Epithelioid Hemangioendothelioma - Dangerous, easy to miss, and nearly impossible to clinically diagnose: Case Report

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Abstract

Epithelioid hemangioendothelioma is a rare vascular tumor with metastatic potential. The extremely heterogeneous clinical presentation and disease progression complicates diagnoses and management. We present the case of a 24-year-old-female with two cutaneous lesions leading to the discovery of metastatic epithelioid hemangioendothelioma. Key clinical and histopathological findings are highlighted to aid dermatologists in diagnosing and managing this uncommon condition.

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Abstract: Epithelioid hemangioendothelioma is a rare vascular tumor with metastatic potential. EHE can have single or multi-organ involvement, with presentations ranging from asymptomatic disease to pain and systemic symptoms. The extremely heterogeneous clinical presentation and disease progression complicates diagnoses and management. We present the case of a 24-year-old-female, with two periauricular erythematous papules, leading to the discovery of metastatic epithelioid hemangioendothelioma through routine biopsy, despite a noncontributory medical history. Histology revealed dermal proliferation of epithelioid cells and vacuoles containing red blood cells. Immunohistochemistry markers consistent with EHE solidified the diagnosis. Although extremely rare, prompt diagnosis of EHE is essential for informed decision making and favorable outcomes. Key clinical and histopathological findings are highlighted to aid dermatologists in diagnosing and managing this uncommon condition.

Ethical Considerations: The patient has given us consent to publish information regarding her case, including photographs and relevant findings. Identifiable patient information has been appropriately masked or omitted to comply with ethical standards and patient privacy.

Introduction: Epithelioid hemangioendothelioma (EHE) is an extremely rare cancer, accounting for less than 1% of vascular tumors, and has been described as demonstrating features between hemangioma and angiosarcoma [1]. Although first described by Dail and Liebow in 1975, it was not until 1982 that Weiss and Enzinger first proposed the term EHE [1]. These tumors can occur at any

age, with 38 years being the median age at diagnosis [2]. The most common presenting symptom is pain, with other symptoms less commonly reported such as cough, palpable mass or fatigue. Nearly one third of patients with EHE are asymptomatic and tumors are discovered incidentally [2]. While likely endothelial in origin, EHE is known to be extremely heterogeneous in presentation and prognosis, complicating diagnosis and clinical decisions[3]. EHE can occur nearly anywhere in the body. Primary cutaneous EHE is rare and should prompt suspicion of metastatic disease, especially if multifocal in the skin [4]. Due to their rarity and similarities to other diagnoses, cutaneous EHE lesions are commonly misdiagnosed [5]. Previous studies suggest the diagnosis of strictly cutaneous EHE incurs a 17% mortality rate at three years, highlighting its relatively aggressive nature [6]. It is paramount for dermatologists and dermatopathologists alike to be aware of EHE and its defining characteristics to minimize the risk of missing this crucial diagnosis. We report a case of two periauricular lesions, with dermal proliferation consistent with EHE, leading to the discovery of underlying metastatic EHE with pulmonary and hepatic involvement in a 24-year-old female. The aim of presenting this case is to enhance understanding of EHE, an uncommon cancer that is not well studied.

Case Report: Our patient is a 24-year-old female with no significant past medical history or social history, including no tobacco or heavy alcohol use. She presented to the dermatology clinic with a left posterior auricular papule and a left preauricular papule present for eight and four months, respectively (Figure 1). Both lesions were painful and progressively enlarging. The patient denied any other symptoms. Shave biopsy was taken of both lesions. The histology of both lesions demonstrated cellular dermal proliferations of epithelioid cells with eosinophilic cytoplasm arranged in cords within a myxohyaline stroma (Figure 2). Subtle vacuoles containing red blood cells were present within some of the cells (Figure 3). Numerous immunohistochemical stains were performed. The tumor cells were diffusely positive for CD31, CD34, ERG and CAMTA1, as well as focally positive for cytokeratin. Tumor cells were negative for SOX-10 and SMA (Table 1). These histological and immunohistochemical findings were consistent with the diagnosis of EHE. Due to multifocal cutaneous disease, there was a high clinical suspicion of metastatic disease. Our patient was referred to medical and surgical oncology for further evaluation and CT scans of the head, neck, chest, abdomen and pelvis were performed. Innumerable bilateral pulmonary nodules, a 1.8 cm hypoattenuated hepatic lesion, and prominent bilateral axillary lymph nodes were noted, all consistent with metastatic disease. After seeking multiple opinions from oncology, our patient elected the watchful waiting approach. Serial CT scans every 3 months were recommended to monitor disease progression.

Discussion: Literature pertaining to EHE is limited with case reports and case series comprising the majority. This can largely be attributed to the prevalence of EHE reported as roughly one in a million [1]. Sites of primary and metastatic involvement in EHE most commonly involve the liver, lung and bone, however the disease has been reported in nearly every part of the body. When cutaneous EHE is discovered, it typically represents metastatic disease rather than primary malignancy. The appearance, location and characteristics of cutaneous EHE varies immensely from case to case, with no clear consensus available [4, 7-8]. The extreme heterogeneity of this disease complicates detection and diagnosis [2]. Often, histopathology and immunohistochemistry are crucial for diagnosis of cutaneous disease. Histologically, tumors typically show circumcised nodules with an overlying acanthotic epidermis. A mixture of pleomorphic spindle and epithelioid cells with sharply eosinophilic cytoplasm will be present, typically embedded in a myxoid or hyaline matrix [8]. Cells typically stain positive for CD 31, CD 34, Factor VIII related antigen, α-smooth muscle actin and cytokeratin [6-7]. When unable to be clearly differentiated from other vascular tumors, the presence

of the WWTR1-CAMTA1 translocation can aid the diagnosis of EHE [3]. This translocation dysregulates the Hippo pathway, promoting cancer proliferation and survival [10]. The prognosis of strictly cutaneous EHE is not readily available. In a small case series of 30 patients with cutaneous EHE, at 36 months follow up, 21% of cases had metastatic disease, 13% had local recurrence, and 17% had died from the disease [6]. In all cases of EHE irrespective of site, one-year overall survival is 90% with a 5-year overall survival of 73% [2]. Given the low prevalence of EHE, no randomized clinical trials exist regarding optimal treatment strategy [7]. Patients with cutaneous EHE should receive additional imaging to evaluate for metastatic disease. When no metastatic disease is found, treatment is surgical resection [3]. A variety of treatments such as cytotoxic chemotherapy, immunotherapy, targeted therapies and organ transplantation have been used for metastatic disease (Table 2). With reports of spontaneous disease regression [9], watchful waiting can also be proposed as a reasonable course following diagnosis of EHE, especially if the nature of the disease is not yet understood or the risks of treatment outweigh benefits.

Conclusion: The heterogeneity of EHE is also demonstrated in its variable course. At times indolent, and others very aggressive, EHE can be unpredictable [7]. Given the uncertain course of the disease, joint decision-making between patient and physician is necessary. Active surveillance includes monitoring progression, and the decision to treat with radiation or surgery often follows once the nature of the tumor is better understood [10]. Systemic treatments have been recorded, but not enough data is currently available to determine a standard approach [10]. Regardless of the course of management, close follow-up for local recurrence and metastatic disease is essential. Future studies should focus on early detection and a standardized approach for the treatment EHE.

Table 1. Immunohistochemistry characteristic of epithelioid hemangioendothelioma (EHE) and results of the patient. Percentages respond to their estimated prevalence in EHE tumors. [3,6-7]

IHC Markers (EHE)	ERG, CD31, SMA, FVIII Ag, CAMTA1/ TFE3, focal cytokeratin (<30%)	
Gene Fusions (EHE)	WWTR1-CAMTA1 (90%)/ YAP-TFE3 (10%)	
Case Results	Positive	Negative
	CD31, CD34, ERG, CAMTA1, cytokeratin (focally)	SOX-10, SMA

Table 2. Possible treatment options based on retrospective studies of tumor involvement and case outcomes/ (R0- microscopic negative margins; R1- gross negative margins). [10]

Involvement	Considerations	Treatment
Unifocal	R0 margins	Surgical resection (70-80% cure rate)
	R1 margins	Surgical resection +/- radiation therapy
	Severe morbidity or R0/R1 not possible	Radiation therapy/ ablative procedure/ isolated limb perfusion
	Not surgical candidate (comorbidities or technical challenges)	Active surveillance
Locoregional	Resection possible	Surgial resection +/- Radiation therapy
	Asymptomatic	Active surveillance
	Symptomatic (surgery not possible)	Radiation therapy/ ablative procedure/ isolated limb perfusion
Systemic	Resection possible	Surgical resection +/- radiation therapy
	Asymptomatic	Active surveillance
	Symptomatic (systemic) or serosal effusion	Systemic therapy (limited evidence)
	Organ involvement	Surgical resection/ transplant (unresectable)

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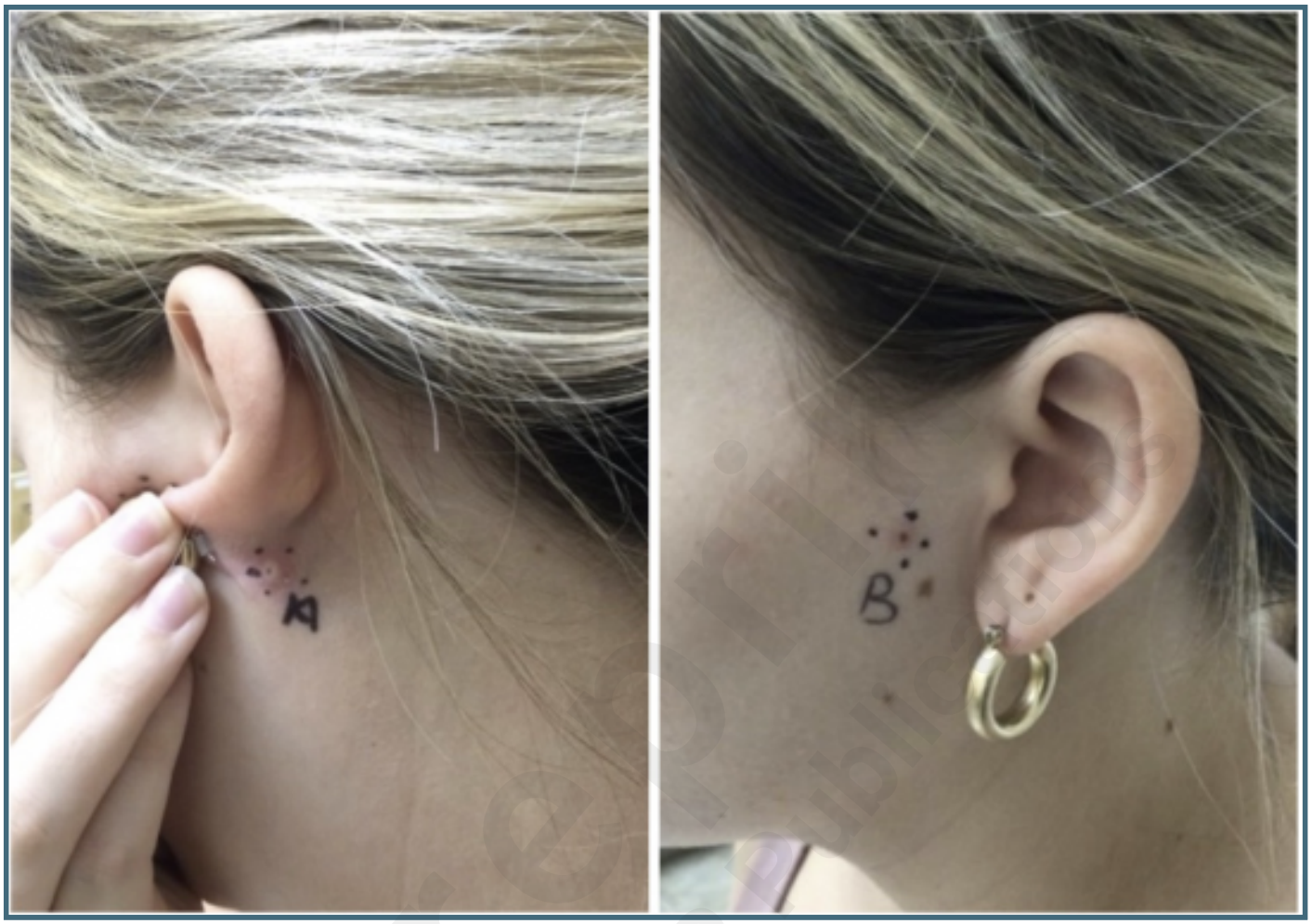
Abbreviations

EHE: Epithelioid hemangioendothelioma

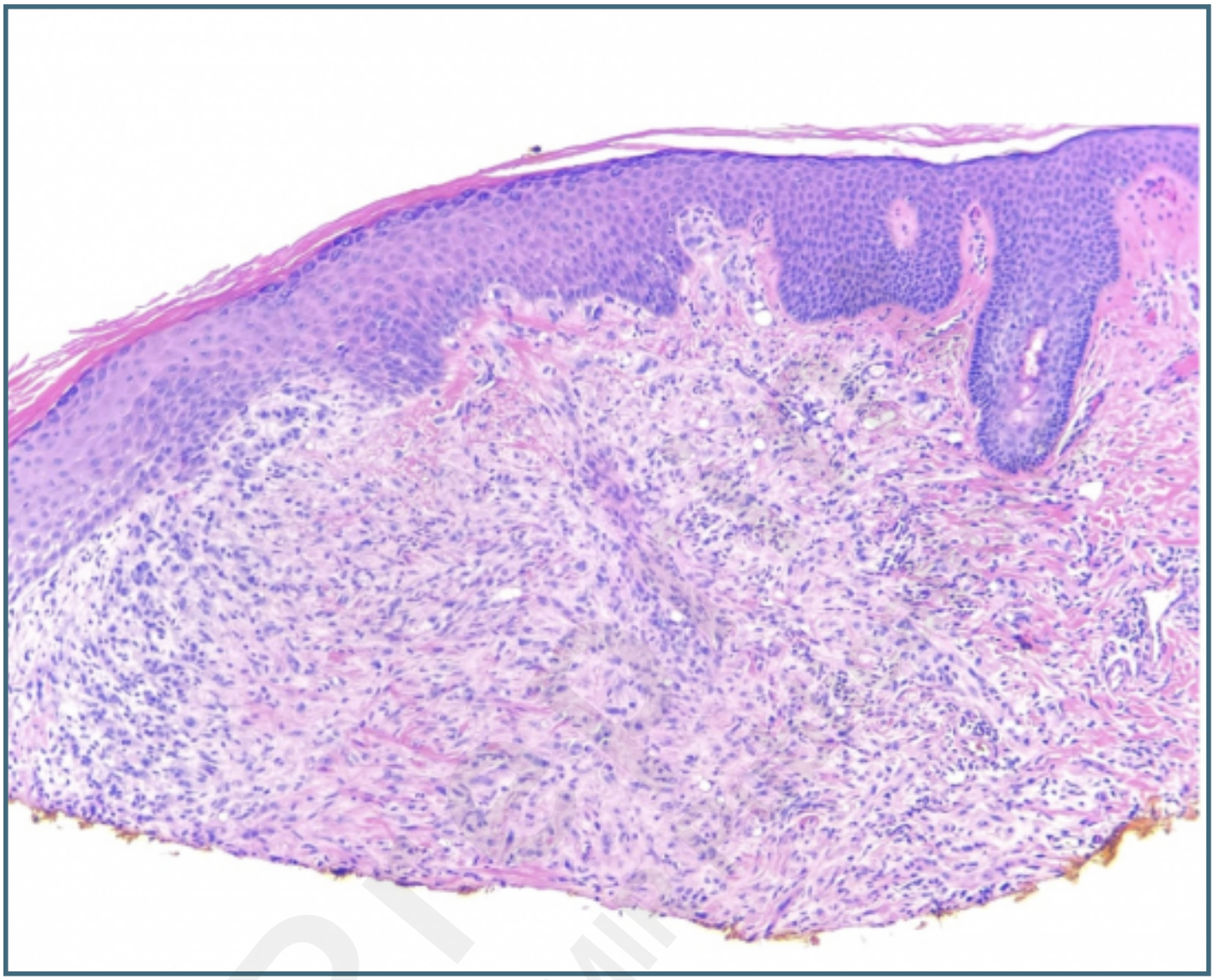
Supplementary Files

Figures

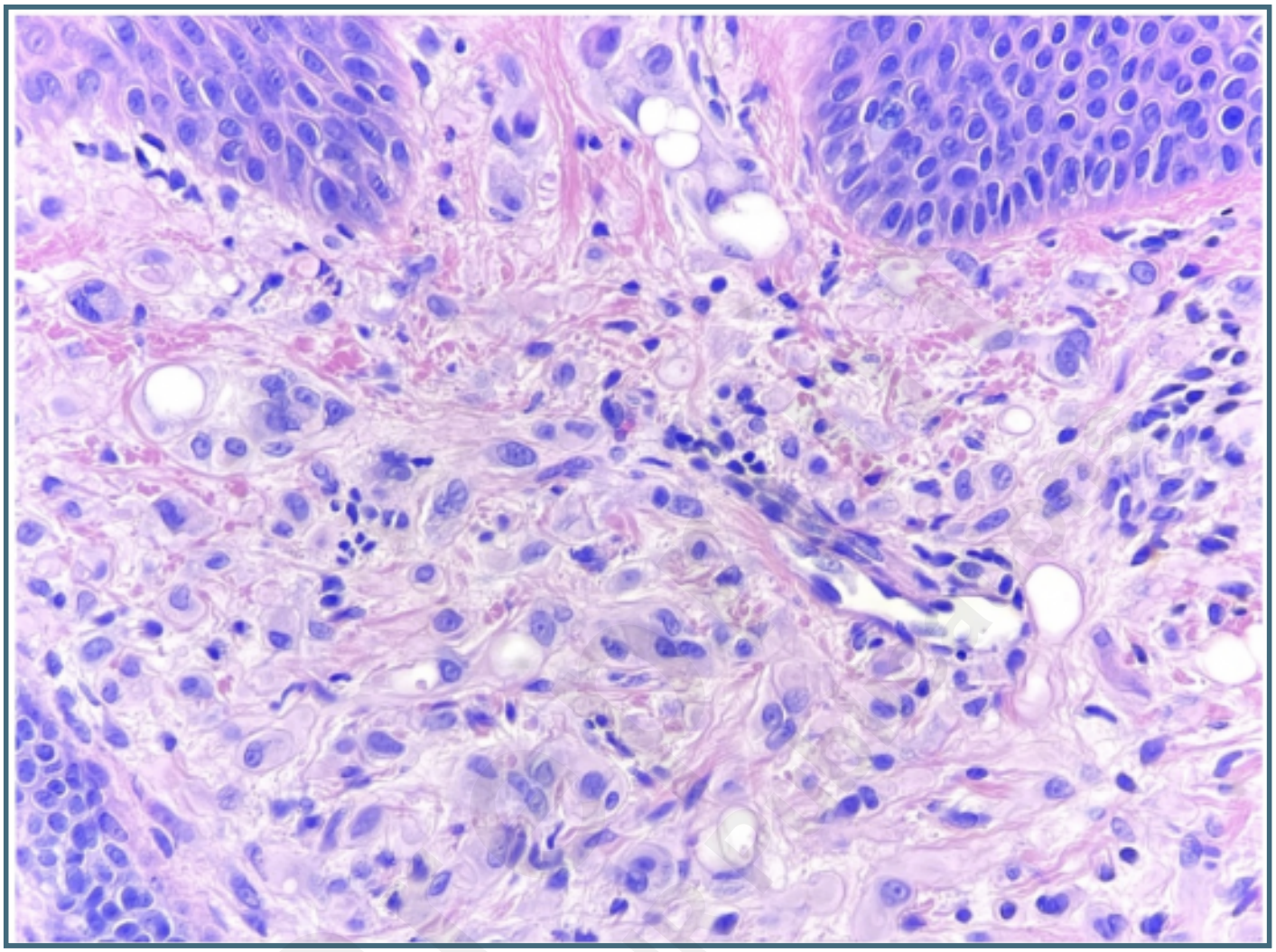
A 3mm umbilicated, skin colored papule on the post auricular neck (left) and a 2mm hyperpigmented papule with surrounding erythema on the preauricular cheek (right).



Dense proliferation of dermal epitheliod cells with no attachment to the epidermis.



Dermal epithelioid cells with eosinophilic cytoplasm and red blood cells in vacuolations identifying them as vascular spaces.



Multimedia Appendixes

Table 1.
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Table 2.
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