Advances in the Medical Management of Vascular Anomalies

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Abstract

Keywords

- ▶ vascular anomaly
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- ▶ sirolimus
- ▶ propranolol
- ▶ timolol
- ▶ interventional radiology

Vascular anomalies comprise a spectrum of diseases that are broadly classified as tumors and malformations. Diagnosis is often challenging, given a wide range of clinical presentations with overlapping signs and symptoms. Accurate diagnosis is critical to determine prognosis and to generate a management plan, which frequently involves multiple subspecialists during different phases of treatment. An updated classification system provides structure and clear, consistent terminology, allowing for improved diagnosis, provider communication, and collaboration. Historically, treatment of vascular anomalies was primarily surgical and medical therapies were limited or ineffective. Recent discoveries of pharmacologic agents effective in treating vascular anomalies have broadened our medical therapeutic options, limiting the need for unnecessary or high-risk procedures and improving patients' quality of life.

Objectives: Upon completion of this article, the reader will be able to (1) discuss why standardized classification and terminology are essential for accurate diagnosis, communication between providers and treatment selection; (2) explain why management of complicated vascular anomalies is often multimodal and multidisciplinary; and (3) explain why sirolimus is an efficacious treatment option for multiple vascular tumors and malformations.

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Vascular anomalies comprise a heterogeneous group of disorders characterized by abnormal growth or development

of blood and/or lymphatic vessels. Diagnosis of vascular anomalies is often challenging due to the large variety of conditions which exhibit phenotypic heterogeneity and a wide range of symptomology and severity. Misdiagnosis may result in unnecessary testing, inadequate monitoring, or the use of potentially harmful and ineffective surgical procedures and medical treatments. Furthermore, usage of incorrect or outdated terminology may cause miscommunication between providers, delays in care, and treatment coverage issues. Accurate terminology and a standardized classification system are imperative for correct diagnosis and the proper management of patients with vascular anomalies.

The first classification system, proposed by Mulliken and Glowacki in 1982, divided benign vascular anomalies into hemangiomas and vascular malformations.¹ This classification was later adopted by the International Society for the Study of Vascular Anomalies (ISSVA) in 1996 and modified to categorize vascular anomalies as either vascular tumors or malformations. Vascular tumors are characterized by the abnormal proliferation of endothelial cells and aberrant blood vessels. In contrast, vascular malformations are networks of abnormal blood and/or lymphatic vessels that form during fetal development and have normal endothelial cell

Table 1 Classification of vascular tumors

Benign	Locally aggressive	Malignant
<ul style="list-style-type: none"> • Infantile hemangioma • Congenital hemangioma • Tufted angioma • Spindle-cell hemangioma • Epithelioid hemangioma • Pyogenic granuloma • Others 	<ul style="list-style-type: none"> • Kaposiform hemangioendothelioma • Retiform hemangioendothelioma • Composite hemangioendothelioma • Kaposi sarcoma • Dabska tumor, papillary intralymphatic angioendothelioma • Others 	<ul style="list-style-type: none"> • Angiosarcoma • Epithelioid hemangioendothelioma • Others

Source: Adapted from 2014 ISSVA Classification.

turn over. The ISSVA classification system was recently updated in 2014 to improve clinical relevancy and to incorporate medical advancements within the field such as newly named diagnoses, identified genes, and associated coagulopathies.²⁻⁴ The current classification system is a clinically useful tool for all medical and surgical specialists with the intended purpose of improving diagnosis, management, and communication between providers.

Vascular Tumors

Vascular tumors are classified as benign, locally aggressive, or malignant and include hemangiomas and rare tumors such as kaposiform hemangioendothelioma (KHE) and tufted angioma (TA; ▶Table 1). In the past, corticosteroids and traditional chemotherapeutics as single agents or as adjuncts to surgical interventions have been used to treat vascular tumors. However, these medical therapies have variable effectiveness and numerous known short- and long-term side effects. Propranolol, timolol, and sirolimus have been utilized in other pediatric diseases for many years but have only recently been recognized to be effective in treating vascular tumors.

Infantile Hemangiomas

Infantile hemangiomas (IHs) are common, benign cutaneous tumors that primarily consist of capillaries and proliferating endothelial cells and histologically stain positive for GLUT-1 during all phases of their life cycle.⁵ IHs characteristically begin to proliferate within a few weeks of life, enlarge for several months, and then slowly involute, sometimes requiring up to 10 years for regression. IHs are most commonly found in the head and neck area but may be located on any part of the body, including the internal organs, most commonly in the liver. IHs are categorized by the location in the dermis and/or hypodermis (superficial, deep, or mixed) and by pattern of distribution (focal, multifocal, or segmental). Hemangioma-associated syndromes include PHACE syndrome (Posterior fossa defects, Hemangiomas, cerebrovascular Arterial anomalies, Cardiovascular anomalies, and Eye anomalies) and LUMBAR syndrome (Lower body hemangioma, Urogenital anomalies and ulceration, Myelopathy, Bony deformities, Anorectal malformations and arterial anomalies and Renal anomalies), also known as SACRAL or PELVIS syndrome. Segmental hemangiomas on the bilateral lower face in a “bearded” pattern may also be asso-

ciated with airway hemangiomas. Five or more cutaneous hemangiomas increase the risk of the presence of liver hemangiomas, which rarely can be associated with an acquired hypothyroidism and cardiac failure. These liver hemangiomas progress through similar growth and involution phases to cutaneous IHs and typically have a benign course.⁶ Very rare cases have been reported of IHs developing into liver angiosarcoma in early childhood, suggesting the need for routine monitoring with ultrasonography during this critical time period.⁷ Because of their natural involution and benign nature, most uncomplicated IHs do not require treatment.

Propranolol, a nonselective adrenergic blocker, is the first-line treatment for complicated IHs and is generally initiated for those that are potentially life-threatening, disfiguring, ulcerated, refractory to other treatments, or causing functional impairment. Since the discovery of propranolol for treatment of IHs in 2008, two randomized control trials (RCTs) and numerous case reports and retrospective studies have been published supporting its safety and effectiveness, with an estimated treatment failure rate of only 1 to 2%.^{8,9} Although both RCTs demonstrated equal efficacy of oral propranolol and corticosteroids, propranolol was better tolerated than steroids and substantially more efficacious than placebo.^{10,11} In 2014, the United States Food and Drug Administration (FDA) approved an oral formulation of propranolol (Hemangeol; Pierre Fabre, Castres, France) specifically for the treatment of IHs in children. Oral propranolol is typically initiated at doses of ≤1 mg/kg/day and escalated to 2 to 3 mg/kg/day divided in two or three doses. In infants, propranolol is generally well tolerated with minimal significant side effects. The most concerning potential side effects are hypoglycemia, bradycardia, and hypotension, which can generally be avoided by incremental dose escalation, close monitoring, and precautionary measures. Propranolol should be held prior to procedures requiring anesthesia and/or fasting. Other oral β-blockers such as atenolol and nadolol also appear to be safe and efficacious but much less evidence is available.¹²⁻¹⁴

Although not yet approved by the FDA for the treatment of IHs, topical timolol has become the favored treatment in less aggressive IHs because of the decreased potential for serious side effects. Timolol maleate is readily available as an ophthalmic preparation in a solution or gel form which is easily and directly applied to IHs. Multiple studies have shown that timolol is effective at diminishing color, size,

and volume of IHs, particularly when used on young infants with superficial IHs in the rapid proliferative phase.^{15–17} Both timolol solution and gel appear to be more effective than topical corticosteroids in reducing the size of IHs.¹⁸ As would be expected, onset of effect with topical timolol is generally more gradual and modest than that typically seen with oral propranolol particularly in large or thick lesions, and is less effective in deep IHs. Several studies have demonstrated that topical timolol is safe with the most common side effect being local skin irritation. Although systemic absorption may occur, the degree is unknown and does not appear to be clinically relevant in the majority of children.^{19,20} However, a recent study suggests that adverse events are more likely to occur in infants who are very young (<1 month adjusted age); weigh less than 2,500 g; or have a history of prematurity, apnea, or bradycardia.²¹ Risk of side effects also increases with timolol application in or near the eye and to mucosal, intertriginous and ulcerated areas.¹⁶

Although no longer a first-line treatment, oral corticosteroids are still an effective method of treatment for IHs and may be used in conjunction with oral propranolol while achieving target dosing and initial responses. Corticosteroids are also considered when β -blockers are contraindicated, causing intolerable side effects or ineffective. Other systemic and more toxic therapies such as interferon and vincristine are now rarely used due to unfavorable side effect profiles and the need for a central venous catheter for administration. Sirolimus, an inhibitor of mammalian target of rapamycin (mTOR), has shown to have an antiproliferative and antiangiogenic effect in in vitro studies of hemangioma endothelial cells, suggesting a potential role in the treatment of IHs.^{22–25} One case report described the successful use of sirolimus in the treatment of a cutaneous hemangioma associated with PHACE syndrome that had otherwise failed conventional therapies.²⁶ As a treatment for complex vascular anomalies, oral sirolimus has been well tolerated and efficacious, but further studies are necessary to determine its role in the treatment of complicated IHs.

Congenital Hemangiomas

Biologically and histologically different from IHs, congenital hemangiomas (CHs) are benign cutaneous tumors that are fully developed at birth and most often found on the head, neck, or limbs. Although CHs can occasionally appear histologically similar to IHs, they are characteristically GLUT-1 negative.²⁷ CHs are divided into two subtypes: rapidly involuting congenital hemangioma (RICH) and noninvoluting congenital hemangioma (NICH). RICHs begin to involute within days to weeks after birth and regress significantly by 1 to 2 years of age. Because of the rapid rate of involution, RICHs are at risk for developing ulcerations and subsequent secondary infections.²⁸ RICHs may also be rarely associated with mild thrombocytopenia, hypofibrinogenemia, and anemia, which is distinctly different from Kasabach–Merritt phenomenon (KMP), as it resolves spontaneously within 2 weeks and is not associated with bleeding complications.^{29,30} Presenting as an asymptomatic abdominal mass in an infant or found incidentally on imaging, single heman-

giomas in the liver involute rapidly like RICHs and rarely cause significant issues.^{31,32} NICHs are present at birth, do not regress, and grow proportionately with the child.³³ A third intermediary type of CH, a partially involuting congenital hemangioma (PICH), has also been proposed to describe CHs that have an initial rapid involution but lack complete regression.³⁴

Management of CHs is based on its complexity and primarily surgical, as systemic medications have no proven effect. If a lesion is painful, function-limiting, or is persistently ulcerated or bleeding, surgical excision may be performed. Pulsed-dye laser may be used to help diminish superficial discoloration. Embolization may be required to control substantial arteriovenous shunting present in large CHs (>7 cm) to prevent cardiac overload and subsequent high-output cardiac failure.³⁵

Kaposiform Hemangioendothelioma/Tufted Angioma with and without Kasabach–Merritt Phenomenon

First described by Zukerberg et al in 1993, KHE and TA are extremely rare vascular tumors that present in infancy or early childhood and are associated with a serious coagulopathy, termed *Kasabach–Merritt phenomenon*.^{36,37} Many experts believe that KHE and TA are variants of the same disease spectrum because they share similar histopathologic and clinical features. TA is classified as a benign tumor, typically located in the superficial tissues and is composed of small tufts of capillaries, characteristically surrounded by a crescentic slit-like vessel in a cannon-ball distribution.³ Similarly, KHE is found in superficial tissues, but is also locally aggressive and commonly infiltrates into the deeper tissues. Histologically, KHE may appear similarly to TA but, characteristically, has coalescing nodules of spindle cells and epithelioid nodules. Both KHE and TA express the lymphatic endothelial markers, podoplanin (D2–40) and PROX-1, and are GLUT-1 negative.³⁸ Classically, KHE/TAs present as solitary lesions which are frequently warm, indurated, red or purple in color, and ill defined.³⁹ KHE/TA lesions are typically located on the extremities, trunk, and neck; however, KHE can infiltrate into the thorax or abdominal cavity. KHE/TA lesions may have intermittent enlargement, pain, skin discoloration, and/or purpura, frequently triggered by systemic infection, local injury, or blood product replacement. KHE/TA lesions may progress if untreated. With treatment, the tumors may decrease in size and become quiescent over time but do not completely regress.

Occurring in approximately 70% of patients with KHE and 10% of patients with TA, KMP is a potentially life-threatening coagulopathy that has a high risk of bleeding and a mortality rate of up to 30%.^{37,40} KMP is characterized by platelet trapping, activation of the coagulation cascade, and secondary consumption of coagulation factors within the abnormal vasculature of the KHE/TA tumor, resulting in profound thrombocytopenia, hypofibrinogenemia, elevated D-dimer and fibrin degradation products, and prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT).⁴¹ Microangiopathic hemolytic anemia and anemia from tumor sequestration of red blood cells (RBCs) may also occur. Risk

factors for the development of KMP are large lesions (>8 cm), mediastinal or retroperitoneal involvement, and infiltration into deep tissues such as muscle or fascia. Superficial tumors, isolated bone tumors, and disease presentation at an older age are less often associated with KMP.⁴⁰

Treatment of KHE/TA is largely medical because the tumors are frequently ill defined or too extensive for complete surgical resection. Over the years, various regimens of therapies including corticosteroids, vincristine, interferon- α , ticlopidine, clopidogrel, aspirin, cyclophosphamide, d-actinomycin, and bevacizumab (Avastin) have been used in the treatment of KHE/TA with inconsistent outcomes. Due to the rarity of these tumors, there are currently no evidence-based guidelines for treatment of KHE/TA. Based on available evidence and clinical experience, consensus-driven recommendations for the management of complicated KHE/TA were proposed by an expert multidisciplinary panel in 2013.⁴² For all patients suspected of having KHE/TA, initial laboratory evaluation should include complete blood count (CBC) with platelet count, aPTT, PT, fibrinogen level, and D-dimer. Imaging with MRI is recommended to evaluate the extent of the tumor and to follow treatment response. When possible, a biopsy should be obtained to confirm the diagnosis, but this is not always possible in the setting of severe coagulopathy and may worsen the underlying disease. Although the management of KHE/TA must be individualized for the symptoms and needs of the patient, treatment is highly dependent on the presence or absence of KMP.

Early recognition and treatment of KHE/TA with KMP is essential, as delays can result in significant morbidity and mortality. To control the severe coagulopathy, the underlying KHE/TA tumor must be treated. If the lesion is small and amenable to resection, complete excision is the preferred treatment. Complete removal of KHE is rarely possible due to its infiltrative nature and high risk of bleeding complications. For KHE/TA with KMP, the consensus panel recommends treatment with a combination regimen of weekly vincristine and daily corticosteroids. Since the 2013 consensus statement, there have been several case reports and case series of the successful treatment of KHE/TA with and without KMP with sirolimus.^{43–46} In the prospective phase II clinical trial on the safety and efficacy of sirolimus for the treatment of complicated vascular anomalies, Adams et al reported excellent disease outcomes for patients with KHE and KMP. More specifically, hematological parameters of the patients with KMP substantially improved on sirolimus.⁴⁷ Everolimus, an analog of sirolimus, also appears to be beneficial in treating KHE with KMP, although no prospective trials have been performed to date.^{48,49} Currently, there is an open randomized phase II clinical trial for high-risk KHE investigating vincristine-based to sirolimus-based treatments, both used in conjunction with corticosteroids in the initial treatment period (ClinicalTrials.gov identifier NCT02110069, funded by the U.S. FDA Office of Orphan Products Development [1R01FD004363] and Pfizer, Inc.).

Maintenance of adequate hematologic parameters in patients with KMP is important, but blood product replacement must be performed with caution. Platelet transfusions

should only be given for active bleeding or immediately prior to or during surgery. Because of platelet trapping within the KHE/TA lesion, platelet transfusions will not only have minimal effect on the platelet count but also cause tumor engorgement, pain, and worsening of the underlying coagulopathy. The consensus panel recommends that patients with hypofibrinogenemia less than 100 mg/dL receive fresh frozen plasma (FFP) or cryoprecipitate; a higher threshold should be considered in the presence of bleeding. Cryoprecipitate is recommended when targeting fibrinogen replacement and/or a smaller volume of plasma is preferred. There are no specific recommendations or restrictions for RBC transfusions but, in general, should be given as needed to maintain oxygenation, perfusion, and symptomatic relief.

Treatment of KHE/TA without KMP is not well defined. If the KHE/TA tumor is small and resectable, complete excision of the lesion is typically advised. Unresectable KHE/TA tumors without KMP lack distinct recommendations. With close monitoring, observation may be considered for asymptomatic tumors that do not involve vital organs or cause functional compromise.⁵⁰ For KHE/TA tumors that require treatment because of growth or symptoms, the 2013 Expert Consensus Group recommended single-agent daily steroids. Propranolol has also been used, but there is no convincing evidence of its effectiveness.⁵¹ In recent years, the use of sirolimus alone to control growth and/or symptoms has been gaining popularity, as it appears beneficial and has a preferred side effect profile over steroids, particularly in children.^{46,47,52} However, no prospective or randomized control studies have been performed to date, given the rarity of KHE/TA without KMP.

Vascular Malformations

Vascular malformations are classified as simple, combined, malformations of major named vessels, and malformations associated with other anomalies (►Table 2). Simple malformations consist of one type of vessel (capillaries, lymphatic vessels, or veins) with the exception of arteriovenous malformations (AVMs). Combined malformations consist of two or more vessel abnormalities in any combination. Both simple and combined vascular malformations are named specifically for the involved vessel(s). Malformations of major vessels generally affect vessels of large caliber and are characterized by abnormalities of the vessel origin, course, length, number (absence, duplication), diameter (hypoplasia, dilation), or valves. Frequently better known as eponymous syndromes, vascular malformations associated with other (nonvascular) anomalies are categorized separately (►Table 3). However, many experts within the field advocate against the use of historically named syndromes and recommend the utilization of the standard nomenclature for vascular malformations, combined with a description of associated abnormalities. Of note, a small number of clinically relevant vascular lesions remain unclassified due to unclear pathologic or histologic characteristics (►Table 4).²

Although sometimes not recognized until months or years of life, vascular malformations are always present at birth and grow proportionally with the child. However,

Table 2 Classification of vascular malformations

Simple	
Capillary malformations (CM) <ul style="list-style-type: none"> • Cutaneous or mucosal CM • Telangiectasias including hereditary hemorrhagic telangiectasia (HHT) • Cutis marmorata telangiectatica congenita • Nevus simplex • Others 	Lymphatic malformations (LM) <ul style="list-style-type: none"> • Common LM (macrocytic, microcytic, mixed) • Generalized lymphatic anomaly • Gorham–Stout disease • Channel type LM • Primary lymphedema • Others
Venous malformations (VM) <ul style="list-style-type: none"> • Common VM • Familial VM cutaneomucosal • Blue rubber bleb nevus syndrome • Glomuvenous malformation • Cerebral cavernous malformation • Others 	Arteriovenous malformations (AVM) <ul style="list-style-type: none"> • Sporadic • In HHT • In CM–AVM • Others
Combined	
<ul style="list-style-type: none"> • CM + VM (CVM) • CM + LM (CLM) • CM + AVM (CAVM) • LM + VM (LVM) 	<ul style="list-style-type: none"> • CM + LM + VM (CLVM) • CM + LM + AVM (CLAVM) • CM + VM + AVM (CVAVM) • CM + LM + VM + AVM (CLVAVM)
Vascular malformations of major named vessels	
Vascular malformations associated with other anomalies	

Source: Adapted from 2014 ISSVA Classification.

Table 3 Vascular malformations associated with other anomalies

Klippel–Trenaunay syndrome (CLVM)	CM + VM +/- LM + limb overgrowth
Parkes–Weber syndrome	CM + AVF + limb overgrowth
Servelle–Martorell syndrome	Limb VM + bone undergrowth
Sturge–Weber syndrome	Facial + leptomeningeal CM + eye anomalies +/- bone and/or soft-tissue overgrowth
CLOVES syndrome	LM + VM + CM +/- AVM + lipomatous overgrowth
Proteus syndrome	CM, VM, and/or LM + asymmetrical somatic overgrowth
Bannayan–Riley–Ruvalcaba syndrome	AVM + VM + macrocephaly, lipomatous overgrowth
Maffucci's syndrome	VM +/- spindle-cell hemangioma + enchondroma
Macrocephaly-CM (M-CM/MCAP)	Megalencephaly-capillary malformation-polymicrogyria
Microcephaly-CM (MICCAP)	
Limb CM + congenital nonprogressive limb hypertrophy	

Abbreviations: AVF, arteriovenous fistula; AVM, arteriovenous malformation; CLVM, capillary lymphatic-venous malformation; CM, capillary malformation; LM, lymphatic malformation; VM, venous malformation.

Source: Adapted from 2014 ISVVA Classification.

Table 4 Unclassified vascular anomalies

Verrucous hemangioma
Angiokeratoma
Multifocal lymphangioendotheliomatosis with thrombocytopenia/cutaneovisceral angiomatosis with thrombocytopenia
Kaposiform lymphangiomatosis
PTEN (type) hamartoma of soft tissue

Source: Adapted from 2014 ISVVA Classification.

vascular malformations may appear to grow unproportionally due to expansion or dilation of the existing abnormal vessels, which commonly occurs during growth spurts and puberty. Vascular malformations may be localized or diffuse and have variable appearances, complications, and severity depending on location(s), proportion of abnormal vessels, involved body structures, and presence of any associated (nonvascular) anomalies. In addition to being categorized by abnormal blood vessel type(s), vascular malformations are also described as either slow flow or fast flow, depending on the presence of an arterial component. This is an important distinction because fast-flow lesions such as AVMs may lead to high-output heart failure.⁵

Historically, vascular malformations have been primarily treated by procedural interventions such as excision, debulking, pulsed dye laser, and sclerotherapy. Medical management was limited to supportive therapies such as compression garments, nonsteroidal anti-inflammatories, and anticoagulation. This treatment approach has been particularly problematic for complex vascular malformations that are diffuse or not amenable to surgery. A multitude of other medications have been used to treat vascular malformations with variable and often disappointing results. Sildenafil has been reported to decrease the size of lymphatic malformations in a small number of case reports; however, other studies have shown no effect of sildenafil.^{53–56} Steroids, vincristine, and interferon have also been used sporadically to treat various malformations with mixed results.⁵⁷ The discovery of sirolimus as an effective treatment changed the management paradigm of patients with complicated vascular malformations.

Sirolimus (Rapamycin)

Sirolimus (Rapamune) is a specific and potent inhibitor of mTOR, a serine/threonine kinase in the phosphoinositide-3-kinase (PI3K)/Akt pathway which regulates numerous cellular processes including cellular catabolism and anabolism, cell motility, angiogenesis, and cell growth.⁵⁸ Prior to its use in vascular anomalies, sirolimus was used to treat patients with

PTEN mutations and hamartoma syndromes including tuberous sclerosis (TS) and lymphangioleiomyomatosis (LAM), all of which involve the PI3K/AKT pathway. Given its effectiveness in these conditions, sirolimus was first trialed as a treatment for vascular anomalies in an infant with KHE and severe KMP, which was refractory to all treatment regimens (steroids, vincristine, cyclophosphamide, bevacizumab, and embolization therapy). The patient not only had complete resolution of the coagulopathy within 2 months of starting sirolimus but also experienced substantial improvements in pain, lesion size, and function.⁵⁹ This initial success prompted the prospective phase II clinical trial assessing the safety and efficacy of sirolimus in the treatment of complicated vascular anomalies. This study demonstrated that sirolimus was a safe treatment option with remarkable responses in patients with microcystic and diffuse lymphatic malformations, capillary lymphatic venous malformations, PTEN-associated vascular anomalies, and venous lymphatic malformations. Many of these patients experienced improvement in clinical symptoms and quality of life regardless of whether improvement was noted radiologically.⁴⁷ Since these initial successes, the use of sirolimus has rapidly expanded and appears efficacious in a multitude of vascular malformations.

In recent years, several studies have demonstrated that sirolimus inhibits lymphatic vessel regeneration and invasion.⁵⁸ Although prospective clinical trials have been limited, numerous reports have been published on the efficacy of sirolimus treatment for macrocystic and microcystic lymphatic malformations as well as combined malformations with a lymphatic component (►Fig. 1).^{60–62} In lymphatic malformations, systemic sirolimus has been shown to reduce disease bulk, lymphatic leakage and blebs, and number of associated infections. In the diffuse lymphatic malformations, generalized lymphatic anomaly (GLA) and Gorham-Stout disease are types of diffuse lymphatic malformations. Gorham-Stout disease, sirolimus has been recently reported to stabilize or improve associated pleural/pericardial effusions (►Fig. 2) and bony disease.^{47,63} Sirolimus has also been shown to

Fig. 1 MRI of a patient with capillary lymphatico-venous malformation with significant disease resulting in right hip dislocation prior to the start of sirolimus (*left*). Hip dislocation resolved and bulk of disease substantially improved at 6 months of sirolimus treatment (*right*).

Fig. 2 Chest X-ray of a patient with generalized lymphatic anomaly with a right-sided pleural effusion before the start of sirolimus treatment (left). Pleural effusion exhibited near-complete resolution at 3 months of sirolimus therapy (right).

stabilize or improve pleural/pericardial effusions, consumptive coagulopathy, and life-threatening hemorrhage associated with the currently unclassified yet aggressive lymphatic anomaly, kaposiform lymphangiomatosis (KLA).^{47,64,65} A recent case report described the benefits of topical sirolimus in treating cutaneous manifestations of microcystic lymphatic malformations.⁶⁶ Based on our institutional experience, many patients experience decreased lymphatic leakage and reduced number and size of blebs with the use of topical 1% sirolimus applied once or twice daily.

Although evidence is limited, sirolimus does appear to have a role in the treatment of some complicated venous malformations. A small number of case reports and series have shown that sirolimus is an effective treatment option for patients with blue rubber bleb nevus syndrome (BRBNS), a rare multifocal venous lymphatic malformation that involves the skin and gastrointestinal (GI) system. Stabilization or decrease in size of lesions, improved GI bleeding, decreased transfusion requirements, and reduction in pain have been reported in patients with BRBNS on sirolimus.^{67,68} One prospective pilot study of six patients with difficult-to-treat venous malformations demonstrated clinical improvement with reduction in pain, bleeding, lesion size, functional impairment, and intravascular coagulopathy.⁶⁹ Another small trial of eight patients with refractory to standard care venous malformations reported that all patients experienced relief of pain and symptoms, and improved self-perceived quality of life.⁷⁰ Additionally, a reduction in phleboliths and superficial phlebitis has been reported in patients with combined malformations with a venous component.⁷¹

The role of sirolimus in the treatment of capillary malformations is unclear at this time. Some small studies report that topical and oral sirolimus may enhance the efficacy of laser treatment for capillary malformations.^{72–74} The benefit of systemic sirolimus is also unknown in the treatment of hereditary hemorrhagic telangiectasia (HHT), an inherited

disease characterized by bleeding from mucocutaneous telangiectasias and/or visceral AVMs. Only one case report documents the resolution of telangiectasias of the skin, buccal mucosa, and upper GI tract in a patient with HHT while on sirolimus therapy.⁷⁵ Other antiangiogenic medications have been more extensively studied in HHT and will be discussed later in this article. The use of sirolimus in the treatment of extracranial AVMs has also not yet been elucidated. The phase II clinical trial assessing the safety and efficacy of sirolimus restricted inclusion of fast-flow lesions to those associated with PTEN.⁴⁷ In a recently published retrospective study, four patients with sporadic AVMs showed no improvement in radiologic imaging or reduction in symptoms; however, these patients also did not exhibit worsening disease while on sirolimus therapy.⁶⁴ In Europe, there currently is an open study investigating the efficacy of sirolimus in the treatment of extracranial AVMs in children and adults (ClinicalTrials.gov identifier NCT02042326).

Based on the phase II clinical trial, sirolimus is generally administered orally as a tablet or liquid suspension at an initial dose of 0.8 mg/m² per dose twice daily at approximately 12-hour intervals and titrated to maintain a goal serum trough level of 10 to 15 ng/mL. This goal drug level was based on the use of sirolimus in pediatric renal transplant patients.⁴⁷ However, lower levels of sirolimus have been efficacious in patients with vascular anomalies, and so many providers now titrate the dose to desired effect with consideration of side effects. Side effects tend to be dose dependent and most commonly include mouth sores, GI upset, headaches, bone marrow suppression, and metabolic/laboratory disturbances. Frequent physical exams and laboratory blood work are necessary while on sirolimus therapy to ensure adequate drug levels and to monitor for toxicities. Because of immunosuppression, *Pneumocystis jiroveci* pneumonia prophylaxis is also recommended. Time to response varies among patients, but maximal effect generally does not occur until months after

achieving adequate doses. Length of treatment is not defined and must be determined on an individual basis. Although data are limited, everolimus also appears to be efficacious in treating patients with vascular malformations and is a treatment option in those with intolerable side effects from sirolimus.^{48,76}

Angiogenesis Inhibitors

Bleeding complications commonly occur with angiodysplasias, telangiectasias, or AVMs involving mucosal surfaces, particularly in the nasopharyngeal and GI tracts, and cause significant morbidity and mortality. Medical management is supportive and surgical interventions may be limited or insufficient due to the diffuse nature of these anomalies. Thus, there has been a growing interest in the use of angiogenesis inhibitors, many of which are currently being used in cancer regimens, to treat these vascular lesions. To date, antiangiogenic therapies have been largely used in patients with HHT or GI angiodysplasias who have frequent or significant bleeding. Although the pathogenesis is not completely known, the telangiectasias and AVMs that arise in HHT are thought to be secondary to disruption in angiogenesis. Studies have shown elevated levels of vascular endothelial growth factor (VEGF) within GI angiodysplasias as well as telangiectasias and AVMs associated with HHT.^{77,78} A small number of studies in animal models have also demonstrated that the blockade of VEGF and other chemokines involved in angiogenesis can prevent progression of AVMs.^{79–81} Additionally, the known mutated genes associated with HHT encode for proteins within transforming growth factor- β (TGF- β) signaling pathway, which is important during the later phase of angiogenesis to induce pericyte differentiation and vessel maturation.^{82,83} Although VEGF and TGF- β are both potent angiogenesis inducers, they have opposing effects on endothelial cells; VEGF protects endothelial cells from apoptosis, while TGF- β induces apoptosis. Dysregulation of this cell signaling balance may induce aberrant angiogenesis in affected tissues.⁸⁴ Studies also suggest that HHT may result from abnormal TGF- β signaling in endothelial cells, causing a defect in pericyte attachment and vessel destabilization.⁸³

Thalidomide was first noted to have antiangiogenic and antitumor properties in 1994 after years of nonuse due to teratogenicity.⁸⁵ The study performed by Lebrin et al suggests that thalidomide acts on pericytes and its precursors to allow vessel maturation and, thus, attenuates angiogenesis by bypassing the TGF- β signaling pathway for vessel stabilization.⁸⁶ In 2011, a randomized study demonstrated that thalidomide was an efficacious treatment for bleeding of GI angiodysplasias. This study showed that patients receiving oral thalidomide versus control (oral iron) had decreased bleeding episodes, hospitalizations, and need for blood transfusions.⁸⁷ Several case reports and series have been published on the use of thalidomide in patients with HHT with similar results. That is, thalidomide seems to be beneficial for HHT patients by reducing the frequency and intensity of nosebleeds, improving hemoglobin level, and decreasing need for transfusions.⁸⁸ Despite these early promising results, the use of thalidomide has been limited. Not only is its use governmentally restricted

due to its known teratogenicity, but thalidomide is also a potent sedative and can cause peripheral neuropathy with cumulative doses. These limitations led to the development of thalidomide analogs with increased potency and fewer side effects, including lenalidomide and pomalidomide, both of which have only been used in a small number patients with HHT.^{89,90} There currently is an ongoing phase I trial investigating the use of pomalidomide treatment for epistaxis and GI bleeding in HHT patients (ClinicalTrials.gov identifier NCT02287558).

Bevacizumab (Avastin) is a recombinant humanized monoclonal antibody that binds to VEGF receptors on endothelial cells and serves as a competitive antagonist. Several small case reports and series in patients with HHT have reported that bevacizumab, when injected locally or sprayed topically, appears to be effective in reducing the severity of epistaxis.^{91–95} Conversely, a multicenter, randomized clinical trial recently showed no difference in epistaxis duration in HHT patients who received the intranasal bevacizumab versus placebo spray.⁹⁶ One phase II clinical trial in patients with severe hepatic forms of HHT demonstrated that the administration of systemic bevacizumab was associated with a decrease in cardiac output and reduced duration and number of episodes of epistaxis.⁹⁷ Furthermore, a recent review of the available literature on the use of intravenous bevacizumab in HHT patients reported improvements in epistaxis frequency and hemoglobin levels. However, the authors cautioned that most citations were case reports and noted inconsistencies in outcome reporting.⁹⁸ Although highly specific for angiogenesis, it remains unclear whether VEGF-targeted therapy is a useful treatment for bleeding of preexisting vascular malformations and additional prospective studies are needed.

Vascular Anomaly Centers

Management of individuals with vascular anomalies often requires the expertise of multiple subspecialists during different phases of treatment. With the goal of providing comprehensive and interdisciplinary care, a growing number of institutions have developed vascular anomaly centers, consisting of providers with diagnostic and therapeutic expertise of vascular anomalies. The physician team ideally consists of specialists from multiple disciplines; those often represented include hematology/oncology, general and plastic surgery, pediatric and interventional radiology, pathology, dermatology, otolaryngology, orthopedics, neurology, ophthalmology, neurosurgery, gastroenterology, and cardiology. These providers, selected based on the unique needs of each patient, work together and collaborate to generate an accurate diagnosis and optimal management plan. Additionally, nurses, technicians, and other caregivers in the center provide vascular anomaly-focused support to patients and their families, and ensure that aspects of care are coordinated and well organized. Ancillary services including physical and occupational therapy, social work, nutrition, genetic counseling, behavioral, and/or psychotherapy should be readily available and incorporated into the management plan as necessary. This comprehensive multidisciplinary approach tailors treatment to the individual based

on the needs of the patient, with consideration not only for physical functioning but also for emotional and social well-being. Members of the vascular anomaly center should act as patient advocates and provide families, community providers, and the general public with education about these uncommon disorders.

Conclusion

During the past decade, clinical and scientific research, along with technological advancements, has enhanced our knowledge of the clinical behavior, pathology, and molecular biology of vascular anomalies. Prompted by this progress, a standardized classification system for vascular anomalies was developed, improving diagnostic and therapeutic management of these complicated lesions. Additionally, the discovery of new medications which effectively treat vascular anomalies, such as propranolol, timolol, and sirolimus, broadened our medical treatment options and provided insight into possible etiologies of these disorders. These advancements stimulated further interest in vascular anomalies, inciting the establishment of vascular anomaly centers around the world and a surge of basic and clinical research. New insight into the genetics and molecular basis of vascular anomalies may lead to novel uses of existing medications or the development of targeted therapies. Dedication of researchers, medical providers, and patients to the scientific study of vascular anomalies is central in expanding our understanding of these conditions, developing new treatments, improving disease outcomes, and enhancing quality of life for patients and their families.

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