PEDIATRIC VASCULAR TUMORS AND MALFORMATIONS

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ABSTRACT

Pediatric vascular tumors and malformations, comprising a broad category of lesions often referred to as vascular anomalies, are a heterogenous group of clinicopathologically distinct entities. Pathologists, clinicians, and radiologists have traditionally lumped these lesions under the generic term, hemangioma, sometimes qualified by modifiers, such as capillary or cavernous. Advances in understanding underlying pathogenetic mechanisms support more specific classification and more specifically targeted therapies. Multidisciplinary consensus has moved toward a biologically based classification system and therapeutic approach for dealing with these lesions. This content focuses on the histologic, immunophenotypical, and clinical features that distinguish the major types of vascular tumors and malformations presenting in infancy and childhood. Pathogenic mechanisms are also briefly reviewed.

OVERVIEW

Vascular anomalies affecting infants and children include tumors and malformations. These have recently generated increasing interest among clinicians and scientists, and several advances in therapy and in understanding of etiology have been made. Physicians now globally realize that these lesions comprise a diverse group of distinct clinicopathologic entities, have differing etiologies and clinical behaviors, and urgently need more effective therapies. Current mainstream treatment options are limited, often ineffective, and may be accompanied by significant clinical complications. Fortunately, recent studies have begun to unveil underlying mechanisms of disease and bring new hope for identification of rational therapeutic targets.

Accurate histopathologic description and knowledgeable clinical and radiologic evaluation are absolute prerequisites for study and meaningful diagnosis of vascular anomalies, but they have not been consistently applied even in major academic institutions. Persistent, overgeneric use of the term, hemangioma, has caused inappropriate lumping of entities that are biologically and clinically dissimilar. Recognizing this problem, the multidisciplinary International Society for the Study of Vascular Anomalies (ISSVA) in 1996 agreed on a general framework of a biologically based nosologic classification system. This scheme derives in part from that proposed by Mulliken and Glowacki, in which vascular anomalies were divided into tumors and malformations, based on presence or absence of endothelial mitotic activity. According to this scheme, the suffix, -angioma (as in hemangioma), should be reserved for benign vascular tumors—whether congenital or acquired or monoclonal or...

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polyclonal—that arise by cellular hyperplasia. Alternatively, the term, malformation, should designate errors in vascular morphogenesis that usually (but not always) become clinically evident at birth and exhibit proportionate growth and little endothelial mitotic activity (eg, venous malformation [VMs]). Presence of endothelial mitotic activity alone is not sufficient as a single factor to separate tumors from malformations, because there are secondary effects, such as ischemia and turbulence, that may stimulate mitotic activity. Combined with correlations with other histologic features, clinical presentation, and behavior, however, this was a rational starting point that has enlightened the approach to these perplexing lesions.

This distinction between angiomas and malformations represents a significant departure from the traditional diagnostic approach of pathologists, in which the term, hemangioma, has been applied without regard to etiology or clinical behavior and at best has been modified by morphologic descriptors, such as capillary or cavernous. To this day, many experienced pathologists refer to VMs, which consist of mitotically quiescent collections of developmentally abnormal veins, as cavernous hemangiomas. Similarly, developmental abnormalities of lymphatic vessel beds (lymphatic malformations [LMs] by the new classification scheme) have previously been referred to as lymphangiomas and arteriovenous malformations (AVMs) as arteriovenous hemangiomas. Continued use of this poor traditional nosology tends to perpetuate past misconceptions despite new etiologic clarity. Similar to other pathology schemae (eg, lymphomas), refinements and additions to the ISSVA-sanctioned scheme will be required as entities that defy classification based on simple criteria are clarified and discoveries in vascular biology and genetics unfold. Nevertheless, this approach has already proved itself in international practice as a useful starting point in a biology-based system of histopathologic diagnosis.

Precise histopathologic diagnosis of the various types of vascular anomalies plays a major role in clinical management of patients with these disorders. For example, different types of vascular malformations show significant variation in their response to sclerotherapy, tendency to recur with renewed strength if incompletely excised, and association with progressive, often massive and life-altering soft tissue and bony overgrowth. Similarly, entities included in the old rubric, capillary hemangioma, vary widely in tendency to regress spontaneously, to cause life-threatening coagulopathy, to present with combined cutaneous and visceral lesions, and to respond to steroids or β-blockers. Despite the fact that capillary hemangiomas share composition by capillary-sized vessels, they are distinguishable in both histologic detail and molecular expression patterns. Thus, beyond the need to separate hemangioma and other tumors from malformation, it is evident that the term, hemangioma, even when modified by capillary, does not function well as a stand-alone diagnosis. Instead, whenever possible, pathologists and clinicians should use descriptors that clearly indicate a specific clinicopathologic entity (ie, infantile hemangioma [IH], noninvoluting congenital hemangioma [NICH], tufted angioma [TA], and so forth).

This article provides an overview of the current clinical, histologic, and immunophenotypical features that distinguish the major types of vascular tumors and malformations presenting in infancy and childhood and it summarizes the diagnostic histopathologic criteria and nomenclature currently applied to these lesions in most major vascular anomalies centers. This nomenclature to some degree represents a departure from the current World Health Organization (WHO) classification scheme for vascular lesions, which was devised before current clinical and scientific consensus. To complement discussion of the new biology-based classification scheme, evidence regarding mechanisms of pathogenesis in the various types of pediatric vascular tumors and malformations also is briefly reviewed. Discussion opens with the vascular tumors, beginning with the classical hemangioma of infancy, IH.

VASCULAR TUMORS
INFANTILE HEMANGIOMA

Clinical
IH is the most common tumor of infancy, affecting approximately 4% of children. Synonyms currently in frequent use by clinicians for this specific clinicopathologic entity include juvenile hemangioma and cellular hemangioma of infancy. The WHO has adopted the term, hemangioma of infancy. Under the general, biology-based nosologic classification scheme endorsed by the multidisciplinary ISSVA and derived in part from that proposed by Mulliken and Glowacki,1 IH is classified as a vascular tumor (an intrinsically proliferative lesion that arises by cellular hyperplasia), rather than a vascular malformation (a congenital error in embryonic vascular morphogenesis with
limited endothelial mitotic activity). Whether or not small and innocuous or large and deforming, their typical and remarkably consistent natural course includes presentation shortly after birth, rapid proliferation in the first year of life, and spontaneous involution over a period of years. Some examples are already evident at birth as relatively inconspicuous precursor lesions, and rare examples, usually small, abruptly abort and regress shortly after appearing. Female infants are three times more likely to develop IH than males. Fair-skinned individuals are at increased risk, although all races are affected. Approximately 60% occur on the head and neck, although they also occur on the trunk, extremities, genitals, and in various viscera, notably the liver, the intestine, and less often the lung. Skin and subcutis seem most commonly affected by IH, whereas deep skeletal muscle is spared. True IH may occur in the brain but have been poorly demonstrated in that location. Most IH present as solitary cutaneous and/or subcutaneous lesions, but a significant percentage of patients (approximately 15%) have multiple skin lesions, in rare cases accompanied by multiple visceral hemangiomas (usually hepatic).

Although all IHs spontaneously involute to a variable degree over a period of years, functional or significant cosmetic sequelae are not uncommon and lead to frequent need for intervention. During the initial proliferative phase, potential complications include skin ulceration and scarring, bleeding, infection, airway compromise, and, rarely, congestive heart failure. Occlusion of the developing visual axis by periorbital IH causes amblyopia, and large lesions of the face may result in jaw malalignment. Psychologic sequelae of deforming facial lesions during early social interactions in preschool and kindergarten can be significant. Although most IH of skin and subcutis show a focal, tumor-like pattern of growth, others show a more plaque-like pattern with a distinctly segmental distribution. Segmental IH of the face are sometimes seen in association with one or more of the following abnormalities: posterior fossa brain malformations, hemangioma, arterial cerebrovascular anomalies, cardiovascular anomalies, and eye anomalies, described by the acronym, PHACE syndrome, or by PHACES syndrome when accompanied by sternal defects and/or supraumbilical raphe. The etiology of this association is not understood.

Common treatment modalities include surgical excision, corticosteroids (topical, intralesional, and systemic), pulsed dye laser, and, most recently, propranolol. Clinically innocuous lesions are often best left alone to regress spontaneously. Recombinant interferon alfa, a known inhibitor of angiogenesis, has been helpful in controlling IH growth, but due to a significant risk of irreversible spastic diplegia, its use is restricted to life-threatening hemangiomas. Topical application of the immunomodulatory agent, imiquimod, has been reported as effective in causing regression of many superficial IHs. Recent clinical studies have shown that propranolol, a nonselective β-adrenergic blocker, can reduce growth of IH in many patients. As a result, relatively widespread off-label use of propranolol for treatment of IH patients has ensued, although treatment must be maintained for several months to prevent rebound.

### Key Features

**INFANTILE HEMANGIOMA**

- Perinatal presentation followed by rapid growth and slow, spontaneous involution
- Variable histology that corresponds to sequential proliferation and involution
- Proliferative phase lesions contain mitotically active, cellular masses of plump endothelial cells and pericytes that form capillaries with small rounded lumina
- Lesional capillaries nondestructively intermingle with local tissue elements, including nerves, eccrine and salivary glands, fat, and superficial skeletal muscle fibers
- Involutive phase lesions show progressive disappearance of lesional capillaries, thickened basement membranes with embedded apoptotic dust, and increased perivascular mast cells
- End-stage lesions consist of loose fibrous or fibrofatty stroma containing a few residual capillary-sized vessels or venules with thickened basement membranes; enlarged feeding and draining vessels persist
- IH has a unique and complex endothelial phenotype shared only by placental capillaries that includes expression of GLUT1, Lewis Y antigen, FcγRII, CD15, CCR6, IDO, and IGF2; GLUT1 immunostains are useful for diagnostic confirmation
**Fig. 1.** IH, proliferative phase. Tumor lobules are composed of cellular masses of plump endothelial cells and pericytes that form capillaries with rounded lumina. Normally configured mitotic figures are identified in each of these two cell populations. Encasing basement membranes are typically multilaminated but still delicate. These thicken and hyalinize during involution.

**Fig. 2.** IH, proliferative phase, characteristic lobularity. The lobules of IH, here seen in the proliferative phase, are well defined and separated by normal stroma rather than by the densely fibrotic bands characteristic of many other vascular tumors, including pyogenic granuloma and KHE.
Gross and Microscopic Features

Grossly, proliferative and early involutive IHs are well-circumscribed, unencapsulated masses with red-to-tan cut surfaces. Later involutive lesions are fibrofatty in consistency and less defined. The histologic features of IHs dramatically change as they proceed through their natural course of neonatal presentation, rapid growth, and subsequent involution, requiring a pathologist to interpret these features within the proper clinical context. There is no sharp dividing line between proliferation and involution, and features of involution typically coexist with features of proliferation during much of the process. Proliferative phase lesions are cellular masses of plump endothelial cells and pericytes that form capillaries with small rounded lumina (Fig. 1). Pericapillary cells with immature dendritic features abound. Basement membranes become increasing multilaminated over time, presumably due to repeated cycles of cell proliferation. The proliferating capillaries are arranged in lobules separated by delicate fibrous septa or normal intervening tissue (Fig. 2). Depending on tissue location, the capillaries nondestructively intermingle with superficial skeletal muscle fibers, adipocytes, peripheral nerve, salivary and eccrine glands, and superficial skeletal muscle fibers (Fig. 3), especially those of facial expression. IHs do not occur within deep skeletal muscle of the extremities or muscles of mastication.

Fig. 3. IH, nondestructive intermingling with local tissue elements. Depending on tissue location, the capillaries of IH freely and non-destructively intermingle with adipocytes (A), peripheral nerve (B), salivary (and eccrine) glands (C), and superficial skeletal muscle fibers (D), especially those of facial expression. IHs do not occur within deep skeletal muscle of the extremities or muscles of mastication.
peripheral nerves, salivary glands, and adipocytes (Fig. 3). Endothelial cells and pericytes show variably enlarged nuclei and abundant clear cytoplasm, and normally configured mitotic figures are easily found. Immunohistochemical stains for cell proliferation markers, such as Ki-67, confirm that both pericytes and endothelial cells are actively dividing. Because proliferative phase IHs are high-flow lesions, albeit without significant arteriovenous shunting, they often contain enlarged draining veins with thickened, asymmetric walls (Fig. 4). Intravascular thrombosis, hemosiderin deposition, and necrosis are rare unless extensive ulceration or presurgical embolization has occurred.

During involution, lesional capillaries begin to disappear (Fig. 5A) and basement membranes continue to thicken and show embedded apoptotic dust (Fig. 5B).\textsuperscript{16} Pericapillary masts cells increase in number (Fig. 5C).\textsuperscript{17} There is no evidence of thrombosis, and inflammation is not prominent. Eventually all that remains in an end-stage lesion is loose fibrous or fibrofatty stroma containing a few residual vessels similar to normal capillaries or venules but with thickened basement membranes (Fig. 6A). Ghost vessels composed of residual, thickened rinds of basement membrane material and containing apoptotic debris and little or no intact cellular lining may also be seen (Fig. 6B). Epidermal atrophy and underlying fibrous scar tissue may be present if the lesion ulcerated while in the proliferative phase. Large arteries and veins modeled during the high-flow proliferative phase do not completely regress when the capillary bed drops out and thus are often present in involuting IH (Fig. 6C).
Fig. 5. IH, early- to midinvolution. During early clinical regression, the capillaries of IH dilate and begin to drop out. Component endothelial cells and pericytes appear less plump, and basement membranes become more thickened and redundant (A). As involution progresses, basement membranes become focally hyalinized and contain embedded apoptotic debris (B). During active involution, perivascular mast cells, evident in hematoxylin-eosin-stained sections but strikingly highlighted by toluidine blue staining (C), increase in number.
Fig. 6. IH, late stage. In the late stages of involution, residual capillary profiles are significantly reduced in number and often appear in isolated clusters (A). Eventually, lesional capillaries appear as ghost vessels with scant endothelium and thickened rinds of fibrotic basement material containing occasional apoptotic debris, as in this lesion from a 5-year-old child (B). During capillary involution, the nonlesional feeding and draining vessels that developed during the high-flow proliferative phase do not involute and remain of abnormally large caliber (C). This may lead to erroneous diagnosis of a vascular malformation.
Histologic examination and routine immunohistochemical studies show that proliferative phase IHs comprise complex cellular mixtures with large complements of endothelial cells, pericytes, mast cells, and interstitial macrophage/dendritic cells (Fig. 7). Electron microscopy demonstrates presence within endothelial cells of a few Weibel-Palade bodies and abundant rough endoplasmic reticulum. Also present are lamellar crystalline inclusions similar to those seen in fetal endothelium. Similarly, isolated IH-derived endothelial cells have been observed to resemble fetal endothelial cells when grown in cell culture. The endothelial cells of IH immunoreact positively for normal endothelial markers of the blood vasculature, such as CD31, CD34, factor VIII–related antigen (von Willebrand factor [vWF]), Ulex europaeus lectin I, Fli-1, and VE-cadherin, although negativity for CD146 has been reported. All stages of IH can be distinguished from other benign vascular anomalies and reactive proliferations by their strong endothelial positivity for a distinct set of antigens that includes GLUT1, Lewis Y antigen, FcγRIII, CD15, CCR6, indoleamine 2,3-deoxygenase, and IGF2 (Fig. 8). Basement membranes strongly express merosin (Fig. 9). GLUT1 immunohistochemistry has become a mainstream tool for pathologists affiliated with centers specializing in the diagnosis and treatment of vascular anomalies.
**Fig. 8.** The distinctive immunophenotype of IH. The lesional endothelial cells of IH, here shown in the proliferative phase, are uniformly positive for the glucose transporter protein isoform 1 (GLUT1). IH endothelial cells maintain strong GLUT1 expression throughout the life cycle of the lesion. Endothelial GLUT1 immunoreactivity is not seen in vessels of normal tissues (other than in placenta, brain, and nerve) or in other benign vascular tumors, malformations, or reactive proliferations. Note the lack of GLUT1 immunoreaction in endothelial cells lining a small intralesional artery (center left). Erythrocytes serve as a positive internal control, as demonstrated in the arterial lumen. IHs are distinguished from other vascular lesions not only by GLUT1 expression but also by an expanded endothelial phenotype that includes but is not restricted to, Lewis Y antigen (LeY), indoleamine 2,3-deoxygenase (IDO), FcγRII, CCR6, and CD15.13,21–24 This phenotype is uniquely shared by placental chorionic villus capillaries and by IH at all stages of growth and involution. In addition, early proliferative phase IH transiently express LYVE-1, a marker of the cardinal vein (lower right).

**Fig. 9.** IH, basement membrane expression of merosin. The basement membranes of IH lesional capillaries, shown here on the right, like those of placental capillaries, are strongly immunoreactive for merosin (α2-laminin). Normal vessels adjacent to the IH capillaries, including the arterial feeder shown here (left), are negative for merosin. Note the normal expression of merosin by periarterial nerve twigs, a positive internal control.
## Differential Diagnosis
### Infantile Hemangioma

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<th>Condition</th>
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<td>IH</td>
<td>Early postnatal presentation, rapid growth, slow spontaneous involution. Proliferative and involutinal phases show shifting histologic features. Locations include skin, subcutis, and some viscera; deep skeletal muscle is spared. Endothelial mitotic figures typical of proliferative lesions, whereas involuting lesions show thickened and multilaminated basement membranes containing apoptotic dust. Lesional capillaries nondestructively infiltrate intralesional nerves and other tissue elements. GLUT1 immunohistochemistry strongly marks the endothelial cells of IH in both the proliferative and involutive phases.</td>
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<td>Pyogenic granuloma (lobular capillary hemangioma)</td>
<td>Acquired, reactive capillary proliferations that can occur in all age groups; when seen in young infants, may be confused with IH. Typically show distinct separation of capillary lobules by thick bands of fibrous tissue, unlike the normal tissue that separates lobules of IH. Grow rapidly and tend to ulcerate and bleed, often taking on the appearance of inflamed granulation tissue. Endothelial cells are negative for GLUT1.</td>
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<td>Intramuscular hemangioma</td>
<td>Present as relatively well-defined tumor-like masses by MRI during childhood or adolescence; congenital nature may be masked by deep location. Probably a vascular malformation rather than a vascular tumor; typically shows angiographic and/or clinical features of AV-shunting; does not regress. Large component arteries and veins are accompanied by beds of capillaries and arterioles that may be mitotically active but lack the characteristic lobular architecture and nondestructive growth pattern of IH. Endothelial cells are negative for GLUT1.</td>
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<td>KHE/TA</td>
<td>May be congenital or acquired. Cellular nodules contain characteristic spindled endothelial cells (absent in IHs) and small platelet-rich fibrin thrombi. Responsible for vast majority of cases of Kasabach-Merritt phenomenon (KMP) due to intratumoral platelet trapping; IHs never cause KMP. Spindle cells coexpress blood vascular (CD34) and lymphatic markers (eg, LYVE1, podoplanin, PROX1). Endothelial cells are negative for GLUT1.</td>
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<td>Congenital nonprogressive hemangiomas (so-called RICH and NICH)</td>
<td>Fully formed at birth and follow either a non-involuting course (NICH) or a rapidly involuting course (RICH). May be confused with either proliferative or involutive phase IH. Consist of capillary lobules with central stellate draining vessels, separated by typically fibrotic stroma containing a prominent interlobular component of veins and small arteries. Intraneural infiltration by lesional capillaries (common in IH) is not seen. Lobular sclerosis, foci of hemosiderin deposition, extramedullary hematopoiesis, thrombosis, and central necrosis are common. Endothelial mitotic figures are scant to absent (also true of involutive phase IH). Thickened and multilaminated basement membranes containing apoptotic dust (typical of involuting IH) are absent or rare. Endothelial cells are GLUT1 negative. Clinical presentation is also extremely helpful, because advanced congenital presence is the norm and postnatal growth is uncommon in congenital nonprogressive hemangioma.</td>
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<td>VMs</td>
<td>Can be confused with involuting and late-stage IH due to persistence of large feeding and draining vessels in the latter. See box: Differential Diagnosis: Vascular Malformations.</td>
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Pathogenesis
The vast majority of IHs are sporadic, although rare families expressing hemangiomas and/or vascular malformations as an autosomal dominant trait with high penetrance have been reported. Some of these familial IH show linkage to chromosome 5q31–33. This suggests that mutation in a gene within this region might predispose family members to IH development. IH are more common in low-birth-weight infants and twins, although a study of 118 twin pairs with IH showed no significant differences in concordance between monozygotic and dizygotic pairs. This argues against a strongly predisposing inherited component.

Although it is the most commonly used marker in surgical pathology practice for the diagnosis of IH, GLUT1 is only one of many markers of IH that distinguish it from other vascular lesions. Together these markers constitute a unique molecular phenotype that is shared only by the fetal capillaries of placental chorionic villi. The etiologic significance of this unexpected expression pattern remains controversial; current evidence favors origin from multipotent vascular precursor cells, possibly arising in the placenta. A recent study reported low VEGFR1 expression in cultured endothelial cells from IH, compared with various controls, with resultant activation of VEGFR2 and its downstream targets. This association suggests possible therapeutic targets. For further discussion regarding the pathogenesis of IH, readers are referred to recent reviews by North and colleagues and Ritter and colleagues.

CONGENITAL NONPROGRESSIVE HEMANGIOMAS (RICH AND NICH)
Congenital nonprogressive hemangioma is a newly recognized clinicopathologic entity that differs from classical, postnatally developing IH in that they present fully formed at birth and then follow a static or rapidly involuting course that proceeds much more rapidly than that of IH. The noninvoluting and rapidly involuting clinical subtypes of congenital nonprogressive hemangioma show considerable, perhaps indivisible, overlap, and are often referred to by clinicians as NICH and RICH, respectively. Traditionally, these congenital lesions have been considered fully developed clinical variants of IH that inexplicably completed their growth in utero rather than pursuing a more typical postnatal growth pattern. These are now recognized as histologically, pathogenetically, and immunophenotypically distinct lesions that differ from classical IH.

Key Features
- Fully formed at birth, without the rapid, postnatal, proliferative phase of IH
- RICH and NICH subtypes
- RICHs seem to melt away in a few months, much more rapidly than IH.
- Prominent arterial phase by Doppler examination, reminiscent of AVM
- Consist of capillary lobules with stellate, thin-walled draining vessels
- Interlobular stroma contains a prominent component of veins and small arteries
- Foci of hemosiderin deposition, thrombosis, extramedullary hematopoiesis, and calcification are common. Peripheral or global sclerosis extends into lobules
- Fully regressed cutaneous RICH often shows marked dermal and subcutaneous atrophy
- Endothelial cells are GLUT1-1 negative and show little or no mitotic activity
Clinical

Congenital nonprogressive hemangiomas often display a peripheral rim of pallor, and those that rapidly involute (RICH) develop a central depression or ulcer before melting away in 3 to 5 months. Occasional examples with progressive clinical growth seem to be exceptions to the rule. Many are first detected by prenatal ultrasound. Unlike IH, but like vascular malformations, congenital nonprogressive hemangiomas occur with equal frequency in men and women. Doppler studies detect prominent arterial flow within the lesion in most cases. Lesions most commonly affect skin and subcutis but also occur in viscera, especially as solitary, centrally necrotic lesions in the liver and occasionally brain. Deep intramuscular location has not been described. Patients with large numbers of NICH/RICH-like lesions in multiple sites, including viscera, have been reported, but their histologic features are as yet poorly documented.

Fig. 10. Congenital nonprogressive hemangioma involving skin. (A) Capillary lobules are separated by fibrotic dermal stoma typically containing a prominent component of large vessels. Note the loss of dermal adnexal appendages. (B) Higher power reveals vessels with moderately plump endothelial cells, focally resembling IH but more button-like in appearance. Intervening stroma is fibrotic. Pericytic coats and basement membranes are less prominent than those of IH, and endothelial mitotic activity is low.
**Microscopic Features**

Whether rapidly involuting or noninvoluting, the capillary lobules that comprise congenital nonprogressive hemangiomas are separated by abnormally dense fibrous tissue, with frequent atrophy and loss of dermal adnexal appendages in overlying skin (Fig. 10A). This contrasts with IH, where tumor lobules are separated by normal-appearing tissue elements. Endothelial cells and pericytes within the capillary lobules can be moderately plump, focally resembling those of proliferative phase IH but lacking increased endothelial mitotic activity and multilamination of basement membranes (Fig. 10B). Foci of hemosiderin deposition, thrombosis, and calcification are commonly present, and peripheral or global sclerosis often extends into the lobules. Foci of extramedullary hematopoiesis are also common, as are thin-walled, centrilobular, draining vessels that are stellate in contour (Fig. 11A). The interlobular vascular

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**Fig. 11.** Congenital nonprogressive hemangioma. Capillary lobules often show stellate, thin-walled central draining vessels (A). Prominent interlobular feeding and draining vessels may suggest a diagnosis of vascular malformation (B).
**Differential Diagnosis**  
**CONGENITAL NONPROGRESSIVE HEMANGIOMA**

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<th>IH</th>
<th>See box: Differential Diagnosis: Infantile Hemangioma</th>
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<td>AVM</td>
<td>Shared congenital appearance and high-flow nature creates resemblance to congenital nonprogressive hemangioma. Clinically significant arteriovenous shunting is typical in AVM but is either absent or low grade in congenital nonprogressive hemangiomas. AVMs often contain foci of capillary proliferation, possibly related to local tissue ischemia, increasing the potential for histologic confusion with congenital nonprogressive hemangioma. The zones of capillary proliferation in AVM are mitotically active and are more infiltrative and ragged in appearance than the well-defined capillary lobules of congenital nonprogressive hemangioma. Sequelae of direct arteriovenous shunting observed in AVMs, such as venous mural arterialization and marked intimal changes, are absent or focal in congenital nonprogressive hemangioma.</td>
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<td>Acquired, reactive capillary proliferations, such as deeply seated lobular capillary hemangioma (pyogenic granuloma)</td>
<td>So-called pyogenic granulomas, although usually small and eruptive, may present in neonates as relatively large, more deeply deeply seated dermal and subcutaneous masses, thus clinically resembling congenital nonprogressive hemangiomas. These entities share several histologic features with congenital nonprogressive hemangioma, including well-defined capillary lobules and stromal sclerosis. The high-flow character of the intralobular stroma and supportive vasculature of congenital nonprogressive hemangioma is absent in reactive proliferations.</td>
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Pathogenesis

The preponderance of clinical, histologic, and immunophenotypic evidence supports the conclusion that the rapidly involuting and noninvoluting clinical subtypes of congenital nonprogressive hemangioma (RICH and NICH) are biologically unrelated to classical IH.\(^{13,14,34}\) Endothelial cells of both are universally negative for GLUT1 and other distinctive markers of IH and placental villous capillaries.\(^{34}\) Pathogenesis is unclear, but the degree of overlap in clinical and histologic features between NICH and RICH, in particular between NICH and initially involuting RICH lesions that arrest short of full regression, suggests that these lesions are part of the same disease spectrum, with RICH perhaps resulting from early complete autoinfarction due to thrombosis of central feeding and/or draining vessels.\(^{13,14}\) NICH and RICH share the early intrauterine development and equal sex predilection of vascular malformations, and they may represent a form of intrauterine vascular injury or malformation with prenatal capillary proliferation and limited potential for continuing postnatal growth. Regardless, the clinicopathologic presentation of congenital nonprogressive hemangiomas of both types is consistent and characteristic.

**HEPATIC HEMANGIOMAS**

**Clinical**

Recent experience reported by two large vascular anomalies referral centers supports division of benign hemangiomas involving the liver in infancy into two major clinicopathologic categories.\(^{35,36}\)
The first major category is that of solitary congenital hepatic hemangioma. These tumors fully develop in utero and typically present as a large perinatal abdominal mass with central necrosis and calcification, not uncommonly complicated by congestive heart failure, anemia, and mild coagulopathy. MRI with T2 weighting shows a high signal heterogeneous mass. Histologic features resemble those seen in RICH variants of skin and subcutis. The second category of hepatic hemangiomas is that of multiple hepatic IHs. These may remain clinically occult or may present in the neonatal period with hepatomegaly and cardiopulmonary distress, often with coexistent hemangiomas in the skin and, more rarely, additional viscera. Like the cutaneous and subcutaneous forms of this entity, hepatic IHs are characterized by early postnatal growth, and spontaneous slow involution. Diffuse involvement of the liver by IH may be complicated by compartment syndrome and/or clinically significant hypothyroidism, the latter due to high tumoral expression of type 3 iodothyronine deiodinase.

**Microscopic Features**

Solitary congenital hepatic hemangiomas show large central areas of infarction and hemorrhage surrounded by more cellular zones of capillaries with flattened to moderately plump endothelial cells admixed with dilated vascular spaces (Fig. 13). Areas of thrombosis, fibrosis, and calcification are common. Extramedullary hematopoiesis is often prominent. The endothelial cells of solitary congenital hepatic hemangiomas are uniformly negative for GLUT1 and other...
IH/placenta-associated antigens. IHs of the liver, like those seen in skin and subcutis, are cellular, well-circumscribed, but unencapsulated collections of small capillaries with moderately plump endothelial cells and pericytes. They are set within in a delicate fibrous stroma sometimes containing entrapped bile ducts and/or hepatocytes (Fig. 14). Clinically evident lesions are multiple and scattered throughout the hepatic parenchyma, although those incidentally discovered at autopsy may be small. Lesional vessels of hepatic IH immunoreact positively for GLUT1 and other markers diagnostic of cutaneous IH (see Fig. 14, inset).

**Fig. 13.** Solitary congenital hepatic hemangioma. Unlike hepatic IHs, which are multiple and perinatal in onset, solitary congenital hepatic hemangiomas fully develop in utero and present as a large solitary perinatal abdominal mass. Histologic features include a central zone of infarction, hemorrhage, and calcification, surrounded by a rim of vascular proliferation histologically similar to congenital nonprogressive hemangiomas of skin and subcutis. Like the RICH variant of the latter, solitary congenital hepatic hemangiomas rapidly regress after birth. These tumors do not demonstrate immunoreaction for GLUT1 and other markers of IH (not shown).

**Fig. 14.** Hepatic IH. IH involving the liver present as multiple well-defined masses, typically scattered about the hepatic parenchyma, often accompanied by multiple skin lesions of like type (not shown). Like the cutaneous lesions, the hepatic lesions are composed of small capillaries with moderately plump endothelial cells and pericytes. Note the entrapped bile ducts (arrowheads) and the adjacent hepatocytes (upper left). Lesional endothelial cells express GLUT1 (inset on upper right) and other markers comprising the IH/placental microvascular phenotype (see text).
Pathogenesis

Hepatic IHs, like IHs in other locations, share the distinctive immunophenotype of placental capillaries and are typically seen in conjunction with cutaneous IH. Pathogenic considerations are thus equivalent. In contrast, current opinion favors classification of solitary hepatic congenital hemangiomas as visceral examples of RICH, based on the fact that most examples of solitary congenital hepatic hemangiomas rapidly and spontaneously regress in a time frame analogous to that of the cutaneous/subcutaneous RICH, which they histologically and immunophenotypically resemble. Mo and colleagues reported the usefulness of GLUT1 in distinguishing between hepatic IHs and large solitary hemangiomas of the liver, although they interpreted the latter as congenital vascular malformation with associated capillary proliferation. Nosology will remain controversial until pathogenesis of these solitary hepatic lesions and their cutaneous counterparts is better understood.

VASCULAR TUMORS ASSOCIATED WITH SEVERE PLATELET TRAPPING: KAPOSIFORM HEMANGIOENDOTHELIOMA AND TUFTED ANGIOMA

Clinical

KMP was originally defined in 1940 as life-threatening thrombocytopenic purpura occurring in the setting of an enlarging hemangioendothelioma. This syndrome is characterized by profound thrombocytopenia caused by platelet trapping within the tumor. It is sometimes compounded by microangiopathic hemolytic anemia and secondary consumption of fibrinogen and coagulation factors. KMP is distinct from the chronic consumptive coagulopathy that can occur in large LMs or VMs in which platelet counts are normal or only modestly decreased, but fibrinogen and clotting factor levels are low. Recent studies have convincingly shown that KMP is not caused by ordinary IH but instead is a complication of two rare types of vascular tumors that histologically overlap: TA and kaposiform hemangioendothelioma (KHE). Many consider KHE and TA variants of the same clinicopathologic entity, with the term, TA, arising from the dermatology literature to describe superficial, often less-aggressive lesions. Both tumor types are equally prevalent in men and women and thus do not show the female predominance of IH. Preferred locations of the KHE/TA spectrum include skin and subcutis, deep soft tissues, bone, and spleen. Rare cases of KMP have been reported in patients with congenital fibrosarcoma or congenital hemangioendothelioma, but the vast majority of cases are associated with KHE or TA. These two latter entities are discussed in this section.

KHE was described as such by Zukerberg and colleagues, although equivalent lesions had been previously reported as “Kaposi-like infantile hemangioendothelioma” and “hemangioma with Kaposi’s sarcomalike features.” Some KHEs are congenital, and most cases present before the age of 2 years. KHE occurring without KMP has been reported rarely in adults. Lesions may present as deeply seated, often bulging, indurated masses or as locally infiltrative vascular stains or plaques. Congenital and more deeply seated tumors are more likely to cause KMP, and patients who develop KMP often have purpura and ecchymoses. Untreated lesions do not regress. Two reported cases spread to regional lymph nodes, thus eliciting the borderline soft tissue lesion term, hemangioendothelioma. Distant metastases have not been reported. The rare instances of lymph node involvement probably reflect multifocal development along a regional lymphatic chain or in multiple separate regions of abnormal lymphatic development; true metastasis is unlikely in KHE. MRI typically shows ill-defined tumor margins with the involvement of multiple tissue layers.

TA was first described as such by Wilson-Jones and Orkin in 1989. Apparently identical lesions had been described earlier as angioblastoma and as progressive capillary hemangioma in 1971. Approximately 15% are congenital, and most present before 5 years of age. Only congenital cases of TA have been associated with KMP. Lesions present as pink-to-red macules and plaques with superimposed papules that spread slowly, then stabilize, and rarely regress.

KHE in the mediastinum or retroperitoneum are often large and unresectable. TA and localized KHE can be cured by wide local excision. Current medical therapeutic options that are successful in some cases include interferon alpha-2a, vincristine, radiation therapy, aspirin plus ticlopidine, multimodal therapy, and a chemotherapeutic regime consisting of cyclophosphamide, vincristine, and actinomycin D. Corticosteroids used as single agents are not effective.

Microscopic Features

The lesions of KHE consist of ill-defined, frequently coalescing nodules composed of fascicles of moderately plump, spindled endothelial cells with bland nuclei and eosinophilic-to-clear cytoplasm.
Similar to Kaposi sarcoma, the spindle cells form slit-like lumina that contain erythrocytes (Fig. 15). The spindle cells often sweep around pericyte-rich nests of more epithelioid cells that surround platelet-rich microthrombi.

Mitotic activity is usually low.

Hemosiderin granules and extravasated erythrocytes are often prominent; tumor cell cytoplasm within epithelioid nests often contains erythrocyte fragments and hyaline globules.

Often displays a prominent component of dilated lymphatic vessels at periphery of tumor nodules and in surrounding fibrotic stroma.

Spindle cells are immunoreactive for CD31 and strongly coexpress blood vascular markers (CD34) and lymphatic markers (podoplanin, LYVE-1, and PROX1).

GLUT1 negative.

TA

Discrete lobules of capillaries scattered within dermis and subcutis in cannonball pattern.

Fibrotic or normal intervening dermal collagen and subcutis.

Tumor lobules are composed of tiny capillaries with pinpoint lumina that may contain microthrombi; the tightly condensed often bulge into peripheral crescentic, thin-walled vessels.

Tumoral endothelial cells may be focally spindled but lack the sweeping fascicles of spindle cells and the nodules of epithelioid cells seen in KHE.

Endothelial cells are focally immunoreactive for lymphatic markers, such as podoplanin, LYVE-1, and PROX1 but less extensively than in KHE; they also express CD34, thus sharing the mixed lymphatic-blood vascular differentiation of KHE.

GLUT1 negative.

Key Features

**KAPOSIFORM HEMANGIOENDOTHELIOMA AND TUFTED ANGIOMA**

KHE and TA are closely related, if not synonymous, entities that together account for the vast majority of cases of KMP, caused by intratumoral platelet trapping.

**KHE**

- Ill-defined, frequently coalescing nodules composed of fascicles of moderately plump, spindled, endothelial cells with bland nuclei and eosinophilic-to-clear cytoplasm.
- The spindle cells form slit-like lumina that contain erythrocytes and sweep around pericyte-rich nests of more epithelioid cells that surround platelet-rich microthrombi.
- Mitotic activity is usually low.
- Hemosiderin granules and extravasated erythrocytes are often prominent; tumor cell cytoplasm within epithelioid nests often contains erythrocyte fragments and hyaline globules.
- Often displays a prominent component of dilated lymphatic vessels at periphery of tumor nodules and in surrounding fibrotic stroma.
- Spindle cells are immunoreactive for CD31 and strongly coexpress blood vascular markers (CD34) and lymphatic markers (podoplanin, LYVE-1, and PROX1).
- GLUT1 negative.

**TA**

- Discrete lobules of capillaries scattered within dermis and subcutis in cannonball pattern.
- Fibrotic or normal intervening dermal collagen and subcutis.
- Tumor lobules are composed of tiny capillaries with pinpoint lumina that may contain microthrombi; the tightly condensed often bulge into peripheral crescentic, thin-walled vessels.
- Tumoral endothelial cells may be focally spindled but lack the sweeping fascicles of spindle cells and the nodules of epithelioid cells seen in KHE.
- Endothelial cells are focally immunoreactive for lymphatic markers, such as podoplanin, LYVE-1, and PROX1 but less extensively than in KHE; they also express CD34, thus sharing the mixed lymphatic-blood vascular differentiation of KHE.
- GLUT1 negative.

Pitfalls in Diagnosis

**KAPOSIFORM HEMANGIOENDOTHELIOMA AND TUFTED ANGIOMA**

- Lack of appreciation of spindle cells may lead to misdiagnosis as the much more common neonatal tumor IH.
- The abnormal component of large lymphatic vessels in KHE may be a prominent feature and can strongly resemble a hemorrhagic LM, with which it shares podoplanin (D2-40) positivity.
- Failure to diagnosis KHE/TA in biopsy material may lead to persistent, even life-threatening hemorrhage during tumor resection by an unsuspecting surgeon.
- Limited biopsy material due to bleeding during the procedure may poorly demonstrate characteristic histologic features—negative immunostaining for GLUT1 (positive in IH) and positivity for PROX1 or podoplanin (negative in IH) can be helpful in distinction from IH.

Similar to Kaposi sarcoma, the spindle cells form slit-like lumina that contain erythrocytes (Fig. 15). The spindle cells often sweep around pericyte-rich nests of more epithelioid endothelial cells and pericytes that surround platelet-rich microthrombi highlighted by CD61 or CD31 immunostaining. Mitotic activity is usually low. At the margin of the lesion, the spindle cells may freely infiltrate into the surrounding adipose tissue and between collagen bundles, or they may be encased by desmoplastic stroma. Hemosiderin granules and extravasated erythrocytes are often prominent, and the tumor cell cytoplasm may contain erythrocyte fragments and hyaline globules. The tumor lobules and marginal soft tissue often display a prominent component of dilated, abnormally distributed lymphatic vessels. Residual KHE lesions after successful medical treatment appear as dormant, often sclerotic, versions of the original disease process.

The spindle cells of KHE are immunoreactive for CD31 and CD34 and for markers of lymphatic differentiation, such as podoplanin (often demonstrated with the D2-40 antibody (Fig. 16), PROX1, and LYVE-1 (see Fig. 16)). Expression of von Willebrand factor is more variable. All lesional endothelial cells are negative for GLUT1 and other IH/placental vascular markers. Electron microscopy demonstrates endothelial cells with interlocking processes and junctions, poorly formed basement membranes, and scant pericytes.

TA is characterized histologically by discrete lobules of capillaries scattered within the dermis.
and subcutis in a so-called cannonball pattern (Fig. 17). Intervening dermal collagen and subcutis are often fibrotic but may be histologically normal. The tumor lobules are composed of tiny capillaries with pinpoint lumina that may contain microthrombi. The tumoral capillaries are tightly condensed and sometimes bulge into peripheral crescentic, thin-walled vessels. Endothelial cells may be focally spindled, but this feature is seen less prominently than in KHE. Also, TA lacks the sweeping fascicles of spindled cells and the nodules of epithelioid cells seen in KHE. Mitotic figures are rare. Endothelial cells within the lobules of TA may focally immunoreact for podoplanin, LYVE-1, and PROX1 but less extensively than is often seen in KHE. As with KHE, lesional endothelial cells are GLUT1 negative.

Fig. 15. KHE. Set within fibrotic stroma, fascicles of spindled endothelial cells form slit-like lumina containing erythrocytes and sweep around epithelioid nodules (A). The epithelioid nodules (B) are rich in pericytes and contain cytoplasmic hyaline globules, erythrocyte fragments, and platelet-rich fibrin thrombi (arrowhead) (the histologic correlate of KMP).
Pathogenesis
The significant degree of histologic overlap between TA and KHE and the association of these two entities with KMP suggest that TA is a milder, more superficial form of KHE. At a minimum, these lie at ends of a disease spectrum. The endothelial expression of lymphatic-associated antigens displayed by these tumors supports the concept that these tumors, like Kaposi sarcoma and a subset of angiosarcomas, have at least a partial lymphatic endothelial phenotype. Human herpes virus 8 sequences, characteristic of Kaposi sarcoma, have not been identified in either KHE or TA and neither has been linked to HIV infection.

Fig. 16. KHE, podoplanin (D2-40) peroxidase immunohistochemistry. Lobules of spindled endothelial cells that stain positively with the D2-40 antibody curve around nests of more epithelioid cells with central microthrombi. Dilated thick and thin-walled vessels, some expressing podoplanin, are present in the surrounding fibrotic stroma. GLUT1 immunoreaction is negative (not shown).

Fig. 17. TA. A cannonball distribution of densely packed capillary lobules in the dermis is classic. The tumor lobules are composed of tiny capillaries with pinpoint lumina, some containing microthrombi. Focally, the capillary endothelial cells are spindled, but less prominently than in KHE. TA and KHE share histologic and immunophenotypic features and likely represent a singular disease spectrum (see text). Together, TA and KHE and account for most cases of KMP.
The selective thrombocytopenia that characterizes the coagulopathy of KMP can be attributed to platelet trapping within KHE and TA vascular beds. Strong coexpression of lymphatic markers and the blood vascular marker CD34 by KHE and TA argues for an abnormal, mixed lymphatic-blood vascular phenotype and may explain the propensity for platelet trapping. Platelet transfusions, although sometimes clinically necessary, have in some cases paradoxically worsened the coagulopathy. This suggests that platelet activation within the tumor may amplify tumor growth by stimulating vascular proliferation, presumably by release of angiogenic agonists, such as platelet-derived growth factor. A self-sustaining cycle of platelet trapping and tumor growth may thus underlie the development of these lesions and KMP.

**Differential Diagnosis**

| IH | See box: **Differential Diagnosis: Infantile Hemangioma** |
| KHE and TA | Strongly associated with KMP | Spindled endothelial cells coexpress blood vascular markers (CD34) and lymphatic markers (podoplanin, LYVE-1, and PROX1) |
| Plasma cell infiltrates absent |
| Kaposi sarcoma | Extremely rare in children | Does not cause KMP | Spindle cells coexpress blood vascular and lymphatic markers, as in KHE/TA, but lack lobularity of KHE/TA |
| Contains characteristic plasma cell infiltrates lacking in KHE/TA |
| Pyogenic granuloma | Those arising in skin affected by a vascular malformation may also mimic the clinical appearance of KHE | Characteristic edematous stroma and granulation tissue-type changes |
| Lack of spindled endothelial cells |
| Generally larger, more loosely packed lesional vessels |
| Lack of lymphatic endothelial markers (except in adjacent normal lymphatic vessels) |

**MULTIFOCAL LYMPHANGIOENDOTHELIOMATOSIS WITH THROMBOCYTOPENIA**

Multifocal lymphangioendotheliomatosis with thrombocytopenia (MLT) is a distinctive disorder characterized by multiple congenital and progressive vascular lesions and complicated by chronic mild-to-moderate thrombocytopenia. It involves skin, viscera, and (in some cases) bone, synovium, or muscle. Clinically significant gastrointestinal bleeding is universally present and may be life threatening. North and colleagues first described MLT in 2004 with highly characteristic histology, multifocal tissue involvement, and consistent expression of the lymphatic-associated marker LYVE-1. A clinically and histologically equivalent series of cases was independently recognized and reported by Prasad and colleagues as congenital cutaneovisceral angiomatosis with thrombocytopenia.

MLT is characterized by cutaneous lesions that often number in the 100s at birth; these are flat or indurated red-brown to burgundy plaques or papules, often with central pallor or scaling, that may measure up to a few centimeters in diameter. Appearance of new lesions and slow progression of existing lesions, without evidence of regression, is typical. Similar lesions in the gastrointestinal tract cause severe gastrointestinal bleeding beginning in infancy. Some patients have extensive pulmonary involvement complicated by hemoptysis and melena. Rare reported cases have involved liver, spleen, kidney, muscle, and/or synovium. Patients have mild-to-moderate, fluctuating thrombocytopenia with essentially normal prothrombin time, partial prothrombin time, and fibrinogen level. Gastrointestinal bleeding may spontaneously stabilize as the child grows, but partial gastrointestinal resection is often needed for effective hemostasis. Corticosteroids, interferon-alfa, thalidomide, and bevacizumab (avastin) have been reported of possible value in some but not all cases. No racial or sexual predilections have emerged.

**Microscopic Features**

MLT lesions involving the skin consist of delicate vessels scattered throughout the dermis/subcutis and lined by a monolayer of slightly hobnailed endothelial cells that focally form papillary projections. These projections are often complex and seem to float in the luminal plane of section (Fig. 18). The endothelial cells show strong immunopositivity for CD31, CD34, and LYVE-1 (Fig. 19) and light-to-absent
positivity for podoplanin. They are negative for GLUT1 and other IH-associated antigens. Mitotic figures are rare or absent, although increased endothelial expression of Ki-67 (approximately 15% of cells) correlates with the clinically observed progression of some lesions.

The initial differential diagnosis of MLT must include many other multifocal vascular skin disorders presenting in infancy or childhood, including diffuse infantile hemangiomas, hereditary hemorrhagic telangiectasia (HHT), blue rubber bleb nevus syndrome, glomuvenous malformations (GVMs) (glomangiomas), and Maffucci syndrome. The skin lesions of MLT, however, are unique in their clinical and histologic appearance and usually far more numerous than is typical for the other conditions (except diffuse infantile hemangiomas). Biopsy and histologic evaluation, if necessary supplemented by immunohistochemistry, is diagnostic.
Fig. 19. MLT, CD31 (A), CD34 (B), and LYVE-1 (C) peroxidase immunohistochemistry. Endothelial cells lining the lesional vessels and their papillary intraluminal projections stain positively with the panendothelial marker CD31 (A). They also strongly coexpress the blood vascular endothelial marker CD34 (B) and the lymphatic endothelial marker LYVE-1 (C). Staining for the additional lymphatic marker podoplanin is typically moderate-to-light and is absent in some cases (not shown). The consistent association of MLT with selective thrombocytopenia (see text) draws parallels to the strong association of thrombocytopenia with the KHE/TA disease spectrum, also characterized by coexpression of lymphatic and blood vascular markers.39,49,58
**Pathogenesis**

It is debatable if MLT lesions are best considered tumors or malformations. Reported cases are sporadic. Component endothelial cells coexpress CD34 and LYVE-1 and may focally express podoplanin, making blood-vascular versus lymphatic-vascular differentiation ambiguous. The association of MLT with selective thrombocytopenia draws parallels to the strong association of severe trapping (KMP) with KHE and TA—two vascular entities that also express mixed lymphatic and blood vascular endothelial markers.39,40,60

**VASCULAR MALFORMATIONS**

Vascular malformations may contain venous, capillary, lymphatic, or arterial components in any combination and have been associated with a number of dysmorphic syndromes.5,64 Both lymphatic and blood vascular malformations represent developmental errors of embryonic vasculature, generally grow slowly and proportionately with the overall growth of the child, and persist throughout life. In contrast, vascular tumors, such as IH, KHE, and pyogenic granuloma, are inherently proliferative lesions that grow out of proportion to the child's growth and (depending on type) may regress spontaneously. Histopathologic distinction between vascular malformation and tumors can be difficult, not only due to lack of clinical history but also because the gross and microscopic appearances of developmental anomalies tend to evolve during postnatal life. Factors causing this evolution include progressive or intermittent vascular ectasia, recruitment of collateral vessels, organizing thrombosis, hormonal modulation, and reactive neovascularization in response to abnormal intralesional hemodynamics. It is also possible that the intrinsic but still undefined molecular abnormalities that cause abnormal in utero vascular development may sometimes continue in postnatal life and cause increased mitotic potential or aberrant responses to angiogenic factors. To complicate things further, rare macrocystic LMs may seem to regress if scarring prevents filling of the cystic vessels. Despite these uncertainties, vascular malformations can usually be recognized by their presence at birth, slow proportionate growth, lack of regressive behavior, and relative mitotic quiescence. Some malformations that are presumed congenital may be temporarily hidden because of their deep location, which complicates preoperative diagnosis. The histopathologist's task is to confirm or dispute the clinical impression and to subclassify malformations based on the constituent vessels and (for blood vascular malformations) presence or absence of histologic evidence of arteriovenous shunting. Correlation with clinical and radiological

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<td>- Represent developmental errors of the embryonic vasculature</td>
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information is often essential. Key clinical features and current histopathologic diagnostic criteria are summarized for each of the major categories of vascular malformations, beginning with those arising from the blood vasculature. Endothelial cells of all vascular malformations, both lymphatic and blood vascular, are immunonegative for markers that are specific for IH, such as GLUT1.13–15,21,22

**CUTANEOUS CAPILLARY/VENULOCAPILLARY MALFORMATIONS (PORT-WINE STAINS)**

**Clinical**

Abnormalities of the superficial cutaneous vascular plexus are heterogeneous in etiology and presentation. They include both capillary/venulocapillary malformations and telangiectasias. Some of these are multifocal and associated with syndromes linked to known genetic mutations. These inherited disorders are rarely encountered by pathologists and recently have been reviewed elsewhere.65–67 This section focuses on a well-recognized clinicopathologic entity of unknown etiology and referred to by clinicians as port-wine stain (PWS). When diagnosing this distinctive venulocapillary malformation, this term is useful to pathologists for communicating a specific clinicopathologic entity to clinicians.

PWSs are congenital vascular anomalies of the skin and occur with an equal gender distribution in 0.3% of all newborns.68 Their histology is characterized by the presence of normal numbers of dilated vessels of mature capillary or venular type, located within the dermis and in some cases extending into the superficial subcutis. They are in essence nonproliferative, congenital lesions that do not involute and are, therefore, best categorized as vascular malformations. Many PWSs, however, become thickened and nodular over a period of many years, primarily due to progressive vascular ectasia. Clinically, PWSs appear as sharply demarcated geographic stains. They are usually unilateral and segmental but may be bilateral and/or multisegmental. PWSs have traditionally been included under the clinical rubric of nevus flammeus, along with the common nevus flammeus neonatorum, known colloquially as salmon patch, stork bite, or angel kiss. The latter differ from PWS, however, in that they are common in newborns and occur as pink macules, most commonly located on the glabella, nape of the neck, and eyelids. They may deepen in color with exercise or emotional upset, often fade with time, and are likely to represent focal areas of physiologic vascular dysfunction. PWSs, alternatively, are relatively rare macular lesions that do not fade over time and, as discussed previously, may become nodular, raised, or darker as patients age. They generally present on the skin of the head and neck, often within the distribution of the trigeminal nerve. Pulsed dye laser therapy lightens the stain in most patients and may clear it in some patients. A significant complication of PWS in some patients is generalized soft tissue and/or bone hypertrophy in the area of the cutaneous stain. Pyogenic granulomas may arise within the stain. PWSs involving the V1 trigeminal dermato-mere may be accompanied by ipsilateral leptome-ningeal and choroid venulocapillary malformations (Sturge-Weber syndrome), resulting in seizures and ocular abnormalities, including glaucoma. Geographic cutaneous stains mimicking PWS may sometimes directly overlie deeper arteriovenous, lymphatic, or mixed LMs/VMs (eg, in Klippel-Trenaunay syndrome [KTS]). These latter PWS-like vascular stains are histologically distinct from true PWS and instead represent cutaneous extensions of an underlying deep malformation.

**Microscopic Features**

PWS biopsies from infants and young children may not reveal the characteristic vessel ectasia that generally does not become prominent in histologic sections until patients are approximately 10 years old, despite clinically evident red discoloration of the skin. Over time, dermal vessels of venulocapillary size and rounded contour become progressively dilated and filled with erythrocytes (Fig. 20A). These vessels are rounded in contour and are lined by thin, elongated endothelial cells associated with peripheral pericytes; neither cell population shows evidence of mitotic activity. Vessels walls become more thickened and fibrous with time. Beyond this fibrous wall thickening, vessels in areas demonstrating generalized soft tissue hypertrophy may develop plump coats of loosely organized, well-differentiated, h-caldesmon–positive smooth muscle fibers.69 The cobblestoning clinically observed in many mature PWSs reflects protrusion of dermis containing dilated vessels between adnexal anchors (Fig. 20B). Gross nodule formation reflects focally exaggerated vascular ectasia and/or late development of complex epithelial, mesenchymal, and neural hamartomatous changes.70

**Pathogenesis**

There is no evidence of an inherited genetic basis of PWS, although the strongly segmental pattern of PWS and Sturge-Weber syndrome suggests the possibility of mosaicism due to somatic mutation of otherwise lethal genes.
Immunohistochemical evaluation for general endothelial and pericytic markers, basement membrane proteins, and fibronectin has not shown differences between normal skin and PWS. Although it remains controversial whether or not dermal vessels are actually increased in number in PWS compared with normal skin, there is no evidence that the number of vessels in these lesions changes with age. Ectasia begins within superficial vessels and progressively extends to deeper vessels, eventually extending into the reticular dermis and focally into the subcutaneous tissue. Studies using S-100 immunostaining have reported a decrease in perivascular nerve density in PWS, suggesting that the progressive vascular dilatation characteristic of these lesions may be due to inadequate innervation. This observation warrants further study.
VENOUS MALFORMATIONS

Clinical

Terms used in the past to refer to lesions now recognized as VMs include cavernous hemangioma and venous hemangioma. Use of these outdated terms as diagnostic labels for lesions that are biologically consistent with VM is confusing to clinicians (and inaccurate) and should be abandoned. So-called cavernous hemangiomas or cavernomas of the brain, terms still firmly entrenched among neurosurgeons, are localized collections of massively dilated capillaries or venules rather than veins.

VMs are typically singular lesions, either localized or segmental, with no associated abnormalities, although some occur as part of complex syndromes. Superficial lesions enlarge under conditions that increase venous pressure (e.g., dependency or exertion) and impart a blue color to skin and mucosal surfaces. Extensive lesions may be complicated by chronic, low-grade consumptive coagulopathy, and phleboliths are common. MRI shows a bright hypersignal on T2-weighted spin-echo sequences due to slow flow.

Multiple VMs occur as a familial mucocutaneous disorder and also in the poorly understood dysmorphic syndrome known as blue rubber bleb nevus syndrome, first described in 1958 by Bean. Blue rubber bleb nevus syndrome comprises an association between multiple VMs of the skin and the gastrointestinal tract, complicated by gastrointestinal bleeding. VMs have also been described in patients with Turner syndrome.

Microscopic Features

VMs are characterized by abnormal collections of veins that are superficial or deep, diffuse or localized, and solitary or multiple. VMs are generally less well circumscribed than IHs and, also unlike IHs, are lined by flat, mitotically inactive endothelial cells (Fig. 21A). The venous nature of these malformations is implied by the presence of a variable amount of well-differentiated smooth muscle in the vessel walls (usually scant relative to luminal diameter), the absence of an internal elastic membrane, and lumina filled with erythrocytes. Vessels of capillary or venular proportions may also be present within the lesion. Component veins vary with regard to luminal size and wall thickness both between and within individual lesions. Those excised from some patients, particularly with KTS, may show extreme disorganization of component smooth muscle fibers. The lining endothelial cells are positive for CD31, vWF, and CD34 and are negative for GLUT1 and other IH-associated markers.

Luminal thrombi in various stages of organization, sometimes including calcified phleboliths, are common in VMs, presumably reflective of stasis in these low-flow lesions. Recanalizing thrombi may demonstrate intravascular papillary endothelial hyperplasia (Fig. 21B). Although it may seem concerning for possible malignancy, this histologic pattern simply represents an exuberant response of endothelial cells to organizing thrombus. It was first described by Masson in 1923 in hemorrhoidal veins and has been referred to alternatively as Masson tumor, Masson vegetant intravascular hemangiendothelioma, and Masson pseudoangiosarcoma. Early stages of this organizing process show growth of endothelial cells into fibrinous thrombus material, which divides it into papillary fronds lined by a single layer of plump endothelial cells with no significant cytologic atypia. In later stages, the fibrin cores of the papillae become collagenized and hyalinized, and the endothelial lining becomes attenuated. Fusion of the lesional papillae may form an anastomosing meshwork of vessels separated by connective tissue stroma reminiscent of angiosarcoma, but the striking pleomorphism, necrosis, and relatively high mitotic rate of angiosarcoma are lacking. Although this type of lesion, due to its etiologic association with organizing thrombi, has a predilection for pre-existing VMs, it can also present as a mass within an apparently normal vein, most commonly in adults; rarely, it occurs within an organizing extravascular hematoma. Foci of intravascular papillary endothelial hyperplasia are common in VM and serve to help distinguish these low-flow lesions from high-flow AVMs.

Pathogenesis

Although the vast majority of vascular malformations are sporadic, rare familial forms of some types have allowed identification of specific genes required for normal vascular morphogenesis and potentially altered by somatic mutation in sporadic malformations. Multiple mucocutaneous VMs inherited as an autosomal dominant trait have been linked to a locus (VMCM1) on chromosome 9p21 and shown associated with activating missense mutations in the endothelial cellspecific TIE-2 tyrosine kinase gene. This may explain the histologic structure of VM, because the agonist ligand for TIE-2, angiopoietin-1, has been shown to induce endothelial sprouting, although many questions remain. Multiple VM also occur without recognized
etiology in Maffucci syndrome, a rare congenital disorder also characterized by dyschondroplasia, multiple enchondromas, and spindle cell hemangiomas. Similarly, blue rubber bleb nevus syndrome consists of multiple gastrocutaneous VM associated with gastrointestinal bleeding and anemia; some cases are sporadic, others autosomal dominant, and all without known etiology.

**GLOMUVEOUS MALFORMATIONS**

Lesions characterized by presence of benign glomus cells have been subclassified historically into various categories, such as solid type, diffuse type, solitary type, multiple type, adult type, and pediatric type. Current evidence supports division of these lesions into two major categories: (1) the glomus tumor proper, a cellular neoplasm that
tends to be well-circumscribed, solitary, and subungual, and (2) the so-called glomangioma, a frequently multifocal lesion, more properly termed, glomuvenous malformation (GVM), that presents in infants or children and histologically resembles a VM in which lesional vessels are surrounded by layers of glomus cells. The following discussion is restricted to this second category, which accounts for 10% to 20% of all glomus cell lesions.

**Clinical**

GVMs are superficial lesions that become evident in childhood or adolescence and generally cover a large cutaneous area. They appear either as multiple, widely distributed to confluent, soft, red-to-blue nodules or as pink to deep blue multifocal plaque-like lesions. Although clinically resembling VMs, GVMs differ in several ways. As recently described by Mounayer and colleagues, they tend to be more nodular or cobblestone-like in appearance, appear bluer and less compressible, and do not swell with exercise or dependency.

GVMs are less painful than the adult-type glomus tumor proper but may be tender to palpation, and attacks of pain may occur during menstruation and pregnancy. Due to their more expansive and multifocal nature, GVMs are less amenable to surgery than common glomus tumors, and residual lesions after subtotal resections may progress locally. Sclerotherapy is less effective for GVMs than for VMs. Argon, carbon-dioxide, and pulsed dye laser therapies may be helpful. Reported cases have behaved in a benign fashion.

**Microscopic Features**

GVMs consist of dilated, thin-walled veins in the dermis and subcutaneous tissue. They are histologically similar to those comprising VMs but instead are surrounded by one or more layers of cuboidal glomus cells (Fig. 22). They are often distributed as separate nodules. Adequate sampling is important, because the glomus cell component can be variable from region to region and vessel to vessel. Some microscopic fields may lack the glomus cells entirely. As in VMs without glomus cells, many GVMs contain organizing thrombi or phleboliths, reflective of stasis.

**Pathogenesis**

Most GVMs are sporadic; some rare familial cases have demonstrated an autosomal dominant pattern of inheritance. Based on linkage disequilibrium studies with these families, a locus for GVMs (termed, VMGLOM) has been mapped to chromosome 1p21-p22. Sporadic glomangiomas may result from somatic mutations at this locus. The VMGLOM locus is unrelated physically to the site on 9p that is linked to familial forms of VM.

**ARTERIOVENOUS MALFORMATIONS**

**Clinical**

Like all vascular malformations, AVMs are the result of errors in vascular morphogenesis and are not neoplastic in origin. Use of the outdated term, arteriovenous hemangioma, is thus inappropriate. AVMs are usually evident at birth and associated with an often clinically significant degree of arteriovenous shunting. Those with superficial extension may raise skin temperature and produce a palpable thrill or pulsation. Clinically significant hemorrhage and local tissue ischemia due to arterial steal are relatively common. Deep lesions may not become apparent until later in childhood or even adolescence or adulthood if shunting is low grade. AVMs tend to progress over time as collateral arterial flow is recruited into the low-resistance vascular bed. For the same reason, they often recur with a vengeance if incompletely excised or inadequately embolized.

**Microscopic Features**

The histologic appearance of AVMs often varies considerably from one area to another, and the actual arteriovenous shunts, which are tiny and numerous, are difficult to find without extensive sectioning or special techniques. Most histologic sections show beds of arterioles, capillaries, and venules within a densely fibrous or fibromyxomatous background, intermixed with numerous larger caliber arteries and thick-walled veins (Fig. 23A). The arteries are often tortuous, and the veins may show impressive adventitial fibrosis and irregular intimal fibrosis. There is no evidence of thrombosis or intravascular papillary endothelial hyperplasia, consistent with the abnormally high venous flow and pressure. Scattered dilated lymphatics may be present but are usually not prominent. Involved skin often contains a prominent pseudoangiosarcomatous proliferation of small vessels, creating a ragged, cellular appearance that lacks the delicate lobularity of IH (Fig. 23B). Isolated foci of mitotically active small vessel proliferation reminiscent of a vascular tumor, such as IH or pyogenic granuloma, can also be seen in more deeply seated regions of many AVMs, admixed with the large vessel component. This proliferative component may dominate the histologic picture in deep intramuscular AVMs, in particular those involving the
tongue, potentially leading to a misdiagnosis of hemangioma. These unusually cellular AVMs, like the more typical forms of AVM, are negative for GLUT1 and other IH-associated antigens. The capillary proliferation in AVMs is likely stimulated by tissue hypoxia resulting from arterial steal, but this has not been proved. Clinical and radiologic correlation with histology is essential in the diagnosis of AVM.

Arterial embolization using polyvinyl alcohol or other foreign materials precedes most surgical resections of AVMs, to reduce intraoperative bleeding. This elicits a variable acute inflammatory response within the involved tissues. Tissue necrosis is a rare complication.

**Pathogenesis**

Unlike AV fistulas, which are often acquired lesions and are characterized by one or a few large AV shunts, AVMs are more complex developmental anomalies with myriad, perhaps millions of, small abnormal AV connections that bypass a normally controlled, high-resistance vascular bed. The vast majority of AVMs are sporadically occurring single lesions of unknown etiology, although it is tempting to speculate that somatic mutation in genes that control arterial and venous differentiation might be involved in their pathogenesis. AV shunts are seen less commonly in familial disorders, such as HHT and the capillary malformation–AVM disorder (CMAVM). CMAVM, characterized by multiple atypical cutaneous capillary malformations and increased incidence of AVMs, is caused by inactivating mutations in RASA1. HHT, also known as Osler-Weber-Rendu syndrome, is an autosomal dominant disorder characterized by multisystemic angiodysplasia leading to frequent epitaxis, telangiectasias, GI bleeding, and arteriovenous shunts in the liver, brain, and lung. It has been linked to mutations in two genes and has therefore been designated HHT type 1 (gene, endoglin; chromosome 9q34.1) and HHT type 2 (gene, ALK-1, chromosome 12q11-q14; this is not the same gene as the ALK-1 of anaplastic large cell lymphoma or inflammatory myofibroblastic tumors). HHT in association with juvenile polyposis has been linked to mutations in SMAD4.

**LYMPHATIC MALFORMATIONS**

**Clinical**

LMs have traditionally been referred to as lymphangiomas, despite general absence of significant endothelial mitotic activity. Just as blood vascular malformations are presumed developmental errors in morphogenesis of the blood vasculature, LMs are thought to be errors in morphogenesis of the lymphatic vascular system. Accordingly, most LMs are usually evident at birth or within in the first year or two of life. In addition to the more common presentations in skin and subcutis, LMs may also involve deeper soft
tissues, bone, or viscera. Those occurring in these deep tissues may not become evident until older childhood or later. They can be localized or regional and may diffusely involve many tissue planes or organ systems.

In current practice it has been found useful to subclassify LMs as either macrocystic, microcystic, or combined. Macrocystic LMs, defined by a cyst diameter of at least 0.5 cm, have traditionally been termed, cystic hygromas. Microcystic LMs are more common and may develop anywhere. Macrocystic LMs most commonly occur in the loose connective tissue of the neck, axilla, chest wall, or groin and often change in size due to progressive distention of the lymphatic spaces by lymph fluid. LMs often enlarge with systemic or local infection, and the macrocystic forms rarely spontaneously regress following
infection, presumably due to destruction and scarring of the dilated cysts. Surgical excision of macrocystic LMs has significant morbidity, and a mainstay of therapy has become sclerotherapy with irritants, such as killed bacteria (known as OK-432) or doxycycline.\(^{93,94}\) Combined microcystic and macrocystic LMs are common. Treatment of microcystic and combined microcystic-macrocytic LMs is problematic, and extensive surgeries may be necessary. Sclerotherapy is generally ineffective. Laser therapy may be helpful.

LMs are often associated with significant soft tissue (in particular fat) and bony overgrowth. Pathogenesis of this intriguing overgrowth phenomenon is not understood. LMs involving the superficial skin or mucosae typically form fragile, clear surface vesicles that often ulcerate or bleed and become dark. Many dermal or mucosal LMs are associated with more deeply seated lesions composed of larger vessels, explaining the frequent recurrence of resected dermal lesions after skin grafting. Upper airway obstruction is a significant risk in LMs involving the tongue or oropharynx. Chylous ascites/intestinal lymphangiectasia or pleural or pericardial effusions may complicate abdominal and thoracic LMs.

Diffuse LM, often called lymphangiomatosis, refers to an extensive LM involving viscera and/or bone, often with coincident involvement of skin or soft tissues of the retroperitoneum or mediastinum. Spleen, liver, lung, and intestine are commonly involved viscera. Clinical morbidity is high due to the lung involvement, effusions, and bone erosion and fracture.

**Microscopic Features**

Microcystic LMs are comprised of dilated small vessels with angular-to-rounded contours lined by a single layer of flattened-to-slightly hobnailed endothelial cells, rimmed by rare pericytes and little or no smooth muscle (Fig. 24A). These are filled with clear fluid and sometimes a few lymphocytes. Traumatized lymphatic vessels may contain erythrocytes. In microcystic LMs involving skin or mucosa, the dilated lymphatic vessels often protrude into superficial vascular papillae, causing bleb formation and epidermal/mucosal hyperplasia. Overlying epidermis may appear hyperkeratotic and verrucous, and the surrounding stroma may be fibrotic and chronically inflamed. The vessels of diffusely infiltrative microcystic LMs often wrap extensively around tissue structures, producing the appearance of free-floating tissue elements and a complex anastomosing vasculature reminiscent of lymphangiosarcoma (Fig. 24B). Focal papillary lymphoepithelial hyperplasia may be evident in some of the lesional vessels of these diffuse LMs. A low but appreciable level of proliferative activity indicated by cell cycle markers, such as Ki-67, may be present.

The vessels of macrocystic LMs have thicker, irregular coats of smooth muscle and/or fibrous tissue and may have valves. Vessel lumens usually contain proteinaceous material and a few lymphocytes and/or macrophages. In many LMs, the enlarged lumina contain abundant blood or organizing myxoid thrombus material resulting from vessel wall injury or communication with the venous system. This makes it difficult to distinguish veins from lymphatics and may suggest a venous or mixed venous-LM. This distinction can usually be made by immunoreaction for antigens, such as podoplanin (with the D2-40 antibody), that are expressed by lymphatic endothelial but not blood vascular endothelial cells (Fig. 25). As with normal lymphatic vessels, the endothelial cells of LM show light-to-absent staining for CD34, unlike the strong staining seen in blood vascular endothelial cells. The surrounding connective tissue often shows a lymphocytic infiltrate varying from a few scattered cells to striking aggregates containing lymphoid follicles.

Intraosseous LMs produce single, or more typically multifocal, cystic bony destruction, referred to as disappearing bone disease, Gorham disease, or Gorham-Stout disease. The affected bones undergo cortical erosion and absorption due to progressively dilated intraosseous lymphatic spaces, resulting in disappearance of bones in imaging studies, particularly plain film. Histologically, dilated, extremely thin-walled lymphatic vessels that may be difficult to appreciate in routine sections expand the marrow space, compressing and eventually thinning the cortical bone (Fig. 26A) sometimes to the point of pathologic fracture. Immunohistochemistry for the panendothelial marker CD31 is useful to identify the endothelial lining of the cystically dilated spaces, and immunohistochemistry for podoplanin confirms lymphatic differentiation (Fig. 26B). In many patients with multifocal bony involvement by LM, viscera (especially spleen) are also affected by LM. Periosseous soft tissue extension is common. Rare cases with similar but localized clinical and radiologic presentation may be associated with VM or AV fistula instead of LM.

Some spontaneously aborted fetuses with posterior cervical swellings, traditionally referred to cystic hygroma, have been shown to have increased cutaneous lymphatics (eg, trisomy 13 and 21) whereas those with monosomy X (Turner syndrome) do not show increased or dilated lymphatics.\(^{95}\)
Pathogenesis

Molecular mechanisms that underlie the developmental dysmorphogenesis of the lymphatic system that results in LM are largely unknown and likely diverse. Most LMs, by far, occur sporadically. Macrocystic LMs probably reflect developmental anomalies of the major regional lymphatic trunks, whereas diffuse microcystic LMs, such as those involving multiple bones and viscera, are more likely to reflect primary abnormalities in lymphatic development and caused by early embryonic somatic mutation or multifactorial germline genetic effects.

Some lymphatic abnormalities interpreted as LMs may be caused by primary or acquired impairment of drainage by large lymphatic collecting...
vessels and thus more properly categorized as examples of lymphedema. Secondary lymphedema is usually caused by lymphatic obstruction or destruction associated with trauma or lymphatic–venous communication, hampering their distinction from capillaries and/or veins in routinely stained tissue sections. This distinction can usually be accomplished by immunoreaction for antigens, such as podoplanin, that are expressed by lymphatic endothelium but not blood vascular endothelium. This facilitates classification of the lesion as lymphatic, venous, or mixed (the latter shown here), a distinction relevant to treatment choice.

**COMBINED VENOUS-LYMPHATIC MALFORMATIONS**

The close relationship between the lymphatic and venous systems during embryonic development may explain why some low-flow malformations include both a significant lymphatic component and a significant venous and/or capillary component. Lesions from patients with KTS most consistently exemplify this phenomenon, but solitary mixed malformations of lymphatic, venous, and capillary vessels are also commonly observed in nonsyndromic patients. KTS is a congenital disorder characterized by a combined lymphatic-capillary VM, usually involving one or more extremities, associated with skeletal and adipose tissue overgrowth in the involved segment.

**Microscopic Features**

The histology of KTS is generally typical of VM and LM, with variably distributed components of each. Overlying areas of cutaneous involvement compounded by reaction to expansion of dermal papillae by ectatic capillaries or lymphatics creates a PWS-like surface stain punctuated by angiokeratoma-like lesions. Eccrine glands are often embedded in myxoid stroma and unusually enlarged. Veins may demonstrate striking mural

**Fig. 25.** Mixed VM-LM, podoplanin peroxidase immunohistochemistry. Lymphatic vessels may contain erythrocytes due to trauma or lymphatico-venous communication, hampering their distinction from capillaries and/or veins in routinely stained tissue sections. This distinction can usually be accomplished by immunoreaction for antigens, such as podoplanin, that are expressed by lymphatic endothelium but not blood vascular endothelium. This facilitates classification of the lesion as lymphatic, venous, or mixed (the latter shown here), a distinction relevant to treatment choice.

Note the strong expression of podoplanin by lymphatic vessels, some containing erythrocytes, and the negativity of other vessels, also containing erythrocytes.
smooth muscle disarray. The malformations are largely cutaneous and subcutaneous but may also infiltrate deep skeletal muscle. Subcutaneous fat is increased.

REFERENCES


