HEMANGIOPERICYTOMA, TRUE PERICYTIC TUMORS AND MIMICS

Christopher D.M. Fletcher, M.D., FRCPath
Department of Pathology
Brigham and Women’s Hospital
and Harvard Medical School
Boston, MA  02115

Bullet points

• Diagnostic criteria for the diagnosis of hemangiopericytoma have shifted since Stout’s first description.
• Very many tumors may show a branching pericytoma-like vascular pattern, as a consequence of which the diagnostic term ‘hemangiopericytoma’ has often been loosely applied.
• The majority of tumors formerly diagnosed as so-called hemangiopericytoma have nothing to do with pericytes.
• The single largest subset of lesions formerly known as hemangiopericytoma (at all sites) would nowadays be classified as solitary fibrous tumors.
• There exists a group of truly pericytic neoplasms, known as myopericytoma, which are being increasingly defined and represent a continuum between myofibroma(tosis), glomus tumor and angioleiomyoma.
Hemangiopericytoma was first described and introduced as a diagnostic concept by Stout and Murray in 1942. They described a series of 9 cases characterized by perivascular proliferation of rounded cells, which they believed to be Zimmermann’s pericytes. They chose the term hemangiopericytoma to contrast with hemangioendothelioma, a type of vascular tumor in which the dominant proliferating component (whether benign or malignant), was endothelial cells. In 1949, Stout published an additional 25 new cases with the purpose of further characterizing and defining the ‘entity’. At this time he noted that the tumor cells consistently grow outside the reticulin sheath of vessel walls, that “the exact nature of these so-variable cells” was uncertain and that it was not possible to distinguish benign and malignant examples of hemangiopericytoma on morphologic grounds. Just 4 years later, in 1953, he stated, during a slide seminar in New York, that it was his “general attitude in regard to hemangiopericytoma to reject it as a diagnosis if he could think of any other reasonable explanation for a tumor.” He already feared that it might represent a possibly heterogeneous tumor type but, nevertheless, he described a further series of 31 cases in pediatric patients, identified from among a total of 307 cases of hemangiopericytoma (at all ages) which he had accumulated by that time. Among these 31 cases, 10 were congenital and more than 50% developed before the age of 5 years. Two patients had multifocal lesions.

In succeeding years, however, the concept of hemangiopericytoma shifted and, in the major series published by Enzinger and Smith in 1976, the definition shifted away from describing cells with rounded glomus-like morphology and a perivascular growth pattern to focus on ovoid-to-spindle-shaped cells arranged in a haphazard fashion in association with variably dilated branching or staghorn vessels.

The proposal that these tumors were composed of perivascular contractile cells was based mainly on the architectural pattern with tumor cells surrounding branching blood vessels, and was supported to some extent (at least in the past) by ultrastructural studies. However, immunohistochemistry has failed to support this theory, as most tumors (at least in adulthood) stain only (and non-specifically) for vimentin and CD34 but not for actin or other myoid markers.
Traditionally, hemangiopericytoma has been classified into adult and infantile variants which have little in common, either clinically or histologically, except for the presence of a branching “pericytomatous” vascular pattern, a feature that is also shared with many other tumors. \(^{12-14}\) Most common among those tumors which consistently share this pattern are solitary fibrous tumor, synovial sarcoma, infantile myofibromatosis, low-grade endometrial stromal sarcoma, mesenchymal chondrosarcoma, deep benign fibrous histiocytoma and infantile fibrosarcoma.

In recent years it has become clear that infantile and adult hemangiopericytoma are two completely independent “entities”, the former being closely related to infantile myofibromatosis and the latter being of disputed nature but, in most cases, essentially synonymous with solitary fibrous tumor.

Among the lesions formerly diagnosed as hemangiopericytoma in adults there seems to have been considerable inhomogeneity, likely reflecting the absence of reproducible diagnostic criteria. In fact the personal opportunity, with Juan Rosai, to review some of Stout’s original cases has suggested that this “entity” may have been heterogeneous and relatively non-cohesive from the outset, as is easy to understand given the absence of more modern diagnostic techniques at that time. In this regard it is worth reminding ourselves that, by 1953, Stout himself indicated that he no longer made this diagnosis if he could come up with any alternative!

As a consequence, hemangiopericytoma has become (like so-called “malignant fibrous histiocytoma”) something of a wastebasket diagnosis, yet there remain discrete subsets (detailed below) for which there is no better name. In parallel with this realization, it is also increasingly appreciated that there probably exists a group of truly pericytic lesions (examples of which were included in Stout’s early work on this topic). \(^{1,2}\) These lesions, which include examples of so-called “myofibromatosis” occurring in adults, \(^{15}\) are best categorized as myopericytoma and are described in more detail below.

**Clinical features**

*So-called adult hemangiopericytoma* has traditionally been said to occur in middle to late adult life with an equal sex distribution. \(^{5,16}\) Probably the majority of the cases so classified in the past would nowadays be regarded as examples of solitary fibrous tumor at the more cellular end of that morphologic spectrum and this view was
codified in the 2002 WHO Classification. This would also include the cellular lesions located in pelvis and retroperitoneum, seemingly most often in adult females, which may be associated with hypoglycemia due to secretion of insulin-like growth factor. A supposedly distinct group comprises those lesions which arise in the meninges (formerly often known as angioblastic meningioma but nowadays often labelled ‘meningeal hemangiopericytoma’). However, many would argue that these also are cellular or malignant examples of solitary fibrous tumor and certainly there seem to be no convincing criteria for distinguishing these tumor types from one another. Although histologic grading of these so-called meningeal hemangiopericytomas is unreliable, many seem ultimately to pursue an aggressive course: a distinctive feature of considerable relevance to general pathologists is the propensity of meningeal lesions to give rise to osseous, intra-abdominal or (less often) pulmonary metastases, often after a prolonged latent period.

*Sinonasal hemangiopericytoma* is a histologically distinct subset composed of more obviously myoid (actin-positive) cells. These cells are short, spindled or ovoid, with uniform nuclear morphology and palely eosinophilic cytoplasm. They are typically arranged in sheets or nodules around small thin-walled vessels and form a submucosal mass which generally measures less than 2-3 cm. Such tumors occur principally in adults and are characterized by the tendency for local recurrence in 15-20% of cases, but not metastasis.

*So-called infantile hemangiopericytoma* can be congenital or else present in the first years of life as a solitary, most often deep dermal or subcutaneous mass. Some patients have multiple lesions, further underlining the overlap with infantile myofibromatosis. Recurrence is common but the ultimate behavior is generally benign. Rare cases with metastasis have been reported; however this might represent an unusual manifestation of multicentricity rather than true metastasis. The clinicopathologic features are virtually identical to those of infantile myofibromatosis and it is nowadays generally agreed that they represent different stages or patterns of the same entity.

*Myopericytoma* is the term we currently prefer to use to embrace lesions described as myofibromatosis in adults, glomangiopericytoma and myopericytoma.
This is essentially the largest group of true pericytic neoplasms. We also believe that this is usually a more appropriate term for infantile myofibromatosis and solitary myofibroma in adults, although general adoption of such changes in terminology is only occurring gradually. As a group, these lesions most commonly develop in superficial soft tissue of the extremities (particularly the distal lower limb) of adults, although often they have been noticed since birth or early childhood. The lesions may be solitary or multiple, are sometimes painful, and (in clinical terms) appear to recur locally in 10–20% of patients, although this probably represents multifocal (or “field change”) disease, rather than true recurrence of a previously excised lesion. A case of glomangiopericytoma associated with oncogenic osteomalacia has been described. Examples of malignant myopericytoma are very rare but seem to behave aggressively.

**Histologic appearances**

*Adult hemangiopericytomas* (so-called) are indistinguishable from (and essentially the same as) cellular examples of solitary fibrous tumor. They are usually well circumscribed, often lobulated, and are composed of cytologically uniform small, basophilic, ovoid to spindled cells with an oval nucleus and ill-defined cytoplasm. These cells are arranged in a patternless fashion around numerous thin-walled ramifying blood vessels, which often adopt a typical staghorn configuration. Focal or diffuse myxoid change and stromal fibrosis can be a feature. A silver stain shows that the tumor cells are located outside the vascular spaces and are each surrounded by a reticulin sheath. Features that have been said to indicate malignancy are the presence of increased cellularity, necrosis, hemorrhage and more than 4 mitotic figures per 10 high-power fields, the latter being the most important feature – these are essentially the same criteria as are nowadays employed in solitary fibrous tumor.

*So-called infantile hemangiopericytoma* is a multinodular tumor in which the lesional cells tend to be more polymorphic and focally spindle-shaped or myoid in appearance. Mitotic figures and focal necrosis are common findings, as is subendothelial proliferation which may simulate vascular invasion. In essentially all cases it is possible to distinguish a second tumor cell population composed of micronodules and fascicles of plump spindle-shaped cells with myoid features that stain positively for smooth muscle actin. This
creates a subtle zoning phenomenon, indistinguishable from (but often less marked than) that seen in myofibromatosis.

Myopericytoma encompasses a morphologic continuum of lesions ranging from those with the appearance of myofibromatosis to those, which almost resemble glomus tumor (but often with “pericytoma-like” vessels) or angioleiomyoma. All are composed of actin-positive perivascular contractile cells showing a variable degree of myoid (spindle-celled or glomoid) cytomorphology. In many cases there are admixed patterns that closely resemble myofibromatosis and so-called “hemangiopericytoma”, except that the perivascular spindle cells in these lesions are eosinophilic and clearly myogenic. It is common, particularly at the periphery of these lesions, to find perivascular proliferation of similar spindle-shaped cells (outside the main tumor nodule), as also occurs in glomus tumors and these cells may also proliferate in either the adventitial or subendothelial layers of vessel walls. The latter closely mimics true vascular invasion, except for the intact overlying layer of endothelium, and this is the feature which has previously been well described in both infantile myofibromatosis and infantile hemangiopericytoma (which in reality are points on this same morphologic spectrum). Examples of true intravascular myopericytoma are seen occasionally.\textsuperscript{34}

**Differential diagnosis**

With the advent of immunohistochemistry the diagnosis of so-called hemangiopericytoma became one of exclusion since many neoplasms can show, at least focally, a pericytoma-like pattern.\textsuperscript{12,13} Most particularly these include:

- synovial sarcoma, which may show a biphasic pattern and is EMA and pan-keratin positive
- mesenchymal chondrosarcoma, which shows islands of mature cartilage
- deep benign fibrous histiocytoma, which is more polymorphic (showing a storiform pattern and inflammatory cells)
- phosphaturic mesenchymal tumor, which has a variety of histologic patterns and is often associated with calcification and osteoclast-like giant cells.

Other tumors which commonly show this vascular pattern are infantile fibrosarcoma and, in truth, almost any type of sarcoma may show focally a perfect resemblance to so-called
“hemangiopericytoma” on occasion, hence this diagnostic term is falling into disuse and should only be employed with great caution and in specific clinical contexts. In the long run, it seems possible that the term may be reintroduced for the family of myopericytic neoplasms – but it seems prudent to ensure that the majority of pathologists (as well as relevant clinicians) understand the demise of the former usage before any such change is made.

REFERENCES

expression: an immunohistochemical study and review of the literature. Mod Pathol 4: 46-52


17. Fletcher CDM, Unni KK, Mertens F (Eds) 2002 World Health Organization Classification of Tumors. Pathology and Genetics of Tumors of Soft Tissue and Bone. IARC Press: Lyon


