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Verrucous Lymphovascular Malformation Versus Verrucous Hemangioma: Controversial Nomenclature

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The International Society for the Study of Vascular Anomalies (ISSVA) divides congenital vascular anomalies into malformations and tumors and subclassified hemangiomas under tumors. However, evidence shows this accepted classification has not been widely employed. Particularly troublesome is the use of the term hemangioma, *commonly used to describe a variety of vascular lesions (both malformations and tumors). The term* verrucous hemangioma *has been used to describe a congenital vascular anomaly with a progressive verrucous epidermal surface persisting throughout life unless surgically excised. Recent evidence suggests that some of these lesions may share histologic features of both hemangiomas and malformations, thereby causing nosologic confusion. We report a 15-year-old adolescent girl with such a lesion and review the literature and controversy of verrucous hemangiomas. In our case, the most appropriate diagnosis is verrucous lymphovascular malformation. Further testing of similar lesions will be necessary to fully understand the nature and classification of these lesions.*

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Nomenclature is the major obstacle to our understanding and management of vascular birthmarks.
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Although Mulliken and Young[1] made this statement in 1988, it is still accurate today. The term *verrucous hemangioma* has been used to describe a congenital vascular anomaly with a progressive verrucous epidermal surface persisting throughout life unless surgically excised. This clinical evolution is suggestive of a vascular malformation rather than a hemangioma. According to Tennant et al,[2] some of these lesions may share histologic features of both hemangiomas and malformations, thereby causing nosologic confusion. We report a case of such a lesion and review the literature on verrucous hemangiomas.

Case Report

A 15-year-old adolescent girl presented to the dermatology clinic complaining of a painful chronic lesion encompassing her left fourth toe. This congenital lesion was first troublesome at 2 years of age when it began to expand and became violaceous. When the patient was 4 years of age, the lesion was removed and pathologically diagnosed as a capillary hemangioma. Recovery after removal was complicated by infection and delayed healing. The lesion subsequently recurred to its previous size and color in less than a year. Two years later, a superficial biopsy of the toe showed changes consistent with lichen simplex chronicus, leading to the temporary use of topical steroids. The same year, 2 intralesional steroid injections resulted in a temporary reduction in lesion size, followed by rapid recurrence. The patient reported numerous bacterial infections and one fungal infection of the lesion that responded to antibiotics and antifungals, respectively. Over the next several years, the lesion and left fourth toe gradually increased in size.

At the time of referral to our clinic, the patient reported that every few months the lesion became

painful and edematous without preceding trauma. The episodes increased in frequency within the past year, preventing the patient from full weight bearing. In addition, the patient reported that the appearance of the lesion had become crusty.

Prior medical history was unremarkable and family history did not reveal vascular lesions or asymmetric extremities.

A hypertrophied left fourth toe with verrucous hyperplasia over the dorsal surface was present upon physical examination (Figure 1). The plantar foot demonstrated multiple tender, exophytic, violaceous nodules with overlying hemorrhagic crusts. The adjacent toes were unaffected. The patient was referred to pediatric plastic surgery for further care. She underwent ray amputation, which was performed without complication. The remainder of the excision was performed using a carbon dioxide laser. The patient healed well with no postsurgical complications.

Histology of the lesion postamputation showed an admixture of angulated thin-walled blood vessels containing proteinaceous lymph, along with smaller numbers of thicker-walled venous structures (Figure 2). This histology was initially interpreted as a verrucous hemangioma. Upon further consultation, the diagnosis was revised to vascular malformation of a predominantly lymphatic type. Radiologic studies and special stains were not performed on this patient.

In the immediate postoperative period, there was no sign of recurrence and her function greatly improved. At 6-month follow-up, the patient had evidence of possible recurrence on the plantar foot near the base of the third toe in the form of a 15×15-mm, firm, flesh-colored, tender

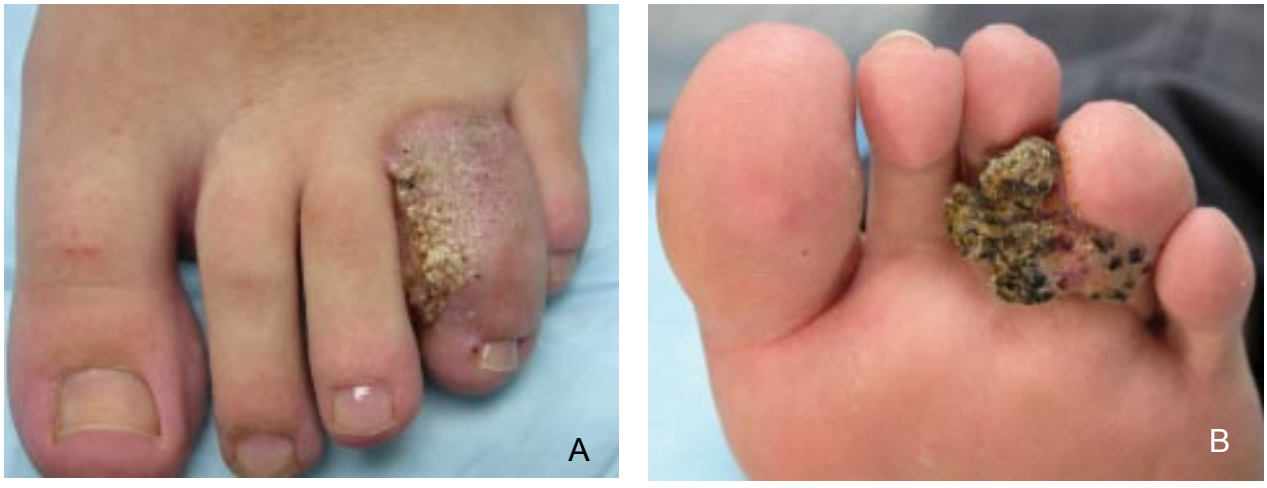

Figure 1. Upon presentation to the dermatology clinic, the patient demonstrated a hypertrophied left fourth toe with verrucous hyperplasia over the dorsal surface and multiple tender, exophytic, violaceous nodules with overlying hemorrhagic crusts on the plantar foot (A and B).

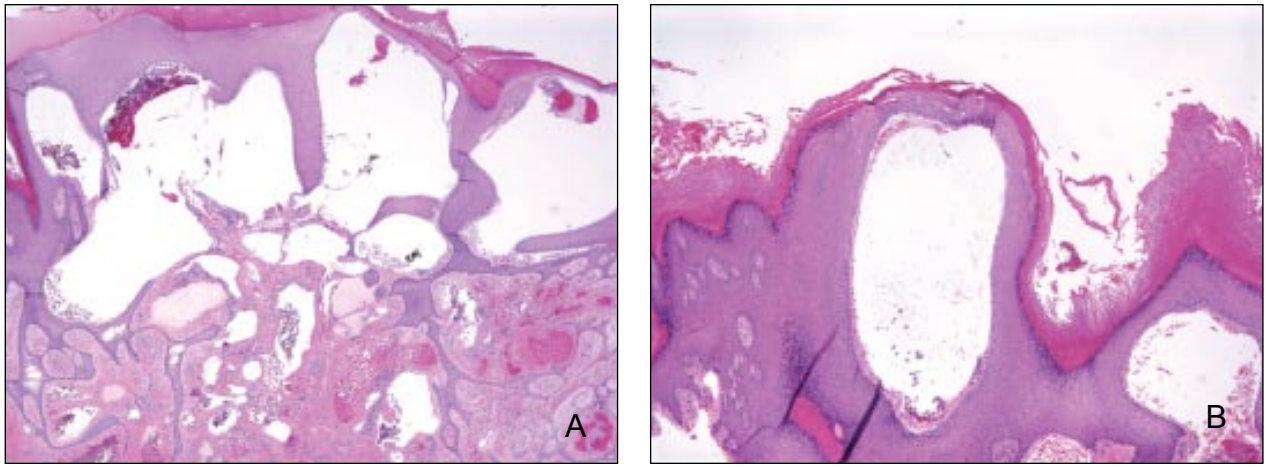

Figure 2. Histology of the lesion postamputation showed an admixture of angulated thin-walled blood vessels containing proteinaceous lymph, along with smaller numbers of thicker-walled venous structures (A and B)(H&E, original magnification ×10 for both).

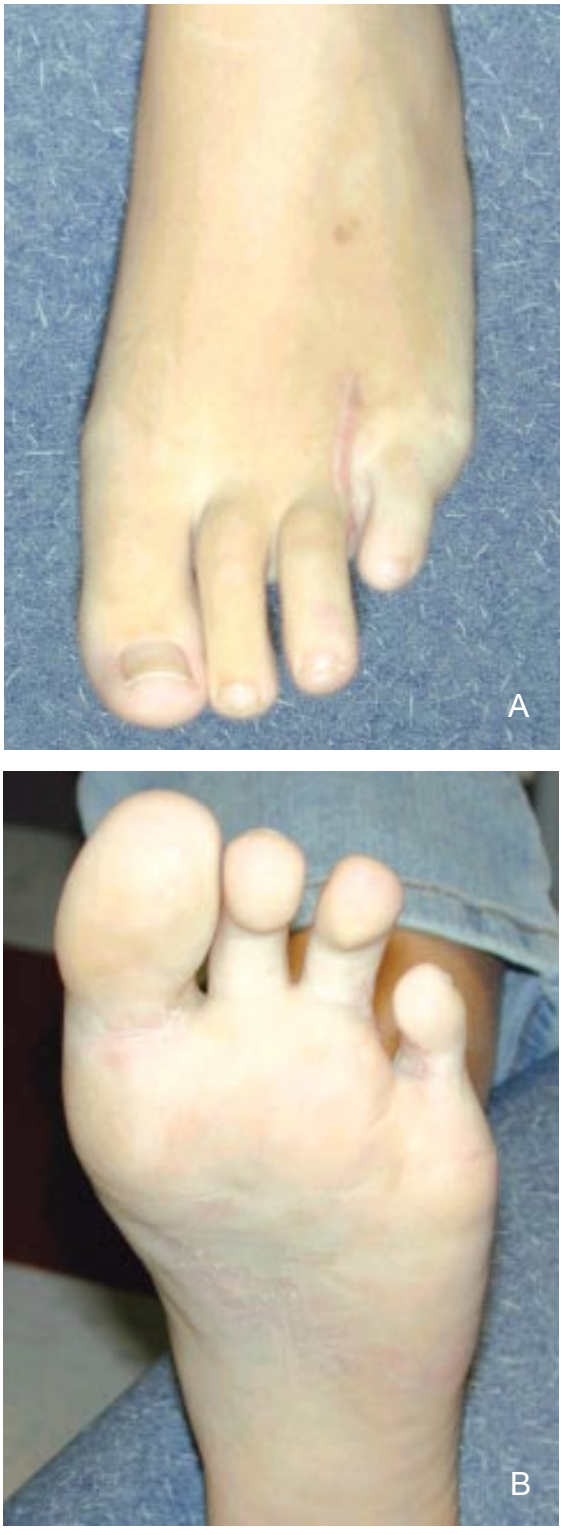

Figure 3. At 6-month follow-up, there was no evidence of residual cutaneous involvement (A and B).

subcutaneous nodule. There was no evidence of residual cutaneous involvement (Figure 3). Because her activity or mobility levels were not affected, the patient and her family elected not to undergo further excision. She currently participates in cross-country running, which she could not do prior to the initial surgery. The loss of the left fourth toe has not interfered with her function.

Comment

In 1982, Mulliken and Glowacki[3] proposed a classification system for congenital vascular anomalies based on clinicohistologic correlations. In this system, congenital vascular anomalies are divided into 2 categories: malformations and hemangiomas. Subsequently, Enjolras and Mulliken[4] refined the classification into malformations and tumors and subclassified hemangiomas under tumors. Both malformations and tumors usually present at or shortly after birth. However, malformations are errors of morphogenesis, whereas tumors are problems of increased proliferation.[4] Malformations, therefore, have a normal rate of endothelial cell proliferation and tend to grow proportionately with the child. In contrast, tumors, specifically hemangiomas of infancy, exhibit a phase of rapid growth during infancy, followed by involution with fibrosis. The International Society for the Study of Vascular Anomalies (ISSVA) adopted this classification system in 1996 and has revised it to include the modifications proposed by Enjolras and Mulliken.[4]

Histologically, hemangiomas of infancy and vascular malformations can be difficult to distinguish. Hemangiomas of infancy go through histologically distinct phases. Proliferating hemangiomas of infancy are neoplasms composed of hyperplastic, densely packed, plump endothelial cells forming capillaries. Involuting hemangiomas of infancy demonstrate fibrofatty infiltration, multilamellated basement membranes, and diminishing cellularity with apoptosis.[3] Involuted hemangiomas of infancy are composed of vascular channels lined with flat mature endothelial cells. Fibrosis may obliterate the blood vessel lumens in the involuted phase. Several immunoreactive markers are characteristically present or absent in proliferating, involuting, and involuted phases. Proliferating hemangiomas of infancy highly express basic fibroblast growth factor, vascular endothelial growth factor, urokinase, E selectin, type IV collagenase, and proliferating cell nuclear antigen, all of which demonstrate the active angiogenesis of these lesions. These angiogenesis markers decrease as hemangiomas of infancy begin to involute and are not present in involuted hemangiomas of infancy. Involuting hemangiomas of infancy express increased levels of tissue inhibitor of metalloproteinase and transforming growth factor β, which inhibits new blood vessel formation and accounts for the involution of these lesions.[4]

Comparison of Hemangioma of Infancy and Verrucous Hemangioma

	Hemangioma of Infancy	Verrucous Hemangioma (Verrucous Lymphovascular Malformation)
Onset	Present at or shortly after birth	Present at birth; may not be visible or diagnosed until later
Clinical appearance	Soft, compressible, well-demarcated, blue-to-red mass; no reactive epidermal changes; typically disappears completely when involuted; ulceration in lip, perineal, and segmental lesions; scarring and fibrofatty residua possible	Early: soft, compressible, well-demarcated, blue-to-red mass Later: reactive epidermal changes and hypertrophy result in a verrucous appearance; satellite lesions are typical; superficial, purulent, or hemorrhagic crusts may be seen; deeper brown to blue-black color Most common on lower extremities
Natural history	Rapid phase of growth during infancy, followed by involution with fibrosis	Normal rate of endothelial cell proliferation and tends to grow proportionately with the child; persists indefinitely without regression
Histology	Proliferating phase: hyperplastic, densely packed, plump endothelial cells forming capillaries Involuting phase: fibrofatty infiltration, multilamellated basement membranes, and diminishing cellularity with apoptosis Involuted phase: vascular channels lined with flat mature endothelial cells; fibrosis may obliterate the blood vessel lumens	Dilated capillaries, venules, and rare lymphatics in the dermis and subcutaneous tissue, along with reactive epidermal acanthosis, parakeratosis, papillomatosis, and hyperkeratosis
Special markers	Angiogenesis markers: bFGF, VEGF, urokinase, E selectin, type IV collagenase, PCNA (all in the proliferating phase; not present in the involuted phase), MIB-1 Angiogenesis inhibitors: TIMP1, TGF-β (in the involuted phase) GLUT1 (present in all stages)	Less frequently than in hemangiomas of infancy, MIB-1 and GLUT1 may be focally positive

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Table. (continued)

	Hemangioma of Infancy	Verrucous Hemangioma (Verrucous Lymphovascular Malformation)
Imaging studies[6]	US: well-circumscribed mass of variable echogenicity containing well-defined lobules and large vessels in the septum; increased flow and high vessel density; in the involuting and involuted phases, the lesion decreases in volume with a reduced number of vessels CT: homogeneous lobular masses with intense enhancement after contrast (proliferating phase); enhancement decreases in involuting and involuted phases MRI: intermediate signal intensity on T1-weighted sequences and increased signal intensity on T2-weighted sequences; necessary for special circumstances (PHACES syndrome, multiple cutaneous hemangiomas, beard distribution)	US: more homogeneous vascular mass with little stroma; if venous, phleboliths and compressible vessels seen; flow demonstrates a venous signal; if arteriovenous, both arterial and venous flow seen; if lymphatic, no flow signal CT: hypodense or heterogeneous lesion with slow peripheral postcontrast enhancement MRI: venous malformations show variable signal intensity; arteriovenous malformations show low signal intensity; lymphatic malformations show low T1 intensity and high T2 intensity; important to ensure full surgical removal

Abbreviations: bFGF, basic fibroblast growth factor; VEGF, vascular endothelial growth factor; PCNA, proliferating cell nuclear antigen; GLUT1, glucose transporter protein; TIMP1, tissue inhibitor of metalloproteinase; TGF-β, transforming growth factor β; US, ultrasonography; CT, computed tomographic scan; MRI, magnetic resonance imaging; PHACES, posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects, eye abnormalities, and sternal or ventral defects.

Vascular malformations, on the other hand, consist of flat mature endothelial cells surrounding ectatic vessels without increased mitotic activity and can be composed of capillary, venous, arterial, and/or lymphatic components. The histologic appearance of vascular malformations is similar to involuted hemangiomas of infancy. North et al[5] delineated a histologic distinction between hemangiomas of infancy and vascular malformations in 2000 by demonstrating the presence of erythrocyte-type glucose transporter protein (GLUT1) as a specific feature of hemangiomas of infancy during all stages, independent of mitotic activity. GLUT1 is a glucose transporter not found in healthy skin. A retrospective study by North et al[5] reported GLUT1 immunoreactivity in 97% of hemangiomas of infancy (139/143) and in none of 66 vascular malformations studied (17 arteriovenous, 33 venous, 11 lymphatic, 5 port-wine stains). The Table provides a comparison of hemangiomas of infancy and lesions that have been termed *verrucous hemangiomas*.

Although an improved clinical and histologic classification system has been officially adopted by the ISSVA, evidence shows that it has not been widely employed. In 2002, Hand and Frieden[7] reviewed genetics textbooks to investigate how often this system was correctly followed. Their data suggest that despite the availability of a practical classification system, standard genetics textbooks still contain a number of discrepancies. They postulate that the use of multiple terms to describe the same anomaly, along with a hesitancy to change well-recognized terminology, might be the cause of such discrepancies. Particularly troublesome is the term *hemangioma*, commonly used to describe a variety of vascular lesions, both malformations and tumors. Use of this term has the lowest rate of agreement with the ISSVA classification criteria.[7] Hand and Frieden[7]

suggest that hemangioma is too generic and should be reserved to describe the hemangioma of infancy.

Halter[8] was the first to use the term *verrucous hemangioma* in 1937. In 1967, Imperial and Helwig[9] identified only 21 previously reported cases. They defined *verrucous hemangioma* as a structural variant of capillary hemangioma that extends into the dermis and subcutaneous tissue. Histologically, the review describes dilated capillaries, venules, and rare lymphatics in the dermis and subcutaneous tissue, along with reactive epidermal acanthosis, parakeratosis, papillomatosis, and hyperkeratosis. The reported lesions were present at or shortly after birth, and 90% of the lesions (17/19) were located on the lower extremities. Age at presentation for medical care ranged from 12 to 43 years.[9] As Mulliken and Young[1] noted in 1988, some of these lesions can be "apparently acquired" because although the structural abnormality is present at birth, it may not clinically manifest until later.[3] Early on, physical appearance of the lesions is similar to hemangioma of infancy, including a soft, compressible, well-demarcated, blue-to-red mass. Later in life, reactive epidermal changes and hypertrophy become increasingly more pronounced, resulting in a verrucous appearance. Satellite lesions typically develop and superficial, purulent, or hemorrhagic crust may be seen.[3] Despite naming it a hemangioma, Imperial and Helwig[9] referred to this tumor as a malformation. It also was noted that because this lesion extends into the dermis and subcutaneous tissue, deep surgical excision is the best method for removal.[9] Some clinicians recommend ultrasonography, computed tomographic scans, or magnetic resonance imaging to delineate the full extent of these lesions prior to removal.[6] However, in our case and in most reported cases of verrucous hemangioma, no radiologic studies were done. Retrospectively, imaging studies to better outline the lesion would have been a useful aid during surgery. Use of the term *hemangioma* rather than *malformation* to describe these lesions may contribute to the tendency to underestimate the need for imaging studies to define their deep and lateral extents.

Since the description in 1967 by Imperial and Helwig,[9] several case reports have been published using the term *verrucous hemangioma* to describe such lesions.[2,10-22] Many of these reports have occurred since the general acceptance of the improved classification system.[10-12,15,21,22] In the 60 cases with available medical history, 55 presented at or near infancy, 4 presented at an unknown time in childhood, and 1 presented in adulthood.[2-5,7-21] Age at presentation for medical care ranged from 5 months to 77 years. The histologic changes of the lesions mimicked those changes described by Imperial and Helwig[9] in the original 21 cases reported. Some lesions also showed inflammation and fibrosis[11] in the upper dermis and superficial purulent[13] or hemorrhagic crusts.[15]

It has been proposed that the reactive epidermal hyperplasia of these lesions is due to suboptimal excision, trauma, and even possibly epidermal growth factors secreted by the underlying lesion. There is no evidence of human papillomavirus, based on immunohistochemical and ultrastructural evaluation of 10 lesions.[22] The verrucous changes in our patient and similar reported cases may signify lymphatic involvement.[9] Hemangiomas of infancy typically do not develop overlying verrucous changes. The verrucous hypertrophy of these lesions is reminiscent of the cutaneous changes seen in chronic lymphedema, elephantiasis verrucosa nostra, and Turner syndrome.

Several authors have proposed new names for this entity. In 1997, Requena and Sangueza[23] correctly pointed out that the term *verrucous hemangioma* is a misnomer because the lesions are not neoplasms but rather errors of morphogenesis. Thus, they renamed the lesions *hyperkeratotic vascular stains*. In their 2000 study on the proper surgical management of verrucous hemangiomas, Mankani and Dufresne[24] proposed the name *verrucous malformation*. In addition, the verrucous hemangiomas described by Imperial and Helwig[9] were subsequently referred to as *venous malformations* by Mulliken and Glowacki.[25]

More recently, Tennant et al[2] reexamined this topic and noted that the clinical presentation and behavior of these lesions is consistent with a malformation. However, the lesions they examined and designated as verrucous hemangiomas contained certain microscopic features that also are present in hemangiomas of infancy, including thick vascular walls, multilamellated basement membranes, relatively uniform channel size, MIB-1 positivity, and GLUT1 positivity. Their evaluation of 11 lesions designated as verrucous hemangiomas revealed focal positivity for GLUT1 in 7 lesions and scattered MIB-1 (a proliferative marker) activity in 8 lesions. The staining in these lesions of accepted hemangioma of infancy markers contradicts their classification as malformations. Despite the potential for confusion, the researchers recommend that the term *verrucous hemangioma* should be retained for these specific errors of morphogenesis until the field of vascular anomalies evolves and a more precise designation becomes available.[2] In our case, staining for GLUT1 was not performed, as it did not impact therapeutic management. At least one group of clinicians, however, routinely performs GLUT1 stains to aid in diagnosing vascular anomalies.[26]

While the initial clinical appearance of vascular malformations can be indistinguishable from hemangiomas of infancy early in life, further investigation will reveal their true nature. Because treatment and prognosis of hemangiomas of infancy and vascular malformations are vastly different, it is important to distinguish them using a clear and precise classification system so patients, families, and physicians can accurately understand potential medical, functional, and psychologic implications. Given our patient's clinical history, presentation, and histologic findings, *verrucous lymphovascular malformation* is more appropriate terminology regardless of any future histologic staining studies.

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