

BRIEF ARTICLE

Malignant Angiosarcoma Masquerading as Benign Epithelioid HemangiomaKarishma Daftary, BA¹, Joaquin Brieva, MD¹, Raj Chovatiya, MD, PhD¹¹ Department of Dermatology, Feinberg School of Medicine at Northwestern University, Chicago, IL**ABSTRACT**

In this report, we describe a case of a healthy 67-year-old female with rapidly growing red nodules on the scalp that demonstrated histological features of benign epithelioid hemangioma on multiple instances yet behaved clinically as a malignant angiosarcoma. Despite multiple rounds of resection, radiation, and chemotherapy, the patient ultimately succumbed from her widely metastatic disease. Diagnosis of vascular neoplasms, including the spectrum of low-grade epithelioid hemangioma, intermediate-grade epithelioid hemangioendothelioma, and high-grade angiosarcoma remains challenging due to overlapping clinical and histopathological features. This report is presented to highlight the need for clinicians to interpret histopathology, whether benign or malignant, in the context of clinical observation as the clinical course may not always match the biopsy.

CASE REPORT

A previously healthy 67-year-old female presented to dermatology clinic with rapidly growing, non-painful, non-tender, dark red nodules on the scalp (**Figure 1**). Three months prior she had noted a single, similar red nodule that was excised and diagnosed as a benign epithelioid hemangioma. A punch biopsy of a newer lesion on the scalp was performed. The epidermis was unremarkable, and the dermis showed multinodular proliferation of immature vessels in myxoid stroma lined by epithelioid and spindled endothelial cells with increased cellularity, mitoses, and vacuolization (**Figure 2 and 3**). Occasional eosinophils and lymphocytes were noted. Immunohistochemistry was positive for factor VIII, CD34, ERG, and SMA. Frank atypia was not identified. These findings suggested a

benign vascular neoplasm consistent with epithelioid hemangioma (EH).



Figure 1. Rapidly growing, non-painful, non-tender, dark red scalp papulonodules on the scalp with central necrotic, vascular plaque.

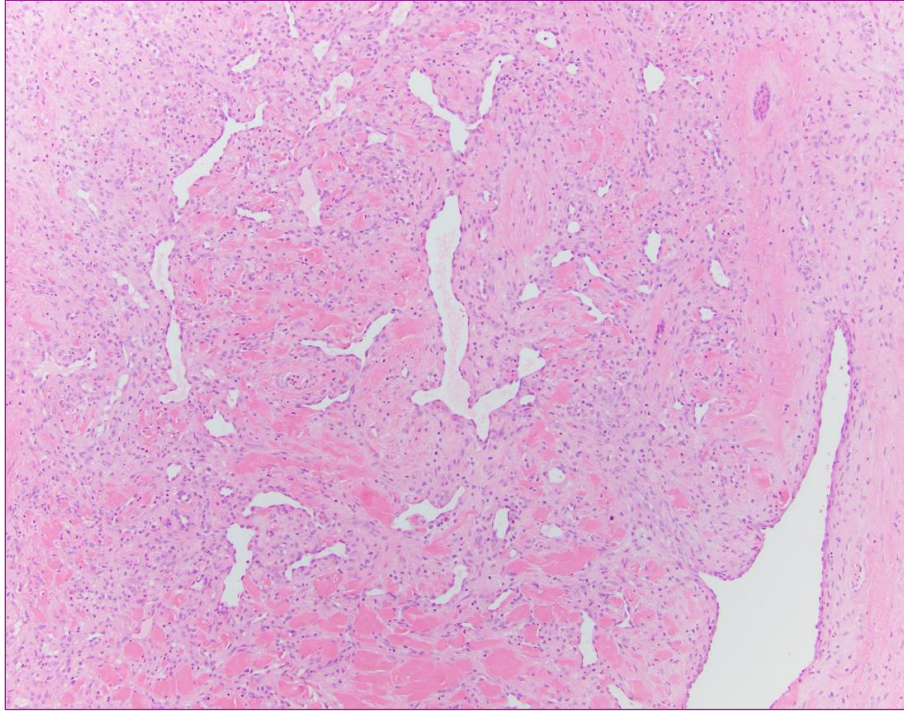


Figure 2. Punch biopsy of a scalp lesion demonstrating a multinodular proliferation of immature vessels in myxoid stroma lined by epithelioid and spindled endothelial cells with increased cellularity, mitoses, and vacuolization (hematoxylin & eosin) at 10X

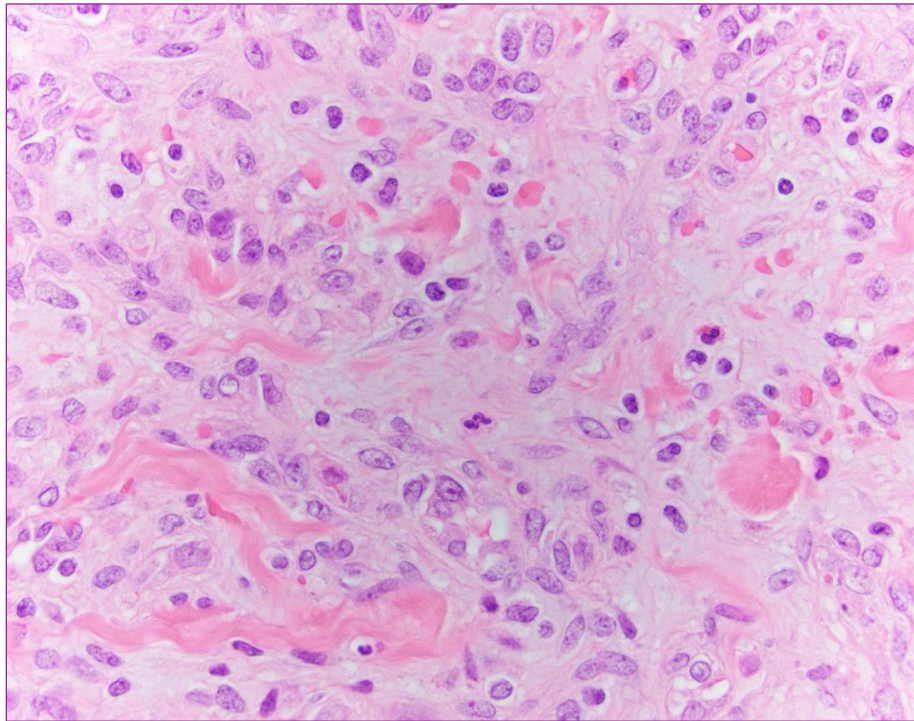


Figure 3. H&E biopsy at 40X

Prior to planned curative excision and over the course of the following month, the lesions showed explosive growth, spreading across the scalp with satellite nodules. During this time the patient also developed headaches and palpable lymphadenopathy. Imaging with PET-CT revealed an infiltrating 1.5cm x 2.1cm x 1.3cm tumor with calvarium invasion, metastatic lymphadenopathy, and innumerable soft tissue masses. Lymph node fine needle aspiration mirrored skin histopathology, which itself had been independently evaluated as EH at four separate academic centers. Clinically, despite benign pathology, these findings were more consistent with an aggressive angiosarcoma. The patient had treatments of radiation, paclitaxel, doxorubicin, and docetaxel/gemcitabine over the next several months, but she unfortunately continued to show progression of disease and ultimately succumbed to her illness.

DISCUSSION

Epithelioid hemangioma (EH), also known as angiolymphoid hyperplasia with eosinophilia, is a benign, slow-growing, dermal vascular proliferation presenting with red-brown, dome-shaped papulonodules. First described in 1969 by Wells and Whimster, the lesions typically appear on the head and neck and more rarely, on the trunk, extremities, and genitalia.^{1,2} The disease commonly presents in the third or fourth decade of life and may have a slight predilection towards females.¹

Patients with EH are often asymptomatic, but some experience pain, pulsations, pruritus, or bleeding due to the vascular nature of the lesions.^{1,2} Histologically, EH is characterized by aggregates of enlarged blood vessels lined with plump endothelial cells and surrounded by lymphocytes and

eosinophils.¹ Diagnosis of EH can be quite challenging, given similarities to other vascular tumors. EH is at the low-grade end of a spectrum occupied by the intermediate-grade malignant epithelioid hemangioendothelioma (EHE) and the high-grade angiosarcoma. Per the classification system set forth by the International Society for the Study of Vascular Anomalies (ISSVA) that categorizes vascular tumors as benign, locally aggressive/borderline, or malignant, EH is designated as a benign whereas both EHE and angiosarcoma are categorized as malignant tumors.³

EHE is a rare malignant tumor with an epithelioid or histiocytoid appearance developing from vascular endothelial or pre-endothelial cells. Similar to EH, the disease presents in middle age, with a median age of onset of 36, and has a slight predilection for females.⁴ 50-76% of patients with this vascular tumor are asymptomatic and diagnosed incidentally on imaging.⁴ When symptomatic, EHE has a broad range of clinical presentations that can affect numerous sites, including most commonly the lung and/or bone, which can present as pleuritic chest pain, pleural effusion, hemoptysis, bone pain, and fracture.⁴ Histological features of EHE include vacuolated endothelial cells growing in nests and cords.^{1,5} Identification of intranuclear inclusions, intracytoplasmic vacuoles, stromal changes, and few mitotic figures may be helpful in differentiating from epithelioid angiosarcoma.^{5,6}

On the high-grade spectrum of vascular tumors is angiosarcoma. There are multiple variants of cutaneous angiosarcoma including angiosarcoma of the head and neck, angiosarcoma associated with lymphedema, radiation-induced angiosarcoma, and epithelioid angiosarcoma.⁷ They differ clinically from EH

and EHE in that they often present in the elderly and the lesions spread rapidly in a centrifugal pattern.⁵ While EH has a benign clinical course, angiosarcoma is a highly aggressive, metastatic, endothelial malignancy with high mortality. Angiosarcoma may mimic EH histologically with certain similar features including vascular channels lined by endothelial cells and a lymphoid infiltrate.⁵ Angiosarcoma is differentiated by increased mitotic activity, necrosis, hemorrhage, irregular vascular channels dissecting through dermis, and an absence of eosinophilic infiltrate.^{5,7}

Prognosis of angiosarcoma is poor; a recent meta-analysis found the mean 5-year survival rate to be 33.35%.⁸ Poor prognostic factors include greater than 70 years of age, tumor size larger than 5cm, and involvement of the head and neck. The standard treatment for angiosarcoma is surgical resection, but this is not always an option in patients with unresectable and/or metastatic disease.⁹ Systemic therapy with paclitaxel is considered to be first-line for advanced cutaneous angiosarcoma.^{9,10} Second-line treatment options include pazopanib, eribulin mesylate, and trabectedin.⁹

There are few examples in the literature demonstrating difficulty in distinguishing between these vascular neoplasms based on pathology alone. Marcum et al. reported a patient who had numerous, rapidly-proliferating, violaceous nodules located on the scalp with pathologic features of EH despite certain clinical features of angiosarcoma.⁵ The patient's lesions showed complete clinical resolution with long-pulsed dye laser therapy and shave excision – standard treatment modalities for patients with EH. Conversely, Zeitouni et al. reported a patient with scalp nodules that showed benign clinical features of EH even though histopathology demonstrated findings

consistent with angiosarcoma.¹¹ The patient's lesions were surgically excised with no recurrence. To our knowledge, an aggressive vascular entity with pathologic features of EH and clinical features of refractory angiosarcoma has not been previously reported.

CONCLUSION

This case serves as a reminder that whether benign or malignant, clinicians should always interpret histopathology in the context of clinical observation. Clinicopathologic correlation and differential diagnosis are especially critical for vascular neoplasms where histopathology may be challenging, as with the spectrum of EH, EHE, and angiosarcoma.

Conflict of Interest Disclosures: Raj Chovatiya has served as an advisory board member, consultant, speaker, and/or investigator for AbbVie, Apogee, Arcutis, Argenx, ASLAN, Beiersdorf, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Dermavant, Eli Lilly and Company, Galderma, Genentech, Incyte, LEO Pharma, L'Oréal, Novan, Inc., Pfizer Inc., Regeneron, Sanofi, and UCB. Karishma Daftary and Joaquin Brieva have no conflicts to disclose.

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