COURSE 13: HISTOPATHOLOGY OF VASCULAR ANOMALIES

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Introduction: Histopathology of vascular anomalies

Vascular malformations are a truly multidisciplinary disease, affecting numerous systems. However, it was not until the last few decades that the histopathology of these often complex lesions was integrated into all phases of research and clinical practice.

Significant research stemming from the histopathology of these lesions has resulted in great breakthroughs, such as immunochemical stains for GLUT1, which has become a definitive diagnosis for most infantile hemangiomas. In addition, the Vascular Endothelial Growth Factor Receptor 3 (VEGF 3) now enables lymphatics to be distinguished from arteries and veins, thus enhancing the accuracy of diagnosis. This module will focus on the various aspects of understanding and distinguishing the various vascular anomalies types, based on understanding the histopathology of these anomalies.

Objectives

Upon successful completion of this activity, participants should be able to:

- Comprehend the basic pathology of vascular anomalies
- Differentiate infantile hemangiomas from vascular malformations based on histopathology
- Distinguish characteristics of vascular malformation types based on pathology
- Ascertain the correlation of vascular anomalies based on histopathology

Vascular tumors

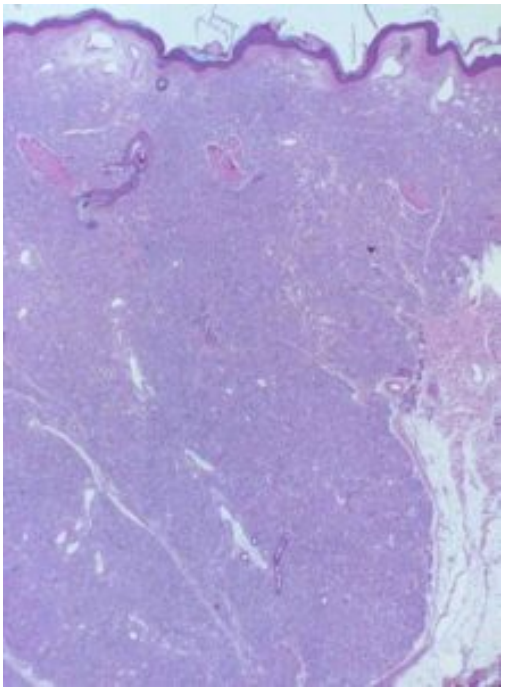
- Vascular tumors may be benign, malignant, congenital, or acquired.
- They may also be divided into high-flow lesions such as the hemangiomas, and low-flow lesions such as the venous malformations.
- Hemangiomas may be divided into infantile hemangiomas, almost always present after birth, and congenital hemangiomas, including Rapidly Involuting Congenital Hemangioma (RICH) and Non-Involuting Congenital Hemangioma (NICH) that are always present at birth.

Infantile hemangiomas

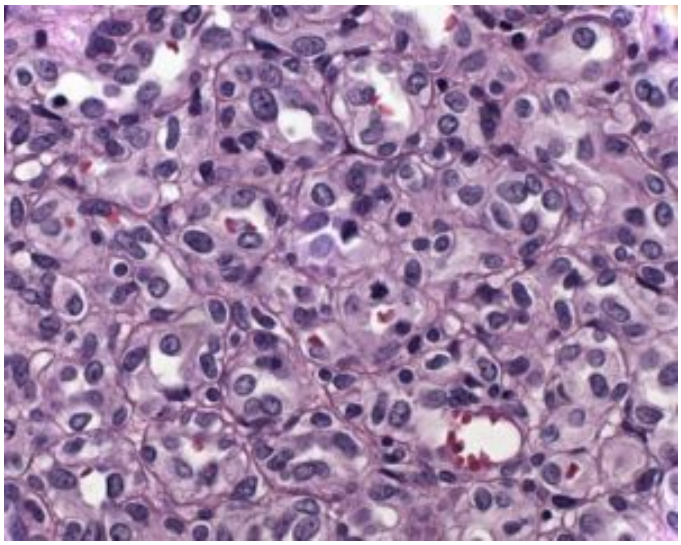
- Proliferative phase associated with a discrete, unencapsulated, densely cellular tumor, often with numerous spindle cells that extend from the superficial dermis to the subcutaneous tissue.
- Fine stroma with mast cells invests capillary structures and increases as the lesion matures.
- Numerous mitoses are easily visible in prominent endothelial cells, as well as apoptotic figures.
- As the proliferative phase ends, the mitoses disappear but prominent apoptosis remains. Infiltration of nerves, skeletal, muscle, and glandular structures is commonly seen.
- Late involution exhibits zones of prominent fibrous tissue with often thick-walled vessels in a background of fat.

Infantile hemangioma

Proliferative phase



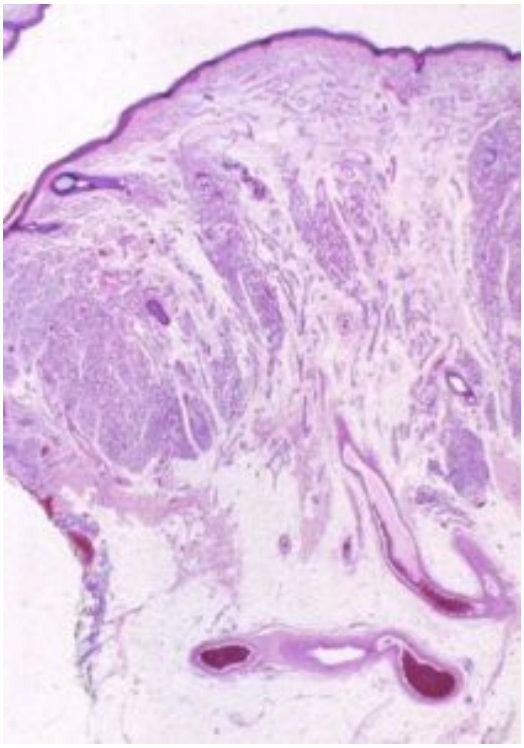
Dermis is replaced by increased numbers of endothelial cells and pericytes. Note increased number of blood vessels and their ectasia.



Endothelial cell mitosis

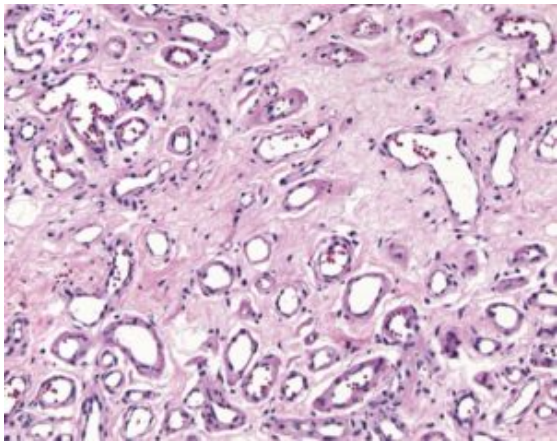
Infantile hemangioma

Involution



Replacement of the IH by subcutaneous fat. Note the residual, well-developed feeding and draining vessels at the base of the capillary proliferation.

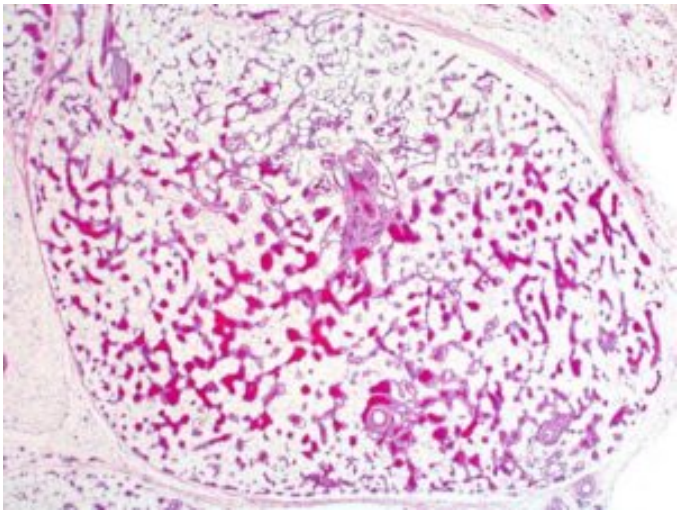
Mid-involution



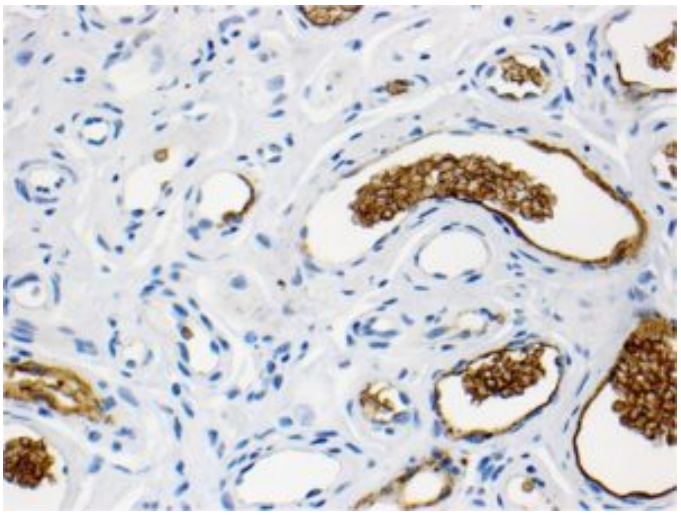
Many lesional capillaries have disappeared, leaving a loosely fibrous stroma. Inflammation is minimal, and there is no evidence of thrombosis.

Infantile hemangioma

Mid-involution (2)



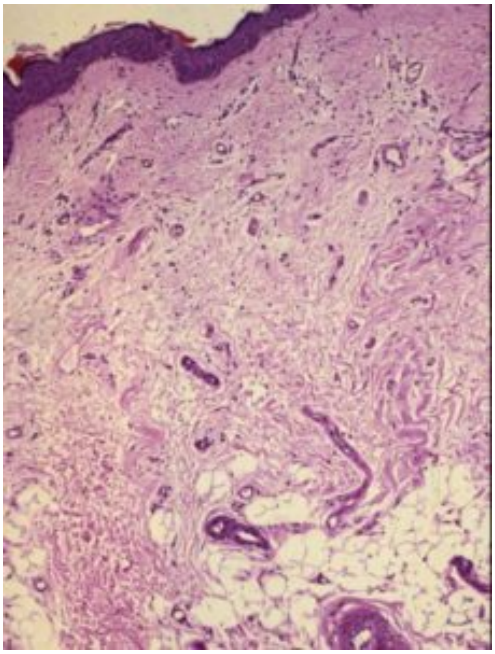
Almost complete replacement of the IH by subcutaneous fat. Residual vessels are still appreciated.



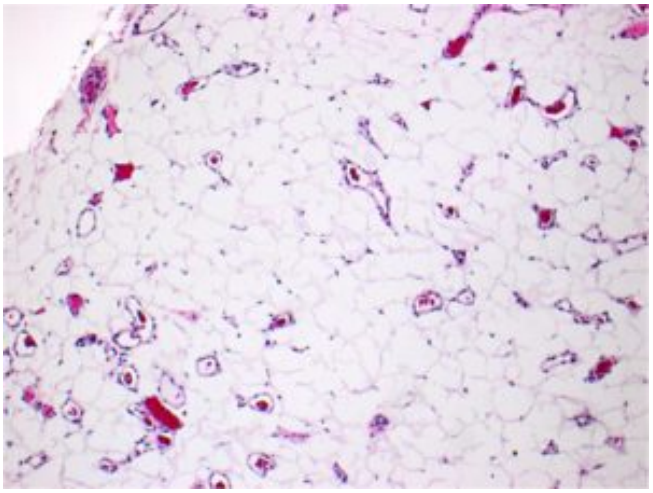
GLUT-1 stains few residual infantile hemangioma capillaries. Glut-1 is a non-energy consuming enzyme that transfers glucose and Vitamin C to the brain at the blood-brain-barrier, and is also present in other metabolically active tissues. The Glut-1 immunohistochemical marker is positive uniquely in infantile hemangioma vasculature, in all phases of the infantile hemangioma life cycle, and negative in normal vasculature.

Infantile hemangioma

End-stage



The dermis is replaced by a loose fibrous stroma containing a few persistent lesional capillaries and supportive vessels. The overlying epidermis in this case is atrophic.



Replacement of the IH by subcutaneous fat. Residual vessels are rare.

Infantile hemangioma

Histological feature

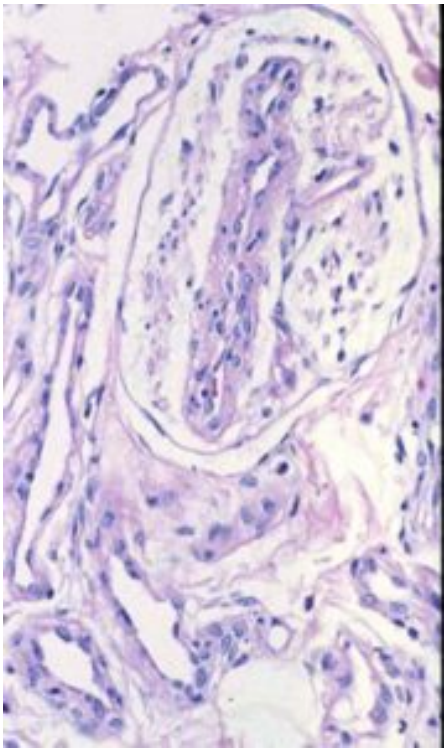


Image courtesy of Dr. Paula North

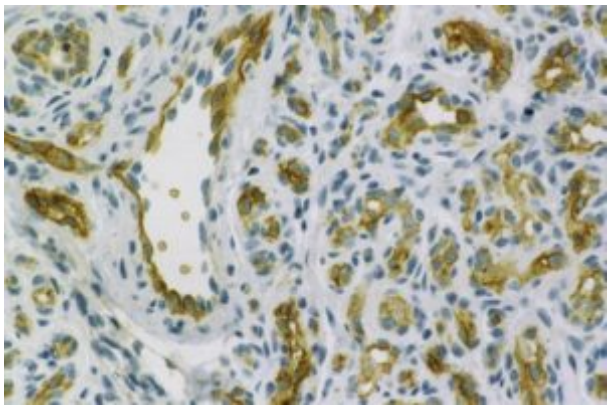
- One prominent histological feature of infantile hemangiomas, the presence of endoneurial pseudoinvasion, led us to investigate blood-nerve barrier competency in these lesions.
- This observation led us to study the blood- brain barrier where there was an enzyme that was a non-energy requiring transporter of glucose, so-called GLUT1.

Infantile hemangioma

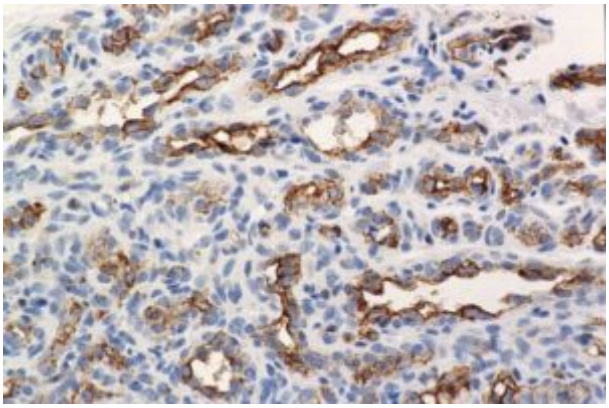
Immunophenotype

Glucose transporter enzyme, type 1, (GLUT-1) has been shown to be a reliable marker for the endothelial cells of the infantile hemangioma.
Lewis-y, Merosin, FcγRII are also positive.
These four markers are identical to placenta, suggesting some relationship between infantile hemangioma and placenta.

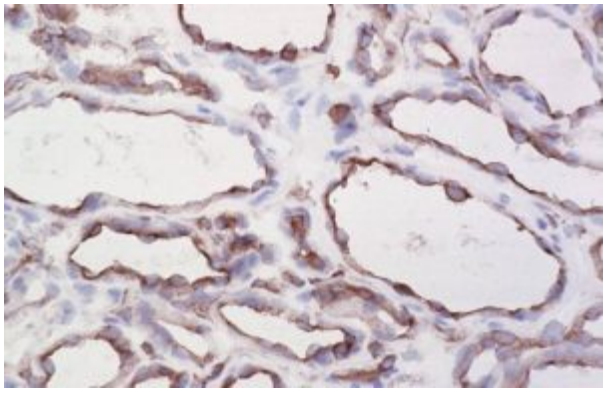
The unique vascular phenotype of infantile hemangioma



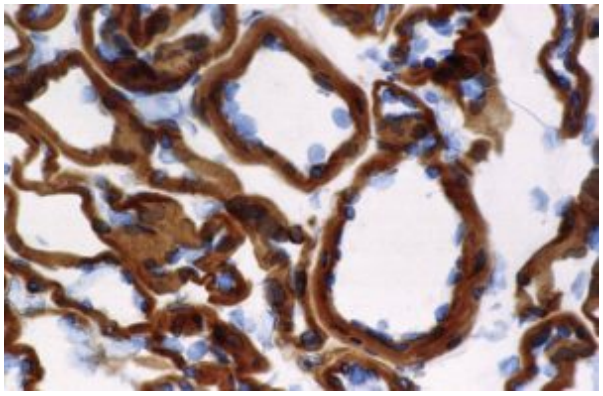
GLUT-1



Le-Y



FcgammaRII



Merosin

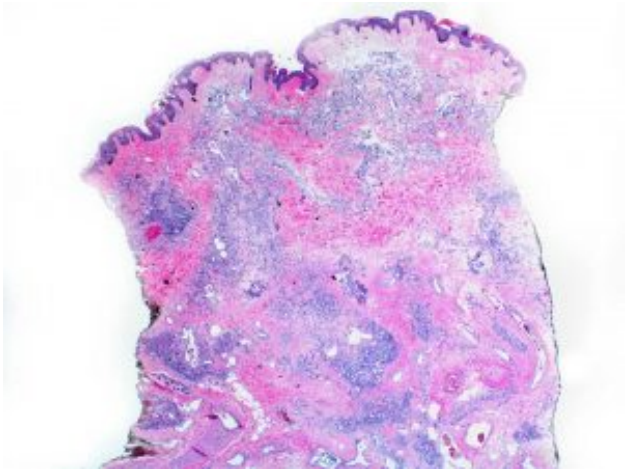
Congenital Hemangioma Histology

- Congenital Hemangiomas are divided into two sub-groups: Rapidly Involuting Congenital Hemangioma (RICH) and Non-Involuting Congenital
- Hemangioma (NICH), both always present at birth.
- Histology is the same for RICH and NICH.
- Low power exhibits large nodules of capillary proliferation associated with large fibrous tracts and ectatic vessels.
- High power of the proliferative areas shows a proliferation of capillaries with prominent endothelial cells, microthrombi, and hemosiderin deposition.
- In some areas, there are large ectatic venous structures intermingled with the capillary malformation or surrounding it.
- Large venous and lymphatic vessels may be scattered in the dermis and subcutanoues fat.
- Foci of extramedullary hematopoesis may be observed.
- The fibrous stroma exhibits hemosiderin deposition and may be hyalinized.
- GLUT-1 is negative, CD31 and CD34 are positive.

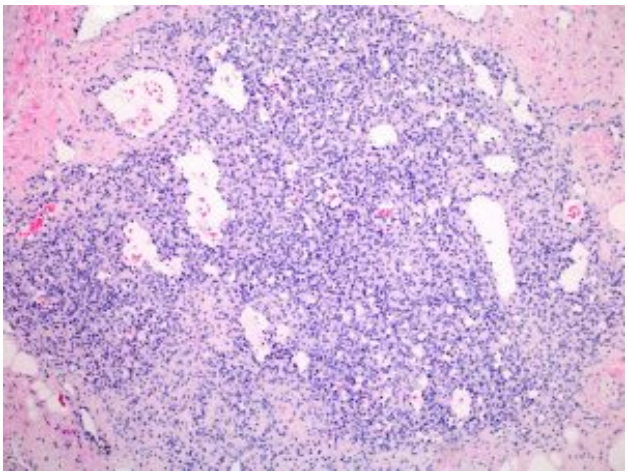
Congenital Hemangioma Histology

- Histology is the same for RICH and NICH
- Low power exhibits large nodules of capillary proliferation associated with large fibrous tracts and ectatic vessels
- High power of the proliferative areas shows a proliferation of capillaries with prominent endothelial cells, microthrombi, and hemosiderin deposition

Congenital hemangioma histology – NICH

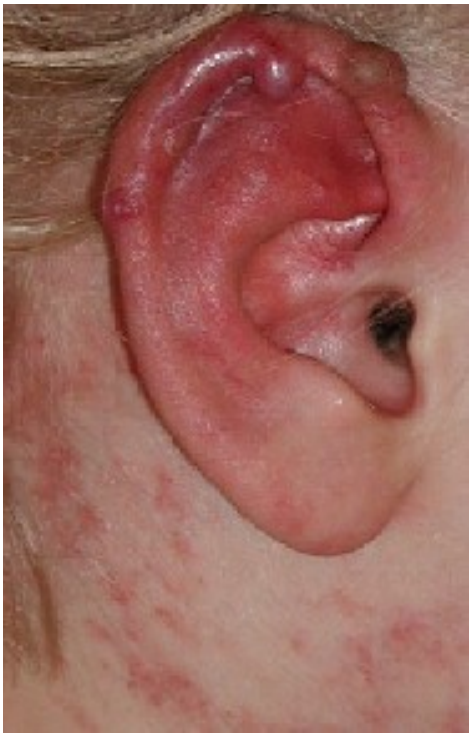


NICH; Multiple nodules of vascular proliferation that follow along the path of the venous structures. There is dense fibrosis.



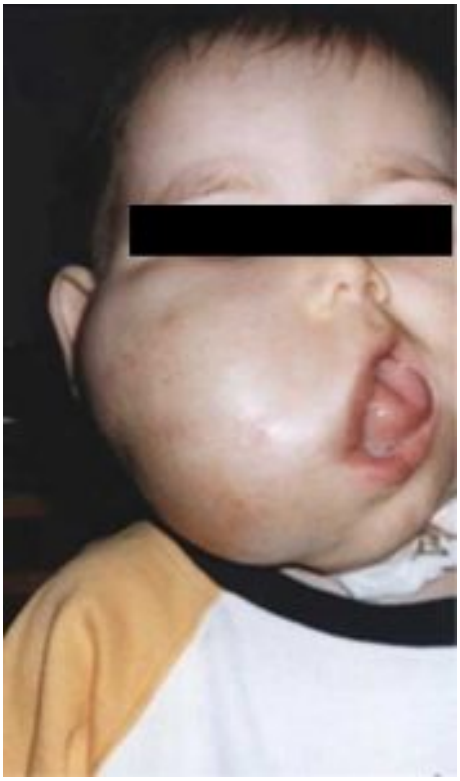
NICH; Nodules of capillary proliferation with small venules.

Vascular malformations



high-flow:

- Arteriovenous malformations
- Arteriovenous fistulas



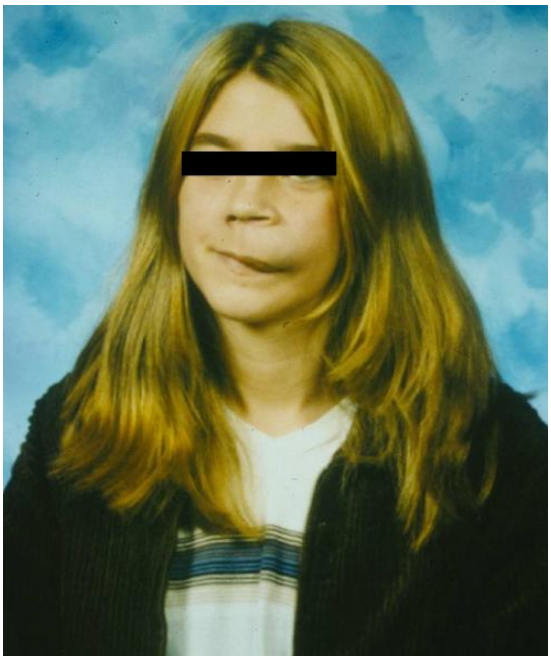
low-flow:

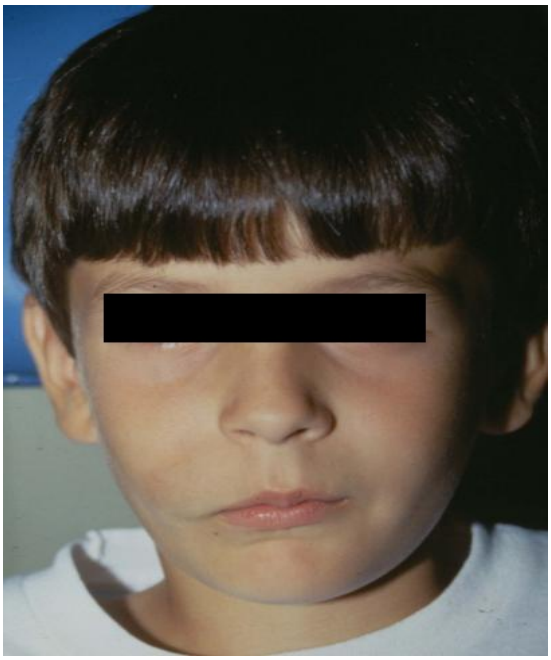
- Lymphatic
- Capillary
- Venous
- Mixed

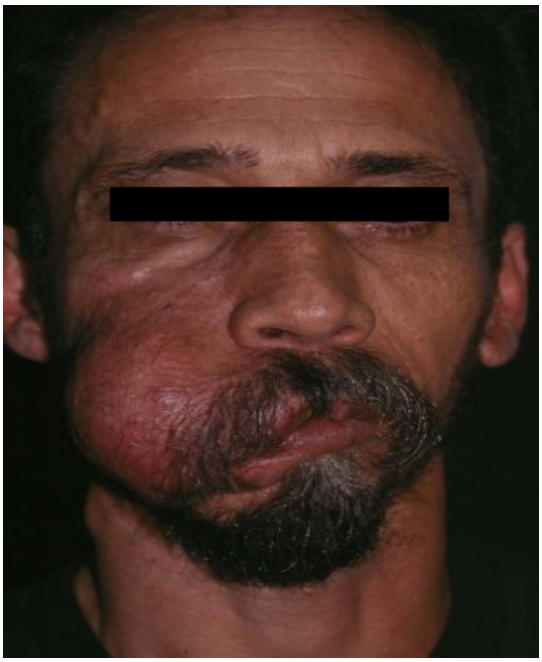
Arteriovenous Malformations

Clinical Features:

- AVMs may occur at any time in life, but commonly occur in childhood.
- They present as small pulsatile areas, often described as throbbing by the patients.
- They favor the head and neck areas.
- Their course is usually one of gradual growth.
- In some advanced cases, there may be such shunting of blood that there is resultant heart failure.
- They may have an overlying port wine-like stain.





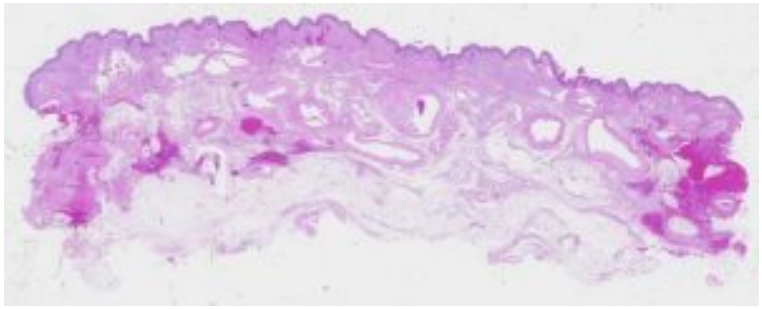


Arteriovenous Malformations

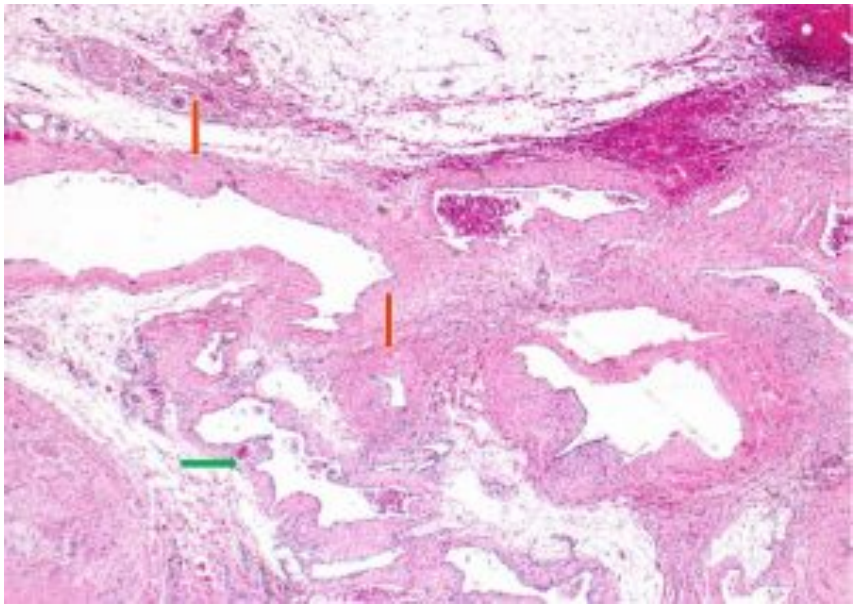
HISTOLOGY

- Low power reveals a central proliferation of variably sized, often tortuous vessels in a fibrous matrix surrounded by areas of prominent capillary proliferation.
- High power reveals arteries of varying shapes with variable wall thickness.
- Large veins with thickened walls containing fibrosis and scattered smooth muscle bundles intimately associated with arteries; chronic lesions may show thin-walled veins.
- Capillary proliferative areas punctuate the fibrous tissue .
- Nidus is area of shunting and is composed of densely packed small capillary-like vessels.
- Hemosiderin deposition may be observed.

AVM Histology



Arteriovenous malformation: Reticular dermis exhibits large ectatic veins and arteries as deep as the superficial subcutaneous fat. Arteries are coated by thickened smooth muscle.



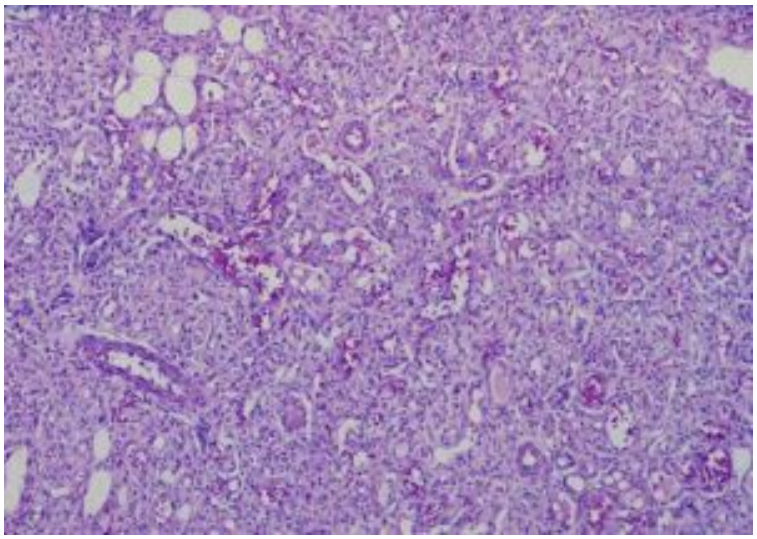
AVM: Red Arrows: dilated arteries; Green arrow: ectatic vein

AVM Histology

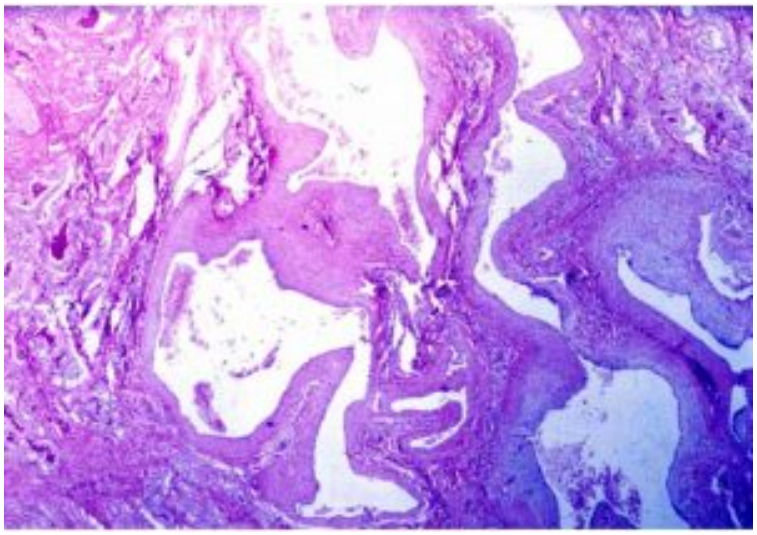
- Areas of capillary proliferation scattered throughout the lesion amidst abnormal vessels
- Occasionally these areas form a palisade around the tangled vessels.
- Stromal changes variable with fibrosis, with admixed fibrofatty tissue and at times foci of myxoid change

Nidus

Successful surgical therapy requires identification and removal of nidus. Otherwise, recurrences may occur.



AVM Nidus: Dense capillary proliferation.

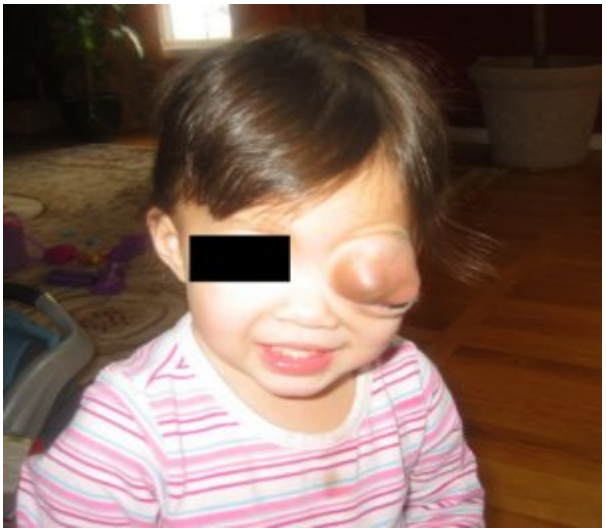


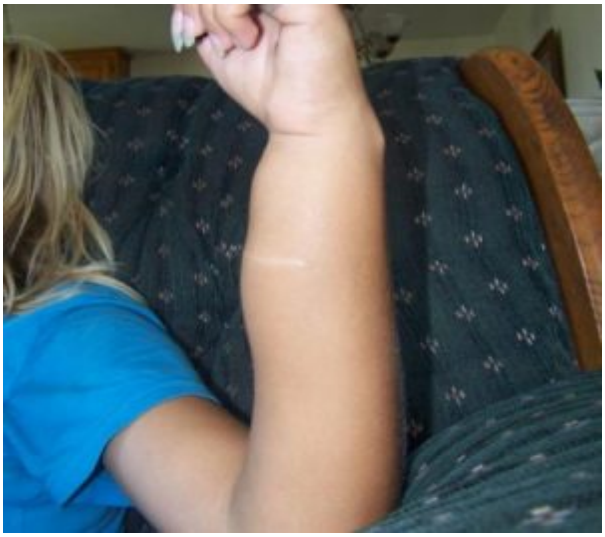
AVM Nidus: Dilated abnormal vessels surround nidus.

Images courtesy of Dr. Paula North.

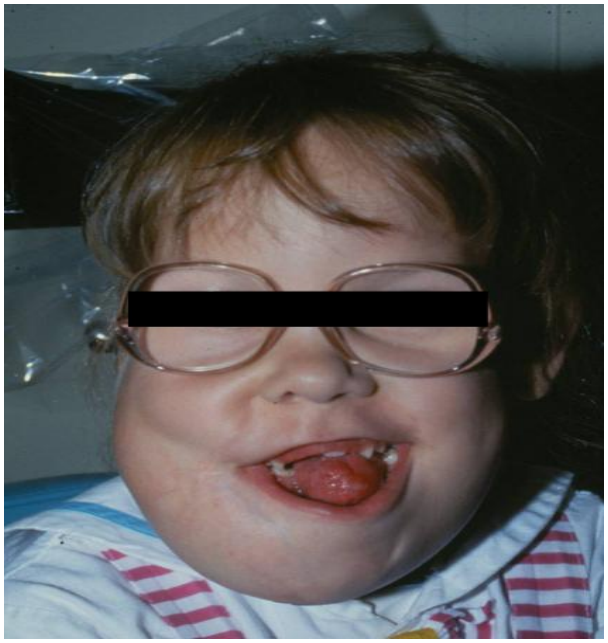
Low flow – Lymphatic malformation

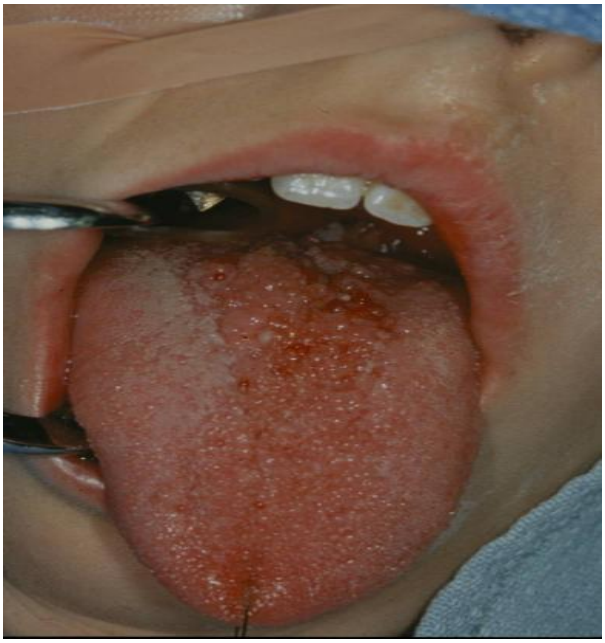
- Lymphatic malformations (previously known as cystic hygroma or lymphangioma are classified as microcystic, macrocystic, or mixed).
- Most lymphatic malformations (approximately 75%) occur in the cervicofacial region.
- The overlying skin can be healthy, or it may have tiny characteristic vesicles.





Lymphatic Malformations



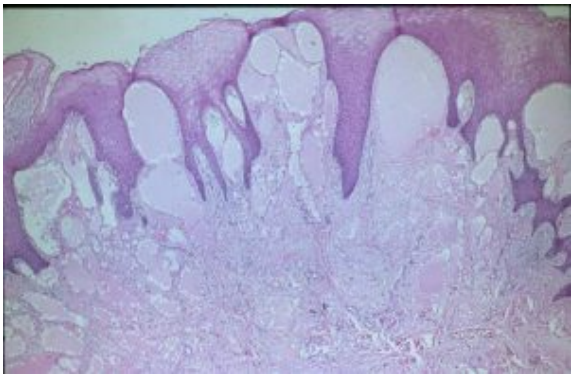


Lymphatic Malformations

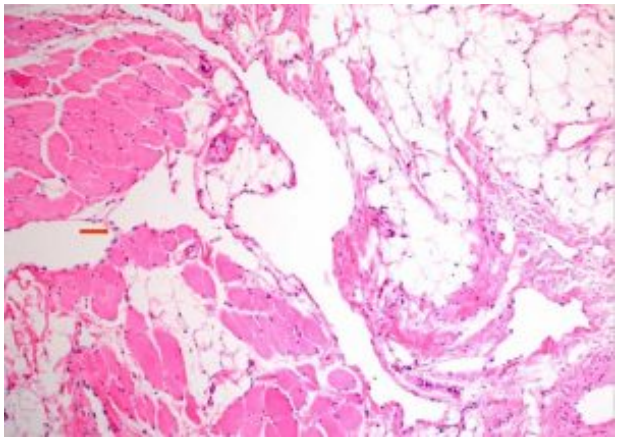
HISTOLOGY

- Low power reveals a highly infiltrative lesion composed of variably sized spaces.
- Wall of small channels very thin; often only one layer of lymphothelium.
- Larger spaces have variable walls composed of loose stroma sometimes with admixed smooth muscle cells.
- Characteristic thin-walled valves found in spaces.
- Lumens may exhibit proteinaceous material, red blood cells and scattered lymphocytes.
- Aggregates of lymphocytes abut many vessels.

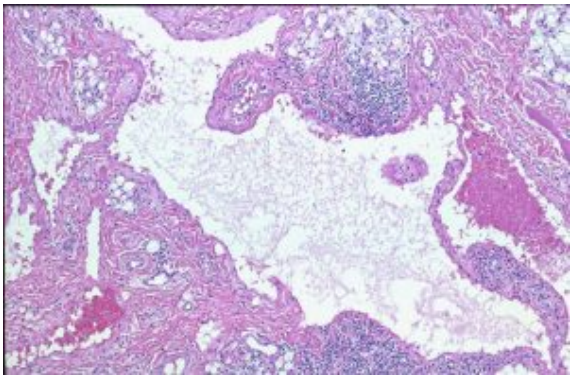
Lymphatic Malformation



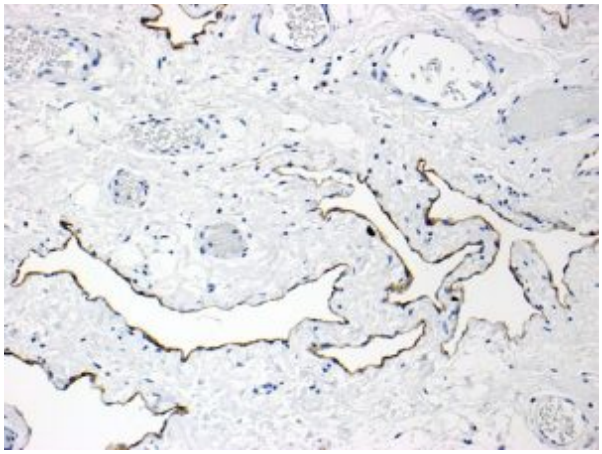
Papillae are expanded by ectatic lymphatics abutting epidermis associated with blebs. Component lymphatic endothelial cells are flattened and show little, if any mitotic activity.



Lymphatic Malformation. Dilated lymphatic vessels. Red arrow: Lymphatic valve



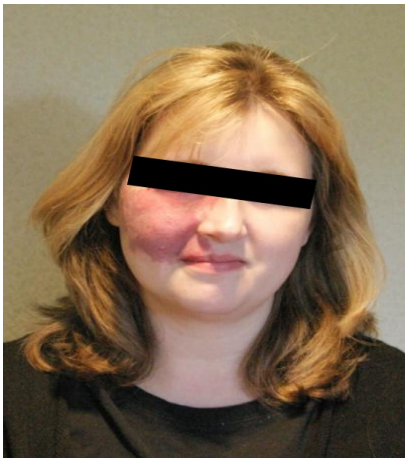
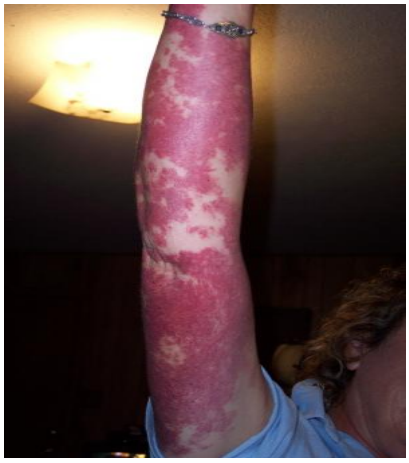
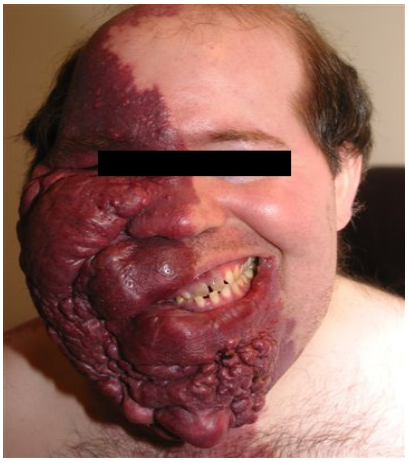
Note the mural lymphoid tissue, often an integral component of lymphatic malformations.



D2-40 highlights ectatic lymphatics

Low Flow – Capillary Malformation Port Wine Stains

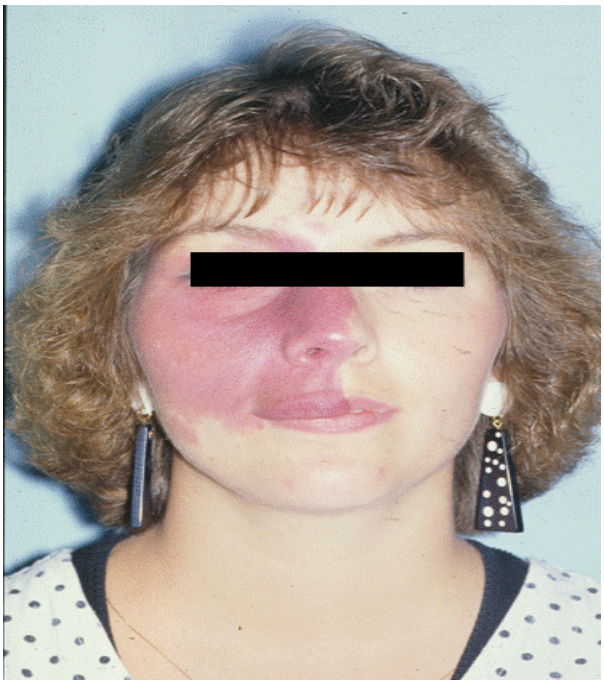
- Also known as port wine stains and nevus flammeus
- Sometimes referred to as venular malformations
- Developmental abnormality of vessels, usually present at birth as a flat red/purple birthmark
- Incidence of cases is 3.05 per 1000
- Never regress
- Some can thicken, become cobbled, and cause tissue overgrowth
- Genetic mutations were detected in one case of port wine stain in the following genes: Guanine Nucleotide-binding protein, Q polypeptide, Alpha subunit (*GNAQ*), *SMARCA4*, *EPHA3*, *MYB*, *PDGFR-β*, and *PIK3CA*.

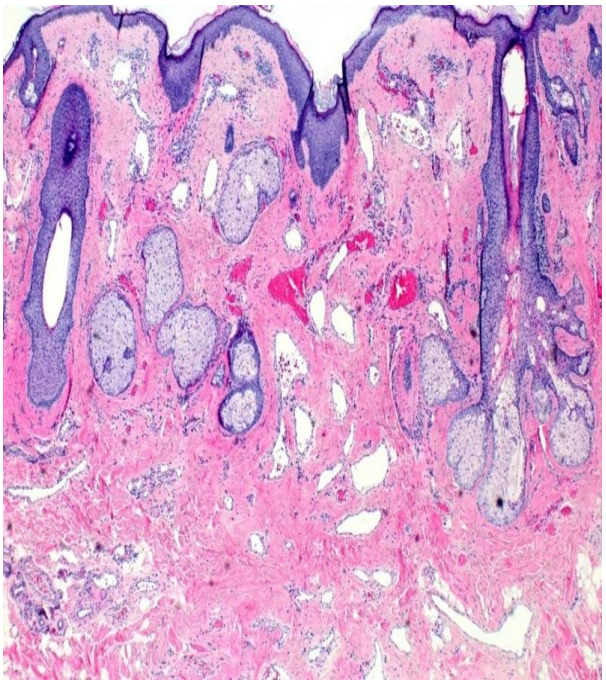
Port Wine Stains

Histologic Features

- Nodular areas may be due to large dilated vessels and are compressible.
- Most nodules exhibit striking, extensive fibrosis, with prominent thickening of scattered vessels scattered amidst numerous dilated vessels
- Some lesions exhibit appendageal hamartomas, even neural hamartomas
- Marked increase in tissue mucins also may be seen
- Early in infancy lesions show increase in superifical vessels that have collapsed lumens and run parallel to each other.
- Thin walled vessels progressively dilate, extending down even into fat by adolescence and adulthood
- Vessel walls appear thickened focally
- Thickening associated with fibrosis, myxoid change in stroma variable scattered inflammation



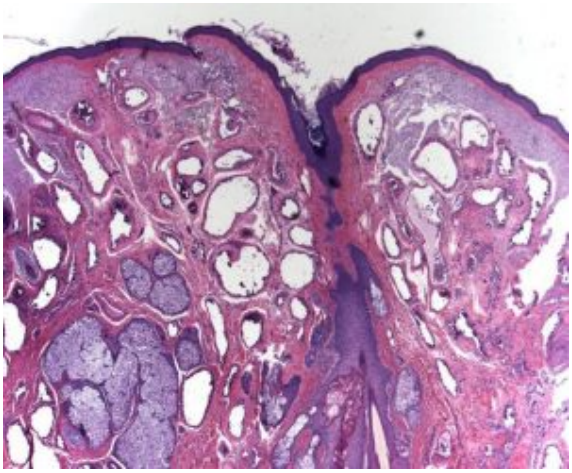
Port Wine Stain

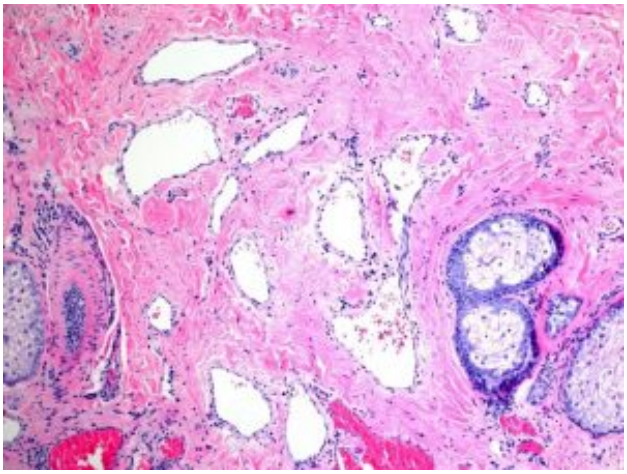


Dermal Venulocapillary Malformation

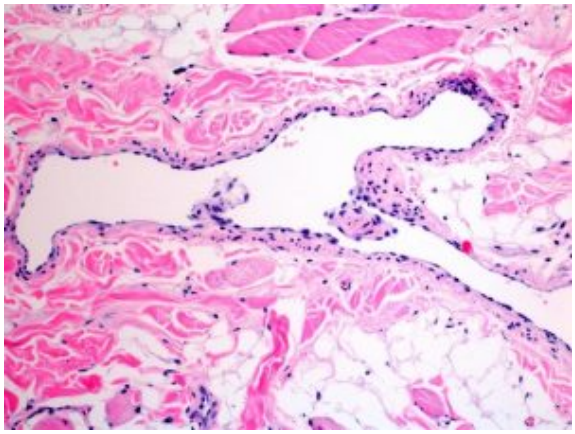
Port Wine Stains

Histology



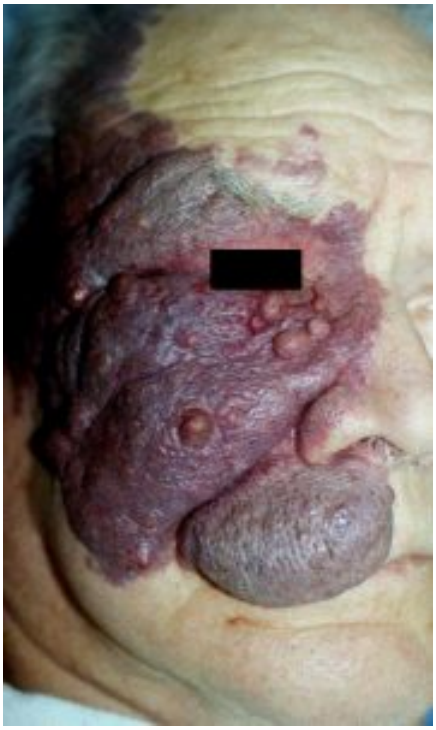


PWS: Dilated venules with abnormal shapes.

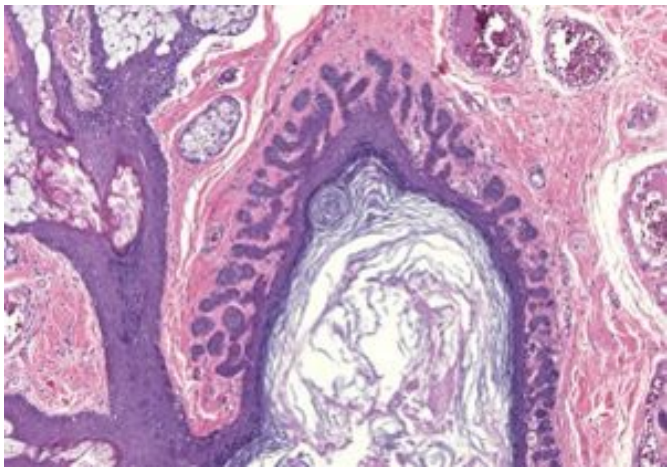


PWS: Dilated venules with abnormal shapes. Often, there is duplication of the basement membrane zone with increased layers of endothelial cells and pericytes.

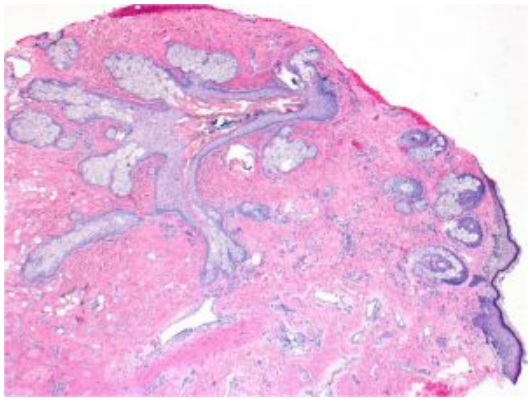
Mature Port Wine Stain: Cobblestoning and Nodularity



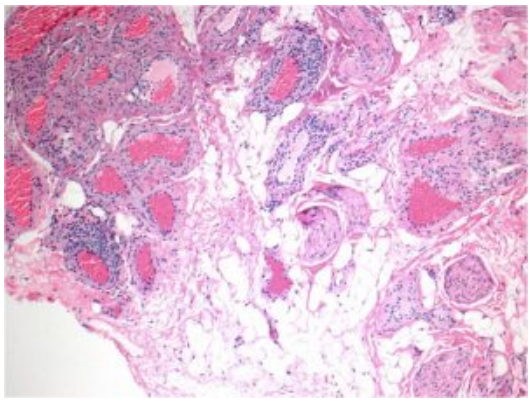
Advanced port wine stain with marked thickening, numerous cobblestone-like areas, as well as bulbous deformity of the lip. These are features typical for an advanced thickened port wine stain.



Cobbled areas frequently exhibit appendageal abnormalities with hamartomas and peculiar structures of the hair follicle wall.



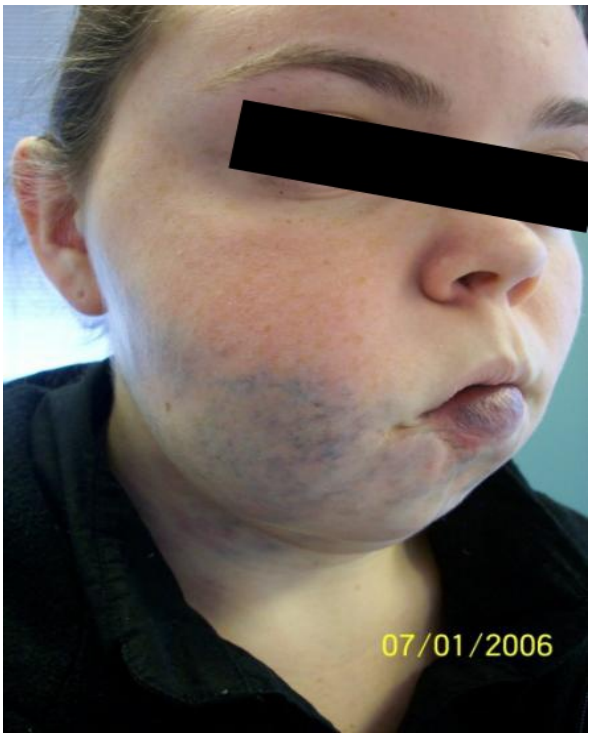
In another cobbled area, there is a sebaceous trichofolliculoma-like appearance to the abnormal structure. Note the dense fibrosis.

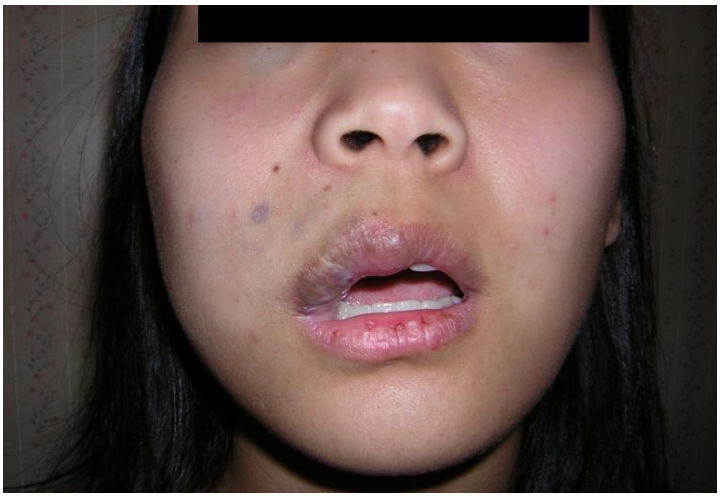


Deep in cobblestone area, there are abnormal blood vessels with irregularly thickened walls. Note the highly irregular vascular structures.

Low-flow – venous malformations

- Venous Malformations are usually a soft and easily compressible soft-tissue mass that is often associated with bluish skin discoloration.
- Increasing engorgement with dependency is typical.
- These birthmarks can be small and localized or extensive and involve the entire extremity or body part.



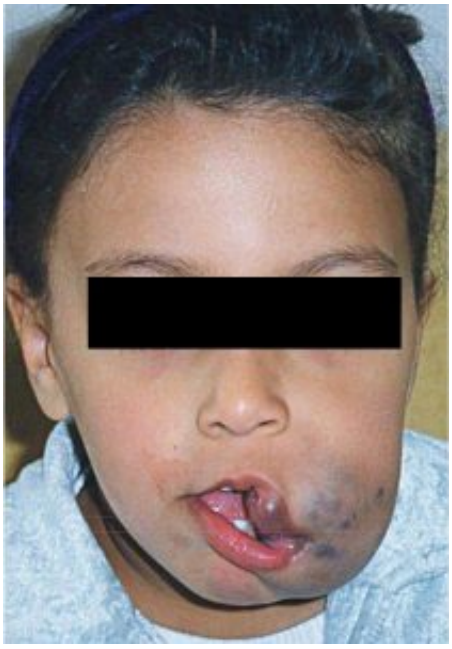


Venous malformation

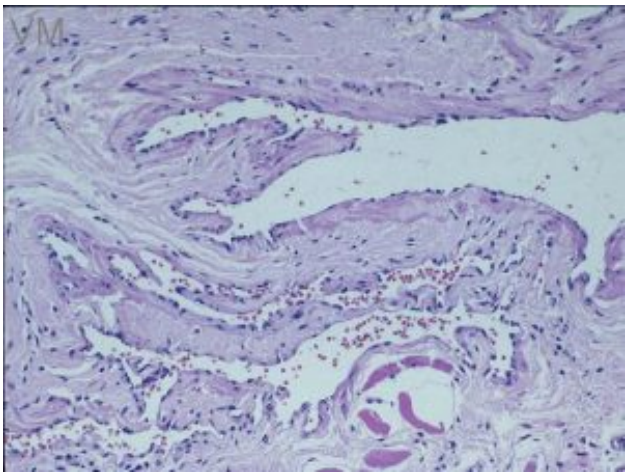
Histologic features

- Aggregate of vessels with irregular sizes and shapes and irregular lumens
- Vessel walls variably thickened with variable smooth muscle component, but most walls are thin, resembling venules
- Fibrosis of walls may be noted, often part of organized thrombus
- Enothelial cells flat and line lumina that may be empty or filled with blood and debris
- Vessels have an arborized often papillated appearance
- Thrombi commonly seen – a characteristic feature
- Organizing thrombi may show papillary endothelial hyperplasia (Masson's effect)

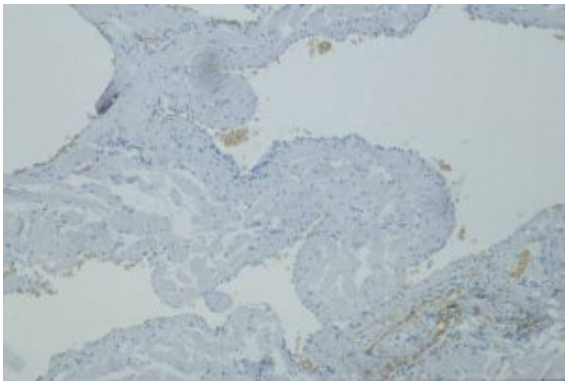
Venous malformation



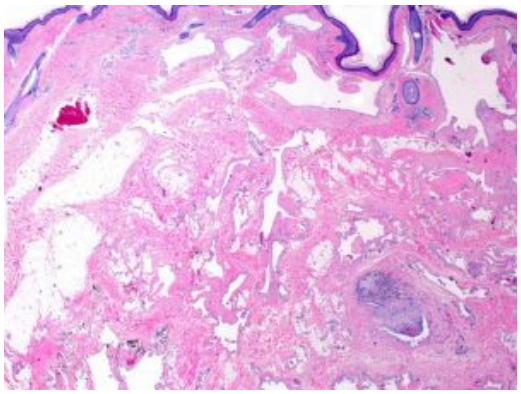
Bluish discolored lesion with enlargement of lips and cheek extending into the mucosa



Large irregularly shaped veins with irregular walls due to abnormal smooth muscle proliferation.



Glut-1 stain is negative in venous malformations. Note irregularly shaped vessels.

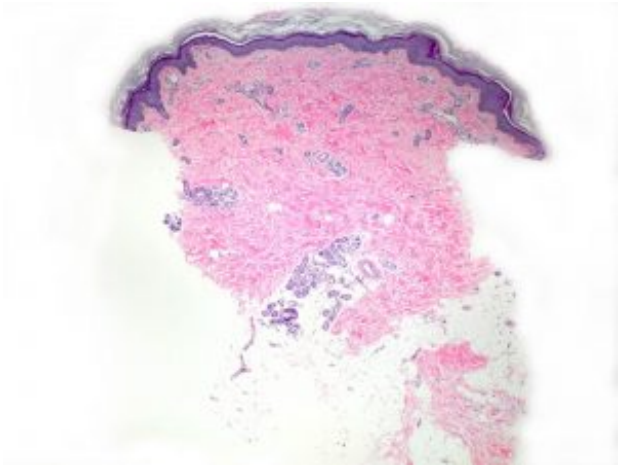


Dilation of vessels extending up to the papillary dermis may give a port wine stain-like appearance to the surface of these lesions.

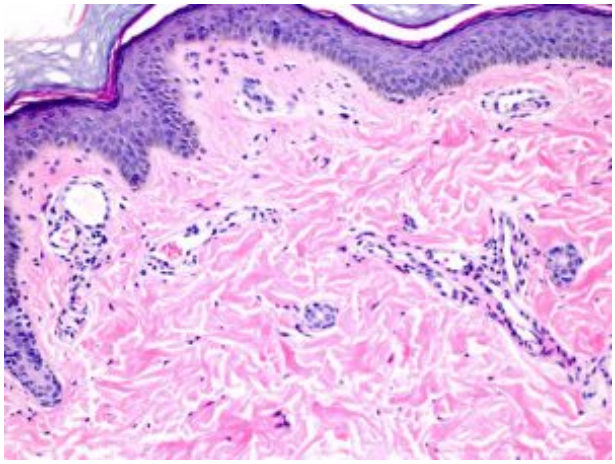
Telangiectases

HISTOLOGY OF ALL TELANGIECTASES:

- Dilated capillary venules in the papillary dermis and rarely the very superficial reticular dermis

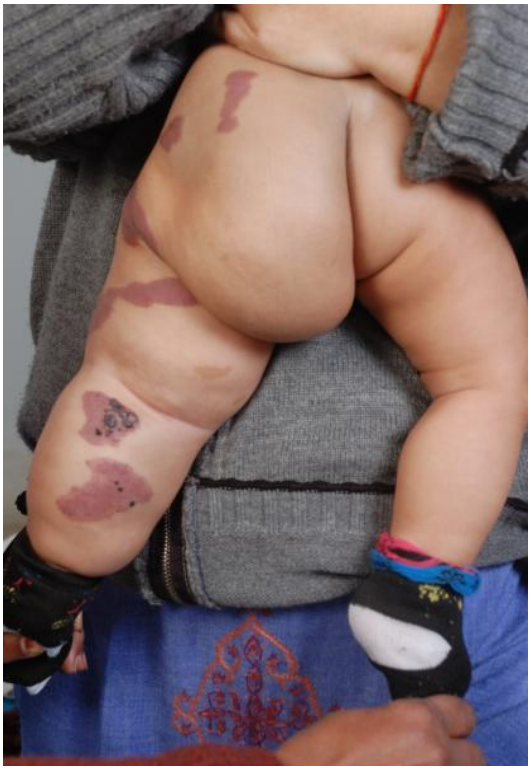


Telangiectasia: Small vessels scattered throughout the upper dermis.

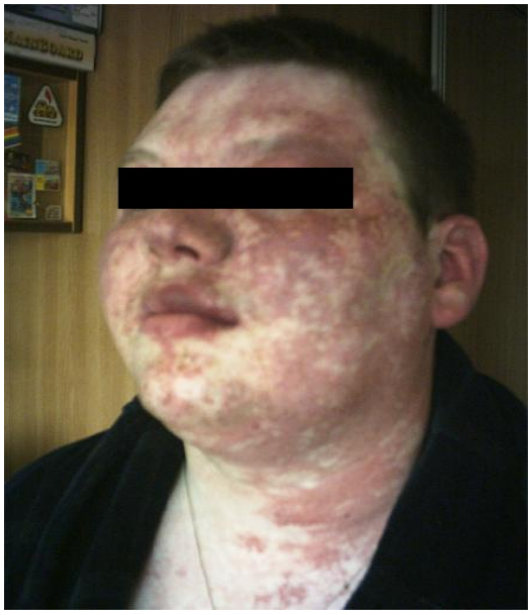


Telangiectasia: Focal dilatation of small vessels.

Malformation syndromes



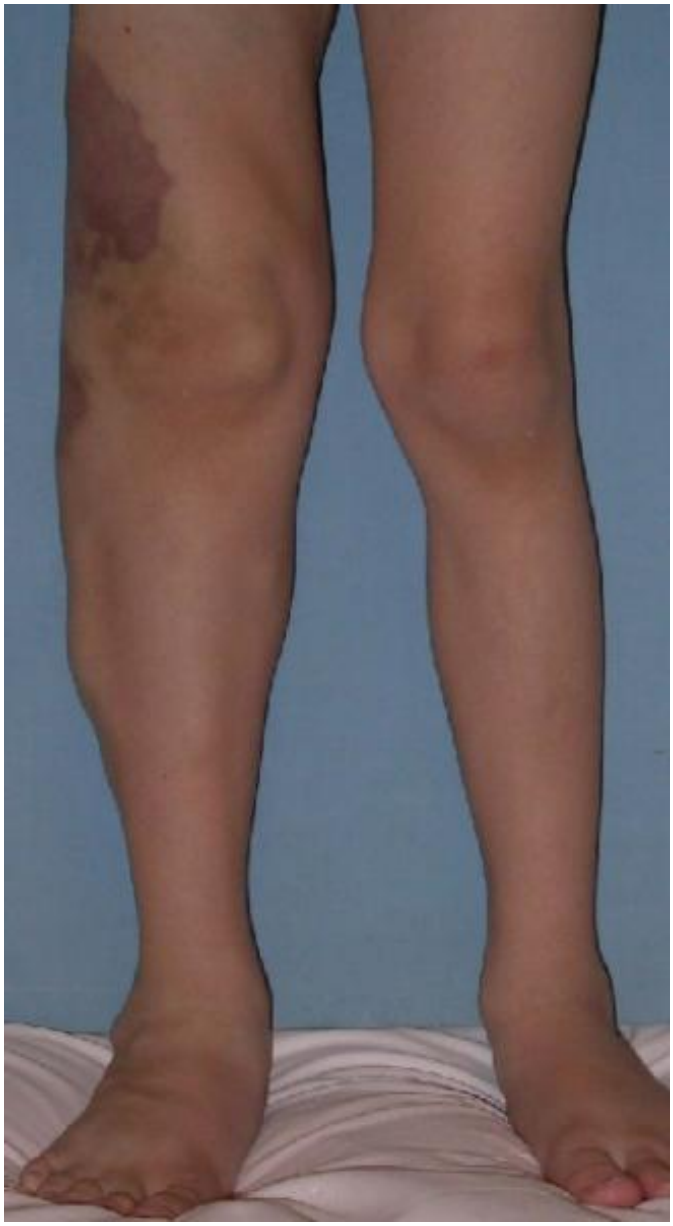
Klippel-Trenaunay Syndrome



Sturge-Weber Syndrome

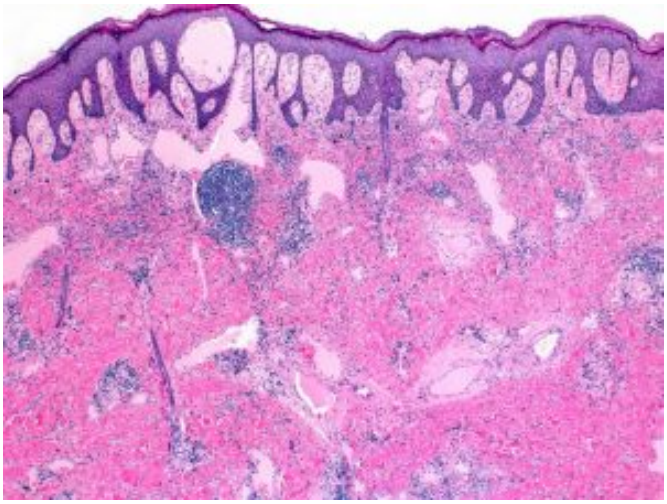
Klippel-Trenaunay Syndrome

- This syndrome involves ectodermal, mesodermal, and endodermal tissues.
- Congenital lesion that consists of a triad of stain, tissue hypertrophy, and bone overgrowth
- Affects one or more limbs (arms or legs) or trunk region.
- Most cases girth of limb is larger but in some cases the non-affected limb can be clinically smaller
- Limb abnormality can be affected with ipsilateral and contralateral hypertrophy of subcutaneous tissue of the trunk
- Stain is different than typical port wine stain and may be present overlying or distal from the affected limb
- Lateral Marginal Vein varicosity diagnostic

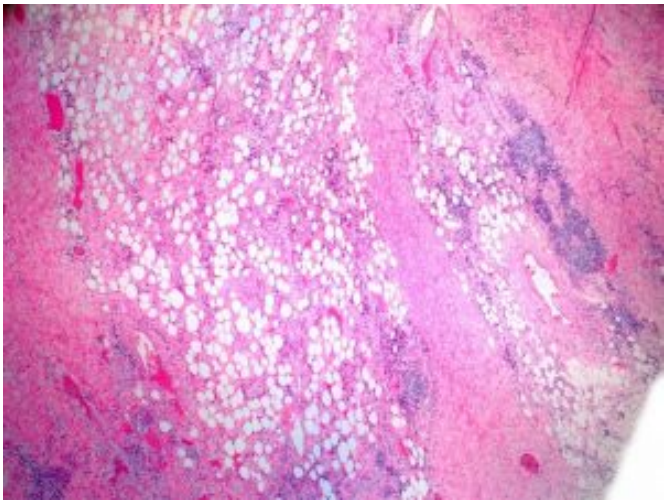


Klippel-Trenaunay Syndrome histology

- The lesion usually exhibits changes of a venous malformation with focal lymphatic involvement
- Venous thrombi are a common occurunce and may be associated with papillary endothelial cell hyperplasia
- Port wine like stain usually develops angiokeratomas and/or superficial lymphatic malformations
- Increased subcutaneous fat is frequently noted in the affected limb and trunk
- Hypertrophy of bone may also be noted



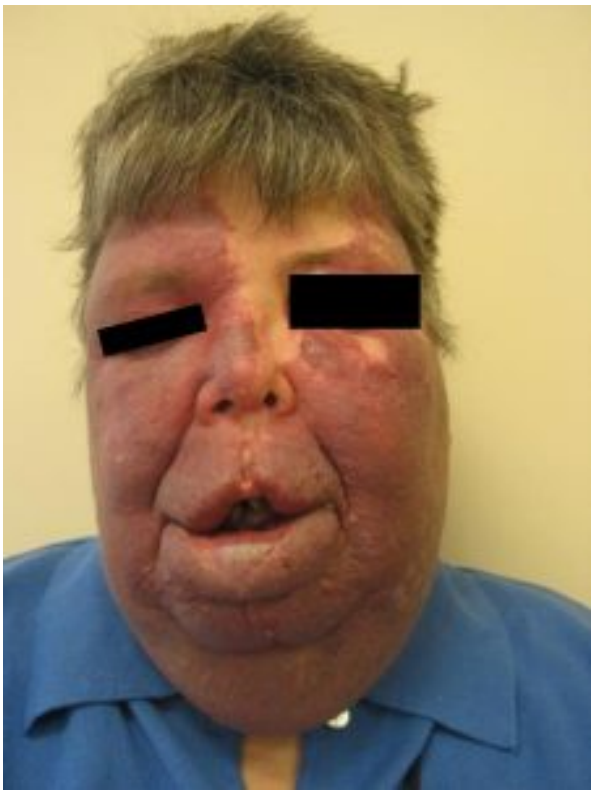
KTS: Malformation involves lymphatics and veins with nidi of inflammation surrounding them. Thickened dermis due to collagen increase. Note superficial dilated vessel surrounded by epidermis, characteristic of angiokeratoma-like skin lesions.

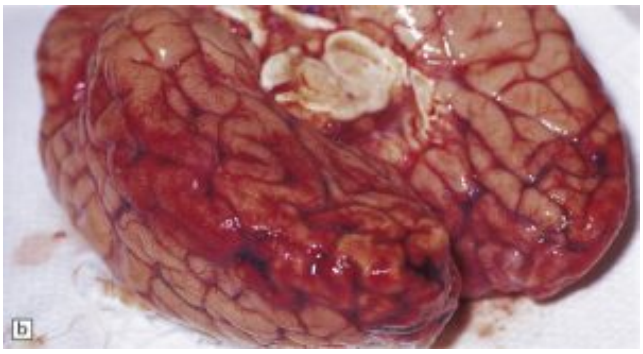


KTS: Vascular abnormality extends throughout the subcutaneous fat.

Sturge-Weber Syndrome

- Classically involves 3 components: vascular stain of the V1 (eye area), leptomeningeal and brain abnormalities including calcification, and glaucoma from increased ocular pressure. However, some patients may present without the full expression of all 3 components.
- Brain may be normal or the involvement may be unilateral or bilateral
- Skin histology equivalent to port wine stain
- SWS has been found to be associated with mutations in the *GNAQ* gene.





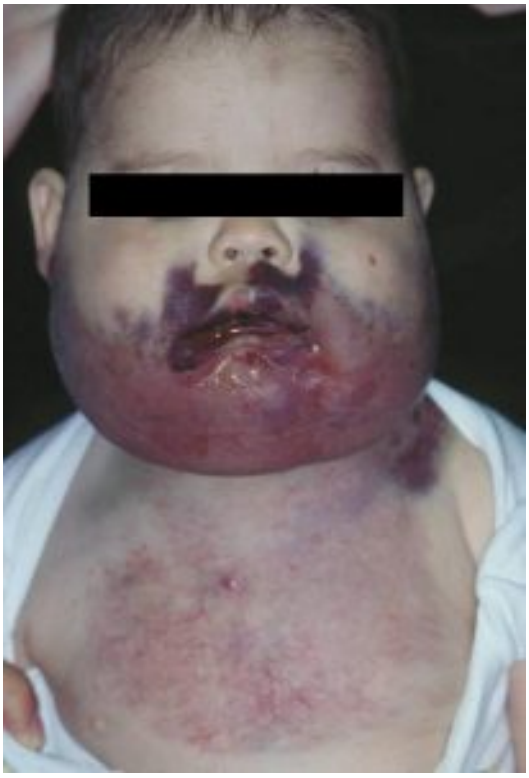
Vascular tumors and malformations associated with coagulopathy

- Mild-to-moderate chronic consumptive coagulopathy – large venous and lymphatic malformations
- Severe thrombocytopenia due to platelet trapping (Kasabach-Merritt phenomenon) – kaposiform hemangioendothelioma and tufted angioma

Tufted angioma histology

- Prominent nodules of vascular proliferation with a “cannon ball” appearance in the mid-to-lower dermis predominantly
- The nodules are composed of numerous small endothelial cells lining closely packed capillaries
- Endothelial cells may be epithelioid or spindled in shape. Rare endothelial cell mitoses are noted
- Occasionally, nodules of spindle cells resemble Kaposiform Hemangioendothelioma
- GLUT-1 is negative

Kaposiform hemangioendothelioma

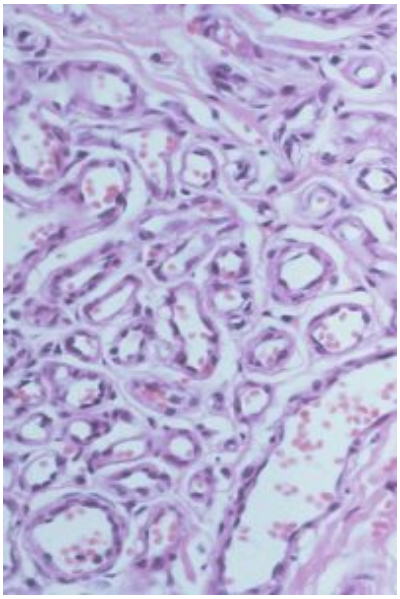


Kaposiform hemangioendothelioma histology

- Large tumor nodules surrounded by prominent ectatic blood vessels, some venous, but mostly lymphatic
- Nodules exhibit very dense proliferative vasculature composed of epithelioid cells resembling, in some areas, the non-ulcerated Pyogenic granuloma or cellular cherry angioma
- Some areas show a dense, epithelioid poliferation with glomeruloid structures
- In other areas, there is dense spindle cell proliferation with slit-like spaces resembling Kaposi's sarcoma **and with focal** glomerulioid structures
- Many of the endothelial cells have a crescent-like appearance, especially in the larger vessels surrounding the tumor nodule
- Endothelial cells exhibit a vacuolated cytoplasm that is slightly eosinophilic
- Mitoses are present
- There is a dense stroma with hyalinization within the tumor
- Platelet fibrin thrombi are present, demonstrated with CD61
- Lesions are positive with CD31, CD34, and FLI-1, and focally D2-40.

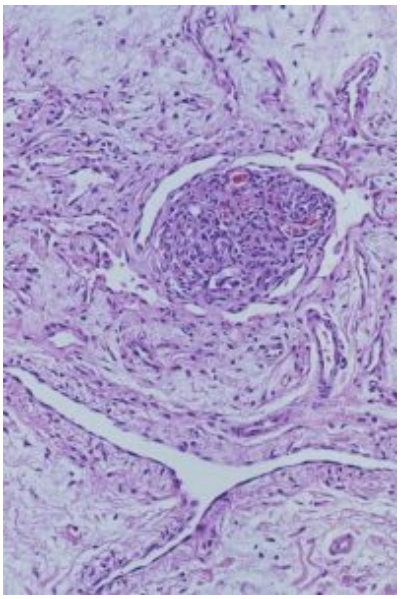
Kasabach-Merritt phenomenon

- While infantile hemangiomas, tufted angioma, and kaposiform hemangioendothelioma exhibit capillary proliferations, they can be distinguished as follows:
- Infantile hemangiomas are Glut-1 positive and do not exhibit the Kasabach-Merritt phenomenon.
- Tufted angiomas and kaposiform hemangioendotheliomas are both Glut-1 negative, and may exhibit the Kasabach-Merritt phenomenon.



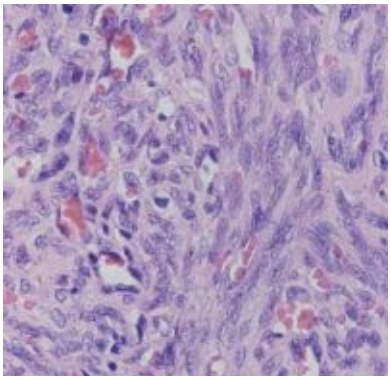
Infantile hemangioma

GLUT-1 positive
No KMP



Tufted angioma

GLUT-1 negative
+/- KMP



Kaposiform hemangioendothelioma

GLUT-1 negative
+/- KMP

In summary

- Vascular tumors of childhood represent a number of distinct entities with diverse etiologies – many with diagnostic histopathological features.
- Some lesions continue to defy classification and are best viewed as complex, dynamic processes responding to as yet unidentified factors. For these, the object for the pathologist is not to “pigeon-hole,” but to describe as accurately as possible.

COURSE 13 QUIZ

1. Which lesion is represented by late involution and exhibits zones of prominent fibrous tissue with often thick-walled vessels in a background of fat?

A. Venous malformation
B. Congenital hemangioma
C. Infantile hemangioma
D. Cystic hygroma

2. Based on histology, which lesion is described as leaving a loosely fibrous stroma, with minimal inflammation, and no evidence of thrombosis?

A. Infantile hemangioma, mid-involution
B. Infantile hemangioma, late proliferation
C. Infantile hemangioma, early proliferation
D. Infantile hemangioma throughout all phases

3. Which of the following statements is NOT true of the change in histology from proliferation to involution for infantile hemangiomas?

A. Late involution exhibits zones of prominent fibrous tissue with often thick-walled vessels in a background of fat.
B. Proliferative phase associated with a discrete unencapsulated densely cellular tumor.
C. Fine stroma with mast cells invests capillary structures and decreases as the lesion matures.
D. Numerous mitoses are easily visible in prominent endothelial cells, as well as apoptotic figures.

4. The dermis is replaced by a loose fibrous stroma containing a few persistent lesional capillaries and supportive vessel in which phase for the infantile hemangioma?

A. Pre-proliferation
B. Mid-stage proliferation
C. Early proliferation
D. End stage

5. Regarding the infantile hemangioma phenotype, which four markers are identical to placenta, suggesting some relationship between infantile hemangioma and placenta?

A. GLUT-1, Lewis-y, Merosin, FcγRII
B. GLUT-1, Lewis-x, Merosin, FcγRIII
C. GLUT-2, Lewis-y, Merosin, FcγRII GLUT-2,
D. Lewis-x, Merosin, FcγRII

6. Which congenital hemangiomas have the same histology?

A. and infantile hemangiomas
B. RICH and infantile hemangiomas
C. NICH and RICH
D. NICH, RICH, and infantile hemangiomas

7. Which vascular malformations (VMs) are high-flow?

A. Arteriovenous malformations and lymphatic malformations
B. Arteriovenous fistulas and capillary malformations
C. Lymphatic malformations and capillary malformations
D. Arteriovenous malformations and arteriovenous fistulas

8. The NIDUS is a critical component of which vascular malformation?

A. Venous malformatIon
B. Capillary malformation
C. Arteriovenous malformation
D. Lymphatic malformation

9. The histology of which lesion is described as follows: “papillae are expanded by ectatic lymphatics and the abutting epidermis associated with blebs”?

A. Lymphatic malformation
B. Infantile hemangioma
C. Capillary malformation
D. Congenital hemangioma

10. Which of the following is NOT associated with the histological features of a port-wine stain?

A. Vessel walls appear thickened focally.
B. Thin-walled vessels progressively dilate, extending down--even into fat--by adolescence and adulthood.
C. Early in infancy, lesions show decrease in superifical vessels that have collapsed lumens and run parallel to each other.
D. Thickening associated with fibrosis, myxoid change in stroma, variable scattered inflammation.

Martin C. Mihm Jr, MD

The last 43 years of my life have been spent in five areas of endeavor. First, I have studied the evolution of malignant melanoma and was involved in the first classification of the tumor into subtypes in 1969 with Dr. Wallace Clark. This work then led to identifying early signs of melanoma and to receipt of the first and only NIH grant to study the biology of this often deadly cancer. This work also led me to study not only the fields of Internal Medicine and Dermatology but also Pathology, in order to understand better the biology and pathophysiology of human tumors.

This work also led to my second great interest: diagnostic dermatopathology. From this work, I went on to found, at the Massachusetts General Hospital, one of the first five institutions in the United States establishing a fellowship program in Dermatopathology, thereafter recognized as an official subspecialty in Medicine.

My third great interest was to understand the evolution of the human immune response. Beginning in 1969 and extending into the early 1980s, I worked with Dr. Harold Dvorak to study and define the human delayed hypersensitivity as presented in experimental contact dermatitis. We also studied human allograft rejection and published one of the first descriptions of the blood vessels as the target in this process. This work served as a segue into a further elaboration of my interest in melanoma with studies of the immune response or TIL's in primary and metastatic melanoma. This work has continued to the present with members of the WHO melanoma program for which I co-directed the pathology panel and currently, with the melanoma pathology group of the EORTC. I also co-direct this endeavor.

Some of the most ground-breaking studies of the host response in mice and man have been carried out with Dr. Glenn Dranoff and his associates as we have studies the importance TILs in patients vaccinated with viral vectors containing DNA that results in autologous tumor cells producing GMCSF with remarkable responses in Stage IV melanoma patients. This work continues with now also Dr. George Murphy, Margaret Shipp, and F. Steven Hodi. These collaborations have blended my interest in melanoma and human delayed response, resulting in highly significant studies in human tumoral immunologic response.

Recent studies in the interest in the glycobiology of melanomas have brought new insights into the potential mediators of T cell infiltration and potential mechanisms of T cell fate within melanomas. I am currently studying the role of galectin-1 (Gal-1) and its ligands in melanoma growth and progression. My interest in prognostication is intrinsically bound to understanding progression. This area should prove to be fertile ground for very meaningful research in understanding melanoma and creating new therapies.

My fifth area is the study of vascular anomalies in collaboration with Drs. Paula North, Milton Waner, Robert Rosen, Stuart Nelson, and Wenbin Tan. We have made seminal observations concerning the importance GLUT1 in the diagnosis and biology of infantile hemangiomas. We also have made other seminal observations in the pathophysiology and pathology of Port Wine stains. I continue to work with all of these physicians in this important area. My prior work qualifies me to be a meaningful collaborator in further vascular studies.

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COURSE 13 QUIZ ANSWER KEY

1. C
2. A
3. C
4. D
5. A
6. C
7. D
8. C
9. A
10. C