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Primary Epithelioid Angiosarcoma of the Breast: A Rare and Challenging Biopsy Diagnosis

Authors' Contribution:
Study Design A
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Literature Search F
Funds Collection G

ABCDEFG **Rachelle Mendoza**
ABCDEF **Kristina Loukeris**

Department of Pathology, SUNY Downstate Medical Center, Brooklyn, NY, U.S.A.

Corresponding Author: Rachelle Mendoza, e-mail: Mendoza@downstate.edu
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Patient: Female, 70
Final Diagnosis: Primary epithelioid angiosarcoma of the breast
Symptoms: Fungating • necrotic breast mass
Medication: —
Clinical Procedure: Biopsy
Specialty: Oncology





Objective: Rare disease
Background: Primary angiosarcoma of the breast is a rare neoplasm, accounting for less than 0.04% of all breast cancers. Epithelioid angiosarcoma is even more unusual with only a handful of cases reported in literature. Differentiating this from other breast malignancy is a challenge. There have been conflicting reports regarding factors that affect prognosis. We present a case of primary epithelioid angiosarcoma of the breast, and also discuss the prognostic and differential diagnostic issues.

Case Report: A 70-year old female presented with slowly enlarging fungating mass in the right breast with a necrotic center and serosanguineous discharge. Initial biopsy done at an outside institution reported the lesion as carcinosarcoma. Histologic sections showed cellular, infiltrative neoplasm with extensive necrosis and ectatic vascular proliferations lined by plump endothelial cells. Infiltrative cells were spindle-shaped with vacuolated cytoplasm and marked anisonucleosis in myxoid background. Mitotic activity was brisk. CAM5.2, AE1/AE3, and CD31 were positive. Proliferation index was high. Estrogen receptors (ER), progesterone receptors (PR), human epidermal growth factor receptor 2 (HER2)/neu were negative.

Conclusions: Primary epithelioid angiosarcoma of the breast can present as a diagnostic dilemma in needle biopsies. This malignancy may mimic carcinoma or benign endothelial lesions. This entity is important to be recognized because it carries poor prognostic risk and requires distinct treatment modalities different from the usual epithelial breast neoplasms.

MeSH Keywords: Breast Neoplasms • Hemangiosarcoma • Sarcoma

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Background

Angiosarcomas are extremely rare forms of primary breast sarcomas, accounting for less than 0.04% of all breast cancers [1]. Histologic subtypes of angiosarcomas include solid epithelioid form, minimal deviation (hemangioma-like) angiosarcoma, granular cell variant, and pleomorphic subtype with the potential to simulate malignant fibrous histiocytoma [2–4].

Primary epithelioid angiosarcoma is an even more unusual variant of angiosarcoma in the breast, and presents as a diagnostic challenge. It is considered a high-grade malignancy, and may mimic histologic appearance of other sarcomas [4], carcinomas [4], or benign endothelial lesions [5]. This entity is important to be recognized because it carries poor prognostic risk. However, literature shows conflicting data regarding the prognostic significance of histologic grade in primary angiosarcoma of the breast.

Case Report

A 70-year-old, African-American female presented with a right breast mass, which slowly enlarged for 7 years. She had no significant past medical and social history. Biopsy done at another institution was interpreted as carcinosarcoma. Computed tomography (CT) imaging showed a heterogeneous, lobulated mass, extending beyond the nipple and infiltrating pectoral muscles. Aside from possible lymph node metastases, no distant metastasis was identified.

Physical examination showed a 10-cm, firm, fungating right anterior breast mass with necrotic center and serosanguineous discharge involving the nipple. Palpable axillary lymph nodes were noted. The left breast and axilla were unremarkable. Core needle biopsy was performed in our institution.

Histologic sections showed cellular, infiltrative neoplasm with extensive necrosis and areas of ectatic vascular proliferations lined by plump endothelial cells (Figure 1). The infiltrative cells were spindle-shaped with vacuolated cytoplasm and marked anisonucleosis. Mitotic activity was brisk. Immunohistochemistry showed positivity for CAM5.2, AE1/AE3, and CD31, with high Ki67. Estrogen receptors (ER), progesterone receptors (PR), human epidermal growth factor receptor 2 (HER2)/neu were negative.

The patient died 4 months after diagnosis.

Discussion

Primary breast angiosarcoma is characterized by proliferation of vascular channels lined by hyperchromatic, pleomorphic

endothelial cells [5]. Epithelioid angiosarcoma is composed of rounded, “epithelioid” endothelial cells with moderate to abundant amphophilic or eosinophilic cytoplasm with rare intracytoplasmic lumina, large, eccentric, vesicular nuclei and prominent nucleoli [4].

An epithelioid morphology can be found in other vascular tumors, such as hemangioendothelioma and hemangioma [5]. The presence of solid growth pattern with necrosis and mitotic activity will differentiate epithelioid angiosarcoma from benign and low-grade vascular lesions. Well-differentiated breast angiosarcoma may also be difficult to morphologically differentiate from pseudoangiomatous stromal hyperplasia, atypical vascular proliferation, perilobular hemangioma, and angiolipoma [4]. Immunostaining for MYC and FLT [4] will help differentiate these vascular lesions from primary breast angiosarcoma [6].

Metastatic carcinoma [4], pleomorphic carcinoma [4], epithelioid sarcoma [4], and melanoma [5] are also difficult to distinguish from epithelioid angiosarcoma. Differentiation is based mostly on immunochemistry and typical morphology. This neoplasm may appear similar to ductal carcinoma in biopsies, showing solid sheets of polygonal cells with abundant cytoplasm and intracytoplasmic clear spaces. The presence of slit-like vascular spaces lined with pleomorphic epithelioid malignant cells favor epithelioid angiosarcoma [5].

Differentiation from other forms of angiosarcomas may be most challenging, but is mostly based on CD34 immunonegativity and typical nuclear morphology (vesicular or indented in epithelioid angiosarcoma) [4].

Immunohistochemistry studies show reactivity for vascular antigens. Von Willebrand factor is most specific, but least sensitive [5]. CD31 has excellent sensitivity and specificity, and is expressed in 90% of angiosarcomas of all types [4]. Epithelioid angiosarcoma is a variant characterized by CD31 reactivity but is classically negative for CD34. More than 35% of epithelioid angiosarcoma stain diffusely positive for cytokeratin [4]. D2-40, Fli-1, factor VIII, and vimentin are frequently found positive in epithelioid angiosarcoma and are useful in differentiating it from carcinomas. Diffuse positive immunostaining for MYC and FLT4 can help differentiate it from other malignant vascular lesions [6]. ER and PR are frequently negative, but HER2/neu positivity had been reported [4].

Epithelioid angiosarcoma is a high-grade sarcoma with aggressive behavior. High-grade primary angiosarcomas are associated with younger age at diagnosis and shorter survival [7]. Rosen et al. (1988) demonstrated in a report of 63 patients that histological grades are associated with prognosis, where 5-year survival for low, intermediate, and high was 76%, 70%,

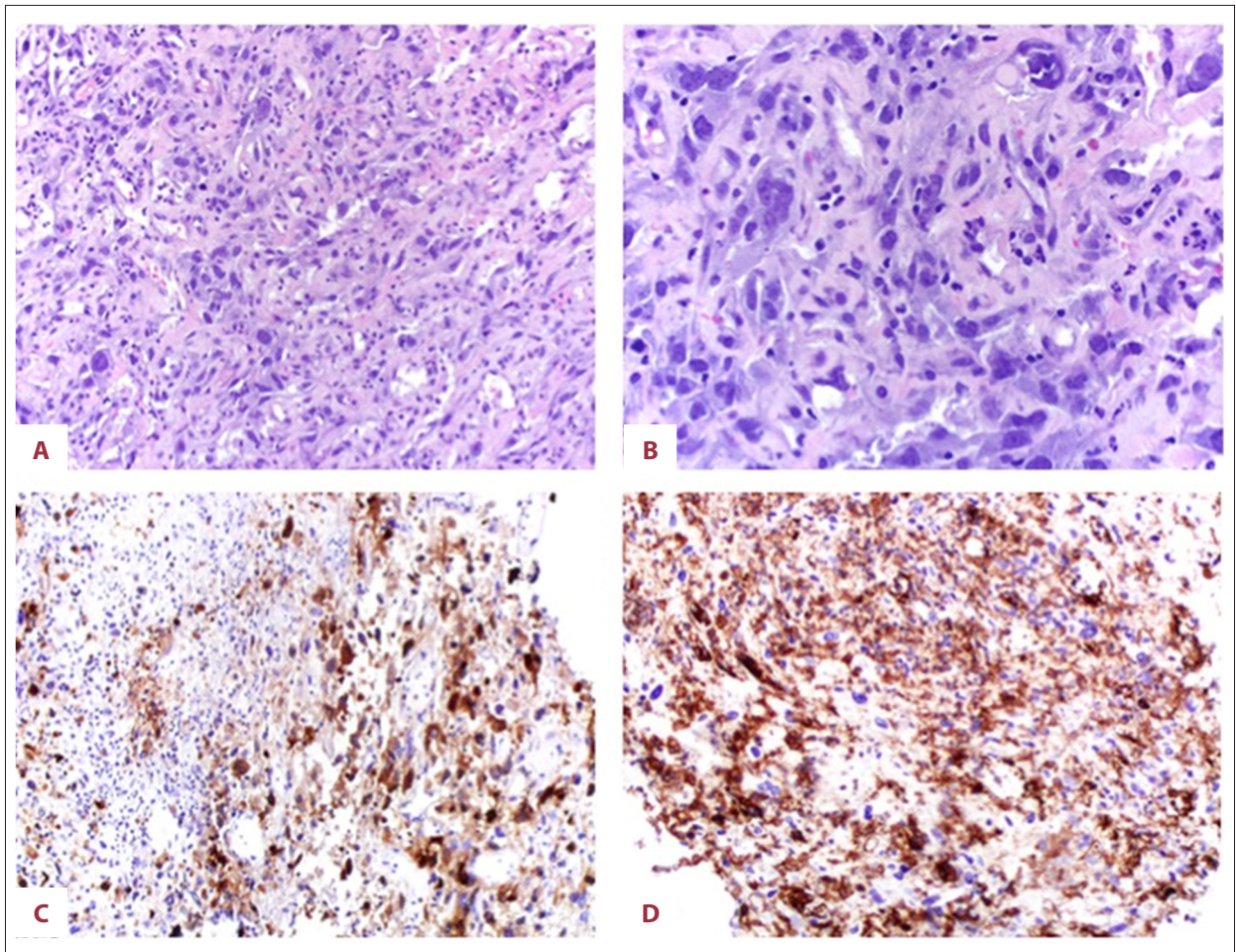


Figure 1. Histologic sections showed spindle-shaped infiltrative cells with vacuolated cytoplasm and marked anisonucleosis: (A) magnification 2000 \times and (B) magnification 4000 \times . (C) AE1/AE3, positive, magnification 2000 \times . (D) CD31 positive, magnification 2000 \times .

and 15%, respectively [8]. However, 2 more recent studies in 2003 and 2008, involving 18 and 49 patients, respectively, concluded no correlation between tumor grade and rate of local recurrence, metastasis, and death [2,3]. These studies, however, were limited by small sample size.

The largest study (2015) involving 226 women with primary breast angiosarcoma confirmed the findings of Rosen et al. [7]. Median overall survival in high-grade lesions was significantly shorter compared to lower grade tumors (172 months in low grade lesions, 24 months in intermediate grade lesions, and 16 months in high-grade lesions) [7].

Other factors reported to affect prognosis were tumor size [7,8] and margin status [7]. Tumor size of more than 5 cm has been associated with distant metastasis and higher 4-year death risk [7,9]. The most common sites of metastasis include contralateral breast, liver, lung, skin, lymph nodes, and bones [7]. Local recurrence has been associated with positive margin status [7].

Conclusions

Primary breast angiosarcoma is a rare and aggressive form of breast cancer. Its rarity limits its consideration during incisional biopsy, leading to diagnostic errors favoring the more common histologic forms of breast neoplasm. Such errors can delay proper management and can lead to poor prognosis. The clinical presentation may be the same as the presentation for usual breast carcinoma, and histology may mimic poorly differentiated ductal carcinoma [10]. The use of immunohistochemical and genetic profiling of the lesion is strongly recommended to narrow down differentials and achieve definitive diagnosis.

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Conflict of interest

None.

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