Pseudomyogenic Hemangioendothelioma
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- First described in 2003 as epithelioid-sarcoma-like hemangioendothelioma and later in 2011 as pseudomyogenic hemangioendothelioma, this rare vascular tumor is of intermediate malignant potential. It was officially included for the first time in the most recent World Health Organization’s Classification of Tumours of Soft Tissue and Bone. It typically affects young adults with a predilection for the distal lower extremity. This tumor lacks morphologic features of vascular differentiation but shows unequivocal evidence of such differentiation with the use of relevant immunohistochemical stains such as FLI1, ERG, and CD31. Pseudomyogenic hemangioendothelioma can be diagnostically challenging and might be confused with other tumors, such as epithelioid sarcoma. In this review we discuss the clinical, morphologic, and immunohistochemical features of this tumor with particular emphasis on the differential diagnosis. Salient molecular and prognostic features are also reviewed.


Pseudomyogenic hemangioendothelioma was recognized as a distinctive entity under the name epithelioid sarcoma-like hemangioendothelioma in 2003; in a series of 7 patients, Billings et al.1 described a tumor that lacked frank histologic evidence of vascular differentiation such as vascular channel formation and intracytoplasmic lumens; however, vascular differentiation was evident with the use of immunohistochemical stains. The name epithelioid sarcoma-like hemangioendothelioma was used to emphasize the similarity of this tumor to epithelioid sarcoma and because 6 of the 7 patients (86%) in that series had a prior diagnosis of epithelioid sarcoma. The first possible description of this tumor occurred in 1992 by Mirra et al.,2 who published a series on 5 patients with morphologically similar tumors; the tumor was considered a variant of epithelioid sarcoma and because of intermediate malignant potential. It was officially named pseudomyogenic hemangioendothelioma (PH) was first introduced to emphasize its myoid-like features. Pseudomyogenic hemangioendothelioma was adopted in the most recent World Health Organization’s Classification of Tumours of Soft Tissue and Bone, in 2013, when the tumor was included for the first time.3 In this review, we refer to the tumor as pseudomyogenic hemangioendothelioma.

**CLINICAL FEATURES**

Pseudomyogenic hemangioendothelioma affects people at many ages, with a mean age in the third or early forth decades,4,5 and has a striking male predominance.3 The tumor has a predilection for the distal lower extremities,1,3 but it has been reported as a primary tumor in different anatomic sites, including bone,6,7 thoracic spine,8 penis,9 lips,10 and scalp and chest.1 Multifocal presentation is not uncommon. Pseudomyogenic hemangioendothelioma often involves different anatomic planes, including dermis, subcutis, and skeletal muscle.

Concurrent bone involvement is estimated to be present in approximately 25% of the cases,1,3 but bone involvement is variable in different series; specifically, 3 of 5 patients (60%) in the study by Mirra et al.,2 and 5 of 5 patients (60%) reported by Amary et al.10 had concurrent bone disease. However, only 29 of 205 lesions (14%) described by Hornick and Fletcher3 showed bone involvement.

Pseudomyogenic hemangioendothelioma varies in size from a few millimeters to a few centimeters. Superficial lesions may present as ulcerated nodules,1 similar to epithelioid sarcoma (ES). Cases that resemble dermatofibroma clinically have also been reported.11 Most patients present with subcutaneous masses particularly on the lower extremities; those masses can be asymptomatic or painful. Some patients present with symptoms related to the mass effect exerted by the tumor on deep structures, such as spinal nerve roots resulting in pain, muscle weakness, or sensory loss.

Imaging studies show a multifocal tumor involving different tissue planes: subcutaneous, intramuscular, and/or intraosseous. The lesions are usually well circumscribed. Intraosseous tumors are usually multiple, well-delineated, lytic lesions with increased uptake and without a periostial reaction or bone destruction.7–9

**Pathologic Findings**

On gross examination, the tumor appears nondescript tan-gray and well circumscribed.1,11 Histologically, the tumor is composed of vaguely nodular architecture, which...
Infiltrates the surrounding adipose or skeletal muscle tissue with an occasional desmoplastic reaction. The tumor cells are arranged in sheets or short fascicles within a background of variably prominent inflammatory infiltrates commonly composed of neutrophils or, less commonly, lymphocytes, plasma cells, or eosinophils. A myxoid background is seen in some cases.

The tumor cells range from spindle to round and epithelioid, and transitional forms have been described. Some cells show voluminous eosinophilic cytoplasm with eccentric nuclei, resembling rhabdomyoblasts. Regardless of the form, the cells typically have a deeply eosinophilic cytoplasm; oval-to-rounded, bland nuclei with fine chromatin; and variably distinct nucleoli. Nuclear pleomorphism is mild to moderate in most cases; a few cases show marked nuclear atypia. The mitotic count is typically less than 5 per 10 high-power fields; however, a few cases have shown higher mitotic counts (Figures 1 and 2). The tumor typically lacks intratumoral hemorrhage or vascular channel formation. Geographic necrosis, distinctive of ES, is not typically seen. Rare cases might show a few intracytoplasmic vacuoles characteristic of epithelioid hemangioendothelioma (EHE). The tumor does not originate from blood vessels.

Dermal-based lesions are occasionally associated with overlying epidermal hyperplasia.

Although PH expresses vascular immunohistochemical markers, morphologic features of vascular differentiation are rare or absent on routine hematoxylin-eosin examination, and ancillary studies are needed to confirm endothelial differentiation.

In addition to the histologic features mentioned, primary bone PH is characterized by intratumoral hemorrhage, woven bone trabeculae lined by osteoblasts, and osteoclast giant cells. The deposited bone can appear similar to that of woven bone trabeculae lined by osteoblasts, and osteoclast bone PH is characterized by intratumoral hemorrhage, differentiation.

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Electron microscopic findings include the presence of prominent rough endoplasmic reticulum and intermediate filaments. In addition, some cells exhibit the presence of submembranous pinocytic vesicles and scattered desmosome-like junctions; no definitive Weibel-Palade bodies were identified in the few cases examined.

### Immunohistochemistry

Most of these tumors stain positively for keratin AE1/AE3, ERG, FLI1, and FOSB. CD31 was positive in 22 of 47 cases (47%) examined by Hornick and Fletcher. Keratin MNF, desmin, CD34, podoplanin (D2-40), S100, H-caldesmon, myogenin, MyoD1, CD68, p63, human herpes virus 8, and factor XIII are typically negative (Figures 3 through 6). Of particular importance, CAMTA1, expressed in most EHE cases, is negative in PH.

Focal positivity for CAM 5.2, smooth muscle actin (SMA), and epithelial membrane antigen is observed in some cases. Importantly, intact nuclear expression of integrase interactor 1 (INI-1) is present in all cases.

### Molecular Pathology

In their study on 11 cases of PH, Trombetta et al showed a balanced translocation between chromosomes 7 and 19 \((t(7;19)(q22;q13))\) in 3 lesions from a single patient. Another case, analyzed by fluorescence in situ hybridization, showed an unbalanced \(t(7;19)\) translocation. Subsequent studies failed to demonstrate the presence of a putative fusion gene until 2014, when Walther et al, using cytogenetics, fluorescence in situ hybridization, messenger RNA sequencing, and real-time polymerase chain reaction, demonstrated a balanced \((t(7;19)(q22;q13))\) translocation resulting in the fusion of the SERPINE1 and FOSB genes in several cases. FOSB is a member of the Fos family (c-Fos, FosB, and its smaller splice variants, Fra-1 and Fra-2), which dimerize with Jun proteins to form AP-1 transcriptional factor complex. This family is implicated in the tumorigenesis of various tumors, including breast, endometrial, and colorectal tumors, among others.

SERPINE1 is believed to be a promoter for FOSB; this translocation is not found in any other soft tissue tumors and is considered pathognomonic for PH. Another case of penile PH was examined using real-time polymerase chain reaction and reproduced the same gene fusion.

### Differential Diagnosis

The most important differential diagnosis is ES. Epithelioid sarcoma and PH share several features: both tumors typically (1) affect young patients, (2) have a predilection for soft tissue in the distal extremities, (3) show epithelioid and spindle cell morphology, and (4) show diffuse expression of keratins. In addition, some cases of ES are positive for FLI1 and ERG (depending on the antibody used; see below). Interestingly, 6 of the 7 patients (86%) examined in the original article that described this tumor had previously been diagnosed with ES. Compared with PH, ES is a more aggressive tumor with a greater tendency for local recurrence and metastasis. In the largest series of patients with ES and available follow-up, 155 of 202 patients (77%) suffered a local recurrence, and 90 (45%) developed distant metastasis. The 5- and 10-year survival rates for ES are reported to range from 34% to 70%, and 17% to 55%, respectively.

In addition, given the high rate of recurrence in ES despite marginal resection, the standard care for ES involves wide local resection, and sometimes amputation, in addition to chemoradiotherapy. Because of these differences, the distinction between ES and PH is important. Epithelioid sarcoma tends to be composed of smaller, well-defined nodules rather than the sheetlike, vaguely nodular growth seen in PH; it also shows greater nuclear atypia in addition to geographic necrosis. Although there is an immunophenotypic overlap with PH, ES typically lacks reactivity to CD31, FLI1, and SMARCB1 (INI-1), unlike PH. Absent or weak immunoreactivity for ERG in ES can be helpful if an antibody to the C-terminus is used, and ESs are frequently ERG+ with antibodies against the N-terminus. In addition, ES was positive for CD34 in 51 of 97 cases (53%) studied by Miettinen et al. Pseudomyogenic hemangiendothelioma is consistently negative for CD34.

In predominantly spindled cases, PH can be confused with leiomyosarcoma.

Pseudomyogenic hemangiendothelioma lacks the intersecting fascicular pattern of a true smooth muscle tumor and is negative for smooth muscle markers, such as desmin, caldesmon, and SMA.

Other epithelioid vascular tumors, such as cutaneous epithelioid angiomatous nodules and EHE, could be considered in the differential diagnosis; however, both have different growth patterns. The cutaneous epithelioid angiomatous nodule is well circumscribed and is positive for CD34 immunohistochemical stain, and EHE has a distinct...
cordlike to nested growth pattern embedded in a myxohyaline matrix that differs from the sheetlike and fascicular growth patterns of PH. Additionally, intracytoplasmic vacuoles found in EHE are typically lacking in PH. The expression of CD34 immunohistochemical stain favors a diagnosis of EHE.\textsuperscript{1,13} CAMTA1 and FOSB immunohistochemical stains are also helpful because CAMTA1 is positive in most EHE cases and negative in PH. Conversely, FOSB is strongly expressed in PH whereas it is negative or focal and weak in EHE.\textsuperscript{14-17}

Figure 1. Pseudomyogenic hemangioendothelioma. Dermal and superficial subcutaneous tumor composed of a mix of spindle and epithelioid cells, some of which have rhabdoid morphology (hematoxylin-eosin, original magnification ×20).

Figure 2. Mild nuclear atypia and no mitosis in a neutrophilic inflammatory background (hematoxylin-eosin, original magnification ×40).

Figure 3. Tumor cells are diffusely and strongly positive for keratin AE1/AE3 (original magnification ×40).

Figure 4. Tumor cells are positive for FLI1 (original magnification ×40).

Figure 5. CD34 is negative. Note the dermal blood vessels as an internal positive control (original magnification ×40).

Figure 6. Keratin MNF1 is negative. Epidermis noted in the left lower part of the image is a positive internal control (original magnification ×40).
Focal nuclear atypia and increased mitotic activity in some cases of PH may lead to consideration of an epithelioid angiosarcoma diagnosis. Unlike PH, most cases of epithelioid angiosarcoma contain vascular channels or cystically dilated spaces lined by malignant endothelial cells. Furthermore, CD34 will help resolve that differential diagnosis because it is typically positive in angiosarcoma and negative in PH.

In primary bone PH, metastases and primary spindle cell bone tumors, such as nonossifying fibroma, osteoblastoma, fibrosarcoma, leiomyosarcoma, and undifferentiated pleomorphic sarcoma, should be considered. An inflammatory neutrophilic infiltrate, mild nuclear atypia, few mitoses, and the peculiar immunohistochemical profile associated with multifocal and well-delineated bone lesions are characteristic of PH in the differential diagnosis with primary bone spindle cell sarcoma.6

The abundance of reactive, woven bone in primary bone PH can make its distinction from osteoblastoma difficult because the quantity of the bone can obscure the neoplastic cells. The presence of spindle cells arranged in fascicles and rhabdomyoblast-like cells located in the inter trabecular tissue are important clues because they are typically absent in osteoblastoma.

Nonossifying fibroma contains fascicles of spindle cells arranged in a storiform pattern; however, the neoplastic cells lack the deeply eosinophilic cytoplasm and rhabdomyoblast-like cells characteristic of PH.

Lack of a history of a previous primary carcinoma, absence of evidence of pulmonary or visceral disease, young age at presentation, regional distribution of the tumor, limited cytologic atypia, and endothelial marker positivity by immunohistochemistry help distinguish PH from metastatic carcinoma.

### Prognosis and Treatment

Pseudomyogenic hemangioendothelioma is a locally recurrent, rarely metastasizing tumor. We looked at several studies in which follow-up was available1–3, 4, 10–12; 82 patients were reported, with follow-up available for 61 (74%). The follow-up periods ranged from 3 months to 19 years. Treatment options included surgery (ranging from simple excision to amputation), chemotherapy, and radiotherapy. Only 3 patients (5%) developed distant metastasis, which was noted 4, 8.5, and 16 years after initial diagnosis. Another patient died of a concurrent squamous cell carcinoma.7 Twenty-six patients (43%) showed evidence of local recurrence or new lesions in the same region as the initial tumor; the recurrences were noted mostly in the first year after diagnosis. Interestingly many of those lesions were stable over time. Two patients (3%) developed regional lymph node metastasis.3,12

Recently, the use of targeted therapy with mammalian target of rapamycin inhibitors, specifically, everolimus25 and sirolimus,26 in children aged 15 and 9 years, respectively, was attempted, with promising results. Everolimus was also used in a 22-year-old patient for 2 months and showed mild shrinkage of the tumors. Interestingly, the same patient had no response to gemcitabine plus docetaxel therapy and was treated initially with surgery in addition to cisplatin and doxorubicin, which resulted in stable disease.27 However, additional randomized studies with more patients are needed to clarify the role of such therapy in PH.

Possible prognostic factors to predict recurrence and metastasis include multifocality, age at presentation, gender, and size of the lesion(s); however, large studies are needed to further elucidate the true potential of this tumor. The mechanism underlying the occurrence of multiple lesions restricted to one anatomic region probably reflects a form of multicentricity rather than regional metastasis.28

### CONCLUSIONS

Pseudomyogenic hemangioendothelioma is a rare vascular tumor of intermediate malignancy that occurs in young adults with a striking male predominance. This tumor has a clinical presentation similar to ES and has been reported in various locations in the body. In the absence of morphologic evidence suggestive of a vascular neoplasm, this tumor can be challenging, and a broad immunohistochemical panel is required to render the correct diagnosis. Pseudomyogenic hemangioendothelioma seems to have a variable clinical course, with frequent local recurrence but a small risk of distant metastases. Given the real, albeit small, risk of distant metastasis occurring long after the initial diagnosis, prolonged periods of follow-up are recommended.

### References