Hemangioma Versus Vascular Malformation

Presence of Nerve Bundle Is a Diagnostic Clue for Vascular Malformation

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Context.—Arteriovenous vascular malformations and hemangiomas are benign vascular lesions that are difficult to distinguish from one another clinically. Also, they may be confused with each other at histopathology. Therefore, histochemical stains for the presence of an artery are frequently used to distinguish between the two.

Objective.—Because it is clinically relevant to differentiate between arteriovenous vascular malformations and hemangiomas, this study was carried out to explore additional diagnostic clues that may help in the diagnosis and differentiation of these lesions.

Design.—A total of 167 cases of benign extracranial vascular lesions were retrieved from the anatomic pathology file of our institution. These comprised 66 cases diagnosed as arteriovenous vascular malformations and 101 cases previously diagnosed as hemangiomas. The hematoxylin–eosin–stained glass slides were reviewed, Movat pentachrome histochemical stain was used to identify elastic vessels (arteries/arterioles), and S100 immunostain was used to identify nerves within these vascular lesions. For immunohistochemistry, the avidin-biotin detection method was used.

Results.—With Movat stain, the presence of thick-walled elastic arteries was detected in 12 of the 101 cases previously diagnosed as hemangiomas, and these cases were therefore reclassified as vascular malformations. Using the same criterion, 2 of the 66 cases originally diagnosed as arteriovenous vascular malformations were reclassified as hemangiomas because they lacked arterial structures. Thus, with this strict criterion, we ended up with 91 cases of hemangiomas and 76 cases of arteriovenous vascular malformations. Intralesional nerves were identified in 91% (69/76) of cases of arteriovenous vascular malformations, including all the 12 arteriovenous vascular malformations previously diagnosed as hemangiomas. In contrast, no intralesional nerve was detected in any of the 91 hemangiomas.

Conclusions.—These results show that nerve bundles are consistently present in vascular malformations and absent in hemangiomas and so can be used as a diagnostic clue to differentiate between these lesions. Also, in addition to describing a previously unreported component of vascular malformations, these data further confirm the hamartomatous nature of these lesions.

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Vascular lesions are very common, with vascular tumors constituting the most common tumors in childhood.1 The diagnosis and treatment of these lesions involve several medical subspecialties, including surgeons, radiologists, internists, and histopathologists. The diagnosis and management of vascular lesions continue to present diagnostic and therapeutic challenges to all. This is in part because of lack of agreement regarding the nosology and classifications of the lesions—both for diagnostic and therapeutic purposes.2 Many authors use the term hemangioma to describe or qualify vascular malformations and a potpourri of vascular anomalies, whereas others continue to use the term cavernous hemangioma for venous malformation and port-wine stain for capillary malformation,3 venous malformation, and arteriovenous malformations (AVMs),4 thus perpetuating the nosologic confusion and the attendant problems. A simple 2-tier classification system proposed by Mulliken and Glowacki5 in 1982, which was later modified and adopted by the International Society for the Study of Vascular Anomalies,6 has helped simplify the clinical classification and management of the lesions. However, the diagnosis and pathogenesis of these lesions continue to challenge histopathologists, who are often called on to help with the definitive diagnosis and classification of these lesions. The presence of arteries, arterioles, or both as an integral part of the lesions (as shown by elastic tissue stains) is often used as a diagnostic criterion for differentiating AVMs from hemangiomas.7 To further characterize the histomorphologic differences between hemangioma and AVM, we used histochemical elastic stains (Movat pentachrome stain) and S100 (an immunohistochemical stain for nerve and nerve fibers) to study the various tissue components present in these lesions.

MATERIALS AND METHODS

The study materials were retrieved from the anatomic pathology file of our institution and consisted of 167 consecutive cases of benign vascular lesions that were diagnosed during a period of 8 years (1995–2002) in our division of surgical pathology. The material consisted of 101 cases originally diagnosed as heman-
Figure 1. Hematoxylin-eosin-stained (A, B, C) and Movat pentichrome stained (D) sections showing the presence of intralesional nerves in arteriovenous malformations. The nerves range from small twigs (A, D) to medium-sized and large nerve bundles (B and C, respectively). Movat stain also shows the presence of thick-walled arterial vessels with elastic lamina (D) (original magnification ×100).

RESULTS

Twelve of the 101 cases originally diagnosed as hemangiomas were reclassified as AVMs based on the presence of thick-walled elastic arteries or arterioles as part of the lesion as demonstrated by Movat stain (Figure 1, B through D). With the same stain, 2 of the 66 cases previously diagnosed as AVMs were reclassified as hemangiomas. Following this reclassification, therefore, we had 91 confirmed cases of hemangioma and 76 confirmed cases of AVM.

Of the 91 confirmed cases of hemangioma, 79 were from skin and subcutaneous tissues, 5 from oral mucosa, 1 from maxillary sinus, 1 from vocal cord, 1 from vulva, 1 from...
Hemangioma Versus Vascular Malformation—Adegboyega & Qiu

Vascular lesions are very common and have been described as the ‘‘oldest tumor’’ because of the discovery of intraosseous hemangiomas in dinosaur vertebrae.1 But to this day, they continue to pose diagnostic and therapeutic challenges to clinicians and histopathologists alike, with consequent and often protracted distress for the patients, who sometimes shuffle from physician to physician seeking help.10 In this study, we show the presence of intrale-sional nerve to be a helpful discriminator that can be of diagnostic utility for histomorphologists for the correct classification and diagnosis of hemangiomas and AVMs. Arteriovenous malformations are the result of errors in morphogenesis and are divided into subtypes based on the constituent vessels: capillary, venous, arterial, lymphatic, and combined forms. Hemangiomas, on the other hand, result from a derangement in angiogenesis with exuberant proliferation of vascular elements due to imbalance between angiogenic and angiostatic forces.3,11,12 Therefore, arteries and arterioles are not part of the lesion. Arteriovenous malformations are a complex network of intercommunicating arterial and venous structures.13 Hence, pathologists rely on elastic stains as ancillary tools for making a definitive diagnosis of AVMs, because arteries and arterioles (with elastic lamina in their walls) are an integral part of AVMs.7 The presence of intrale-sional nerve in AVM, as reported in this study, provides an ad-ditional diagnostic criterion that is simple and reliable and can be readily used to differentiate AVMs from hemangiomas, even in H&E-stained tissue sections. Also, the presence of nerve in AVMs supports the theory that AVMs are hamartomas, which by definition are mass lesions composed of an abnormal architectural organization of tissues that are normally present at a particular site or organ.7

Only a handful of previous studies have focused on the presence or distribution of nerves in benign vascular les-sions. Rydh et al14 reported absence of nerve bundles and paucity of nerve fibers around the dilated vessels in 9 cases of port-wine stains (which they called venous malfor-mations) and concluded that loss of vascular tone due to absence of adequate nerve supply may be responsible for the vascular ectasia that characterizes those lesions. Con-sidering the absence of nerve bundles in those lesions, we suggest they are better classified as venous hemangiomas. Robinson et al14 studied the innervation of 6 intramuscular hemangiomas using S100 immunohistochemical stain. They reported the nerve content of hemangiomas to be the same as that in normal tissue and that in surrounding margins of the lesions. They also observed increased pres-ence of nerves in the immediate (1–3 mm) vicinity of the intramuscular hemangiomas. Increased neuropeptides (substance P and calcitonin gene–related products) were found within the lesions, and the authors surmised that these neuropeptides were responsible not only for creating the symptom of pain but also for inducing growth of the lesions by stimulating proliferation of fibroblasts and endothelial cells. The nerve bundles observed in that study and also previously reported in other benign intramuscu-lar vascular lesions15,16 were likely to be nerve bundles that are normally present within the richly innervated skeletal muscles in which those hemangiomas are located.

Jang et al17 studied 15 hemangiomas (6 proliferating and 9 involuting) and 7 vascular malformations of unspecified
types and looked at nerve fiber (not nerve) contents of these lesions. They reported an increased number of nerve fibers in proliferative hemangiomas compared with their involving counterparts and AVMs, and based on that, they hypothesized that neuropeptides released by nerve fibers in proliferating hemangiomas may play some angiogenic role in promoting the growth of hemangiomas. In our study, we found nerve bundles to be present only in AVMs and not in hemangiomas, but small nerve fibers (highlighted by S100 immunostain) were observed in both lesions. In agreement with the finding reported by Jang et al.,\textsuperscript{17} we noticed comparable presence of nerve fibers in the hemangiomas and AVMs we studied, which may be because all the hemangiomas we studied were past the proliferative phase (which usually occurs in infancy).

Additional fundamental differences between hemangiomas and AVMs include (1) the timing of their clinical appearance, (2) their growth patterns, (3) the biologic behavior or growth characteristics of their endothelial lining in cell culture, (4) the stromal cellular and extracellular matrix compositions, and (5) the response of the lesions to pharmacotherapeutic agents.

Hemangiomas appear very early in life, either at birth or within the first 2 weeks of life.\textsuperscript{3,5} Arteriovenous malformations by definition are technically present at birth but may not become noticeable until much later in life, with some coming to sight as late as during puberty or even during the postpubertal period. The timing of the clinical appearance of vascular malformation depends on the type of vessels involved.\textsuperscript{14} Capillary and lymphatic malformations are usually evident at birth or within the first year of life, venous malformations any time between birth and early adulthood, and arterial malformations and AVMs often at puberty or during pregnancy because of the associated hormonal changes.\textsuperscript{15,16} Hemangiomas grow with a rapid growth phase during the first year of life and usually involute within the first decade of life.\textsuperscript{5,19} In contrast, AVMs grow proportionately with the patient; do not involute; and may sometimes increase in size because of vascular ectasia induced by conditions such as sepsis, trauma, puberty, and pregnancy.\textsuperscript{18} The endothelial lining of hemangiomas (particularly in the proliferative phase) is plump, and when cultured, they proliferate and form tubular structures reminiscent of vascular channels. The endothelial cells that line AVMs are quiescent flat cells that neither proliferate nor differentiate into vascular structures in vitro.\textsuperscript{19} Immunohistochemical studies have shown that, unlike the extracellular matrix of vascular malformations or normal tissues, the extracellular matrix of hemangiomas contains increased fibronectin, perlecain, and laminin,\textsuperscript{1,20,21} increased growth factors (basic fibroblast growth factor, insulin-like growth factor, and vascular endothelial growth factor),\textsuperscript{22-24} proteases (type IV collagenase and urokinase); and adhesion molecule E selectin.\textsuperscript{25} Also in line with their divergent growth characteristics, hemangiomas (especially in the proliferative phase) respond to corticosteroids, interferon α2a, ionizing radiation, and laser photocoagulation,\textsuperscript{18,26,27} all of which have no growth-inhibiting effects on AVMs.

Considering the differences in the pathobiology and natural history of these lesions, as well as the therapeutic and prognostic implications of accurately distinguishing between hemangiomas and AVMs, it is important that these lesions be correctly diagnosed. Not only will AVMs that are misdiagnosed as hemangiomas and treated as such fail to respond to medical treatment with pharmacologic agents, error in surgical management of such lesions may also result in treatment failure and loss of angio-access for proper management of the lesion in the future.\textsuperscript{28} We here show the presence of intraleisonal nerve to be a simple, reliable, and cost-neutral diagnostic criterion for correctly distinguishing between hemangiomas and AVMs.

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References