Epithelioid Angiosarcoma
A Brief Diagnostic Review and Differential Diagnosis

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Epithelioid angiosarcoma is a highly aggressive endothelial cell malignancy, most commonly arising in the deep soft tissues, but a variety of primary sites, including the adrenals, thyroid, skin, and bone, are encountered. On hematoxylin-eosin-stained sections, the pathologist encounters sheets of large, mildly to moderately pleomorphic epithelioid cells, with abundant eosinophilic cytoplasm, vesicular nuclei, and prominent nucleoli. Obvious vasoformative foci may not be present, creating confusion with metastatic carcinomas, malignant mesothelioma, melanoma, anaplastic lymphoma, epithelioid peripheral nerve sheath malignancies, and epithelioid sarcoma. Moreover, malignancies with apparent vascular differentiation must be distinguished from less aggressive vascular neoplasms, including epithelioid hemangioendothelioma. Given the range of clinical presentation, the diversity of primary sites, and the nonspecific initial histopathologic appearance, here we review the histologic findings and immunohistochemical profiles of epithelioid angiosarcoma and neoplasms in its differential diagnosis. (Arch Pathol Lab Med. 2011;135:268–272)

Angiosarcomas are rare malignancies of endothelial origin. These neoplasms are classified into cutaneous, visceral, and soft tissue subtypes. Histologically, angiosarcomas range from well-differentiated tumors with variable endothelial atypia to high-grade spindle cell malignancies. In contrast to this conventional appearance, a unique morphologic subtype of angiosarcoma, in which the malignant endothelial cells have a predominantly (or exclusively) epithelioid appearance, has been defined as epithelioid angiosarcoma.1

Epithelioid angiosarcoma most often arises in the deep soft tissues (usually intramuscular) of the extremities, but a variety of primary sites, including the thyroid gland, skin, adrenal glands, and bone, are encountered.1,2 Consequently, most cases of epithelioid angiosarcoma are soft tissue angiosarcomas, with a minority falling into the visceral and cutaneous categories.

Epithelioid angiosarcoma has a male predilection and, although isolated pediatric cases have been reported, they generally occur in adult life, with the highest incidence in the seventh decade.2,3 A variety of clinical presentations may be encountered, owing to the diversity of primary sites and the highly aggressive nature of the tumor. These range from painful, enlarging soft tissue masses to long bone fractures to arteriovenous shunting and subsequent high-output cardiac failure.4 In one study, approximately one third of patients with soft tissue angiosarcoma had complaints attributed to a hypocoagulable state, including hemothoraces, peritoneal bleeds, ecchymosis, gastrointestinal bleeding, and persistent hematomas.5 The nonspecific initial presentation depends on the size of the tumor, the tissue involved, and its resultant dysfunction. Furthermore, lesions infrequently occur within schwannomas,5 or in association with foreign bodies/truma, solid and hematologic malignancies (status postsurgical, radiation, and/or chemotherapeutic intervention), synthetic vascular grafts, and orthopedic hardware/prostheses.6,7 Angiographic and computerized tomographic studies help identify the lesion’s location and its relationship to the native vasculature.

Epithelioid angiosarcoma often demonstrates early nodal and solid organ metastasis, especially to the lungs, bone, soft tissue, and skin. Within 2 to 3 years of diagnosis, more than 50% of patients are dead of disease, but 20% to 30% of people are disease free.7 Adverse prognostic factors include advanced age, increased tumor size, a retroperitoneal primary site, and an increased proliferative index (MIB-1 ≥10%).3 Treatment modalities vary among individual cases of angiosarcoma, but surgical resection of the primary tumor and radiation therapy are usually used.6 There is evidence that paclitaxel-based chemotherapeutic regimens may improve survival.9 Additionally, reports of remission after the combined use of adjuvant radiation therapy and bevacizumab, followed by surgery, have been described.10 Endothelial malignancies are derived from mesenchymal cells, which undergo blood vessel and/or lymphatic-endothelial differentiation. Current evidence supports that individual epithelioid angiosarcomas follow either or both (vascular and lymphatic) endothelial cell lines.11,12 The diversity of primary sites is attributed to the ubiquity of blood vessels and lymphatics throughout the body. Larger tissues with a vast lymphovascular supply (eg, deep soft tissues) and tissues with high concentrations of endothelial cells (eg, adrenals and thyroid) seem to be at the highest risk for developing these malignancies.
Epithelioid angiosarcoma contains large, mildly to moderately pleomorphic, round to polygonal epithelioid cells, with central to eccentrically located nuclei containing prominent nucleoli. Within the nucleus, the chromatin is peripherally marginated, yielding a vesicular appearance. Most malignant endothelial cells are filled with abundant eosinophilic cytoplasm, but occasional cells with intracytoplasmic lumina containing erythrocytes can usually be identified, aiding in diagnosis. Architecturally, cells are primarily arranged in sheets, but cellular islands or cords may be seen (Figure 1). On hematoxylin-eosin (H&E)-stained sections, focal areas of irregularly anastomosing vessel formation are usually present; purely epithelioid lesions are uncommon, but a completely epithelioid focus may be encountered with scant biopsy material. In areas of malignant vasoformation, cellular stratification may create a papillary appearance. Sheeted areas contain a scant amount of stroma, but in less cellular regions it is often abundant, with a desmoplastic to fibromyxoid appearance. Malignant endothelial cells are closely approximated to pericytes, which may be highlighted with α-smooth muscle actin. In poorly differentiated areas of sheeted epithelioid cells, there is actually external laminal cellular organization into primitive tubules, in which the tumor recapitulates vascular structures lacking canalization. This rudimentary vasoformative architecture is clearly demonstrated with reticulin staining (Figure 2). Throughout the tumor, mitotic figures are numerous, and varying degrees of necrosis and hemorrhage are present (Figure 3). In epithelioid angiosarcoma of the bone, foci containing prominent neutrophilic infiltrate (not associated with necrosis) have been described (Figure 4, A and B).7

As with all types of angiosarcoma, the epithelioid variant is strongly vimentin positive. Immunostaining for factor VIII has been consistently positive among studies, with stronger staining of malignant cells than in traditional nonepithelioid vascular sarcomas (Figure 5, A).2,3,6 CD31 is a sensitive marker, being at least weakly positive in almost all cases (Figure 5, B). CD34 positivity ranges from 40% to 100%, and it tends to stain areas with readily apparent vessel formation. Consequently, its utility in sheeted, poorly differentiated lesions is limited. Pancytokeratin stains more than 35% of angiosarcomas,3 with positivity ranging from 78% to 100% in smaller studies specifically investigating the epithelioid variant (Figure 5, C; Table).2,7 In one study, staining for Ki-67 with MIB-1

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Figure 1. Epithelioid angiosarcoma of the adrenal gland. Nests of large, mildly pleomorphic epithelioid cells with vesicular chromatin and prominent nucleoli in a fibromyxoid stroma. There are focal areas of vascular formation and malignant endothelial cells with intracyto-

plasmic lumina containing erythrocytes (center) (hematoxylin-eosin, original magnification ×200).

Figure 2. Metastatic epithelioid angiosarcoma of the soft tissue, left flank. Reticulin staining demonstrates cellular organization into primitive vessels in this densely sheeted tumor (original magnification ×100).

Figure 3. Hematoxylin-eosin staining of tumor in Figure 2. The primary lesion (left-sided cutaneous breast angiosarcoma) developed 4 years after a segmentectomy, axillary dissection, and radiation therapy (with complicating lymphedema) to treat invasive ductal carcinoma in an 82-year-old woman. There are multiple necrotic foci in the dense sheets of malignant endothelial cells, confirmed immunohistochemically (original magnification ×100).
Figure 4. Epithelioid angiosarcoma of the right femur. A, Sheets of malignant epithelioid cells fill the marrow cavity (hematoxylin-eosin, original magnification ×100). B, High-power view demonstrates moderately pleomorphic epithelioid cells, intermixed with acute inflammation (hematoxylin-eosin, original magnification ×400).

Figure 5. Immunostaining of the epithelioid angiosarcoma seen in Figure 1. A, Factor VIII clearly outlines the membranes of the malignant cells (original magnification ×200). B, CD31 demonstrates intense membranous and cytoplasmic staining (original magnification ×200). C, Most malignant cells stain with cytokeratin AE1/AE3 (original magnification ×200).
Epithelioid angiosarcoma and epithelioid hemangioendothelioma may or may not contain erythrocytes, revealing the endothelial nature of the cells composing epithelioid angiosarcoma. This feature is not a feature, many individual cells display intracytoplasmic vacuolization, focal areas of necrosis, and a variable degree of mitotic activity, giving the impression of epithelioid angiosarcoma. Although both tumors may coexist at any age and a variety of sites, epithelioid sarcoma is generally seen in the distal upper extremities of adolescents and young adults. Epithelioid sarcoma almost always displays epithelial membrane antigen, a feature only occasionally seen in cutaneous angiosarcomas. Despite frequent CD34 positivity, epithelioid sarcoma does not usually express factor VIII or Fli-1 (Table).^{14,15}

Less aggressive vascular malignancies are not primarily composed of dense sheets of epithelioid cells, characteristic of epithelioid angiosarcoma. Epithelioid hemangioendothelioma may show focal high-grade areas, with cellular atypia and a sheathed architecture, but most cells reside in small nests and trabeculae. Plump endothelial cells without significant pleomorphism invade a hyalinized to myxoid stroma. Nuclei are vesicular and have less conspicuous nucleoli. Although frank vascular formation is not a feature, many individual cells display intracytoplasmic lumina, containing red blood cells. The tumor may be contiguous with a parent vessel, filling its lumen or extending concentrically/radially into the surrounding tissue. The mitotic count is rather low (<2 mitoses per 10 high-power fields), compared with epithelioid angiosarcoma.\(^a\) Epithelioid hemangioendothelioma and epithelioid angiosarcoma should be differentiated based on the growth pattern comprising most of the malignancy. The latter having a greater degree of cytologic atypia and a sheeted architecture, but most cells

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Positive IHC</th>
<th>Negative IHC</th>
<th>Variable IHC</th>
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<tbody>
<tr>
<td>Carcinoma</td>
<td>CK, mucin (signet ring cells), EMA</td>
<td>Factor VIII, CD31, CD34, Fli-1</td>
<td>S100, EMA (in cutaneous lesions), CK (usually positive), CD34</td>
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<tr>
<td>MPNST</td>
<td>S100</td>
<td>Factor VIII, CD31, CD34</td>
<td>Vimentin</td>
</tr>
<tr>
<td>ES</td>
<td>EMA, CK, vimentin</td>
<td>Factor VIII, Fli-1, S100 (^a)</td>
<td>CD34, CD31</td>
</tr>
<tr>
<td>Malignant mesothelioma</td>
<td>HMB-45, S100, Melan-A, vimentin</td>
<td>Factor VIII, CD31, CD34, Fli-1</td>
<td>CD34, CD31</td>
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<td>Anaplastic large cell lymphoma</td>
<td>CD45, CD30, pan-T-cell marker</td>
<td>Factor VIII, CD31, CD34, Fli-1</td>
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<tr>
<td>EH</td>
<td>CD31, factor VIII</td>
<td>Factor VIII, CD31, CD34, Fli-1</td>
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Abbreviations: CK, cytokeratin; EA, epithelioid angiosarcoma; EH, epithelioid hemangioendothelioma; EMA, epithelial membrane antigen; ES, epithelioid sarcoma; IHC, immunohistochemical stain; MPNST, malignant peripheral nerve sheath tumor; SMA, smooth muscle actin; WT-1, Wilms tumor-1.

\(^a\) Epithelioid sarcoma demonstrates focal S100 positivity in ~1% of cases.\(^1\)

was 10% or greater in 72% of angiosarcomas (of all subtypes) evaluated, confirming the highly proliferative nature of these neoplasms. Eighty-three percent of patients with a high proliferative index (MIB-1 ≥10%) eventually died of disease, whereas 67% of patients with a low proliferative index (MIB-1 <10%) were disease-free; expectedly, increased tumoral proliferation is adversely correlated with prognosis.

As previously alluded to, the histologic features of epithelioid angiosarcoma frequently preclude a straightforward diagnosis on routine H&E-stained microscopic evaluation. In some cases, the sheeted epithelioid appearance, along with positive cytokeratin staining, makes metastatic (or primary) carcinoma a strong diagnostic consideration. Distinguishing features present on H&E evaluation include areas of intracellular lumina, which may or may not contain erythrocytes, revealing the endothelial nature of the cells composing epithelioid angiosarcoma. Lumina may mimic signet ring cells, but mucin staining will differentiate between the two. Moreover, most noncutaneous angiosarcomas do not stain with epithelial membrane antigen,\(^3\) giving it a strong negative predictive value to help rule out carcinoma. Carcinomas will not stain for endothelial markers, including factor VIII, CD31, CD34, or Fli-1 (Table). Due to its mesenchymal intermediate filament expression, epithelioid angiosarcoma is almost always strongly positive with vimentin staining, a feature common to a limited number of carcinomas (ie, renal cell carcinoma, endometrial adenocarcinoma, salivary gland carcinoma, and follicular thyroid carcinoma), melanoma, and mesothelioma.

Hematoxylin-eosin–stained sections of melanoma, mesothelioma, and anaplastic lymphoma may display histologic characteristics reminiscent of epithelioid angiosarcoma. These tumors can be easily differentiated with a panel of immunohistochemical stains. Unlike epithelioid angiosarcoma, melanoma will stain for HMB-45, Melan-A, and S100, and mesothelioma will demonstrate calretinin and Wilms tumor-1 positivity. The T lymphocytes of anaplastic large cell lymphoma will express lymphocytic antigens, specifically CD45 (common leukocyte antigen), CD30, and at least one pan-T-cell marker, which will be negative in most epithelioid angiosarcomas (Table). There has been one reported case of CD30-positive cutaneous epithelioid angiosarcoma, which was CD45 negative.\(^13\)

Approximately 5% of malignant peripheral nerve sheath tumors have a distinctly epithelioid cytomorphology. These malignancies can appear identical to epithelioid angiosarcoma, but malignant peripheral nerve sheath tumors will not stain with vascular markers (factor VIII, CD31, Fli-1, and CD34) and they will be at least focally positive for S100. Epithelioid angiosarcoma demonstrates the opposite immunoprofile (Table).

Epithelioid sarcoma is composed of sheets, nodules, and trabeculae of infiltrative epithelioid to spindled cells, with intensely eosinophilic cytoplasm. Vesicular nuclei and prominent nucleoli may be present. These tumors can have focal vasomorphological areas, vimentin and cytokeratin positivity, CD34 positivity (~50%),\(^14\) intracytoplasmic vacuolization, focal areas of necrosis, and a variable degree of mitotic activity, giving the impression of epithelioid angiosarcoma. Although both tumors may present at any age and a variety of sites, epithelioid sarcoma is generally seen in the distal upper extremities of adolescents and young adults. Epithelioid sarcoma almost always displays epithelial membrane antigen, a feature only occasionally seen in cutaneous angiosarcomas. Despite frequent CD34 positivity, epithelioid sarcoma does not usually express factor VIII or Fli-1 (Table).\(^14,15\)

In rare cases of epithelioid angiosarcoma that are not clearly elucidated by routine H&E in concert with
immunohistochemical techniques, electron microscopy can help confirm endothelial differentiation. Ultrastructurally, large round to oval cells (endothelial cells) are seen adjacent to smaller polygonal to spindle cells (pericytes). Red blood cells are seen in vascular channels formed by closely approximated, circumferentially orientated endothelial cells. Moreover, erythrocytes may be observed within intracytoplasmic lumina, which traverse individual malignant endothelial cells. Cords of cells are encased by an external lamina, which may display focal areas of duplication. The cytoplasm contains aggregates of intermediate filaments and a linear array of perimembranous pinocytotic vesicles. Most studies have demonstrated at least some cells containing Weibel-Palade bodies, but in one study, where the ultrastructural characteristics of 12 angiosarcomas were examined, no such structures were identified. According to the authors, the identification of Weibel-Palade bodies is not necessary to diagnose angiosarcoma and is expected to be absent in poorly differentiated tumors. Other ultrastructural findings include peripheral chromatin margination against the nuclear membrane and prominent nucleoli.

In summary, epithelioid angiosarcoma is a rare, aggressive vascular malignancy characterized by sheets of epithelioid endothelial cells, which can mimic multiple other epithelioid malignancies. Although these neoplasms can arise in a variety of locations in a variety of age groups, the most common presentation is a deep soft tissue mass in the extremity of an individual in the seventh decade of life. Age and clinical history may help lower the suspicion of malignancies in the differential diagnosis. Furthermore, initial evaluation of H&E-stained sections and appropriate immunostaining can usually provide a definitive diagnosis.

References

Submissions Now Accepted for CAP ‘11 Abstract Program

Abstracts and case studies are now being accepted for the College of American Pathologists (CAP) 2011 meeting, which will be held September 11th through the 14th in Grapevine, Texas. Submissions for the CAP ‘11 Abstract Program will be accepted through Friday, April 1, 2011.

Accepted submissions will appear in the September 2011 issue of the Archives of Pathology & Laboratory Medicine. Visit the CAP ‘11 Web site at www.cap.org/cap11 for specific abstract program information as it becomes available.