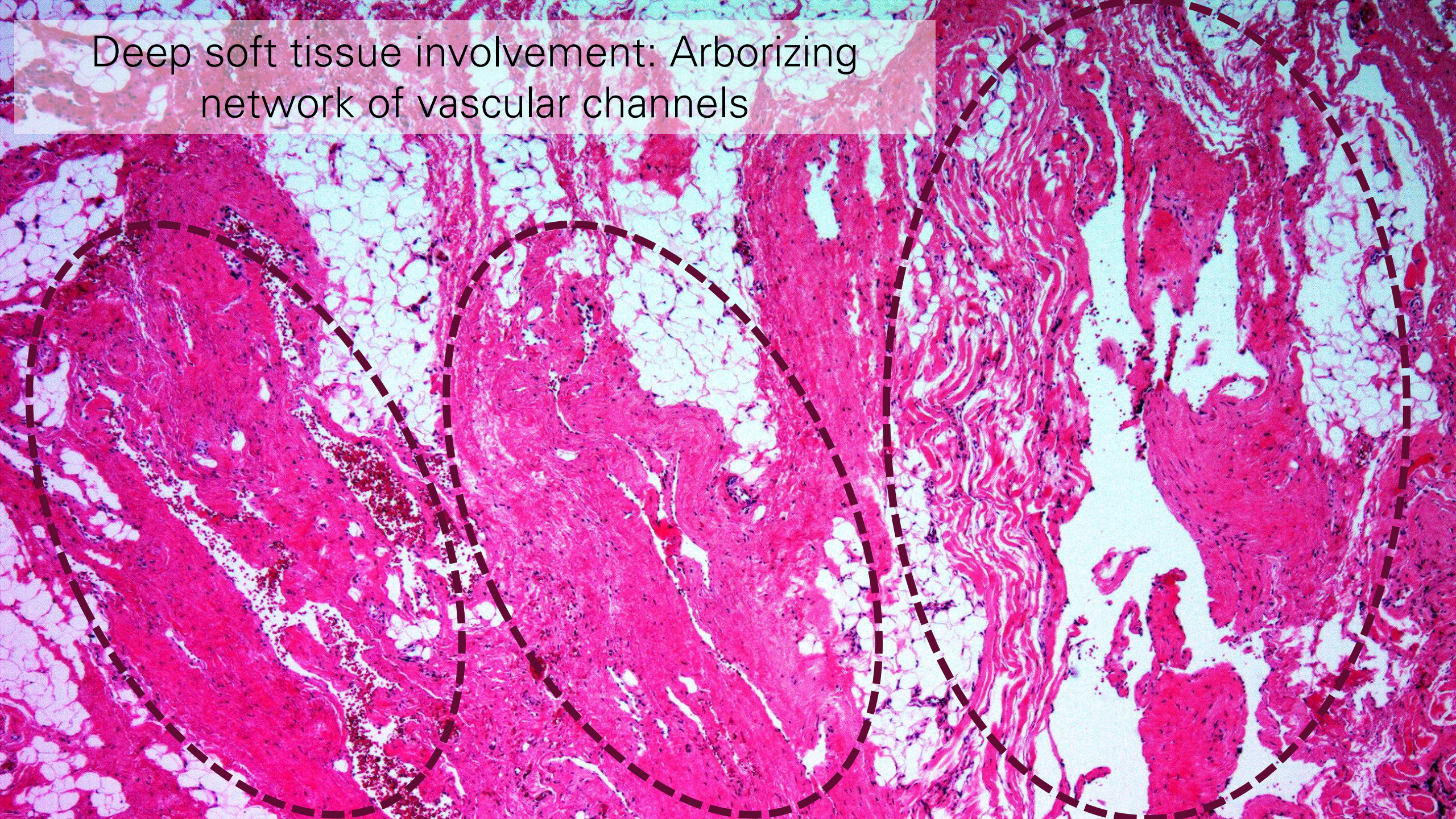
9/3/2019

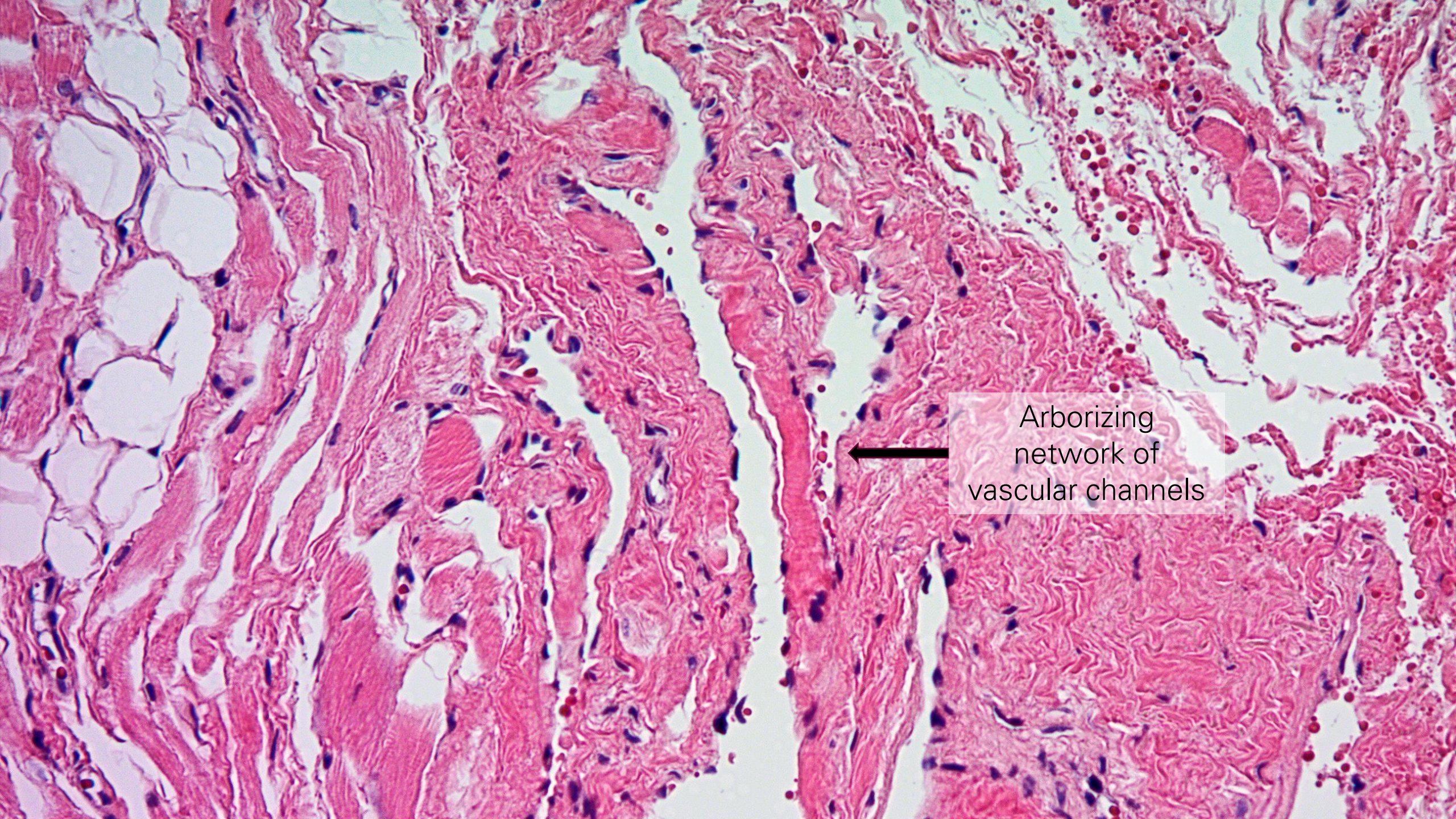

Squamous mucosa
Small capillary-sized proliferation
Vascular spaces: Empty to a few erythrocytes
Vascular space: congested erythrocytes to thrombus

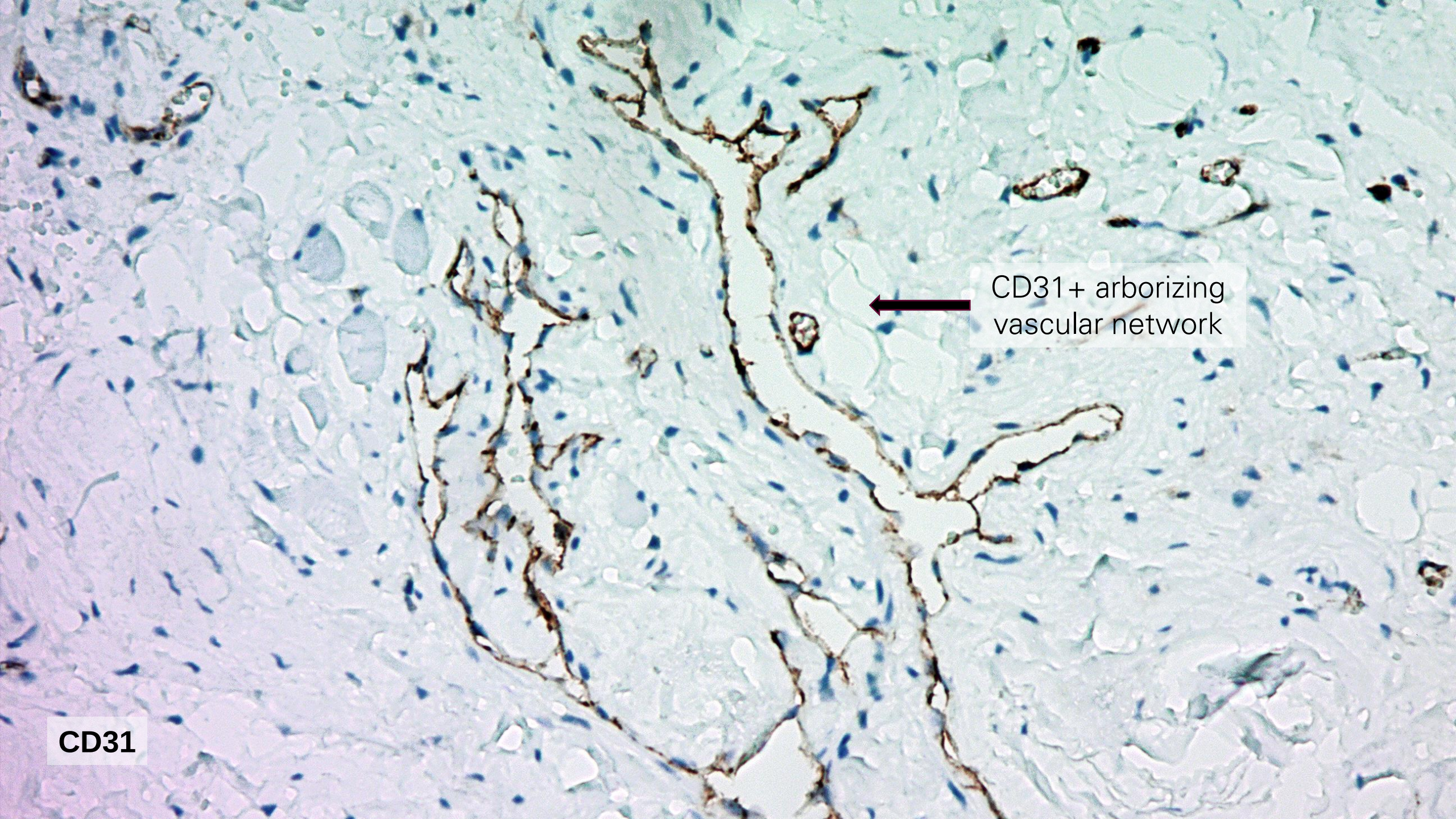

Mucinous glands
Valve-like structure
Pseudomalignant perineural invasion
Large, dilated vascular space with thin walls and valve

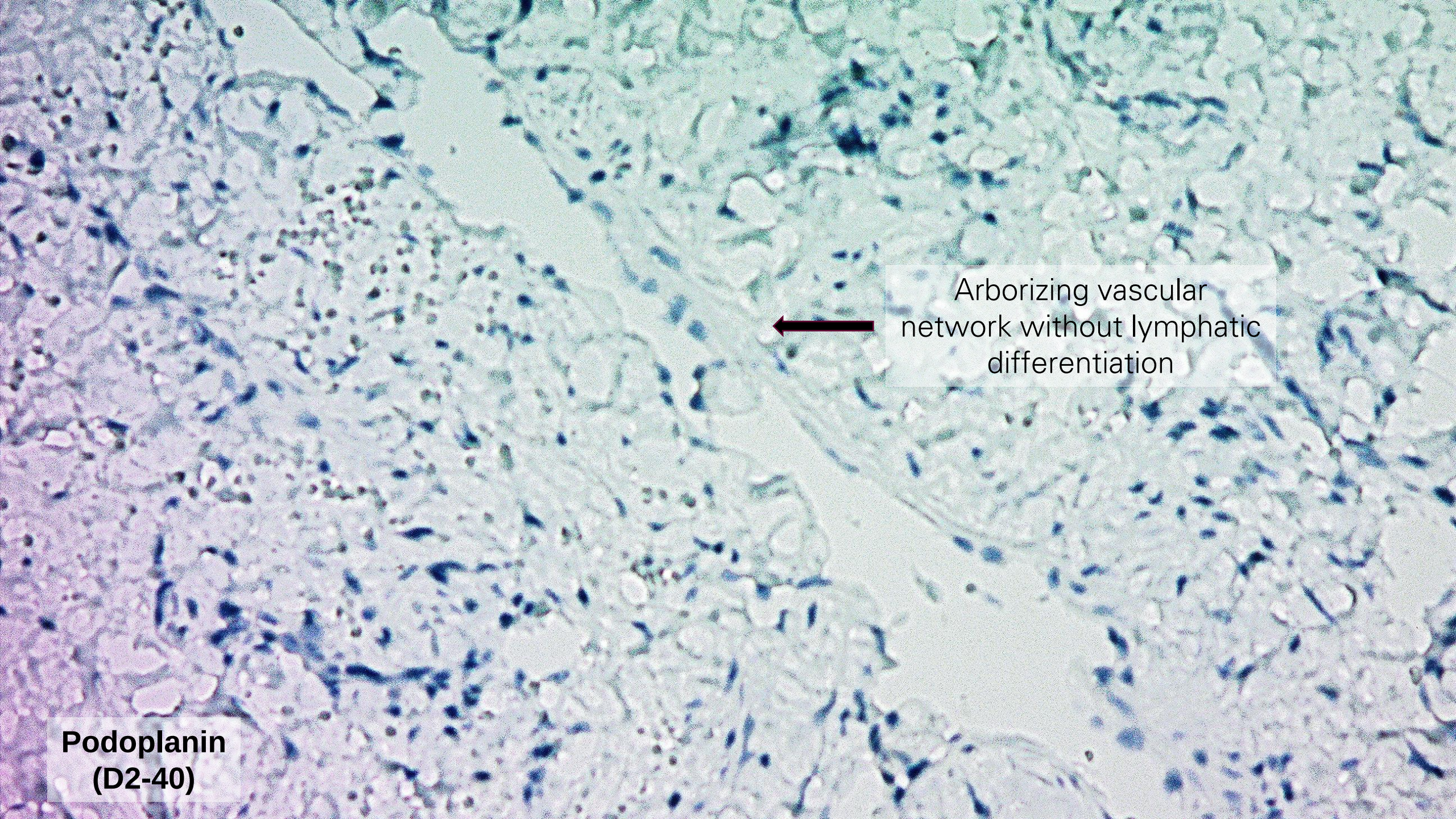


At 5 years of age
11/29/2023


Deep soft tissue involvement: Arborizing network of vascular channels


Arborizing
network of
vascular channels


CD31+ arborizing
vascular network
CD31


Arborizing vascular network without lymphatic differentiation
Podoplanin (D2-40)

- **Clinical Information:** 5-year-old male with vascular lesion of the lip that has been a diagnostic challenge. It was initially considered to benign hemangioma (including on path from first excision), but after a poor response to propranolol the diagnosis was reconsidered. A second excision sample from 2020 was more consistent with a venous malformation, but a lymphatic component couldn't be excluded.
- **DIAGNOSIS:**

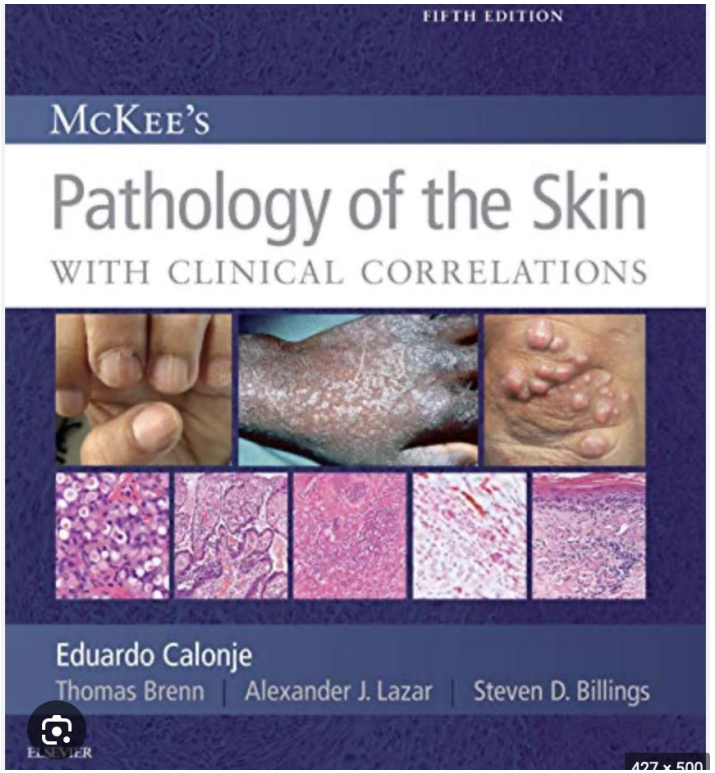
  Skin, Left Upper Lip, Excision :

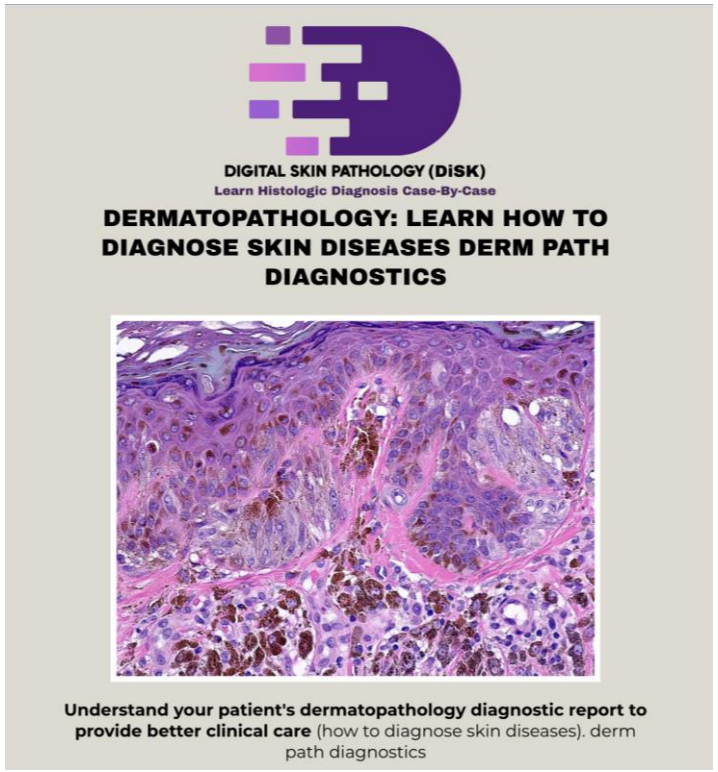
  - Venous malformation without lymphatic component.

  Comment: Per the request of Dr. X, the current excision was reviewed. The prior excisions from 2019 and 2022 were also reviewed in conjunction. All three excisions demonstrate similar features of vast areas of cystically dilated venous structures that are collapsed or contain fibrin thrombi.

  By immunohistochemistry, CD31 highlights numerous collapsed venous structures while Podoplanin (D2-40) is negative for lymphatic differentiation.
- **Minimal Diagnostic Criteria:**
  - Large, empty dilated vascular spaces with thin walls and valve-like structures
  - Immunohistochemistry (IHC) markers (Podoplanin, PROX-1, & LYVE-1) are negative for lymphatic component
- **Differential Diagnosis:**
  - Venous lymphatic malformation (IHC markers positive for lymphatic differentiation)
  - Microcystic lymphatic malformation
  - Sinusoidal malformation (hemangioma)

References

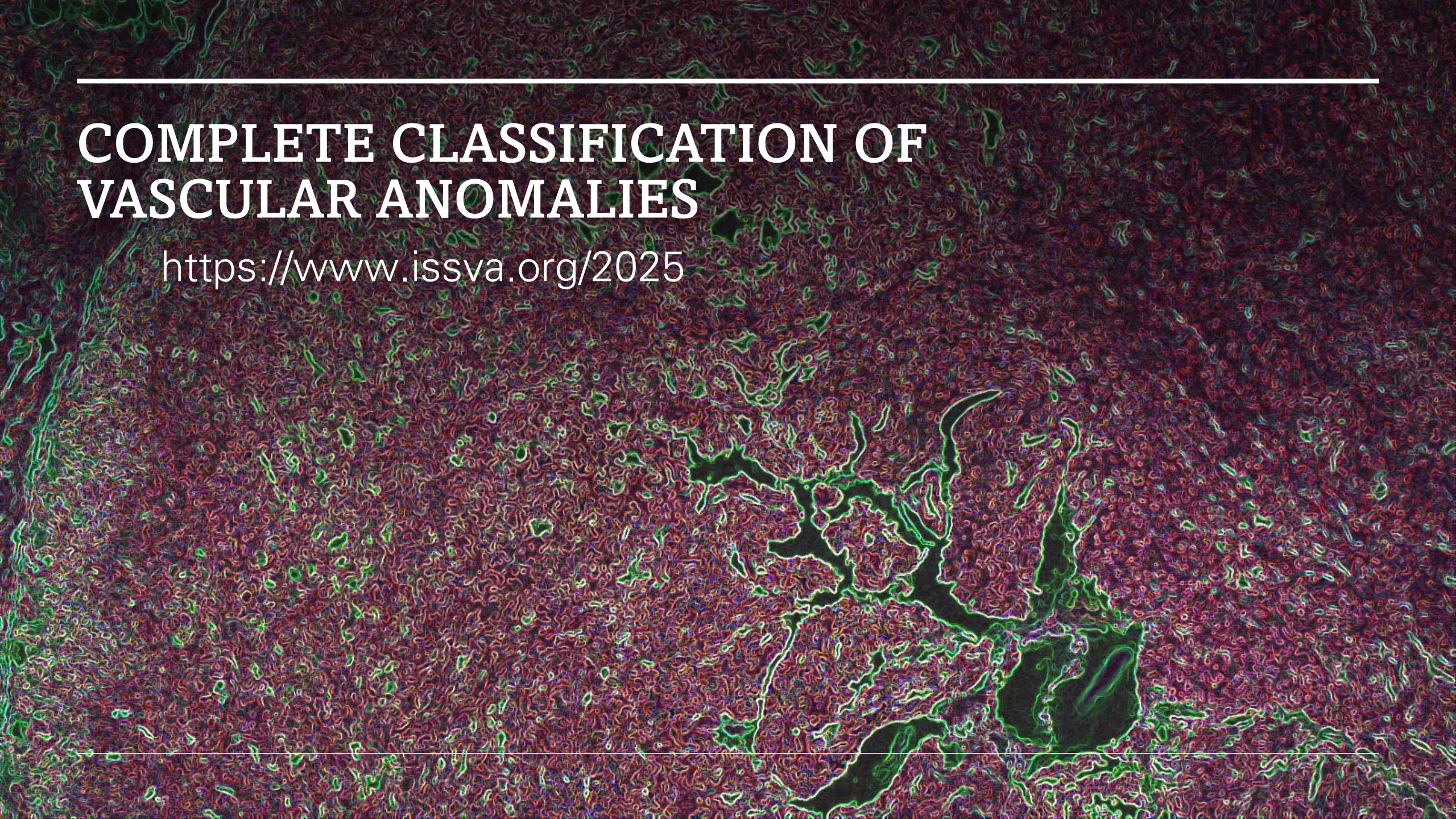


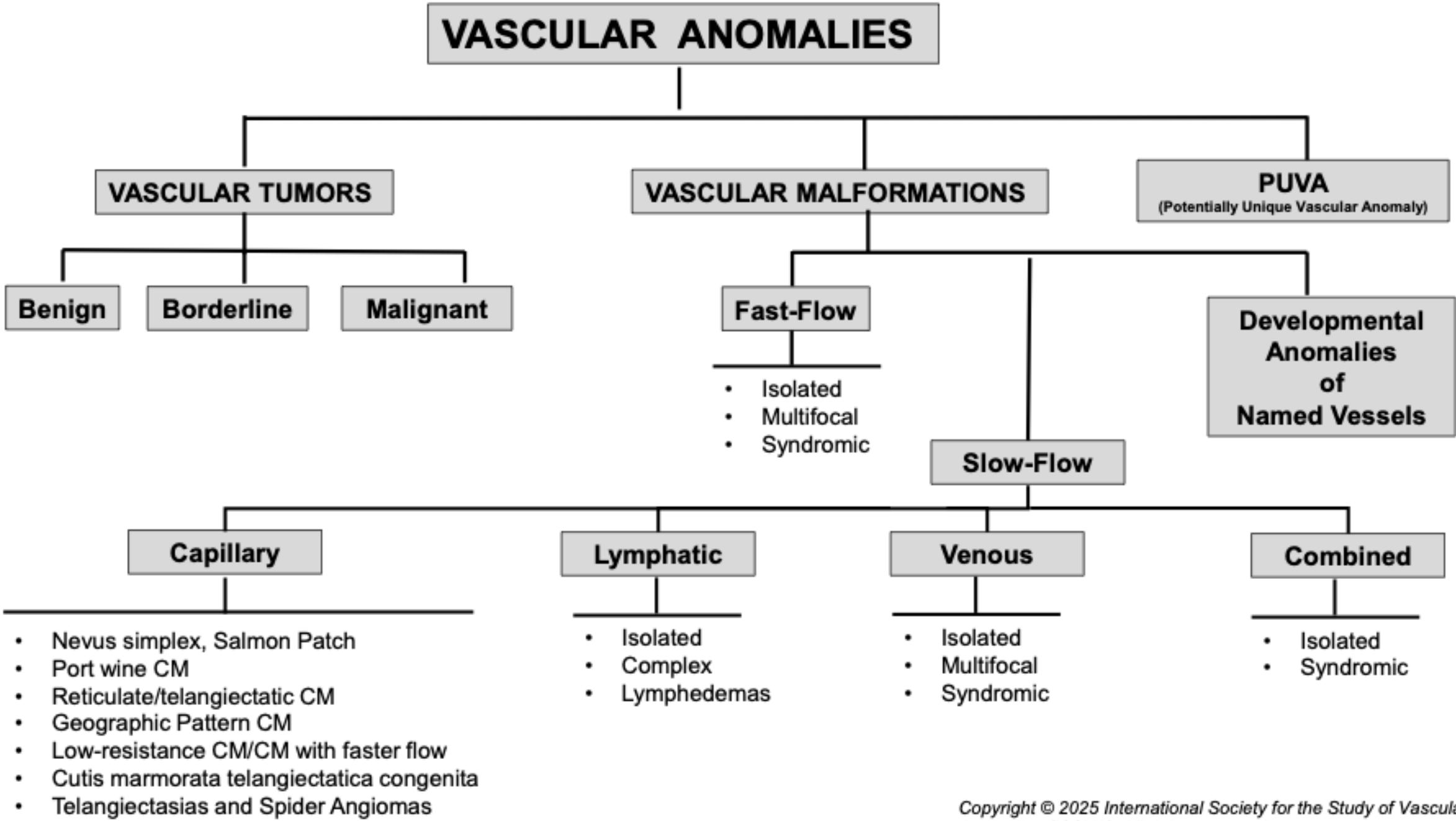


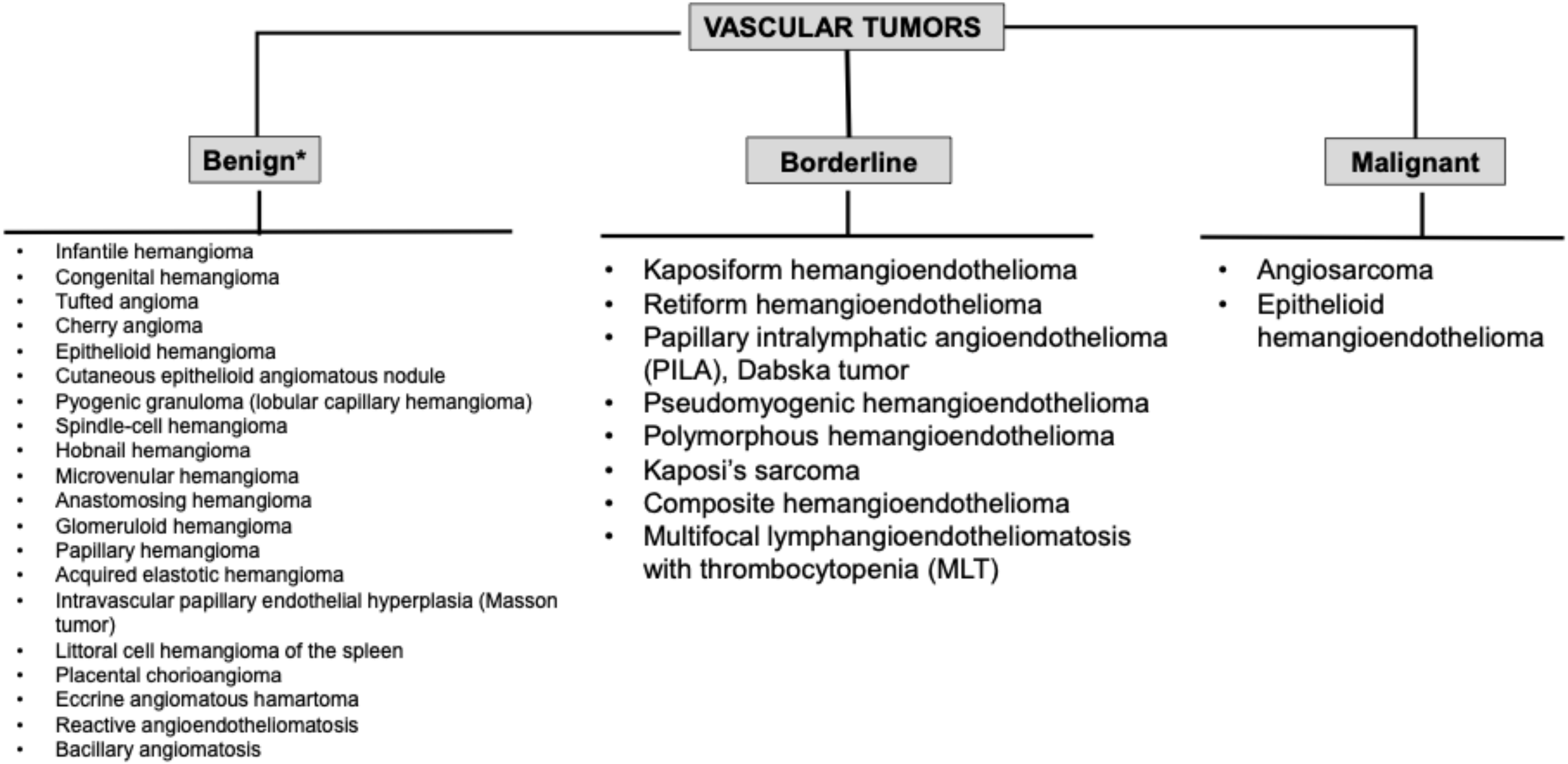
- Dadras Image collection
- Digital Skin Pathology https://digitalskinpathology.com
  - Current lecture
  - Examples of cases
  - Quizzes
- *McKee's Pathology of the Skin* Eduardo Calonje
- ISSVA.org
- WHO Classification of Tumors (Skin Tumors 5th edition)

COMPLETE CLASSIFICATION OF VASCULAR ANOMALIES

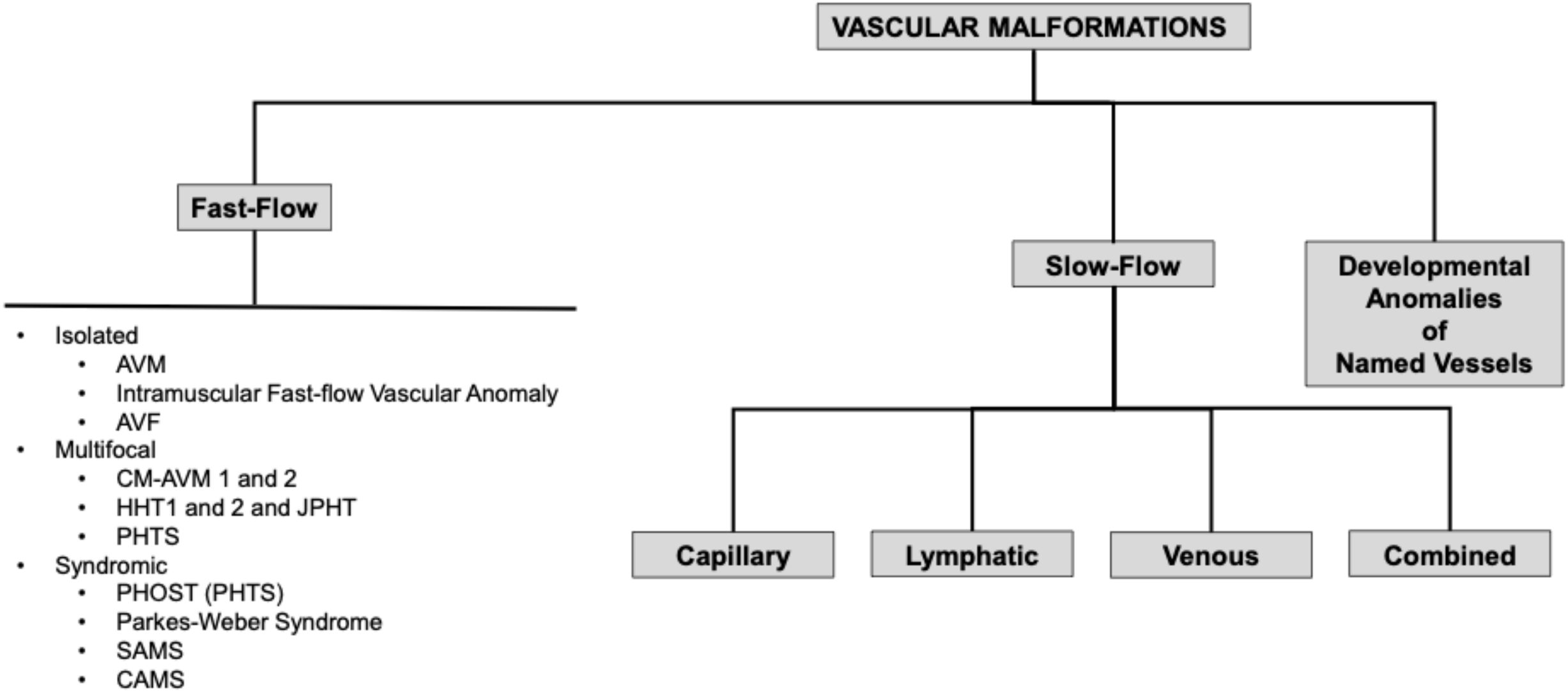
https://www.issva.org/2025







*Reactive proliferative vascular lesions are listed with benign vascular tumors



- Isolated
  - AVM
  - Intramuscular Fast-flow Vascular Anomaly
  - AVF
- Multifocal
  - CM-AVM 1 and 2
  - HHT1 and 2 and JPHT
  - PHTS
- Syndromic
  - PHOST (PHTS)
  - Parkes-Weber Syndrome
  - SAMS
  - CAMS

VASCULAR MALFORMATIONS

SLOW-FLOW

Capillary

- Nevus simplex, Salmon Patch
- Port wine CM (Port wine Birthmark, Nevus flammeus)
  - Isolated (includes Phacomatosis Pigmentovascularis)
  - Syndromic
    - With hypertrophy or extracutaneous disease
    - Sturge-Weber Syndrome
    - DCMO
- Reticulate/telangiectatic CM
  - Isolated
  - Syndromic
    - M-CM
    - MIC-CAP
    - DCMO
- Geographic Pattern CM
  - Isolated
  - Syndromic
    - KTS
    - Associated with CLOVES/Disorders of PROS
- Low-resistance CM/CM with faster flow
  - Isolated
  - Syndromic
    - CM-AVM 1 and 2
    - Parkes-Weber Syndrome
- Cutis marmorata Telangiectatic Congenita
- Telangiectasias and Spider Angiomas
  - Isolated
  - Syndromic
    - CM-AVM 1 and 2
    - HHT 1 and 2 and JPHT (see AVM category)

Lymphatic

- Isolated
  - LM
    - Macrocystic
    - Microcystic
    - Mixed Macro-microcystic
  - Angiokeratoma
- Complex
  - GLA
  - KLA
  - GSD
  - CCLA
    - Isolated
    - Syndromic (RASopathy)
  - GLD
- Lymphedemas
  - Primary
    - Isolated
    - Syndromic
  - Secondary

Venous

- Isolated
  - VM
    - Phlebectatic
    - Spongiform
  - VVM
  - FAVA
- Multifocal
  - VMCM
  - MSVM
  - BRBNS
  - GVM
  - HCCVM/CCM
  - VMOS
- Syndromic
  - PHTS
  - CLOVES
  - Mafucci Syndrome
  - Sinus Pericranii

Combined

- Isolated
  - CLVM
  - LVM
  - CLM
  - CVM
  - HCCVM/VVM
- Syndromic
  - PROS
  - KTS (CLVM with hypertrophy)
  - CLOVES
  - CLAPO
  - Proteus Syndrome

Developmental Anomalies of Named Vessels

- Vena cava
- Aorta
- Vein of Galen
- Others