## Supplement 1

## Criteria for diagnosis of vascular lesions

### A. Tumors

Infantile hemangiomas

Clinical
Presentation as bright red or bluish-red lesions on the skin, which may be raised or have a nodular appearance, with onset within the first few weeks to months of life, but not at birth. Usual evolution in phases of growth/increase in size, plateauing, and spontaneous decrease in size till involution. Phases decided as per history from attendants, in conjunction which any previous available photos and clinical examination.
Clinical subtype classification-

- Bright red coloured plaque with finely lobulated surface “strawberry like” in superficial IH
- Warm, ill defined, light blue purple mass with minimal/no overlying skin changes in deep IH
- Well delineated, red vascular plaque over large, poorly circumscribed violaceous nodule in Mixed IH

Histopathology
Proliferative phase- characterized by lobular arrangement in form of well-demarcated cellular lobules with interspersed small round or slit-like capillaries/vascular spaces having plump oval-to-spindle shaped endothelial cells with some mitosis, along with many pericytes, and minimal stroma.
Involuting phase- shows lesser capillaries, capillaries with larger lumens, better identifiable capillaries as cellularity decreases and vascular spaces increase, less-plump flattened endothelial cells, more stroma with increased fibrosis and fatty change, and less cellularity and pericytes between endothelial channels, and increased presence of mast cells. The vessels entrap but spare the adnexal structures. GLUT1 positivity of endothelial cells on immunohistochemistry.

Radiology
Ultrasound (USG) in the proliferative phase shows well-defined lobulated masses with heterogenous/mixed echotexture (although most commonly hypoechoic, but can be iso and hyperechoic too) and variable echogenicity, with internal echogenic septa and marked diffuse increased vascularity on doppler. There is no arteriovenous shunting, but high-flow feeder arteries can be seen. In the involuting phase, the boundaries become less-defined and indistinct, and more echogenic due to fibrofatty change. On doppler, the vascularity decreases. Magnetic Resonance Imaging (MRI) in the proliferative phase shows a solid well-defined lobulated mass/plaque with intermediate or increased T2 signal intensity, and isointense with muscle in

T1-weighted images. On contrast, they show rapid, homogeneous, and intense contrast enhancement with variable washout.

Congenital hemangiomas

Clinical
They usually present as single violaceous nodules or plaques with associated telangiectasias and peripheral halo. Their morphology resembles mixed and plateau/involuting hemangiomas but differ in onset, as present since birth. On the basis of evolution, classified in to-

Rapidly Involuting Congenital Haemangioma (RICH)- raised, violaceous nodule with large, radiating veins or with overlying telangiectasia and a halo of pallor. Undergoes rapid involution during the first year of life, faster than infantile hemangiomas. It may occasionally ulcerate and bleed, and have pain.

Non Involuting Congenital Haemangioma (NICH)- well-circumscribed round to oval, slightly indurated, or raised soft-tissue plaque with overlying telangiectasias and a rim of pallor. Does not involute spontaneously.

Partially Involuting Congenital Haemangioma (PICH)- involutes partially for few months then stops, leaving active proliferated vessels. Completely involuted infantile hemangiomas that leave behind persistent fibro-fatty sequelae can be a differential, but they have onset after birth and no proliferated vascular component.

Histopathology
Similar to infantile hemangiomas, except that they are GLUT-1 negative on immunohistochemistry. The rapidly involuting variant shows dermal and subcutaneous lobules of capillaries, occasionally coalescent, surrounded by abundant fibrous tissue. Non-involuting congenital haemangioma on histopathology shows lobules that are variable in size and most often large and composed of curved, thin-walled capillaries.

Radiology
It is similar to infantile hemangiomas. They have more heterogenous and hypoechoic echotexture, and can have surrounding soft-tissue edema and calcifications, in contrast to infantile hemangiomas. RICH frequently has venous ectasias and venous lakes presenting as large hypoechoic spaces, and NICH can have microshunts.

Tufted angiomas

Clinical
Present as solitary (more commonly) or multiple (less commonly) firm erythematous, dusky erythematous, bluish-purple or violaceous macules, plaques or nodules, which may appear together as a confluent poorly-demarcated firm indurated plaque with a cobblestone-like surface over the skin. Clinically, they may be asymptomatic or associated with pruritus or tenderness, although tenderness is usually seen in associated Kasabach-Merritt phenomenon.

Occasionally lesions can have hypertrichosis and/or hyperhidrosis. Some early stage lesions may be mostly macular and can resemble a portwine stain, but are distinguishable through ill-defined margins and some firmness/induration. They can develop at any age but often arise in infancy or early childhood. Usual age of onset is 1-5 years but may even present at the time of birth. While typically benign, tufted angiomas can have a variable course, with some lesions showing slow progression with lateral extension for few years followed by stabilization, and others remaining largely stable. Lesions usually persist, but uncommonly can regress spontaneously. Can rarely be associated with coagulopathy alone or coagulopathy with thrombocytopenia (consumptive coagulopathy) , known as Kasabach-Merritt phenomenon, which manifests as thrombocytopenia, microangiopathic hemolytic anemia, and coagulopathy, leading to bleeding tendencies and potentially life-threatening complications such as hemorrhage and organ dysfunction, although this phenomenon is much more commonly seen in kaposiform hemangioendothelioma. In some cases of uncommon presentations, histopathology might be essential in establishing the diagnosis.

Histopathology
Characterized by cellular lobules dispersed mostly in the mid and deep dermis and also in the superficial subcutaneous tissue, which have rounded or slit-like vascular spaces, similar to the proliferative phase of infantile hemangiomas. The appearance of multiple lobules, or tufts of vessels, is often referred as “cannonball”, because of their frequent rounded shape. The elongated cleft-like vessels are seen at the periphery of lobules in a semilunar/crescentic fashion, and may give a glomeruloid appearance. There are occasional lymphatics which occur as large dilated channels which are clear or filled with plasma but lack erythrocytes. Rest dermis may show fibrosis. It is GLUT-1 negative, and if it shows lymphatics, those are D2-40/podoplanin positive. Some crescentic vessels and cells can also show D2-40 positivity. In contrast the lobules of infantile hemangiomas usually lack the round appearance and peripherally located vascular spaces, and are GLUT-1 positive.

Radiology
Not very well known, available only from few case reports. Mostly similar to kaposiform hemangioendothelioma, except more superficial location, better definition, and less tortuous vessels.

<u>Kaposiform hemangioendothelioma</u>

Clinical
Presents similar to tufted angioma, and both diseases are considered to be on a spectrum. Soft pointers that increase the likelihood of kaposiform hemangioendothelioma over tufted angioma include more purpuric lesions, more ill-definition of lesions, deeper lesions involving underlying muscles and bones, and significantly more association with Kasabach-Merritt phenomenon
Histopathological examination reveals infiltrative growth of spindled endothelial cells within the dermis and subcutaneous tissue.

Histopathology

Histopathology is similar to tufted angioma, with differences including more depth of lobules extending to deep subcutaneous tissue and beyond, more infiltrative and less well-defined/rounded lobules with more cells being spindle-shaped, and increased slit-like spaces rather than rounded vascular spaces or peripheral semi-lunate crescents (hence 'kaposiform'), more lymphatics, and significantly more hemosiderin suggestive of sequelae of hemorrhagic episodes.

Radiology

On sonography, they show heterogenous echotexture like other hemangiomas, are usually moderately echoic, but can be hypoechoic and hyperechoic too. They can show features like striate hypoechoic bands, punctate hyperechoic foci, and tortuous feeder vessels. On doppler, they usually show abundant blood flow, but can be patchy too. On computed tomography, they show striated or flocculent soft-tissue shadow, and deeper muscle or bone involvement. On magnetic resonance imaging, they show heterogeneous and high signal intensity on T2-weighted images, compared with the muscles. They show mixed high and low signal intensities on fat-saturated T2-weighted images, and no significant diffusion restriction on diffusion-weighted imaging.

Pyogenic granulomas

Clinical

Also known as lobular capillary hemangiomas, they are characterized by rapidly growing, friable, and often ulcerated nodules with granulation tissue on the skin or mucous membranes. They typically present as solitary, red to violaceous papules or nodules that can vary in size, and frequently have a peripheral collarette of scales. The lobulation can be apparent clinically too. These lesions may arise spontaneously or develop at sites of minor trauma or irritation.

Histopathology

Pyogenic granulomas typically exhibit a polypoid or exophytic architecture, characterized by a central core of fibrovascular tissue covered by an ulcerated or eroded epithelium. The epidermis is usually hyperplastic with parakeratosis, but can also be atrophic. The sides of the lesion may show some clawing, which corresponds with the collarette of scale seen clinically. Within the vascular stroma, there is a proliferation of thin-walled capillary-sized vessels, often arranged haphazardly and surrounded by edematous or fibrous stroma. Endothelial cells lining the vessels appear plump and hyperchromatic, with occasional mitotic figures, indicative of active angiogenesis. Surrounding inflammatory infiltrate, mainly composed of lymphocytes and plasma cells, may also be present, and neutrophils are present when they are ulcerated. They lack encapsulation and demonstrate an infiltrative growth pattern into the adjacent dermis or mucosa. Early lesions are more cellular and have less capillaries and fibrosis, so can resemble infantile hemangiomas especially when well-lobulated, but compared to infantile hemangiomas, they can have significant inflammatory infiltrates, and are GLUT-1 negative.

Radiology
In USG, they are poorly demarcated hypoechoic lesions, usually extending till the level of subcutis. Doppler shows diffuse vascularity. MRI shows features suggestive of a soft tissue lesion with significant contrast enhancement.

**B. Malformations**

Capillary malformations

Clinical
They present as well-demarcated, pink, red or purple patches with onset since birth, and lack spontaneous involution. They grow in proportion to the child's growth/rest of the anatomical site where they are present, but can darken or thicken with age.

Histopathology
haphazardly arranged ectatic vessels, with small venular morphology in the papillary and occasionally reticular dermis.

Radiology
As they are usually present in dermis alone, on USG they cannot be differentiated from normal vasculature of dermis. As they are very slow-flow malformations of small size, the doppler is also usually normal.

Venous malformations

Clinical
Present as soft, bluish or purplish lesions that may be macular, barely elevated, elevated, or subcutaneous nodules or plaques. They have a distinctive bluish or greenish hue. They are usually soft and compressible, can occasionally have a bag-of-worms feeling in larger lesions, and have a tendency to increase in size with dependency. They can vary in size from small patches to larger, irregularly shaped areas, and they may be present at birth or develop later in life. They usually increase in proportion to child's growth, although progression may occur and newer lesions may arise. They do not resolve by themselves. The lesions may be asymptomatic, causing only cosmetic concerns, or they may be associated with symptoms such as pain, swelling, or functional impairment, particularly if they involve deeper tissues. Complications such as thrombosis or bleeding may occur, especially if the malformation is traumatized.
A subtype, verrucous venous malformation presents with isolated or grouped or confluent dusky red-to-purple papules or plaques that are initially not keratotic, soft, flat or barely raised at birth or early childhood, but with age become hyperkeratotic, verrucous, and elevated.

Histopathology
Venous malformations are composed of irregular venous-type channels, characterized by variably sized irregular and angular shaped profiles. Due to the vessels being very large, some venous malformations were previously termed as 'cavernous hemangiomas'. The wall

thickness of these venules is variable and very heterogenous owing to the variable thickness of muscle layer in the tunica media, in the same section wall thickness may vary considerably. The arrangement of these vessels also vary considerably, they may be arranged haphazardly, or in clusters with intervening thin stroma, or back-to-back without any intervening stroma, and can even appear as anastomosing. There can be thrombi, calcifications, valvular structures, and papillary hyperplasia. They can extend from dermis to the subcutis and underlying tissue, including the muscle and bone.
Verrucous venous malformation has epidermal papillomatosis/verrucosity and acanthosis, and vessels which are present both in the papillary dermis (which shows large dilated channels) and deep dermis and subcutis, unlike angiokeratomas, in which dilated vessels are present only in papillary dermis. It is the only type of malformation (or vascular lesion other than infantile hemangioma) which can show focal GLUT-1 positivity. It can also show lymphatics (channels which do not have blood but only plasma, and are D2-40 positive).
The characteristic histopathologic feature of glomuvenous malformation is the presence of ectatic and malformed veins with smooth muscle focally, or totally replaced by one or multiple layers of cuboidal "glomus" cells.

Radiology
Frequently show multicystic pattern with large anechoic to hypoechoic channels, but can also show solid mass-like features, resembling hemangiomas. Hyperechoic foci of thrombi and calcifications are important clues to differentiate. On doppler, they show monophasic low velocity flow, or even absent color flow, in contrast with hemangiomas. In MRI, they are usually more hyperintense than muscles (or hemangiomas) on T2-weighted images. Fluid-fluid levels can be seen due to slow flow.

<u>Lymphatic malformations</u>

Clinical
Present as soft, translucent, fluid-filled vesicles or cystic lesions that may vary in size and shape from small papules to large, disfiguring masses. The fluid is usually clear but can have blood too due to leakage from vessels, or associated venous component, when they are termed as veno-lymphatic malformation. They may present at birth or develop later in infancy or childhood. They usually increase in proportion to child's growth, although progression may occur and newer lesions may arise. They are often asymptomatic and larger lesions causing cosmetic disfigurement, functional impairment, pain, or recurrent infections. Complications such as bleeding, lymphatic fluid leakage (lymphorrhea), or cellulitis may occur, particularly if the malformation is traumatized or infected. Morphologically they can be-

- Microcystic lymphatic malformation- plaques with crops of clear or hemorrhagic vesicles scattered on their surface with intermittent leakage of fluid from superficial vesicles
- Macrocytic lymphatic malformation- large, soft, translucent mass under normal skin

Histopathology
They show large dilated elongated channels with angular margins and a very flat endothelium. They may have valves. The walls lack any tunica media or muscle/elastic layer, in contrast to

venous malformations. The lymphatics usually are empty or contain some plasma, which presents as an amorphous hyaline material. Although they lack erythrocytes, presence of erythrocytes and hemosiderin does not exclude lymphatics, as owing to their thin walls, hemorrhage in to lymphatics is not uncommon. Veno-lymphatic malformations may have components of both venous and lymphatic malformations.

Radiology
They usually show non-compressible multilocular anechoic cystic spaces with internal septa of variable thickness, but the cysts might be hyperechoic too if they contain debris or blood. Occasionally, solid masses can also be seen. Doppler rarely shows any flow.

Arteriovenous malformations

Clinical
Peripheral (extra-cranial) arteriovenous malformations frequently present with cutaneous lesions. It progresses to 4 stages as per Schobinger-

- Quiescent- where the skin is warm and discolored (pink or blue). It lacks other examination findings like elevation, nodularity, thrill or bruit, so it can be frequently confused with a port-wine stain, but the shunting can be detected on doppler.
- Expansile- has swelling- so elevation/nodularity, can be palpated, has bruit, thrill, pulsation, and tortuous veins
- Destructive- has pain, ulceration, bleeding
- Decompensation- cardiac decompensation/failure

Histopathology
Arteriovenous malformations on histopathologic examination reveal malformed arteries and veins, along with intermediate vessels. Malformed arteries have a thick muscular wall but have disruption of the internal elastic lamina. Veins show thick fibrotic wall with severely reduced elastic fibers due to exposure to high blood pressure. Multiple foci of microvascular proliferation are seen.

Radiology
On USG, they show marked increase in color vascularity along with pulsatile arterial flow. On MRI, they show rapid enhancement and rapid washout, early venous drainage.

**C. Unclassified lesions**

Angiokeratomas

Clinical

They present as well-circumscribed dark red to purple, hyperkeratotic papules and nodules that may become confluent, forming plaques. They usually present during infancy or early childhood and persist.

Histopathology

Angiokeratomas have epidermal papillomatosis/verrucosity and acanthosis, and dilated vessels present only in papillary dermis, unlike verrucous venous malformation, in which vessels which are present both in the papillary dermis (which shows large dilated channels) and deep dermis and subcutis.

Radiology

Usually shows a linear hypoechoic soft tissue mass with mild vascularity and no deep involvement.

Angioma serpiginosum

Clinical

It presents with dusky erythematous macules arranged in a serpiginous fashion. There is usually variable hue in the lesions, which some patches appearing dark purple and some light purple, unlike a port-wine stain which usually has a uniform hue. Some clinicians consider it a superficial type of capillary malformation.

Histopathology

On histopathological examination, it shows features of a capillary malformation.

Radiology

Similar to those of a capillary malformation.