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Case Report

Epithelioid hemangioendothelioma with actin+/cytokeratin+myoblast-like cells: Report of a case

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ABSTRACT

An unusual case of epithelioid hemangioendothelioma (EHE) with immunohistochemical positivity for cytokeratin (CK), alpha-smooth muscle actin, and calponin (CALP) is presented. The lesion occurred in a 43-year-old man in the right frontal region, with clinical suspicion for an epidermoid cyst. It was excised completely. Grossly, an 8 mm nodule was well circumscribed, soft, and it had gray cut surface. Histologically, typical features of EHE were seen, such angiocentric localization, epithelioid cytomorphology with mild atypia, myxohyaline stromal matrix, a few slit-like vascular channels, and isolated vacuolated cells. In addition, the stroma contained numerous spindle cells resembling myoblasts or myofibroblasts. They showed, besides scattered positivity for vascular markers, focal positivity for CALP and diffuse strong expression of alpha-smooth muscle actin and pancytokeratin AE1/AE3. This observation of numerous actin+/CK+cells is unusual. The lesion resembled other CK-positive vascular tumors and actin-positive myofibroblastic lesions, all of which has to be considered in differential diagnosis.

KEY WORDS: Cytokeratin, epithelioid hemangioendothelioma, epithelioid hemangioma, epithelioid sarcoma-like/pseudomyogenic hemangioendothelioma, smooth muscle actin

INTRODUCTION

Epithelioid hemangioendothelioma (EHE) is rare lesion which occurs in adults, most often in soft tissues, liver, bones, and lung [1-4]. The tumor is regarded as "borderline" or low-grade malignant, with propensity for local recurrence and with low risk of metastasis [1-4]. EHE shows epithelioid cytomorphology and frequent immunohistochemical positivity for cytokeratin (CK), and therefore, it can be confused with carcinoma. Expression of smooth muscle actin in EHE was described in only several cases [2,5]. Here, we present a case of EHE which contained, in addition to epithelioid endothelium, an unusual population of myoblast-like cells with strong co-expression of smooth muscle actin and pancytokeratin.

MATERIALS AND METHODS

The tissue was fixed in 4% formalin and processed routinely. All of the tumor tissue was paraffin-embedded. The sections were stained with hematoxylin and eosin. Immunohistochemical studies were performed on formalin-fixed, paraffin-embedded sections using the following antibodies: CD31 (JC70A), CD34 (Qbend 10), D2-40 (D2-40), alpha-smooth muscle actin (1A4), desmin (D33), calponin (CALP), pancytokeratin (AE1/AE3), CK5/6 (D5/16B4), CK high molecular weight (34betaE12), epithelial membrane antigen (EMA) (E29, Dako), glial fibrillary acidic protein (GFAP) (polyclonal), cyclin D1 (EP16) (all from Dako), Fli-1 (MRQ-1, Cell Marque), and S-100 protein (15E2E2, Biogenex). Immunostaining was performed according to standard protocols using streptavidin-biotin complex labeled with peroxidase (Dako). The positive and negative controls were applied.

CASE REPORT

In 43-year-old and otherwise healthy man, a small lesion growing slowly for several months in the right frontal region was excised completely. It resembles clinically an epidermoid cyst. Grossly, an 8 mm dermal/subcutaneous nodule was well circumscribed and non-encapsulated, soft, with pale gray cut surface. Histologically, it showed circumscribed sharp margin [Figure 1a] and contained slit-like vascular channels with epithelioid endothelium [Figure 1b and c]. Among these vessels, many spindle to epithelioid cells with abundant cytoplasm were seen [Figure 1d and e]. The spindle cells resembled myoblasts or myofibroblasts. Some of the epithelioid cells contained intracytoplasmic vacuole. The stroma was myxoid to myxohyaline, with foci of extravasated red cells and fibrin. The nuclei showed mild nuclear atypia. Small nucleoli were often seen in both endothelium of the vessels and stromal cells. Mitotic activity was 1/20 high power field, and atypical mitotic figures were not found.

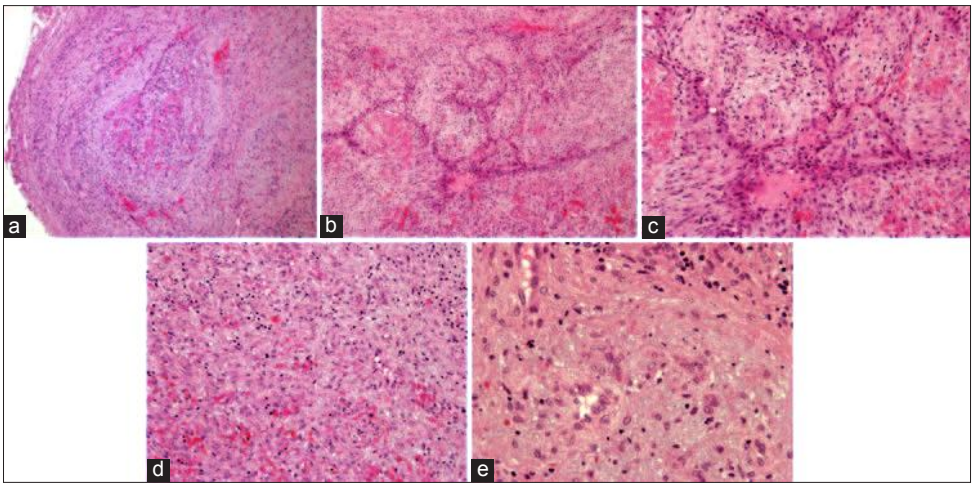

Figure 1: Histological features. (a) Low power shows well-circumscribed lesion with eosinophilic tumor cells, abundant myxoid matrix, slit-like vessels, extravasated fibrin, and scattered mononuclear inflammatory cells. (b and c) An area with slit-like vascular channels. The stromal cells are either epithelioid or spindle myoblast-like (below left). (d) Spindle cell proliferation with extravasated erythrocytes, resembling that of nodular fasciitis. (e) Epithelioid cells in myxohyaline matrix (HE, original magnifications ×100, ×200, and ×400 in c-e, respectively)

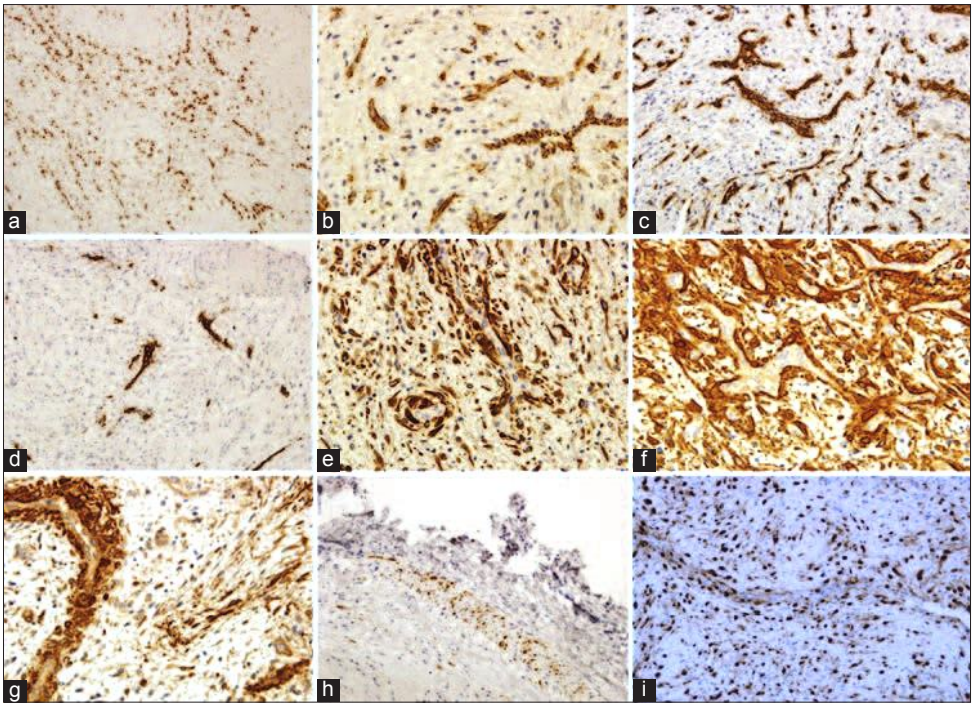

Figure 2: Immunohistochemical findings. (a) Fli-1 positivity in vascular channels and in cells of the stroma. (b) CD31 positivity. (c) CD34 positivity. (d) D2-40 is expressed by vascular channels and rare stromal cells. (e) Cytokeratin AE1/AE3 positivity is strong in the cells of the stroma, whereas epithelioid endothelium of primitive-appearing vascular channels is negative. (f) Alpha-smooth muscle actin positivity is similar to that of cytokeratin. (g) Calponin is expressed by many cells of the stroma. (h) Desmin positivity highlights a remnant of muscular vessel wall. (i) Cyclin D1 positivity predominate in the stroma. (original magnifications ×100 in a, d and h, ×200 in c and i, ×400 in b, e-g, respectively)

Immunohistochemically [Figure 2], endothelial cells of vascular channels and scattered cells in the myxoid stroma were positive for endothelial cell markers Fli-1, CD31, CD34, and D2-40 [Figure 2a-d]. In addition, approximately 80% of the cells in the stroma among vascular channels were positive strongly for pancytokeratin AE1/AE3 [Figure 2e] and alpha-smooth muscle actin [Figure 2f]. One-third of these cells expressed CALP [Figure 2g]. Desmin was negative in the tumor cells, and it revealed a remnant of muscular vessel wall in the margin of the lesion [Figure 2h]. Cyclin D1 stained some epithelioid cell of vascular channels and many cells of the stroma [Figure 2i]. Following antibodies gave negative results: CK 5/6, cytokeratin 34betaE12, p63, EMA, GFAP, and S100 protein.

We diagnosed the lesion as EHE with very low risk of recurrence, and we recommended follow-up. The patient is without a recurrence 7 months after the excision.

DISCUSSION

The present tumor shows typical features of EHE, such as angiocentric growth, epithelioid cytomorphology, primitive vascular channels and isolated cells with vacuoles, myxoid intercellular matrix, immunohistochemical positivity for endothelial markers and CK [1-5]. However, we have seen also some unusual features. In the myxoid matrix among primitive vascular channels, numerous spindle cells were seen. Cytomorphology of these cells resembles that of nodular fasciitis cells [6] or myoblastic cells [7]. It shows abundant eosinophilic cytoplasm and nucleus with well-visible nucleolus. However, although these cells appeared like myofibroblasts or myoblasts, they were positive not only for actin but also expressed in addition CK, and some of them were positive for endothelial cell markers. Histogenesis of this cell population is difficult to explain. They could represent a phenotype of immature vascular cell having both endothelial and myoid features, with aberrant CK expression. Recently, myoblast-like endothelial cells were reported as a major component of so-called pseudomyogenic hemangioendothelioma [7], a tumor that is probably identical to previously described epithelioid sarcoma-like hemangioendothelioma [8,9]. Hornick and Fletcher found that myoblast-like cells in pseudomyogenic hemangioendothelioma were positive for both CK and actin, although actin expression was usually only focal [7]. We suggest that in our case, the CK-positive myoblast-like cells show differentiation similar to that seen in pseudomyogenic HE. In addition, CK+/actin+cells described rarely in EHE [2,5] could represent the same phenomenon.

Differential diagnosis in our case included various vascular and myofibroblastic lesions with epithelioid and/or myoid morphology, such as epithelioid hemangioma (EH), cutaneous epithelioid angiomatous nodule (CEAN), epithelioid sarcoma-like/pseudomyogenic hemangioendothelioma, epithelioid angiosarcoma, and nodular fasciitis. EH [10] shows striking resemblance to our case, and it was necessary to exclude it first of all. Like the presented tumor, EH occurs in the head and neck region in mid-aged patients [3], it is typically well circumscribed, and it is often associated with a vessel wall [3,11]. In addition, EH shows epithelioid cytomorphology, contains actin+ cells, and rare cases of EH express CK [11]. However, our case lacked prominent infiltration with mononuclear inflammatory cells and eosinophils, and vascular differentiation appeared to be more primitive, i.e., with non-luminized endothelial cell groups and with isolated cells, of which some showed intracytoplasmic vacuole. The vessels in EH are well differentiated, and the stroma of EH is collagenous and distinct from myxoid to hyaline stroma of EHE. Expression of CK was strong and diffuse in our case, whereas CK-positivity in EH is at most focal [11]. CEAN [12] is predominantly solid-appearing proliferation of epithelioid endothelial cells. This lesion overlaps with EH, and some authors regard it as a variant of EH [12-14]. In CEAN, actin-positivity is limited to pericyte cell layer [12,13], and CK expression was not observed in this lesion (although number of reported cases is still low). Myxoid stroma and primitive-appearing vasoformation typical of EHE is not present in CEAN. Pseudomyogenic/epithelioid sarcoma-like hemangioendothelioma is an infiltrative tumor, in contrast to our well-circumscribed lesion. It contains CK+myoblast-like cells which resemble those observed in our case, but it lacks vascular channels and cell groups composed of epithelioid endothelium. Actin positivity observed in this tumor was never prominent [7]. Epithelioid angiosarcoma [15,16] is, in contrast with our case, an infiltrative neoplasm with high nuclear atypia and mitotic activity. Expression of actin was described in some cases, but it was only focal [15] or it was limited to the pericytes of more differentiated vascular channels [16]. Myofibroblastic lesions such as nodular fasciitis (including its intravascular form) lack features of vasoformation both morphologically and immunohistochemically [6,17].

CONCLUSION

We described an unusual case of EHE which contained numerous cells resembling myoblasts or myofibroblasts. These tumor cells co-expressed actin, CALP, and CK. Pathologists should be aware of the possible occurrence of such unusual immunophenotype in EHE.

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