

# Vascular malformations part 2 — current classification of vascular malformations

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For many the subject of vascular malformations remains shrouded in mystery and confusion resulting from a lack of understanding of the nature of the pathology compounded by the confusing nomenclature still associated with these lesions. For example, the term 'haemangioma' has been used to describe a variety of vascular lesions with different aetiologies and natural histories. Names utilising a mixture of descriptive and histologic terms, such as 'strawberry angioma', 'nevus flammeus', or 'cavernous haemangioma' still abound in current medical usage. The classification of vascular anomalies outside of the central nervous system (CNS) is based on the seminal works of Mulliken and Glowacki.<sup>1,2</sup> They divided vascular anomalies into those exhibiting rapid endothelial cell growth (proliferation) followed by a period of stabilisation (quiescence) and finally spontaneous involution, termed haemangiomas, and those having a rate of growth commensu-

rate with the growth of the individual termed vascular malformations (VMs). As opposed to haemangiomas, VMs reach stability by adulthood or continue to grow by hypertrophy rather than cellular proliferation. The current classification of CNS vascular anomalies remains primarily a pathoanatomically-based one and is based on the works of McCormick *et al.*<sup>3-5</sup> and Russel and Rubenstein.<sup>6</sup>

In this review we will present a synopsis of CNS and non-CNS vascular anomalies based on the abovementioned classification schemes in the hope that this will dispel much of the confusion surrounding the subject of vascular malformations or anomalies.

## Classification of CNS vascular malformations

The current classification is based on the pathoanatomic works of McCormick *et al.*<sup>3-5</sup> and Russel and Rubenstein.<sup>6</sup> This assumes vascular malformations to be congenital or developmental hamartomas rather than neoplasms, and is based on the microscopic and gross pathologic features of these lesions (Table I). Already confounding this classification is the identification of mixed malformation

**Table I. Classification of CNS vascular malformations**

Arteriovenous shunts
Classical AV Malformations
Pial AV fistulas
Dural AV shunts
Galenic shunts
Cavernous malformations
Capillary telangiectasias
Venous malformations
Developmental venous anomalies
Mixed malformations

types,<sup>7</sup> together with the identification of increased endothelial cell proliferation within CNS vascular malformations further blurring the distinction between malformation (hamartoma) and tumour (proliferation).<sup>8</sup>

Although intracranial arteriovenous shunts are similar angioarchitecturally to AV shunts elsewhere in the body, the cerebral and spinal cavernous malformation (cavernoma) does not have a similar counterpart in the rest of the body. Analysis of structural proteins within the wall of cavernomas shows these lesions to be developmentally immature unlike the walls of venous malformations elsewhere in the body. Furthermore the so-called venous angiomas or developmental venous anomalies (DVAs) of the brain actually represent persistent normal embryological venous drainage of regions of the brain rather than true vascular malformations.<sup>9</sup>

Although most CNS vascular malformations occur in isolation, some are found in association with cutaneous and mesodermal vascular anomalies. This mirrors the development of both the skin and nervous system from the ectodermal plate and neural crest of the early embryo, often

also involving the adjacent subectodermal mesoderm. The most classic examples of such syndromes would include the Wyburn-Mason syndrome (or Bonnet-Dechaume-Blanc syndrome) and the Sturge-Weber syndrome. The Wyburn-Mason syndrome is an association of cerebral (diencephalic), retinal and maxillofacial arteriovenous malformations, hence its alternative name of 'unilateral retinocephalic vascular malformation'.<sup>10</sup> Recognition of the metameric nature of this disorder has led to a revised classification of such craniofacial vascular malformation syndromes as the cerebrofacial arteriovenous metameric syndromes (CAMS).<sup>11,12</sup> A similar developmental metameric distribution would also explain the development of the rare type III or juvenile spinal AVM syndromes (cutaneomeningospinal angiomas, Cobb syndrome), now termed the spinal arteriovenous metameric syndromes (SAMS).<sup>13</sup> The Sturge-Weber syndrome, also 'encephalo-trigeminal angiomas', involves capillary-venous malformations of the brain, usually affecting a single cerebral hemisphere, associated with retinal vascular malformations and cutaneous facial capillary malformations (previously nevus flammeus, cutaneous angioma or port-wine stain). Again the association of a telencephalic venous malformation with facial involvement usually within the V1 distribution suggests a venous metameric syndrome (cerebrofacial venous metameric syndrome (CVMS) — Lasjuanias, personal communication). However, often the cutaneous malformation involves the V2 or V3 distributions as well or may even extend to the neck and upper trunk, thus showing a spectrum of

expressivity. Forty-five per cent of children having V1 and V2 involvement will develop glaucoma due to associated venous malformations affecting the canal of Schlemm or other disruption of the ocular venous drainage.<sup>14</sup>

Other associations between CNS and other vascular malformations include the association of craniofacial vascular malformations such as cutaneous capillary malformations and venous and lymphatic malformations with intracranial DVAs,<sup>15,16</sup> and the heritable association between cerebral cavernous malformations and cutaneous or other systemic venous malformations.<sup>17,18</sup> Finally there is the development of CNS arteriovenous malformations as part of the spectrum of multisystemic vascular malformation development in hereditary haemorrhagic telangiectasia.<sup>19</sup> These associations with non-CNS vascular malformations suggest a particular phenotypic expression peculiar to the environment of the brain and spinal cord of the same underlying vascular malformative processes found elsewhere in the body, hinting that the classic pathoanatomical classification of CNS vascular malformations may well later be revised along more biologically-orientated lines.<sup>20</sup>

## Non-CNS vascular malformations

As mentioned above the current classification of these disorders as adopted by the International Society for the Study of Vascular Anomalies (ISSVA) is that described by Mulliken and Glowacki. Initially they differentiated between true vascular malformations and haemangiomas, based

upon endothelial cell growth characteristics.<sup>1</sup> Haemangiomas show initial rapid endothelial cell proliferation more typical of a tumour followed later by variable spontaneous regression in many cases. Conversely VMs show no (or rather minimal) endothelial cell proliferation and are characterised by a growth rate commensurate with the rate of growth and development of the child. They then divided the VMs into high-flow (arteriovenous shunts) and low-flow VMs. The low-flow VMs were further subdivided according to their histological origins into the capillary, venous, lymphatic or mixed malformations (Table II).

**Table II. Classification of non-CNS vascular malformations**

Haemangiomas (proliferative lesions or tumours)
Vascular malformations (non-proliferative)
High flow
• Arteriovenous malformations
Low flow:
• Capillary malformations
• Venous malformations
• Lymphatic malformations
• Mixed malformations

## Haemangiomas

The term haemangioma has traditionally been used as a generic term to describe a large variety of vascular lesions with different aetiologies.<sup>1</sup> Currently the term haemangioma is restricted to a distinct proliferative lesion of early childhood being more a tumour than a vascular malformation. Haemangiomas are the most common vascular tumour, with an incidence of 1 - 2.6%.<sup>21</sup> Thirty-three

to 40% of lesions are apparent at birth, with 70 - 90% appearing during the first 4 weeks of life and none beyond the age of 5 years. Haemangiomas may be superficial (cutaneous), deep (covered by normal overlying skin) or visceral.<sup>22</sup> They can occur in any race, but are more common in girls (3:1), light-skinned whites and premature infants (20%) especially those with a birth weight < 1500 g.<sup>23</sup> The superficial cutaneous lesions tend to show a bright red colour initially that deepens during the first year of life (Fig. 1a).



Fig. 1a. Small cutaneous haemangioma on the cheek of an infant.

Haemangiomas tend to show a firm, rubbery consistency compared with venous malformations that are compressible.<sup>22</sup> The prevalence of haemangiomas is approximately 1 - 3% of neonates, increasing to about 10% of white children and 1.4% of black children at 1 year of age.<sup>21</sup> Sixty percent of haemangiomas occur in the head and neck region, with 25% on the trunk and 15% on the extremities. Occasionally they may involve oral or genital mucosa. In about 15 - 20% of cases the lesions are multiple (benign neonatal haemangiomatosis). They

initially present with an erythematous patch or pink macule often referred to as a 'herald spot'. They then undergo a proliferative (growth) phase of 3 - 12 months followed by a variable plateau or stabilisation phase and finally by a phase of involution. All lesions inevitably show some degree of spontaneous involution or regression.<sup>1,22</sup> Approximately 30% of infantile haemangiomas will regress by the third birthday, about 50% by the fifth, and 70% by the seventh.<sup>24,25</sup>

If a haemangioma fails to show evidence of regression by 5 - 6 years of age, then it is unlikely to regress completely. Lesions exhibiting early changes of involution are associated with more rapid disappearance and a better cosmetic result. Regression is heralded by the appearance of white streaks (fibrosis) on the surface of the lesion. Occasionally haemangiomas may ulcerate or bleed or develop secondary infections, mainly during the proliferative phase.<sup>22</sup> The tumour in the proliferative phase is characterised by endothelial cell proliferation producing plump, hyperplastic endothelial cells together with a variable number of mast cells. During the involutinal phase there is a conversion from proliferation to apoptosis of the endothelial cells with progressive deposition of perivascular and interlobular fibrous tissue.<sup>26</sup> An increase in basic fibroblast growth factor (BFGF), proliferating cell nuclear antigen, type IV collagenase, E-selectin and monocyte chemoattractant protein is seen during the proliferative phase, whereas during the involutive phase there is an increase in metalloproteinase tissue inhibitor and a fall in BFGF levels.<sup>27</sup> BFGF can thus be used as marker to assess the cessation of proliferation and onset of involution.

Most haemangiomas are recognised clinically. Imaging is only required in cases where there is diagnostic uncertainty or where intervention is required. Ultrasound (with doppler) will rapidly distinguish solid haemangiomas from vascular malformations. Computed tomography (CT) and magnetic resonance imaging (MRI) will help to assess the depth and extent of lesions. Angiography, while showing a characteristic homogeneous contrast blush without evidence of AV shunting, should rather be reserved for therapeutic purposes.<sup>27</sup> In most cases no treatment is required because of spontaneous regression. However 10 - 20% of lesions will require treatment because of impending (or established) loss of function or a threat to life (Fig. 1b). Treatment for cosmetic reasons alone is a controversial indication given the natural history of these lesions. More often than not the parents are more affected by appearance than the children themselves except as the children approach school age. Examples of indications for active treatment (i.e. 'alarming')



Fig. 1b. Large maxillary and periorbital cutaneous haemangioma. Its anatomical position threatens the function of the eye.

haemangiomas) would include:<sup>27,28</sup> (i) periocular lesions threatening vision; (ii) lesions obstructing the airway; (iii) large lesions associated with high-output cardiac failure; (iv) facial lesions with rapid growth and distortion; (v) lesions with severe persistent cutaneous ulceration or haemorrhage (Fig. 1c); and (vi) Kasabach-Merritt syndrome.



Fig. 1c. Ulceration of scalp haemangioma.

The Kasabach-Merritt phenomenon or syndrome, first described in 1940, consists of very large haemangiomas complicated by severe thrombocytopenia, microangiopathic haemolytic anaemia and consumption coagulopathy. It is seen most frequently in young infants during the first week of life and carries a mortality of 20-30%, thus requiring aggressive treatment when recognised.

Multiple cutaneous haemangiomas may rarely co-exist with visceral haemangiomas in a condition termed 'diffuse neonatal heman-giomatosis' or 'disseminated haemangiomatosis'. Visceral lesions may be found in the liver, GIT, spleen, pancreas, adrenals, lungs, heart, skeleton, muscle, salivary glands, kidney, bladder, testes, thymus, thyroid, bone,

meninges, brain and eyes. The mortality rate is high, with extensive visceral involvement mainly during the first months of life and mainly due to high-output cardiac failure.<sup>22</sup>

Large facial haemangiomas may be associated with posterior fossa brain malformations, arterial developmental anomalies, cardiac anomalies, aortic coarctation and eye anomalies in the PHACE syndrome, a strange association of proliferative and non-proliferative vascular anomalies.<sup>29,30</sup>

Medical treatment for haemangiomas includes local and systemic steroids, interferon  $\alpha$ -2a and  $\alpha$ -2b, and Pentoxifylline. Other options include intralesion injection of sclerosing agents, cryotherapy, laser therapy, embolisation, radiation therapy and surgical excision.<sup>21,22</sup> Several groups, including the Pretoria Vascular Malformation Group, have reported successes in treating haemangiomas using the antiangiogenic properties of the antimetabolic antibiotic derivative bleomycin.<sup>31</sup> Other treatment types used when other methods have failed included vincristine or radiation therapy.

## Arteriovenous (high-flow) malformations

Arteriovenous malformations (AVMs) are high-flow lesions with direct communications between an artery (or arteries) and a vein (or veins) bypassing the capillary bed (Fig. 2). The term 'arteriovenous fistula' is often reserved for direct single hole communications usually related to trauma or other acquired condition, whereas the term 'arteriovenous malformation' should be reserved for

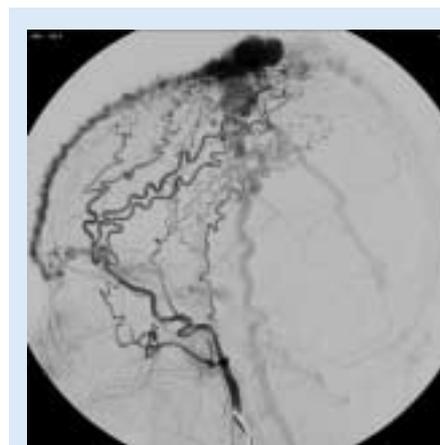


Fig. 2. High-flow (arteriovenous) malformation of the scalp. This composite digital subtraction angiogram combines both the arterial and venous phases in one image.

congenital lesions.<sup>32</sup> They are much less common than low-flow malformations and often become symptomatic following trauma (including biopsy) or around puberty. Clinically they can present as a pulsatile mass with a thrill, bruit and occasionally local hyperthermia, skeletal overgrowth, trophic changes with ulceration or bleeding, congestive heart failure or functional impairment due to arterial steal and ischaemia. The diagnosis is generally made clinically with deep lesions identified as being high-flow with the aid of doppler ultrasound. CT, MRI and angiography are all used to assess the extent of a lesion during the planning of therapy. AVMs are the most difficult and dangerous lesions to treat, and for this reason quiescent AVMs should be followed clinically, with treatment delayed until complications such as pain, ulceration, haemorrhage or cardiac failure intervene.<sup>21</sup> Treatment options include direct percutaneous and transarterial embolisation and surgical excision, with the treatment best left to those specialists well versed in the management of such lesions.

## Venous malformations

Venous malformations (VMs), often incorrectly termed cavernous haemangiomas, are low-pressure, low-flow malformations. They are present at birth, although not always visible at that stage, and undergo slow growth commensurate with the growth of the child.<sup>1,27</sup> VMs are soft, compressible, non-pulsatile masses that expand after a Valsalva's manoeuvre or in a dependent position. They have a bluish colour often with normal overlying skin (Figs 3a, b). Forty per cent are found in the head and neck region, 20% on the trunk and 40% on the extremities. VMs can be superficial (cutaneous) or occur in



Fig. 3a. Small venous malformation of an upper lip. Note the characteristic bluish colouration.



Fig. 3a. Large venous malformation of a lower limb. No leg length discrepancy was noted.

buccal and intestinal mucosa and in other organs. Sudden enlargement can occur after trauma, haemorrhage, surgery, or with hormonal changes. VMs can become painful due to the development of thrombophlebitis or in cases with muscular or articular involvement. Calcified phleboliths may be present in the lesions, hence the previous term phlebangioma. Ultrasound features include low (or absent) flow and compressibility of the widened vascular spaces. In some lesions a biphasic flow pattern suggests the presence of a mixed malformation such as a capillary-venous or lymphatico-capillary-venous malformation.<sup>33</sup> CT and MRI are useful in delineating the full extent of the lesion.<sup>21,34</sup>

There is no role for angiography although direct puncture venography may be useful in documenting the extent of a lesion and pattern of its draining veins.

VMs may be associated with other anomalies as a component of several complex syndromes such as: (i) Blue Rubber Bleb Nevus syndrome or Bean syndrome; (ii) Maffucci's syndrome; (iii) Klippel-Trenaunay syndrome; or (iv) Gorham's syndrome (Gorham-Stout syndrome).

The Blue Rubber Bleb Nevus syndrome is a rare condition consisting of multiple VMs involving several organ systems, especially the skin and GIT. Most cases are sporadic, but some are inherited with an autosomal dominant inheritance pattern.<sup>35,36</sup> The skin lesions are present at birth but other lesions only become apparent later in life.

The Klippel-Trenaunay syndrome (KTS) is a complex constellation of VMs including abnormal develop-

ment of the normal deep and superficial limb venous drainage, lymphatic malformations and limb asymmetry (hemi-hypertrophy).<sup>37</sup> The lower limb is most commonly affected, rarely affecting the upper limb or both upper and lower limbs. The hypertrophy is mainly due to muscle hypertrophy, thickened skin and subcutaneous fat and occasionally lymphoedema. There is usually relatively little increase in bone size.<sup>36</sup> This indicates a combined ectodermal and mesodermal maldevelopment. Deep venous thrombosis (DVT) and pulmonary embolism are common in patients with KTS. A variation of KTS where limb hemihypertrophy is associated with a high-flow AVM within the affected limb and also in other organ systems is the Parkes-Weber syndrome.<sup>20</sup>

VMs may be associated with osseous abnormalities e.g. in Maffucci's syndrome and the Gorham-Stout syndrome. VMs may be associated with a low-grade consumption coagulopathy.<sup>27,36,38,39</sup> Therefore prior to any intervention a full assessment of coagulability is required. As many VMs are asymptomatic no treatment other than reassurance may be necessary in many cases. Discomfort due to localised lesions may respond to external compression, e.g. with elasticated stockings. More aggressive treatment is indicated in lesions producing pain, discomfort, significant cosmetic disturbance or functional impairment. This generally involves either percutaneous sclerotherapy or surgical excision. Percutaneous sclerotherapy involves the use of a number of agents including absolute alcohol, Ethibloc, Sodium Morrhuate, Sodium Tetradecyl Sulphate and

Sotradecal.<sup>27,33,40-44</sup> Intralesional bleomycin injections have also recently been shown to be effective in treating VMs.<sup>31,45</sup>

## Capillary malformations

Cutaneous capillary malformations (also termed port-wine stains or nevus flammeus) are due to ectatic vessels within the upper dermis. They are present at birth with an equal sex distribution. They are flat sharply demarcated lesions that are pink during infancy deepening in colour to red in young adulthood and purple in middle age.<sup>21</sup> Forty-five per cent of facial lesions are restricted to one of the three trigeminal sensory areas, whereas 55% overlap dermatomes, cross the midline or occur bilaterally.<sup>46</sup> The malformation may extend over the trunk or extremities. Port-wine stains are often associated with numerous malformative syndromes. The best known of these is the Sturge-Weber syndrome where they are associated with cerebral capillary-venous malformations (resulting in the so-called angiomatous lesions of the leptomeninges), retinal angiomas, cerebral atrophy and cortical calcifications. VMs may also be found in other organs, and Sturge-Weber syndrome may also occur in association with Klippel-Trenaunay syndrome.<sup>36</sup> Clinically these patients develop seizures that are difficult to control medically, hemiparesis, hemisensory deficit, homonymous hemianopia and mental retardation. Although the strict definition of Sturge-Weber syndrome includes VMs of the brain, eye and upper facial skin, the disorder can present with considerable variation in expressivity, with skin lesions fre-

quently covering the entire face, neck, trunk and extremities. Overgrowth of facial soft-tissues and facial bones may occur under the area of the port-wine stain, although this overgrowth is rarely seen in black patients.<sup>14</sup> Other variations include the occurrence of facial skin lesions with ocular anomalies but without the intracranial abnormalities, or where the leptomeningeal angiomas occur without the port-wine stain.<sup>47,48</sup> Port-wine stains may also be found in association with a number of other congenital syndromes including Cobb syndrome (spinal metameric arteriovenous malformation), Wyburn-



Fig. 4a. Mucocutaneous telangiectasias on the tongue of a patient with hereditary hemorrhagic telangiectasia (HHT).



Fig. 4b. Mucosal telangiectasias seen in the duodenum at endoscopy.

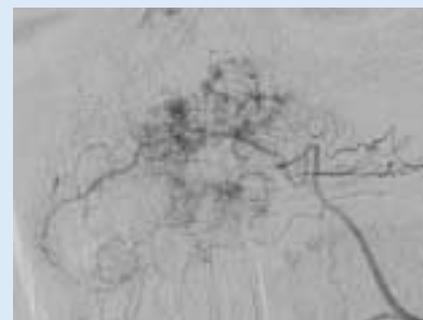


Fig. 4c. Selective facial arterial digital subtraction arteriogram showing multiple enhancing telangiectasias in the nasal mucosa of the same patient.



Fig. 4d. Nasal endoscopic view showing multiple nasal telangiectasias seen through a septal perforation that has resulted from repeated surgical procedures for intractable epistaxis.

Mason syndrome (CAMS 2), Von Hippel-Lindau disease, Proteus syndrome, Roberts's syndrome and thrombocytopenia-absent radius (TAR) syndrome.<sup>36</sup> Treatment of the port-wine stains includes dermabrasion, tattooing, laser and surgery.

Hereditary haemorrhagic telangiectasia is an inherited multisystemic vascular dysplasia syndrome in which the most commonly encountered VMs are mucocutaneous capillary telangiectasias. (Figs 4a-d).<sup>49-51</sup> Patients may also develop AVMs of the brain, spinal cord, lungs and liver.

## Lymphatic malformations

There are two types of lymphatic malformations (LMs), firstly abnor-

malities of lymph vessels and nodes leading to inadequate clearance of lymph (primary lymphoedema), and secondly solitary or multiple cystic lymphatic malformations.<sup>52</sup> LMs occur either due to defective origin of lymphatics together with the venous system or abnormal development of the lymphatics themselves. Cystic LMs result from sequestered lymphatic sacs that fail to communicate with normal lymphatic vessels.<sup>33</sup> Most (70–80%) occur in the head and neck region where they tend to be more cystic. These were previously referred to as cystic hygromas (Fig. 5a). Twenty per cent of cystic LMs are found in the axilla, with other uncommon sites being the superior mediastinum, mesentery, retroperitoneum, pelvis and extremities. Cystic LMs can be subdivided into macrocystic, microcystic and mixed types. Microcystic LMs were previously called lymphangiomas.

Although present at birth, cystic LMs become clinically apparent later in life, usually before 2 years of age.<sup>33</sup> Sudden enlargement may be due to bleeding or inflammation.<sup>21</sup>



Fig. 5a. Macrocystic lymphatic malformation of the neck. Previously termed cystic hygroma.



Fig. 5b. Lymphatic malformation of the upper lip.

LMs may be associated with a number of syndromes including Turner's syndrome, Noonan's syndrome, multiple pterygium syndrome, fetal alcohol syndrome, Klinefelter's syndrome, Down's syndrome, and Klippel-Trenaunay and Parkes-Weber syndromes.<sup>33,53</sup>

Treatment is again dependent on the presence of functional impairment or cosmetic defect (Fig. 5b). An upper respiratory tract infection may frequently cause enlargement of head and neck LMs that may compromise the airway. Macrocystic lesions are probably best treated with percutaneous sclerotherapy. Various agents have been used including alcohol, Ethibloc, hypertonic glucose, bleomycin, triamcinolone and more recently OK-432.<sup>27,31</sup> Microcystic LMs have a high risk of recurrence after surgery and therefore conservative management is recommended for quiescent lesions.<sup>33,54</sup>

## Mixed vascular malformations

Given the common vasculogenic origin of arteries, capillaries, veins and lymphatics it is hardly surprising that mixed or combined malformation

types occur.<sup>55</sup> Combinations include capillary-venous (e.g. Sturge-Weber) arteriovenous, lymphaticovenous, capillary-lymphatic, capillary-arteriovenous (Parkes-Weber), capillary-venous-lymphatic (Klippel-Trenaunay) and more complex combined forms.

## Conclusion

Mulliken and Glowacki<sup>1</sup> wrote: 'A classification is clinically appropriate only when it provides clinicians with a common language through which ideas can be exchanged. A classification is necessary because there is such a large list of clinical congenital vascular lesions with a complex variability in signs, symptoms, and clinical behaviour. Each lesion has its own little story of happiness or grief, particularly as to whether it will require conservative or aggressive management and whether it will become acceptable with this form of treatment. Therefore we must continue to strive for an easy yet efficient method of labelling our patients' problems.<sup>1</sup> A good working classification of any group of pathologies should thus be 'a comprehensive and clinically relevant means of simply and uniformly describing (vascular) anomalies that occur within any human organ system.'<sup>20</sup> Each of the classification systems described above (CNS and non-CNS) is simple and easy to understand and follow, although each is far from complete. There are still lesions that do not comfortably fit into these classifications such as the hepatic cavernous haemangioma and the spinal osseous haemangioma, both of which are technically low-flow vascular malformations. And what of the aneurysmal bone cyst? These classifications will certainly change with a more thor-

ough understanding of the genetic and molecular biology underlying the development of VMs, but for now they will suffice.

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