

Epithelioid angiosarcoma of bone and soft tissue: a report of seven cases with emphasis on morphologic diversity, immunohistochemical features and clinical outcome

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ABSTRACT

Aims and background. Epithelioid angiosarcoma is a rare histopathologic variant of angiosarcoma characterized by an epithelioid morphology. This subset can histologically mimic non-vascular neoplasms and impose serious challenges in reaching a correct diagnosis, especially in the context of limited tissue sampling (e.g., needle core biopsy). To improve recognition of epithelioid angiosarcoma – and the spectrum of morphologic diversity associated with this rare variant – and to avoid a misdiagnosis, we describe the clinical, histopathologic, and immunohistochemical findings of cases of epithelioid angiosarcoma diagnosed at our institution.

Methods and study design. Seven cases of epithelioid angiosarcoma with appropriate pathologic material were identified from our archives. Immunohistochemistry was used to detect the expression of CD31, CD34, Factor VIII, cytokeratin, epithelial membrane antigen, vimentin, HMB45, CD1a, CD68, lysozyme, CD45, desmin, and smooth muscle actin in all cases. Follow-up information was obtained by reviewing medical records or by direct communication with family members.

Results. The lesions involved the bone (n = 4) and soft tissues (n = 3). Microscopically, all tumors had a predominantly diffuse growth pattern, with a focal nested architecture in 6 cases, which closely mimicked metastatic carcinoma. The initial biopsy was performed in 2 of 6 patients and revealed the presence of a malignant neoplasm suggestive of metastatic carcinoma. Immunohistochemically, the epithelioid endothelial cells usually showed strong reactivity for CD31 (7/7), variable or focal positive staining for CD34 (5/7), Factor VIII (4/7), cytokeratin (6/7), epithelial membrane antigen (2/7), vimentin (7/7), and CD68 (3/7). In contrast, they were negative for CD1a, HMB45, lysozyme, CD45, desmin, and smooth muscle actin. Three patients died of disease within one year of the diagnosis, 2 patients developed local recurrence or metastases, and another 2 were disease-free at this writing.

Conclusions. With any unusual epithelioid neoplasm displaying some or all of the morphologic features described above, epithelioid angiosarcoma should be included in the differential diagnosis. In such an instance, endothelial markers should be incorporated in the immunohistochemical analysis to avoid misdiagnosis, particularly with limited sampling.

Introduction

Epithelioid angiosarcoma (EA) is a rare histopathologic variant of angiosarcoma characterized by an epithelioid morphology. It is associated with a poor prognosis and early metastases¹⁻⁴. Histologically, the tumor is composed of sheets, nests and cords of epithelioid endothelial cells with areas of vascular differentiation, necrosis, and hemorrhage²⁻⁸. Immunohistochemical analysis reveals that the neoplastic cells

Key words: differential diagnosis, epithelioid angiosarcoma, histopathology, immunohistochemistry, prognosis.

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frequently express epithelial markers, in addition to endothelial cell markers, thereby potentially leading to the erroneous diagnosis of metastatic carcinoma, especially in the context of limited sampling⁹⁻¹⁰. The current trend towards small biopsies obtained with computed tomography-guided techniques exacerbates this possibility. To our knowledge, most studies on EA are limited to case reports, with several large series providing more detailed morphologic, immunohistochemical and prognosis information^{2-6,11}.

With the present study, we contribute to the literature 7 additional cases of EA arising in the bone and soft tissue, emphasizing their clinical features, morphologic diversity, immunohistochemical phenotype, and differential diagnosis, to improve the recognition of the tumor and to avoid potential misdiagnosis.

Materials and methods

All cases diagnosed as angiosarcoma with available slides and clinical information, coded between 1996 and 2009, were retrieved from the Department of Pathology, Peking University People's Hospital. The tumors were re-reviewed and classified on the basis of hematoxylin and eosin (H&E) morphology and immunohistochemical findings. Seven cases of EA with appropriate formalin-fixed, paraffin-embedded material were identified.

The tumor size was defined as the largest tumor dimension based on clinical, gross, or microscopic slide measurement. If the clinical size was provided, it was given preference over the gross size when lesions were received in a fragmented state. For the purposes of the study, we defined EA as an angiosarcoma in which >90% of the tumor cells had an epithelioid phenotype as described by Deshpande *et al.*¹¹. Immunohistochemistry was performed according to the following method of the EnVision+ system¹². Immunohistochemistry was used to detect the expression of CD31, CD34, Factor VI-II, cytokeratin (CK), epithelial membrane antigen (EMA), vimentin, HMB45, CD1a, CD68, lysozyme, CD45, desmin and smooth muscle actin in all cases. Ap-

propriate controls were performed according to the manufacturer's instructions.

Pursuant to Research Ethics Committee approval at the Beijing University People's Hospital, follow-up information was obtained by review of medical records or direct communication with patients or their family.

Results

Clinical information

A summary of the clinical details is presented in Table 1. The 7 patients ranged in age from 23 to 84 years (median, 61) at the time of diagnosis, and the ratio of male to female was 4:1. Two of the 4 bone lesions involved the femur, one involved the radius, and one involved the sacrum. Two of the 3 soft tissue lesions involved the thigh and one involved the leg. Six patients presented with a solitary mass, one patient presented with two separate lesions (femur and thoracic vertebra). Localized pain or tenderness were the most common clinical symptoms. All 7 patients were initially treated by surgical resection, 2 patients were diagnosed on biopsy preoperatively. None of the patients had a history of prior radiation or known risk factors for angiosarcoma.

Follow-up information is summarized in Table 1. Three patients died of disease within one year, one of whom developed local recurrence and lung metastasis prior to death. Two patients are alive with disease: one developed local recurrence within 4 months and the other recurred four times and developed a metastasis to the lymph node within 16 months. Two patients are alive without evidence of disease 1.5 and 46 months after diagnosis, respectively.

Pathological findings

Grossly, the tumors were gray-tan in 5 cases (Figure 1A). In the initial surgical resections, the lesions ranged from 1.5 to 35 cm in the greatest dimension. Several samples were received fragmented with sizes provided in aggregate.

Histological examination showed a diffuse pattern of

Table 1 - Clinical information, therapy, and outcome

Case	Age (y) /sex	Location	Multifocality	Treatment	Recurrent	Metastasis	Outcome
1	23/F	Distal radius	No	Radical resection	No	No	NED (46 mo)
2	28/M	Thigh	No	Amputation	x4	Lymph node	AWD (16 mo)
3	70/M	Femur	No	Radical resection, chemotherapy	No	No	DOD (11 mo)
4	62/F	Femur, thoracic vertebra	Proximal femur, thoracic vertebra	Amputation of femur, radiation treatment	No	No	DOD (10 mo)
5	84/M	Calf	No	Radical resection	After 40 d	Lung	DOD (6 mo)
6	53/M	Sacrum	No	Radical resection	No	No	NED (1.5 mo)
7	60/M	Thigh	No	Radical resection	After 4 mo	No	AWD (4 mo)

NED, no evidence of disease; AWD, alive with disease; DOD, dead of disease.

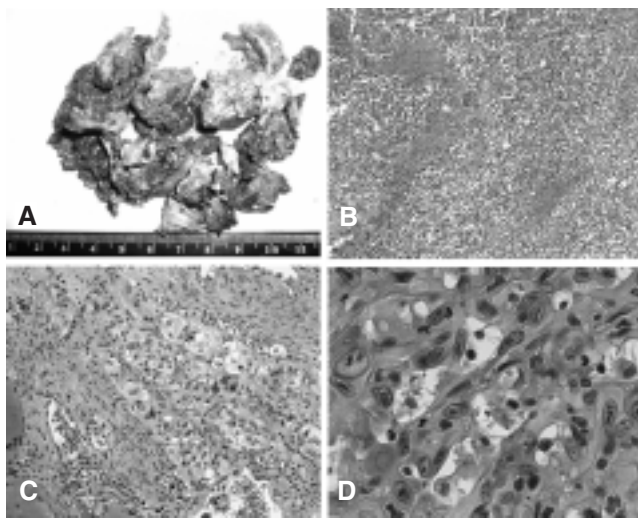


Figure 1 - Typical gross and morphologic features of epithelioid angiosarcoma. A) Gross appearance showing a fragmented tan-white tumor. B) Low-power photomicrograph showing a sheet-like architecture and so-called geographic necrosis (H&E, $\times 100$). C) Area with a nested architecture (H&E, $\times 200$). D) Vasoformative differentiation with red blood cells (H&E, $\times 400$).

growth with a geographic pattern of necrosis in 5 cases (Figure 1B) and a focal nested architecture in 6 cases (Figure 1C). The tumors were composed of large epithelioid cells with abundant eosinophilic cytoplasm. The neoplastic cells showed pronounced nuclear pleomorphism, a vesicular chromatin pattern, and large central nucleoli. Each case was associated with an infiltrate of lymphocytes, neutrophils and occasionally eosinophils, of varying proportions. Three cases contained cytoplasmic vacuolization suggestive of vasoformative properties (Figure 1D). In most cases, numerous mitotic figures were identified. In some areas, dilated and anastomosing vascular channels were adjacent to – or intermixed with – the solid areas. Most of the vascular spaces were lined or filled by plump epithelioid cells identical to those seen in the solid areas. The intratumoral stroma was infrequent or absent. Extensive hemorrhage, necrosis, and cystic degeneration were present.

Minor histologic differences included the presence of a pseudoglandular pattern ($n = 1$), signet ring cells ($n = 3$), bizarre pleomorphic cells ($n = 1$), and abundant eosinophils ($n = 1$). The pseudoglandular configuration was lined by neoplastic cells, reminiscent of an adenocarcinoma (Figure 2A). In case 4, signet ring cells were focally present (Figure 2B). In case 6, a minority of the cells were bizarre and pleomorphic (Figure 2C). Abundant eosinophils were identified in case 7, a potential diagnostic pitfall for histiocytic sarcoma (Figure 2D). No clear association between the number of inflammatory cells and the growth pattern of the epithelioid endothelial cells was observed.

In 2 cases (cases 5 and 6), both of which had preresection biopsies, lumen formation was not identified either

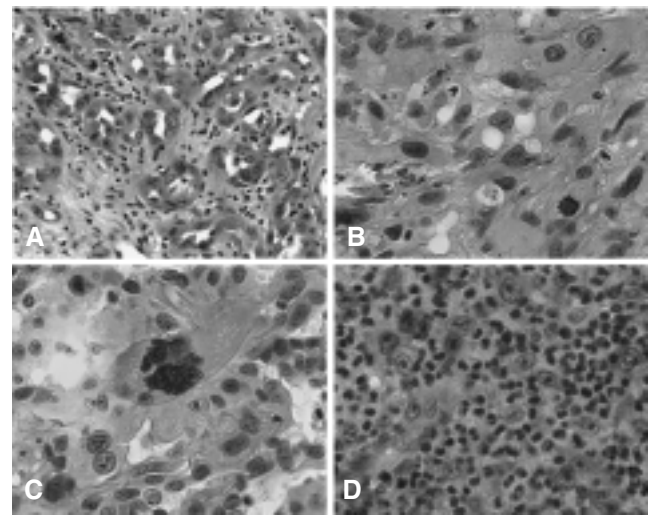


Figure 2 - Uncommon morphologic features of epithelioid angiosarcoma. A) pseudoglandular pattern (H&E, $\times 400$). B) Signet ring cells (H&E, $\times 400$). C) Bizarre pleomorphic cells (H&E, $\times 400$). D) Abundant eosinophils (H&E, $\times 400$).

on biopsy or resection. The tumors were composed of poorly differentiated epithelioid cells and were immunoreactive for CK. They were initially favored to represent metastatic carcinoma. On careful re-review of the biopsies, intracytoplasmic vacuolization, suggesting vasoformative properties, could be identified. Interestingly, the histopathologic features of the resected specimens differed slightly from the biopsies: case 5 showed a cord-like pattern, and case 6 contained dilated vascular channels.

Immunohistochemical findings

The immunohistochemical findings are summarized in Table 2. The tumors were immunoreactive for CD31 in all 7 cases (Figure 3A), and in 6 cases more than 50% of the cells demonstrated strong membrane reactivity. CD34 was expressed in 5 cases, and 3 had $>25\%$ positive cells (Figure 3B). Factor VIII was expressed in 4 of 7 cases, but $<10\%$ of the cells were deemed positive (Figure 3C). Immunoreactivity for CK varied: 1 case was negative, 1 had rare positivity, 3 had focally staining, 1 case had moderately extensive reactivity (Figure 3D), and another had diffuse reactivity. Two cases contained scattered EMA-positive cells. Four cases were moderately positive for vimentin, whereas 3 were mildly positive. Immunohistochemical staining was moderate to strongly positive for CD68 in 4 cases. All cases were negative for HMB45, CD1a, lysozyme, CD45, desmin, and smooth muscle actin.

Discussion

Angiosarcoma constitutes less than 1% of all sarcomas. EA represents a rare variant of angiosarcoma with

Table 2 - Summary of immunohistochemical findings

Case	CK	EMA	Vim	CD31	CD34	F8	HMB45	CD1a	CD68	Lyso	CD45	Desmin	SMA
1	+	-	+	+	-	+	-	-	-	-	-	-	-
2	+	+++	++	++	++	+	-	-	+	-	-	-	-
3	-	-	++	+	++	+	-	-	-	-	-	-	-
4	+	+	+	++	+	-	-	-	-	-	-	-	-
5	+	-	+	+	+	-	-	-	-	-	-	-	-
6	++	-	++	++	++	+	-	-	++	-	-	-	-
7	+++	-	+++	++	-	-	-	-	++	-	-	-	-

F8, Factor VIII; Lyso, lysozyme; SMA, smooth muscle actin; -, negative; +, mildly positive; ++, moderately positive; +++, strongly positive.

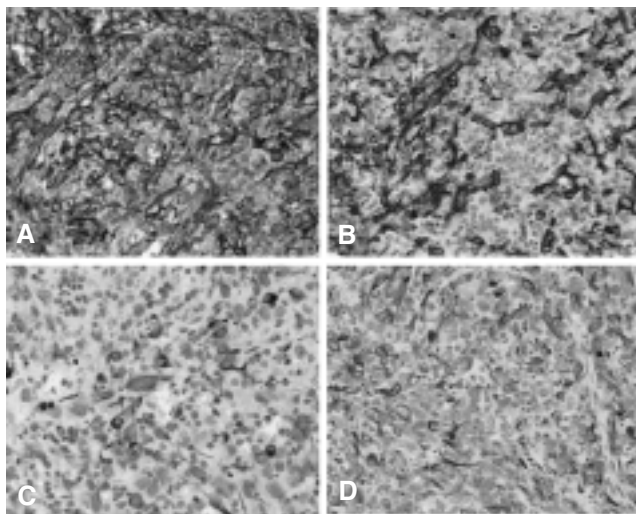


Figure 3 - Representative immunohistochemical findings. A) A tumor with diffuse staining with CD31 (IHC, $\times 200$). B) A lesion with focal immunoreactivity for CD34 (IHC, $\times 200$). C) Neoplastic cells with scarce positivity for Factor VIII (IHC, $\times 200$). D) A tumor showing moderate staining for CK (IHC, $\times 200$).

a characteristic epithelioid morphology. In this study, we describe the clinical and histopathologic attributes of an additional 7 cases of EA. Although the clinical findings are similar to those described in previous reports²⁻⁶, this report emphasizes several additional histopathologic findings observed in these rare neoplasms.

In the present series, we observed a wide age of involvement ranging from the second to eighth decades. There was a predisposition towards males and the lower extremities. Roughly equivalent numbers of cases arose in the bone and soft tissues. The lesions were usually solitary, but multicentric bone involvement was recognized in 1 patient. Two patients developed local and/or distal metastasis. All patients were treated by radical resection or amputation; 1 patient also received radiation therapy.

In each case, the diagnosis of EA was made on the basis of morphology and supported by immunohistochemistry. The observed histologic features highlight the recognized morphological diversity of EA, which has been emphasized in prior reports^{3,4}. Typically, tumors

were composed of large polygonal-epithelioid cells with marked nuclear pleomorphism, organized in sheets and nests with rare abortive vascular formation. Immunohistochemistry confirmed the expression of one or more endothelial markers (CD31, CD34, Factor VIII); vimentin and CK were also generally positive. Two cases were EMA positive.

On the basis of morphology and immunohistochemistry, the differential diagnosis frequently included: undifferentiated carcinoma, malignant melanoma, histiocytic sarcoma and other sarcomas with epithelioid features¹³.

An erroneous diagnosis of metastatic carcinoma, especially on limited core biopsy, is a realistic consideration because both tumors tend to affect older individuals and are composed of sheets of epithelioid cells bearing expression of epithelial markers. In this series, 2 patients underwent initial biopsies for a focal nodule and multifocal lesions, respectively. On the basis of the biopsy, the results were considered suggestive of metastatic carcinoma. However, on radical resection, vascular channels lined by tumor cells were identified and confirmed by immunohistochemistry to represent a neoplasm of endothelial origin. Angiosarcoma is widely recognized by staining for CK^{2,3,13}, hence caution should be exercised in this circumstance. The presence of cytoplasmic vacuoles containing red blood cells, anastomosing vascular channels, and the lack of a desmoplastic reaction are helpful in distinguishing EA from metastatic carcinoma. Minimal vasoformative differentiation is also strong evidence in support of an EA, although this can be difficult to appreciate on biopsy. Immunohistochemical confirmation is necessary with specific endothelial markers, namely CD31, even when CD34 and Factor VIII antibodies are negative. It is noteworthy that a proportion of metastatic carcinomas are positive for CD34 (15%) and CD31 (38%)¹⁴.

Epithelioid hemangioendothelioma (EHE) is a low-grade malignant vascular tumor that is also in the differential diagnosis. It is less aggressive than EA. The treatment of EHE is varied and includes curettage, en bloc resection, and radiotherapy¹⁵. In order to avoid over treatment, EHE should be distinguished from EA. Although EA and the EHE share a number of

histopathologic features, including the presence of epithelioid endothelial cells and an inflammatory infiltrate, they differ in several respects. EHE often contains small central areas where the epithelioid endothelial cells have an indeterminate growth pattern. At the periphery of the lesions, there are typically well-developed vessels with a defined smooth muscle coat, and some of these also have an epithelioid endothelial cell lining. In contrast, the following features help establish a diagnosis for EA: the pronounced cellular atypia, less frequent cytoplasmic vacuoles, lack of chondromyxoid matrix and intimate association with a central muscular artery.

Other potential diagnostic considerations include melanoma, histiocytic sarcoma, and anaplastic large cell lymphoma. In addition to subtle morphologic differences, markers of melanocytic, histiocytic, and hematolymphoid differentiation aid in differentiating these respective neoplasms.

Similar to previous reports, the prognosis of EA in our patient population was poor, with most patients succumbing to their disease shortly after diagnosis. Most patients died within one year, and only 2 patients lived longer than one year. Analyzing the clinical and pathologic features of these patients, we suggest advanced patient age and the presence of tumor necrosis may be associated with a poor prognosis. However, larger sample numbers are necessary to further evaluate this possibility.

In summary, we contribute 7 additional cases of EA to the literature. This report highlights the clinical details, morphologic diversity and immunophenotypic attributes of these rare tumors.

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