Multifocal vascular lesions

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Abstract

Multifocal vascular lesions are important to recognize and appropriately diagnose. Generally first noticed on the skin, multifocal vascular lesions may have systemic involvement. Distinguishing among the different types of multifocal vascular lesions is often based on clinical features; however, radiological imaging and/or biopsy are frequently needed to identify distinct features and guide treatment. Knowledge of the systemic associations that can occur with different vascular anomalies may reduce life-threatening complications, such as coagulopathy, bleeding, cardiac compromise, and neurologic sequelae. This review provides a synopsis of the epidemiology, pathogenesis, presentation, workup, and treatment of several well-recognized multifocal vascular tumors and malformations.

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Vascular tumors and malformations may present as single or multiple lesions. Multiple vascular anomalies may involve visceral organs and merit an index of suspicion for systemic involvement. Both cutaneous and visceral vascular anomalies have been associated with coagulopathy, bleeding, cardiac compromise, and neurological sequelae; and as such, these anomalies are important to recognize and diagnose early. Distinguishing among the different types of vascular lesions is often based on clinical features, however radiological imaging and/or biopsy are frequently needed to identify distinct features. Knowledge of the systemic associations of various vascular growths is essential for comprehensive care. This review provides a brief synopsis of the epidemiology, pathogenesis, presentation, workup, and treatment of several well-recognized vascular tumors and malformations that present with multiple lesions. A chart of distinguishing features is also provided with the goal of highlighting both overlapping and unique features to aid in proper diagnosis (Table).¹

Vascular malformations

Multiple venous malformations

Venous malformations (VMs) are slow-flow vascular malformations composed of irregular blood vessels that grow over time and may lead to varying complications including disfigurement, bleeding, thrombosis, and pain.

Diagnosis is generally made clinically based on characteristic skin lesions. Classic histological findings reveal ectatic vascular channels lined by a single layer of cuboidal or flattened endothelial cells in the dermis or subcutaneous fat surrounded by a fibrous stroma or a smooth muscle cell wall. The differential diagnosis of VMs, includes other vascular lesions, such as hemangiomas, glomuvenous malformations and lymphatic malformations.

Pharmacologic interventions have yet to show consistently successful results; however, recent studies have made advances in the specific genetic mutations associated with VMs leading to improvement in diagnosis and hopefully more effective and targeted therapies.²

The TIE2-PI3K-AKT axis has been implicated as a key pathway that is mutated in venous malformations and specific types of mutations affecting this pathway correlate with different presentations of VMs such as blue rubber bleb nevus syndrome (BRBNS), inherited venous malformation cutaneomucosal (VMCM), and sporadic venous malformations, briefly reviewed below.

Blue rubber bleb nevus syndrome

BRBNS or Bean syndrome, first described in 1860 by Gascoyen and later described in 1958 by William Benett Bean, is a rare disorder characterized by cutaneous and visceral venous malformations, most commonly within the gastrointestinal (GI) tract, and less commonly in other organ systems, such as the central nervous system (CNS) and musculoskeletal system.³,⁴

BRBNS is a sporadic disorder, though cases have been reported in the literature with autosomal dominant inheritance perhaps describing families with multiple cutaneomucosal venous malformations.³ Somatic mutations have been reported in the endothelial cell tyrosine kinase receptor TIE2 (encoded by TEK) on chromosome 9p21.2.⁶ Males and females are equally affected.

Venous malformations present at birth or shortly thereafter and gradually increase in number and size with age. These lesions may vary in number from few to hundreds of skin lesions and have variable cutaneous clinical appearances ranging from small blue-black papules to large vascular appearing venous malformations, with the most common presentation described as a “rubber nipple.”⁷ In a minority of cases, GI involvement may present in the absence of cutaneous lesions.⁵

The cutaneous venous malformations may occur anywhere on the body, but favor the trunk and extremities. They may be asymptomatic or associated with hyperhidrosis and nocturnal pain specifically overlying the involved skin.³ Local consumptive coagulopathy can occur with abnormalities including elevated D-dimer and decreased fibrinogen. Cutaneous venous malformations tend not to bleed and are benign in nature.
Gastrointestinal malformations may present throughout the entirety of the GI tract, though there is a predilection for the small intestine. Lesions are prone to occult or obvious bleeding with resultant iron deficiency anemia. Less commonly, significant GI bleeding can occur with transfusion dependence. Rare complications such as intestinal torsion, intussusception and perforation have also been reported.

Evaluation should include a complete history and physical exam, complete blood count, local intravascular coagulopathy studies (D-dimer, fibrinogen, prothrombin time, partial thromboplastin time) and stool guaiac testing to detect anemia and GI bleeding; an elevated D-dimer has been found to be highly specific for VMs. Positive guaiac testing and anemia necessitate a full investigation of the GI tract to identify bleeding sites.

Treatment of cutaneous lesions is usually dependent on cosmetic disfigurement or functional impairment. Treatments include sclerotherapy, electrodesiccation, laser ablation and surgical excision.

The GI lesions are generally treated conservatively with treatments to address associated anemia, including iron supplementation and transfusions. Surgical intervention with resection, endoscopic sclerotherapy, photocoagulation, or banding may be necessary in cases of troublesome bleeding or severe anemia recalcitrant to medical therapy. Medical therapies including corticosteroids, octreotide and interferon-α have been historically utilized; recently sirolimus has been reported to be helpful in the treatment of symptomatic lesions. Management of associated coagulopathy may also be indicated.

Inherited cutaneomucosal venous malformations
Inherited cutaneomucosal venous malformations, also known as familial cutaneous and mucosal venous malformations or venous malformation cutaneous and mucosal (VMCMs), are rare and account for approximately 1% of patients with venous anomalies. VMCM is thought to be caused by a germline activating TIE2.
mutation with autosomal dominant inheritance and shows varying phenotypes within affected family members. An additional somatic mutation in TIE2 was found in one case of resected VMCM, suggesting the need for “second hit” mutation for formation of the venous malformation.

Though there is significant variation in skin findings, even among individuals from the same family, VMs typically appear as small (<2 cm) multifocal bluish purple soft and compressible lesions on the skin and mucosa. Ninety percent of patients with a mutation in TIE2 will develop mucosal lesions by the age of 20 years. Lesions are usually present at birth and increase in size with maturation. New lesions may also appear over time. While smaller venous malformations are generally asymptomatic, larger lesions (up to a few centimeters in diameter) may invade muscle and cause discomfort.

Few reports demonstrate the presence of VMs in the muscle, intestines, and lungs. Unlike BRBNS, VMCM malformations have a better prognosis as they tend not to bleed and life expectancy is that of the general population. Nonetheless, repeated examinations are recommended to assess for new onset pain as well as assess for localized intravascular coagulopathy (LIC) as may occur in an enlarging venous malformation.

Symptomatic lesions may necessitate treatment surgically with sclerotherapy and possibly excision. In the case of LIC treatment, an anticoagulant may be necessary to halt progression and relieve pain.

### Multifocal sporadic venous malformations

Over half of sporadic VMs were found to have heterozygous somatic mutations in TIE2. The most common mutation, L914F, has not been found to occur as a germline mutation suggesting it is incompatible with life. In contrast, the most common germline mutation in TIE2 found in inherited VMCM, R849W, has potentially weaker effects, likely necessitating an additional somatic mutation, or “second hit,” for VM development.

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<th>Cerebral cavernous malformations</th>
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<th>Capillary malformation-arteriovenous malformation syndrome</th>
<th>Multiple pyogenic granulomas</th>
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<tr>
<td>Congenital or acquired</td>
<td>Congenital</td>
<td>Congenital</td>
<td>Variable (infancy to adulthood)</td>
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<td>CCM1 (KRIT1), CCM2 (CCM2), CCM3 (PDCD10)</td>
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<td>(RASA1)</td>
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<td>Variable, stable to slowly progressive</td>
<td>Rapid onset over the course of several weeks</td>
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<td>Poor response to most pharmacologic interventions</td>
<td>Responsive to surgical modalities, reports of beta blocker therapy</td>
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<td>Severe, in most if not all</td>
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<td>Never</td>
<td>Intermittent depending on amount of bleeding</td>
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Multiple glomuvenous malformations

Multiple glomuvenous malformations (GVMs), or glomangiomas, are benign vascular neoplasms described by Touraine in 1936, roughly 6 years after Masson’s first description of a solitary glomus tumor in 1924. Multiple GVMs are rare and account for approximately 10% of cases of glomus tumors with the majority occurring in children. The solitary variant accounts for approximately 90% of cases and occurs more commonly in young adults.

GVMs arise from glomus cells which are modified smooth muscle cells, derived from the Sucquet-Hoyer canals comprised of arteriovenous anastomoses that make up specialized thermoregulatory units. Glomus cells are normally found in acral skin; however, glomus tumors may occur anywhere on the body suggesting derangement of these units. Glomus cells are normally found in acral skin; however, glomus tumors may occur anywhere on the body suggesting derangement of these units. Glomus cells stain positive for smooth muscle differentiation markers including smooth muscle actin (SMA) and muscle specific actin. Glomus cells have more recently been shown to have cytoplasmic positivity for smoothelin and Wilms tumor 1 (WT1); absence of WT1 in the endothelium of vascular structures helps to differentiate GVMs from glomus tumors.

Distinctive radiographic features on magnetic resonance angiogram (MRA) have been reported to include subtle arterial enhancement with early venous shunting and progressive filling of dilated venous spaces.

Surgical excision is considered the gold standard of treatment for symptomatic lesions and may pose challenges with multiple lesions. Treatment with neodymium-doped yttrium aluminum garnet (Nd:YAG), pulsed-dye, argon and carbon dioxide lasers, as well as sclerotherapy have been reported.

Cerebral cavernous malformations

Cerebral cavernous malformations (CCMs) are vascular lesions composed of clusters of dilated sinusoidal endothelial lined channels without intervening neural parenchyma, occurring within the CNS. CCMs differ from other vascular malformations such as arteriovenous malformations in that they are slow flow without smooth muscle or elastin in their lining.

Patients with CCMs may develop vascular malformations in areas other than the CNS, including the vertebrae, retina and skin, which show similar histological features.

CCMs may be inherited in an autosomal dominant fashion or occur sporadically and are estimated to have a 0.1%-0.5% prevalence in the general population. There is no clear gender predilection. Mutations at 3 chromosomal loci have been detected encoding Krev interaction trapped 1 (KRIT1), CCM2, and PDCD10 in CCM1, CCM2 and CCM3 respectively. CCM3 appears to have a more severe phenotype than CCM1 and CCM2 and affects a different pathway.

Patients typically present with malformations in the fourth decade of life. At the cerebral capillary level, these malformations range in severity from asymptomatic and found incidentally on imaging, to causing severe neurological symptoms, including hemorrhagic stroke, seizures, headaches or focal neurologic deficits. Surgical modalities are considered standard treatment for asymptomatic, accessible CMs. Observation should be elected for asymptomatic, incidental or surgically inaccessible lesions. Radiosurgery has been considered in highly symptomatic surgically inaccessible lesions.

Cutaneous lesions occur in 9% of patients with familial CCM (FCCM), particularly with KRIT1 mutations. Cutaneous lesions have been described as red macules, vascular nodules and hyperkeratotic vascular lesions; skin biopsy shows abnormal dilated thin-walled blood vessels. In 2009, Sirvente et al prospectively classified the cutaneous vascular malformations in 417 patients with FCCM based on the International Society for the Study of Vascular Anomalies (ISSVA) criteria. Three distinct categories were found: hyperkeratotic cutaneous capillary venous malformations (HCCVMs), capillary malformations and venous malformations in 39%, 34% and 21% of the patients respectively. Cutaneous lesions were most commonly single and found on an extremity. KRIT1 was found to be the most frequently mutated gene in cutaneous vascular malformations-FCCM patients.
Capillary malformation-arteriovenous malformation syndrome

Capillary malformation-arteriovenous malformation (CM-AVM) syndrome is an autosomal dominant disorder characterized by capillary malformations with or without arteriovenous malformations in the skin, muscle, bone, brain or spine. Capillary malformations (CMs) occur in approximately 0.3% to 0.5% of the population, most commonly on the head and neck, and are generally thought of as a benign, isolated finding or as a marker for underlying neurological or soft-tissue abnormalities. However, the presence of CMs should also prompt consideration of CM-AVM syndrome given a now recognized association with fast-flow lesions throughout the body.

The prevalence of CM-AVM syndrome is unknown. CM-AVM syndrome is primarily a familial autosomal dominantly inherited disorder caused by heterozygous inactivating mutations in the RAS p21 protein activator 1 (RASA1) gene, located on chromosome 5, though de novo mutations may also occur. While the penetrance of CM-AVM syndrome is over 95%, there is a wide clinical spectrum within affected family members.

Patients generally present with a solitary or multifocal congenital or acquired CMs with characteristic round or oval, pink, <1 cm to 3 cm macule or patch, 50% of which have a blanched peripheral rim or halo. Arterial flow on doppler may be seen within some of the CMs and large CMs are most likely to overlie an AVM and should be evaluated with ultrasound with Doppler (Figure 2).

AVMs are found in approximately 30% of affected patients with RASA1 mutations and may be cutaneous, subcutaneous, intramuscular, intrasosseous and intracerebral. Patients in whom the AVM involves the extremity in association with bony and soft tissue overgrowth (approximately one-third of patients with AVMs) are thought to have Parkes Weber Syndrome (PKWS) as part of CM-AVM syndrome.

Diagnostic criteria and management guidelines have been proposed for evaluation and management of patients with CM-AVM, though none have been firmly established. If more than 3 CMs or atypical CMs are identified, it is important to consider CM-AVM syndrome. If a family history of CMs is present or a RASA1 mutation has been confirmed, then the diagnosis is definite. Management of CM-AVM syndrome should include screening radiographic studies of the neuroaxis (MRI/MRA) to assess for fast-flow lesions and subspecialty evaluation pursued. Genetic testing is recommended for those in whom the diagnosis is uncertain. Of note, the presence of both CMs and AVMs may evolve over time; therefore, continued surveillance is advised even if initial screening studies are negative.

Vascular tumors and provisionally unclassified vascular anomalies

Multifocal infantile hemangiomas

Infantile hemangiomas (IHs) are the most common tumors of infancy. They have a predictable growth cycle including a proliferative phase, marked by rapid growth; a plateau phase, marked by minimal-to-no growth; and an involuting phase, during which the hemangioma slowly regresses. IHs are rarely life threatening and have variable health and cosmetic consequences depending on their size and location. Specifically, hemangiomas located along the airway or within the liver pose a significant morbidity and mortality risk and are associated with poor outcomes including death from airway obstruction and cardiac heart failure, respectively, among other complications.

Infants may present with different patterns of hemangiomas, each with distinct associations and prognoses. Most patients have one cutaneous infantile hemiogima; in 30% of cases there are multiple cutaneous lesions. The presence of 5 or more cutaneous hemangiomas accounts for approximately 3% of cases. The occurrence of multiple cutaneous hemangiomas, in particular 5 or more, is reviewed based on this presentation’s, probable pattern of behavior, and known associations (Figure 3).

Of note, it has been recommended that the terms “benign neonatal hemangiomatosis” and “diffuse or disseminated neonatal hemangiomatosis” (DNH), referring to varying presentations of cutaneous and/or visceral hemangiomas, be abandoned to avoid diagnostic confusion and potential grouping of in fact disparate conditions. Glick et al highlighted that the literature needs to be carefully reviewed because many cases may have been reported as IHs prior to recognition that there are other entities, such as multifocal lymphangioendotheliomatosis with thrombocytopenia (see below), that are associated with higher mortality.

Studies support that patients with 5 or more focal cutaneous hemangiomas are at a significantly higher risk of having internal hemangiomas, particularly in the liver, with the potential for serious complications. Therefore, routine screening with imaging and blood work is recommended for infants who present with 5 or more skin lesions. Segmental hemangiomas, even in isolation, have been reported in association with visceral hemangiomas. Most commonly, segmental facial hemangiomas were associated with visceral hemangiomas. Visceral involvement most commonly involved the liver, followed by the GI tract, brain, mediastinum, and lungs. Internal hemangiomas can occur without cutaneous IHs; however, the presence of multifocal IHs can herald visceral involvement.

Of interest, not all hepatic hemangiomas confer equal risk to affected patients. Christison-Lagay et al retrospectively analyzed

*FIGURE 2. Vascular patches on the trunk and arm of a child. A single pathogenic mutation in RASA1 gene was identified. An AVM may underlie the largest patch, as in this patient.*
Hepatic hemangiomas can range from asymptomatic to life threatening with congestive heart failure, fulminant hepatic failure, hypothyroidism and abdominal compartment syndrome. Early detection is important for prompt intervention and reduction of potential sequelae. In some cases enteroscopy or laparotomy was necessary to confirm diagnosis. The authors suggest that infants with profound anemia, melena, or hematochezia should be evaluated for GI hemangiomas even in cases without cutaneous IHs.

Although most hemangiomas eventually involute as part of their tripartite growth/regression cycle, many require medical and surgical management. With the influential report of propranolol for treatment of infantile hemangiomas, the traditional treatment approach for patients with both cutaneous and hepatic IHs dramatically shifted in 2008. Please see the first article in this issue, “Infantile hemangiomas complications and treatment” by Cheng et al, for details of management of infantile hemangiomas.

**Multifocal lymphangioendotheliomatosis with thrombocytopenia**

Multifocal lymphangioendotheliomatosis with thrombocytopenia (MLT), also known as congenital cutaneous angiomatosis with thrombocytopenia (CCAT), was described by North et al in 2004 as a newly recognized congenital vascular disorder. MLT is characterized by multifocal cutaneous and extracutaneous vascular lesions with thrombocytopenia, and is associated with a high mortality often linked to GI bleeding and lack of effective treatment.

MLT is a rare condition and as such, much remains unknown regarding its pathogenesis, full characterization as well as effective medical management. Case reports suggest that MLT is a congenital disorder without a familial pattern of inheritance.

Cutaneous findings have been described as slow, progressive onset of numerous distinctive red-brown plaques, papules or nodules without regression. Vascular lesions within the GI tract are associated with severe bleeding and localized consumption of platelets within the abnormal vascular tissue causing thrombocytopenia.

Skin biopsy shows distinctive dilated, thin-walled vessels in the dermis and subcutis lined by hobnailed, proliferative endothelial cells (10%-15% immunoreactive for Ki-67), with occasional endothelial tufts projecting into the lumen. Immunoreaction for the lymphatic marker lymphatic vessel endothelial receptor 1 (LYVE-1) is uniformly present while staining for GLUT1 is uniformly negative, helping to differentiate MLT from other multifocal vascular conditions.

The differential diagnosis of MLT includes other multifocal vascular conditions, such as multifocal IHs and BRBNS. Other vascular entities with lymphatic marker staining (D2-40 or LYVE-1) include kaposiform hemangioendothelioma, tufted angioma, Kaposi sarcoma, and lymphatic malformations, but the clinical features differ from MLT.

Management can be challenging and reported treatments have...
inclusion of medications utilized for other vascular anomalies such as oral prednisone, propranolol, interferon-α, and vincristine. Other agents, including thalidomide, bevacizumab and most recently sildenafil, have been reported.

Multiple (eruptive) pyogenic granulomas

Solitary pyogenic granulomas (PGs), also called lobular capillary hemangiomas or less often granuloma telangiectasicum, are well-described benign vascular tumors that occur in all ages, although they have a predilection for children and woman of reproductive age. The presence of multiple PGs is a rare phenomenon.

The occurrence of multiple PGs, termed eruptive pyogenic granulomas, is considered a benign self-limited disorder that may occur spontaneously in an otherwise healthy individual though case reports suggest many associated instigating factors. Eruptive PGs may be “localized” or “disseminated” depending on their distribution. Eruptive PGs are generally characterized by rapid growth in a matter of weeks. Lesions commonly appear as smooth pedunculated or sessile vascular papules ranging in size from approximately 2 to 20 mm, that bleed easily with minor trauma. Biopsy typically demonstrates hyperplastic clusters of capillaries arranged in a lobular architecture. Despite similar histologic features, GLUT1 staining can differentiate pyogenic granulomas from IHs, the latter with negative staining.

Though the pathogenesis remains unclear, it has been suggested that PGs evolve in the setting of an angiogenic stimulus, such as endothelial growth factor and fibroblast growth factor. A range of associations has been reported in prior case reports of multiple PGs including exclusion of an existing lesion, prior trauma (burns, laser), infection, states of high estrogen levels (pregnancy), medications (etretinate, isoretinoin), as well as underlying vascular anomalies (CMs, microscopic arteriovenous anastomoses). There have also been reports of associated malignancy.

With the exclusion of rare reports of congenital onset or intravascular or subcutaneous location, PGs typically appear to be located primarily on the skin or visible mucosa without systemic involvement and no algorithm or formal recommendations for systemic evaluation have been delineated. Review of the literature suggests that the common driving force behind the eruption of PGs may be an angiogenic factor and therefore physical examination and review of systems is warranted to attempt identification of potential triggers as outlined above. In fact, Strohal et al speculated that while the occurrence of localized PGs is likely due to trauma, disseminated PGs may indicate an endogenous and potentially occult angiogenic source and investigation for an underlying malignancy and infection should be pursued.

Although multiple PGs may regress or resolve spontaneously, typically over the course of 6–12 months, intervention may be indicated to minimize bleeding. Treatments vary from excision, electrocautery, and laser, most commonly CO2-laser and pulsed-dye laser therapy. Surgical excision was found more effective in limiting recurrence when compared to other surgical options. More recent literature cites the use of β-adrenergic receptor antagonists, topical and oral, in the management of these lesions.

References

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