Case Report

Isolated Cutaneous Epithelioid Hemangioendothelioma of the Nose: Case Report and Comprehensive Literature Review

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Abstract

Here, we report a rare case of isolated cutaneous epithelioid hemangioendothelioma (EHE) occurring on the nose of a 56-year-old female patient, without any systemic involvement. This article will also briefly highlight the clinical, pathological, as well as the molecular features of EHE.

Keywords: Borderline tumor, epithelioid hemangioendothelioma, vascular lesion

Introduction

The term epithelioid hemangioendothelioma (EHE) was first introduced by Weiss and Enzinger in 1982, to describe a vascular tumor that shows features between a hemangioma and an angiosarcoma.[1] Originally, EHE was considered to be a borderline or an intermediate malignant vascular tumor. However, the current classification of vascular anomalies considers EHE to be a fully malignant vascular tumor.[2] The Rationale for this is that EHE has a more aggressive biological behavior along with a higher metastatic potential than other lesions classified as hemangioendotheliomas, reaching up to 30%.[2-5] The epithelioid morphology of EHE makes the diagnosis of such tumors extremely challenging. The epithelioid cytomorphology has a broad differential diagnosis, and the vascular nature of these tumors can be difficult to recognize. We report a case of a rare vascular tumor, with usual cutaneous involvement, occurring in an atypical location. A high index of suspicion is required to identify such cases.

Case Report

A 56-year-old Caucasian woman presented with a solitary erythematous, firm, nonpulsating nodule located on the left nasal ala and sidewall of the nose. The lesion measured 2 cm × 2 cm in size with sharply defined borders. On close inspection, the surface appeared smooth and shiny with an erythematous to skin-colored nodule at the inferolateral margin that is surrounded by a telangiectatic base [Figure 1].

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Website: www.jddsjournal.org

DOI: 10.4103/jdds.jdds_23_19

The patient first noticed the lesion a few months ago, which started as small papule that gradually increases in size. Initially, the progression was slow, but in the last month prior to seeking medical help, the mass became large enough to worry the patient. The patient denied a history of pain, itching, or bleeding of the lesion or any other systemic symptoms. Both full skin evaluation and complete physical examination were negative. A review of the medical history of the patient was insignificant. An incisional skin biopsy was performed. The histopathological examination revealed an infiltrating neoplasm composed of atypical deeply infiltrative epithelioid cells with large eosinophilic cytoplasm and round hyperchromatic nuclei forming channels in between collagen bundles [Figure 2]. Immunohistochemically, the atypical cells were positive for CD31, CD34, Factor VIII, CD68, CK7, CD10, and vimentin [Figure 3], whereas it was negative for CD3, CD20, CD1a, S-100, HMB-45, ASMA, GCDFP-15, Ki-67, and CK5 [Figure 3]. The differential diagnosis of EHE was epithelioid angiosarcoma versus EHE. The low Cytologic atypia, low mitotic rate, and absence of necrosis were helpful to rule out angiosarcoma. The overall picture was suggestive of a low-grade malignant vascular neoplasia most likely EHE. Screening for extracutaneous disease including magnetic

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How to cite this article: Alramthan A, Abdulkader A, Alenezi M. Isolated cutaneous epithelioid hemangioendothelioma of the nose: Case report and comprehensive literature review. J Dermatol Dermatol Surg 2019;23:102-5.

resonance imaging brain, chest, and abdomen as well as a bone scan was negative. The tumor was excised completely with a safety margin of 0.2 cm, and the defect was repaired with a full-thickness skin graft [Figure 4]. Follow-up was arranged every 3 months for a period of 3 years. The patient is doing well with no history of recurrence nor metastases.

Discussion

EHE is a rare vascular tumor of endothelial cell origin that represents <1% of all the vascular tumors.[6] It is a tumor of adulthood, with a peak incidence in the 4th–5th decade. Females are affected more commonly than males.[3] It arises most frequently in deep soft tissue, liver, lungs, and bones. EHE also occurs within the skin in a range of anatomic locations.[6] Skin involvement as a primary presentation is rare. Cutaneous lesions often are associated with an underlying bone or soft-tissue tumor. However, isolated cutaneous lesions may exist, although extremely rare.[7] Although the most commonly reported sites of cutaneous involvement are the extremities,[1,5] many recent publications described the occurrence of EHE in the head-and-neck region.[8-10] EHEs have a propensity for angiocentric growth and obliterating the vascular lumen.[3,4] As a result such tumors more likely to manifest with symptoms of vascular occlusion rather than manifesting as a mass lesion.[4] However, the angiocentric growth pattern is less commonly observed in cutaneous tumors, that is, why most cutaneous tumors present as a solitary skin-colored painful or tender soft-tissue mass that does not resemble a vascular neoplasm clinically.[1,4,5] Nevertheless, the cutaneous presentation may be

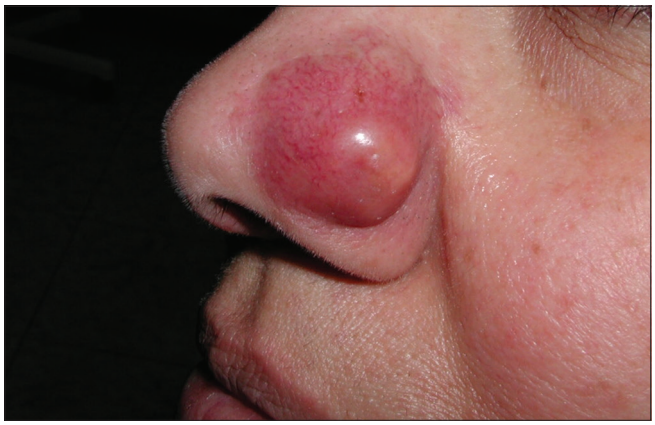

Figure 1: A solitary erythematous, firm, nonpulsating nodule located on the left ala and sidewall of the nose. The lesion measured 2 cm × 2 cm in size with sharply defined border. The surface of lesion appeared smooth shiny with erythematous to skin-colored area in inferolateral margin that is surrounded by telangiectatic base

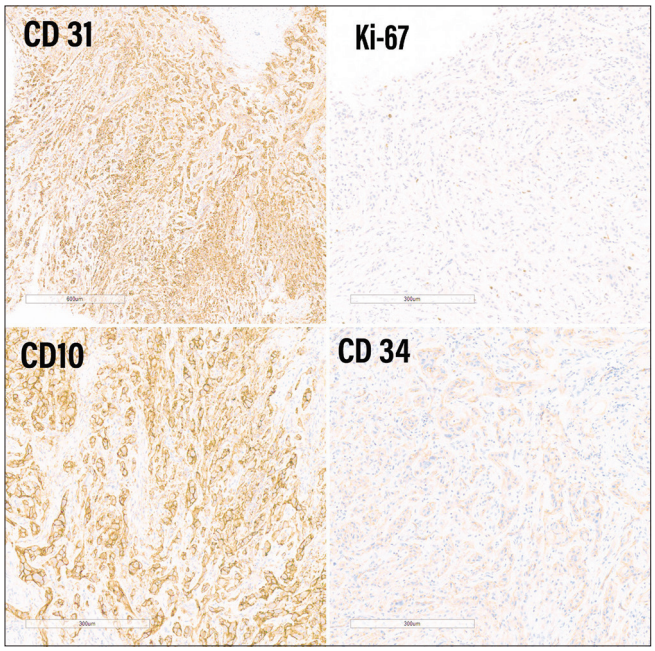

Figure 3: Immunohistochemical study showed a positive reaction of the atypical cells to CD1, CD34 as well as CD 10, and a negative reaction to Ki-67

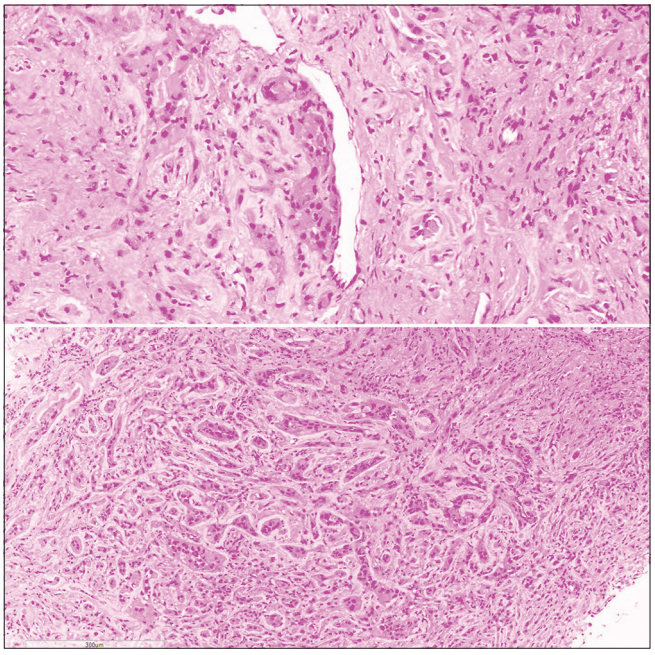

Figure 2: An infiltrating neoplasm composed of atypical deeply infiltrative epithelioid cells with large eosinophilic cytoplasm and round hyperchromatic nuclei forming channels in between collagen bundles

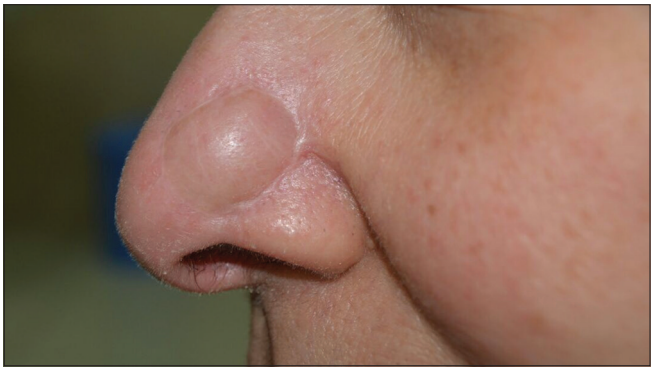

Figure 4: Tumor was excised completely with a safety margin of 0.5 cm, and the defect was repaired with a full-thickness skin graft

quite variable. Solitary, multiple, eruptive, and ulcerative skin lesions have all been reported.[11-14] EHE might masquerade as verruca vulgaris, an occipital artery aneurysm, or pyogenic granuloma.[15-17] Approximately 30% of EHE metastasizes to regional nodes, lung, liver, or bone.[3,4]

The patient described in this case report is unique despite the fact that we describe EHE occurring in a female with a typical age of onset. Yet, our patient presented with an isolated skin lesion, which is very rare, in an atypical location. Although there have been reports of EHE occurring in the head-and-neck area, they are still limited in number.[8-10] The first report of a patient with a solitary cutaneous EHE was in 1993 by Resnik *et al*.[18] Over a period of more than a decade, a minority of cases with isolated skin involvement have been reported.[19] Nevertheless, a solitary EHE arising in the skin is seen in exceptional cases. In a review of the literature, only two cases have been reported with EHE occurring in the nasal cavity, but none have ever described cutaneous involvement of the nose.[20,21] We report the first patient who presented with a solitary and purely cutaneous involvement of the nose.

EHE is characterized by an infiltrative growth pattern of epithelioid and histiocytoid tumor cells that form poorly canalized cords or small nest embedded within a myxohyaline stroma. The tumor cells have an eosinophilic cytoplasm containing vacuoles, hence the name "blister cells." The vacuoles represent a primitive lumen formation, which may contain red blood cells. Nuclear features vary from low to marked nuclear pleomorphism. The latter is seen in one-quarter of cases. EHE with hyperchromasia, nuclear pleomorphism, and increased mitotic activity may be quite challenging to separate from angiosarcoma.[3,4] Approximately 50% of EHEs are associated with a preexisting vessel. Histologically, EHE can be seen growing within or around the affected vessel, and tumor cells radiate out from the associated vessel. EHE stains were positive to at least one of the vascular makers, e.g., CD31, CD34, FLI-1, or ETS-related gene (Erythroblast Transformation-Specific). About 25% of EHEs are immunoreactive for cytokeratin but typically negative for epithelial membrane antigen.[1,4]

Cytogenetic studies reveal a chromosomal translocation (1;3) involving WWTR1 and CAMTA1 that are characteristic of EHE. WWTR1, which is located on chromosome 3 and normally highly expressed in endothelial cells, is a transcriptional coactivator involved in the Hippo pathway. CAMTA1, on chromosome 1, is a member of the calmodulin-binding transcription activator family that is normally found only in the brain. How this WWTR1/CAMTA1 fusion gene relates to the pathogenesis of EHE is not known yet. The WWTR1/CAMTA1 fusion gene is found in most cases with the classic morphology. A small group of cases lack WWTR1/CAMTA1 fusion gene and have YAP1-TFE3 fusion instead. Recently, YAP1–TFE3 fusion gene was identified in a small subset of EHE who were lacking the WWTR1–CAMTA1 fusion gene. The YAP1 transcriptional regulator which acts as a coactivator as well as a corepressor in the Hippo pathway shows homology to WWTR1. The tumors with YAP1TFE3 fusion gene tend to have more abundant eosinophilic cytoplasm, relatively more well-formed vessels, and mild-to-moderate cytologic atypia, compared with the more common EHE variant.[3-5,22]

Accurate diagnosis of vascular tumors can often be quite challenging and yet critical for determination of appropriate clinical management. The differential diagnosis of EHE includes epithelioid angiosarcoma, epithelioid sarcoma-like hemangioendothelioma, and epithelioid sarcoma.

Angiosarcomas display a wide spectrum of histological appearances, ranging from areas of well-developed, anastomosing vessels lined by epithelioid endothelial cells to solid sheets of atypical endothelial cells without clear vasoformation. Tumor cells have prominent nuclear atypia and abundant amphophilic to grayish to lightly eosinophilic cytoplasm with intracytoplasmic vacuoles. Apoptotic cells, tumor necrosis, and extensive hemorrhage are commonly present. When epithelioid cells predominate, angiosarcomas are classified as "epithelioid angiosarcomas." Angiosarcomas have immunoreactivity for typical vascular markers including CD31, CD34, and ERG and occasionally podoplanin which is a lymphatic marker. Angiosarcomas co-express cytokeratin, neuroendocrine markers, and CD30.[3-5]

Epithelioid sarcoma-like hemangioendothelioma is composed of solid sheets and nodules of epithelioid to spindled endothelial cells with dense eosinophilic cytoplasm. Well-formed vessels are not seen, and only in rare occasions, intracytoplasmic lumens may be evident. Immunophenotyping is consistently positive for keratin, Fli-1, and ERG. They are frequently positive for CD31 and consistently negative for CD34. Epithelioid sarcoma-like hemangioendothelioma retains the nuclear expression of SMARCB1 (INI-1). It also has a different cytogenetic abnormality, a balanced t (7;19) (q22;q13) resulting in a SERPINE1-FOSB fusion.[4,5]

Epithelioid sarcoma typically has a nodular growth pattern of epithelioid cells, often with central necrosis. Epithelioid sarcoma, in addition to strong keratin expression, is positive for CD34 in approximately 50% of cases. Epithelioid sarcoma may be positive for ERG as well. However, it is negative for CD31, lacks myxohyaline stroma, and lacks vacuolated tumor cells. Epithelioid sarcoma shows loss of SMARCB1 (INI-1).[4]

Regarding our patient, the tumor cells have an epithelioid morphology, co-expressing keratin and endothelial markers with the tendency to form vascular channels. Epithelioid sarcoma was excluded based on the tendency of the tumor to form vascular channels. The low cytogenic atypia, low mitotic rate, and absence of necrosis and extensive hemorrhage were helpful to rule out angiosarcoma. Epithelioid sarcoma-like hemangioendothelioma was crossed out from the differential diagnosis because tumor cells were reactive to CD34. The histological analysis of our patient was clear and straight

forward, but this is not the case in all epithelioid vascular tumors. In such difficult instances, the identification of nuclear expression of CAMRA1 can aid in the diagnosis.

Deyrup *et al.* proposed that epithelioid hemangioendothelioma can be stratified into high-risk group and low-risk group based on mitotic activity (>3 mitotic figures/50 high-power fields) and tumor size (>3 cm). The two risk groups had markedly different clinical courses.[23] In general, superficial cutaneous EHE has a better prognosis than deep soft tissue and visceral EHE. EHE is best treated by complete surgical excision with adequate margins.[5] A single report described a complete clearance of EHE with topical application of imiquimod. However, this study is limited to one patient.[24]

In conclusion, EHE is a rare vascular malignant tumor that is usually associated with deeply seated tumors. However, pure cutaneous involvement can occur. Vigilance is needed when diagnosing such patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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