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CASE REPORT

# Epithelioid Hemangioendothelioma of the Maxillary Sinus

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**Abstract** The clinical course and pathologic features of a 72 year old female who presented with epistaxis are presented. Radiographic findings were notable for a large, soft tissue lesion filling the maxillary sinus with significant bony erosion and expansion. The patient was ultimately diagnosed with epithelioid hemangioendothelioma (EHE) and underwent endoscopic resection. She has no evidence of local, regional or distant recurrence 14 months post-surgery. The rarity of this neoplasm, the unusual anatomic location and non-specific symptoms present diagnostic and management challenges. Epithelioid vascular tumors encompass a spectrum of benign and malignant tumors. EHE itself is thought to have an intermediate malignant behavior pattern, though cases with indolent behavior have been reported. Differentiation of EHE from other lesions has historically based on histopathology. Additionally, recent studies have described a recurrent genetic fusion WWTR1–CAMTA1 in EHE, involving t(1;3) (p36;q25). This represents the second reported case of EHE arising in a paranasal sinus. The histopathologic findings of this lesion are reviewed.

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## Introduction

Epithelioid hemangioendothelioma (EHE) is a rare, vascular, soft tissue neoplasm with an estimated body-wide incidence of approximately one person in every 1,000,000. Due to the rarity and histological similarity to other tumors, correct diagnosis can be challenging. Delay in diagnosis may occur, especially when the lesion presents with non-specific symptoms and in an unusual location, such as the paranasal sinuses. We present a case of a patient who presented with a 1-year history of epistaxis who was ultimately diagnosed and treated for maxillary sinus EHE. This represents the second reported case of paranasal sinus EHE in the literature. The clinical, radiographic and pathologic findings are reviewed.

## Case Report

A 72-year-old female presented with a 1 year history of episodic right sided epistaxis, occurring multiple times per week, with variable severity and described as bright red bleeding from the right nare lasting minutes–hours. The bleeding had been mostly self-limited, but she had received a nasal packing for heavy bleeding in the emergency room 1 month prior to otolaryngology evaluation. The patient's past medical history was notable for coronary artery disease, cerebrovascular disease (history of stroke), hypertension, type II diabetes mellitus, gastroesophageal reflux, osteopenia. She was not taking anticoagulant medications during this period. She denied any other sinonasal

symptoms. Office evaluation including nasal endoscopy was notable for soft tissue fullness in the right middle meatus and dark colored nasal secretions consistent with old blood. There were no mucosal masses and the remainder of the otolaryngologic exam including remainder of the nasal endoscopy, oral cavity, neck and cranial nerve exams were clear. The patient's history, examination findings and lack of an identified bleeding source prompted a computed tomography (CT) scan that revealed a complex mass in the right maxillary sinus (Fig. 1).

An endoscopic approach to the lesion was recommended given the clinical history, examination and CT findings. The patient underwent resection of the lesion for both diagnostic and treatment purposes. The procedure involved creation of a large maxillary antrostomy with preservation of the inferior turbinate and the anterior 2/3 of the lateral nasal wall. Gross findings were notable for a bulky, friable mass filling the maxillary sinus cavity. The entire lesion was mobilized and resected endoscopically with gentle manipulation. Of note, there were no identified bony attachment points within the maxillary sinus or soft tissue extension of the lesion beyond the maxillary sinus walls. Based on the intraoperative and radiographic findings, the origin of the lesion was consistent with the medial maxillary sinus wall. Following pathologic diagnosis, positron emission tomography (PET)–CT was performed and was notable for no evidence of lesion at the primary site, nonspecific contralateral axillary [maximum dimension 0.8 cm, standard uptake value (SUV) 5.5 and contralateral cervical level IIA, 0.9 cm, SUV 2.9] lymph node enlargement. Fine needle aspiration of the cervical and axillary lymph nodes revealed a mixed population of lymphocytes without concerning features. The patient's case was discussed at the institutional multi-disciplinary head and neck tumor board including the options of additional surgical resection and adjuvant radiation therapy. The decision was made to observe without additional therapy. The patient has had serial clinical evaluation and serial PET–CT, most recently 18 and 14 months after surgery, respectively, with no clinical or radiographic evidence of recurrence. The patient is asymptomatic from a sinus-nasal perspective. A well-healed right maxillary sinus cavity without evidence of lesion or inflammatory changes was noted on nasal endoscopy at most recent office follow up.

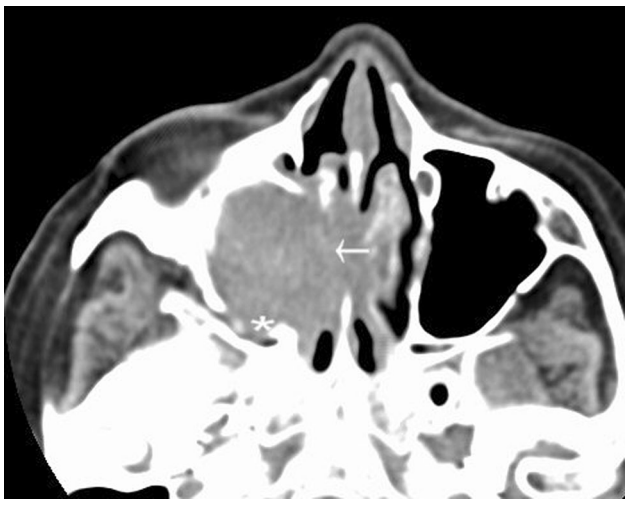

**Fig. 1** Axial, non-contrast, CT scan demonstrating a complex mass filling the right maxillary sinus with erosion of the medial (*arrow*) and posterior maxillary sinus walls (*asterisk*)

## Histology

The tumor was composed of nests and, at places, cords of predominantly large, round and polygonal eosinophilic epithelioid cells embedded in a hyalinized matrix (Fig. 2a). The nuclei were uniform in size with diffuse fine chromatin and many with prominent nucleoli. Cytoplasmic vacuolation was remarkable and most had a few red cells in the neolumina (Fig. 2b), indicative of primitive vascular channel formation. Mitotic figures were rare (less than 1 mitoses per 10 high-power fields). Extensive ischemic necrosis was noted. The tumor cells showed strong and uniform reactivity for pancytokeratin (Fig. 2c), CD31 (Fig. 2d), factor-VIII antigen, ERG and FLI-1 and were negative for HMB-45, chromogranin, CD56, TFE3 and desmin. The above features confirmed the diagnosis of an EHE.

## Discussion

EHE is a rare, vascular, soft tissue neoplasm that was first described by Weiss and Enzinger in [1]. The lesion is felt to originate from the intima of the blood vessels, and is usually venous in origin. There is no sex predilection, and age of onset is variable [2]. The most common anatomic locations include skin, bone, soft tissue, or the parenchyma of the lung or liver [3–5]. Rare locations in the head and neck, such as the gingiva, palate, parotid gland, and submandibular region, have previously been described [6]. The nasal cavity is also an extremely rare location for this tumor, with only 4 cases reported in the literature since 2003 [6–9]. Even rarer, however, is an EHE primarily originating within a paranasal sinus. To date, only one case of EHE originating in the maxillary sinus has been previously described in the literature [10]. These tumors have an intermediate and variable malignancy pattern in terms of both local recurrences and metastatic potential. This results in an unpredictable, yet oftentimes, indolent clinical course, and patients can survive for decades even with

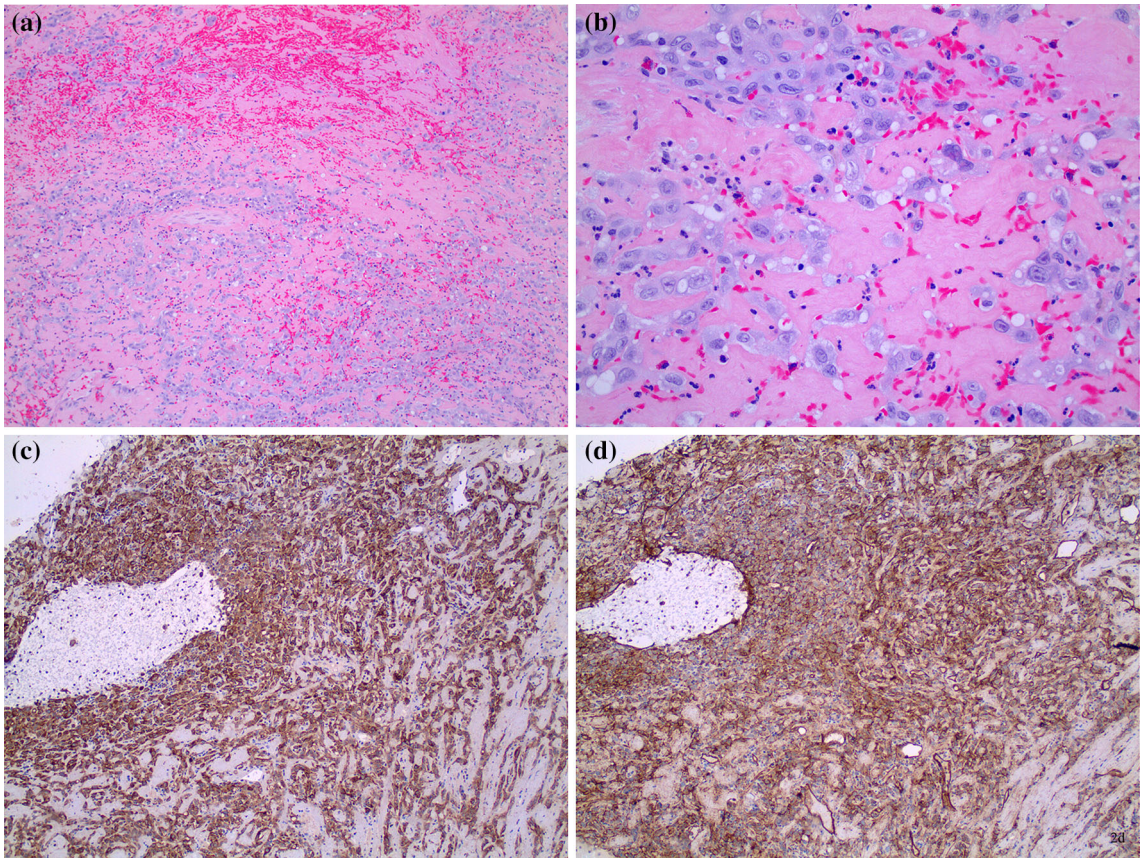


**Fig. 2** **a** The tumor consists of epithelioid cells and spindle cells, with bland nuclei, arranged in cords, and occasional nests in a predominantly hyalinized stroma (100×, H and E stain). **b** Epithelioid cells with neolumina formation and red blood cells inside the neolumina (400×, H and E stain). **c** Tumor cells show positivity for pancytokeratin (100×) and **d** CD31 (100×)

multi-organ disease [11, 12]. Mentzel et al. [12] noted 20 % of tumors metastasized and 17 % of patients died in their study. In our patient, the clinical history of a 1-year period of symptoms and radiographic findings of bony erosion and remodeling without soft tissue extension beyond the maxillary sinus suggests a low grade, slowly evolving process. However, some tumors do grow rapidly and can quickly become fatal. Given the limited clinical data, evidence based treatment protocols for treatment for sinonasal EHE are not possible. Based on the pathologic and clinical aspects of this disorder in other anatomic locations, complete surgical resection and a consideration of adjuvant therapy for high-risk patients may be indicated.

Microscopically, EHE consists of epithelioid cells or spindle cells arranged in cords, clusters or occasionally in solid sheets in a myxoid to chondromyxoid matrix. The tumor cells often have intracytoplasmic vacuoles, some with red blood cells, suggesting a primitive vascular origin. Mitotic figures are usually rare. The nuclei are usually bland but nuclear atypia has been described. Immunohistochemically, these tumors are positive for cytokeratin (especially CK18), and vascular markers including CD31, factor VIII-antigen, ERG and FLI-1. Recent studies have described a recurrent genetic fusion WWTR1–CAMTA1 in EHE [13], involving t(1;3) (p36;q25). This results in a reciprocal chromosomal translocation involving a fusion of the promoter of the WWTR1 gene with the carboxyl terminus CAMTA1 gene. These have not been seen in other vascular tumors and, hence, some authors have suggested that it could be used in difficult cases to distinguish EHE from its morphological mimics [13, 14]. YAP1–TFE3 gene fusions have been identified in a subset of EHEs where WWTR1–CAMTA1 fusion was not identified [15]. Tumors with this fusion have been reported to demonstrate a strong expression of TFE3 (nuclear). Our case did not show nuclear TFE3 expression.

Epithelioid vascular tumors broadly include epithelioid hemangioma, EHE and, at the malignant end of the spectrum, malignant EHE and epithelioid angiosarcoma. Epithelioid hemangiomas have a lobulated architecture with the hallmark "tombstone" appearance of the endothelial cells in the well-formed vessels. The lesions have an inflammatory component in the background with a predominance of eosinophils. Though they are no definite criteria for a diagnosis of a malignant hemangioendothelioma, a tumor size >3 cm and greater than 3 mitoses per

50 high power field is highly suggestive. Pseudomyogenic hemangioendothelioma (also termed epithelioid sarcoma-like hemangioendothelioma) is a recently described tumor which occurs more commonly in men, predominantly in the 2nd to 5th decade, most commonly reported in the extremities [16]. The tumor predominantly consists of spindle cells with bright eosinophilic cytoplasm resembling rhabdomyoblasts. These lesions have a characteristic infiltrative pattern and very commonly have stromal neutrophils. They are strongly positive for cytokeratin (AE1/AE3), diffusely positive for FLI1 and show variable reactivity to CD31. They are negative for EMA and CD34, and retain INI1 expression. Often they have a minor component of epithelioid cells which can be a pitfall. Sinonasal angiosarcomas are histologically low-grade tumors but can infiltrate the adjacent tissue including bone. These tumors are composed of anastomosing vascular channels including capillary like vessels and cavernous vascular spaces. The lining endothelial cells are often plump or spindly with nuclear pleomorphism and atypia. Atypical mitotic figures may be present. These tumors may have intracytoplasmic vacuoles containing erythrocytes as in EHE. Epithelioid angiosarcomas are typically high grade lesions comprising atypical endothelial cells with round nuclei and prominent nucleoli, increased mitotic activity and necrosis. Often, though focal, vascular differentiation can be identified in the form of irregular, vaguely formed vascular channels, which can be helpful to differentiate from so called "malignant hemangioendothelioma".

The differential diagnoses of EHE also include intravascular papillary endothelial hyperplasia, glomangiopericytoma, Kaposi sarcoma, malignant melanoma, carcinoma and large cell lymphoma. Most can be differentiated with microscopic examination and immunohistochemistry. However, one has to be careful to consider metastatic carcinoma. In the present case, keratin was diffusely and strongly positive and this can be a potential pitfall. The immunohistochemical positivity for endothelial markers is very helpful to differentiate EHEs from carcinomas.

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