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Abstract

The epithelioid cell histiocytoma (ECH) is a polypoidal benign tumor of superficial connective tissue that is often diagnosed as a pyogenic granuloma. ECHs are speculated to originate from dermal

dendritic subunits and are composed of 2 primary cell populations, ie, CD34^{+} primitive fibroblastic dendrocytes and factor XIIIa^{+} histiocytes. Although dendritic subunits are distributed throughout most collagenous tissues inclusive of oral mucosa, to date, all reported cases of ECH have been cutaneous lesions. ECHs' putative pathogenesis entails activation of CD34^{+} "sentinel" reserve dendrocytes, followed by an influx of histiocytes and mast cells. Juxtacrine communication increases release of wound healing factors; suggesting a reactive etiologic component. In this current case, the location (ventral tongue) and history (recent increase in size) suggest the possibility that trauma could have initiated the dendritic subunit "wound healing" cascade. Consistent with its benign course, the ECH is managed by local excision, and has an excellent prognosis.

The epithelioid cell histiocytoma was first described in 1989.[1] It is a benign, exophytic connective tissue neoplasm with a vascular appearance giving it the silhouette of a pyogenic granuloma. Several papers have characterized its clinical and histopathological features.[1, 2, 3, 4, 5, 6, 7, 8, 9, 10] To date, however, all reported lesions presented as cutaneous tumors (Table I). We describe, for the first time, a case of an epithelioid cell histiocytoma (ECH) arising on the mucous membrane of the ventral surface of the tongue.

Table I. Demographic and clinical features of reported epithelioid cell histiocytomas

Reference	No. of cases	Male/Female	Age range, y	Site (skin)	Size, cm	Duration	Clinical diagnosis
Jones et al, 1989[1]	19	8/11	24-63	Lower limb: 14	0.5-1.5	Months-years	Pyogenic granuloma: 8
							Fibrous histiocytoma: 6
							Melanotic lesion: 3
							Glomus tumor: 1
							Basal cell carcinoma: 1
							Papilloma: 1
							Eccrine poroma: 1
Mehregan et al, 1992[6]	8	6/2	19-76	Lower limb: 5	0.7-1.5	6 mo-2 y	Intradermal nevus: 5
				Back: 1			Fibroma: 3
				Upper limb: 1			
				Nasolabial fold: 1			
Estrada et al, 1992[11]	2	0/2	12-46	Lower limb: 1	NA	NA	Angiofibroma: 1
				Upper limb: 1	NA	NA	Dermatofibroma: 1
Glusac et al, 1994[9]	10	8/2	19-72	Lower limb: 9	06.-1.7	3 mo-1 y (in known cases)	Melanotic lesion: 3
				Upper limb: 1			Uncertain: 3
							Pyogenic granuloma: 2
							Adnexal tumor: 2
							Angioma: 2
							Fibroma: 1
							Basal cell carcinoma: 1
							Dermatofibroma: 1
Gomez et al, 1994[3]	20	12/8	7-80, NA 1 case	Lower limb: 6	0.5-2.0	5 mo-18 y (10 cases)	NA: 11
							Cyst: 2
				Upper limb: 8			Lipoma: 2
				Abdomen: 2			Pyogenic granuloma: 1

				Eyelid and canthus: 2			Fibroma: 1
							Nevus: 1
				Anus margin: 1			Hemangioma: 1
				NA: 1			Keratoacanthoma: 1
Dezfoulian et al, 1995[4]	2	2/0	38-46	Lower limb: 1	0.8, NA	3 mo, NA	NA, NA
				Neck: 1			
Wilk et al, 1996[12]	7	4/3	28-56	Lower limb: 5	0.6-1.1	NA	NA
				Upper limb: 2			
Manente et al, 1997[8]	1	1/0	13	Groin: 1	0.6	3 mo	Epithelioid histiocytoma
Zelger et al, 1997[10]	1	0/1	34	Upper limb: 1	0.7	< 9 mo	NA
Glusac and McNiff, 1999[7]	15	10/5	23-65	Lower limb: 8	0.3-1.4	1 mo-15 y (9 cases)	Melanotic lesion: 5
				Upper limb: 4		NA: 4	Squamous carcinoma: 3
				Face: 2		Several years: 2	Basal cell carcinoma: 2
				Abdomen: 1			Dermatofibroma: 2
							Uncertain: 2
							Fibroma: 1
							Pyogenic granuloma: 1
							Keratoacanthoma: 1
							Seborrheic keratosis: 1
Cook and Theaker, 2001[5]	1	1/0	34	Neck: 1	NA	NA	NA
Stewart et al, 2003[13]	1	1/0	66	Lower limb: 1	1.5	Many years	NA
Our case	1	0/1	84	Ventral tongue: 1	1.0	NA	Pyogenic granuloma: 1
TOTAL	88	53/35 (1.5:1)	Average: 45.5	Lower limb: 50	0.3-2.0		
				Upper limb: 18			

				Abdomen: 3			
				Neck: 2			
				Back: 1			
				Groin: 1			

NA, Not available.

Clinical presentation

An 84-year-old white woman presented with a nodule on the left ventral surface of her tongue of unknown duration that appeared to suddenly increase in size over the previous month. The 1.0 × 0.7 cm asymptomatic lesion was exophytic and polypoidal with a granular surface that was red to focally white in color. The lesion was firm and nontender on palpation. The clinical impression was of a pyogenic granuloma. A simple uneventful excisional biopsy was conducted and the tissue specimen was submitted in 10% neutral buffered formalin for routine processing and histopathological examination.

Microscopic and immunohistochemical features

Hematoxylin and eosin–stained sections demonstrated the exophytic nature of the tumor. Lesional tissue was enclosed by collarettes of surface epithelium that were contiguous with a focally ulcerated surface epithelium (Fig 1). Granulation tissue covered lesional cells in areas of ulceration. In other areas, the lesional cells were distributed in the papillary lamina propria (Fig 2). The lesional cell distribution appeared homogeneous and did not extend into the deeper connective tissues. The lesional cells displayed both an epithelioid and a spindled morphology. Mast cells were frequently observed in close proximity to the epithelioid cells. Lush vascularity as well as scattered, normal-appearing mitotic figures were apparent (Fig 3). As the overall features suggested a well-vascularized benign epithelioid neoplasm, diagnostic considerations included a lobular capillary hemangioma, epithelioid spitz nevus, and a benign histiocytic neoplasm.
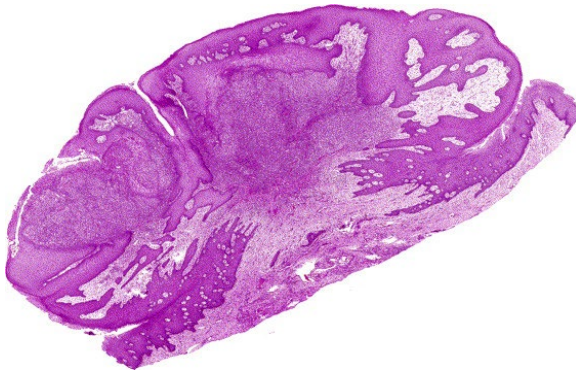

Fig 1. The lesion projects above the surrounding mucosa. Collarettes of epithelium enclose lesional cells (hematoxylin and eosin [H&E], ×10 image scale).
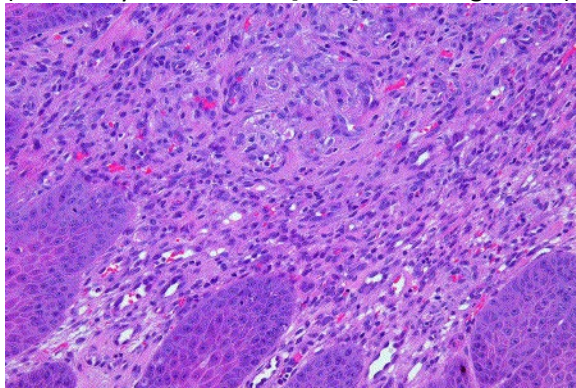

Fig 2. Epithelioid and spindle-shaped lesional cells closely approximate the surface epithelium (H&E, ×250 image scale).
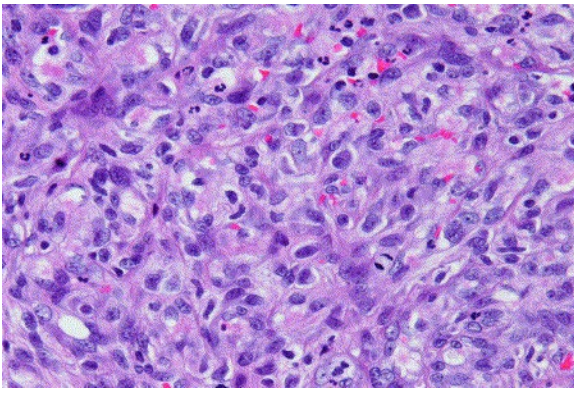
Fig 3. The lesional tissue composed of epithelioid to spindle-shaped cells with vesicular nuclei and small nucleoli. Scattered inflammatory cells and normal appearing mitotic figures are also seen (H&E, ×400 image scale).

A battery of immunohistochemical stains were then conducted to provide a definitive diagnosis (Table II). Standard positive (known positive tissue) and negative (positive tissue without antibody) controls were conducted with each immunohistochemical stain. The immunohistochemical staining profile of this case is shown in Table III. Despite the epithelioid appearance of many of the lesional cells, only the surface epithelium demonstrated cytokeratin positivity. While CD31 and CD34 staining was prominent, positivity was primarily demonstrated by endothelial cells associated with the extensive vascularity (Fig 4). Occasional mild to moderate CD34 positivity was observed in dermal dendritic cells. Alpha smooth muscle actin as well as muscle-specific actin (HHF 35) highlighted the myopericytes surrounding the tumor vasculature (Fig 5). Scant S100 positivity was noted within intraepithelial Langerhans cells as well as scattered connective tissue dendritic cells (Fig 6). While the cytoplasm of the epithelioid histiocytes stained weak to moderately with factor XIIIa, strong nuclear and cytoplasmic reactivity to factor XIIIa was demonstrated within the S-100 negative dendritic histiocytes (Fig 7). CD117 positive mast cells were noted in areas that strongly expressed factor XIIIa positive dendrocytes (Fig 8). Focal CD68 positivity, consistent with infiltrating macrophages, was noted within the specimen. Stronger CD68 reactivity was apparent at sites with a more extensive inflammatory infiltrate, ie, areas underlying ulceration. Collectively, the light microscopic features, including abundant neovascularization in a background of epithelioid and spindled cells in conjunction with the immunohistochemical staining profile, were consistent with a diagnosis of an epithelioid cell histiocytoma, a lesion hitherto undescribed in the oral cavity.

Table II. Immunohistochemical antibodies, retrieval techniques, dilutions, and antibody source

Antibody	Antigen retrieval (Target retrieval solution, DAKO)	Dilution	Source/clone
Cytokeratin	Yes	1:100	DAKO/AE1/AE3
CD31	Yes	1:80	DAKO/JC70A
CD34	Yes	1:500	IMMUNOTECH/QBEND10
Actin, α-smooth muscle	No	1:500	DAKO/1A4
Actin, muscle	Yes	1:250	DAKO/HHF35
S100	Yes	1:4000	DAKO/POLYCLONAL

Factor XIIIa	Yes		1:60	CELL MARQUE/POLYCLONAL
CD68	Yes		1:3000	DAKO/KP1
CD117	Yes		1:300	DAKO/POLYCLONAL

Table III. Immunohistochemical results of current case

| Antibody	Result
CKC	Surface epithelium stained strongly. All other tissue stained negative.
CD31	Intense staining of vascular endothelium.
CD34	Positive staining of vascular endothelium.
Actin, α-smooth muscle	Highlighted perivascular myopericytes.
Actin, muscle (HHF35)	Highlighted perivascular myopericytes.
S100	Less than 10% of cells in tumor stained positive. Dendritic morphology. Also stained similarly dendritic cells within epithelium suggesting a Langerhanian origin.
Factor XIIIa	Weak to moderate staining by epithelioid histiocytic cells. Strong nuclear and cytoplasmic staining by dendritic histiocytes. Weak blush by matrix collagen and intravascular fibrin.
CD68	Strong expression by macrophages in areas underlying ulceration and in connective tissue septa.
CD117	Strongly expressed by mast cells.
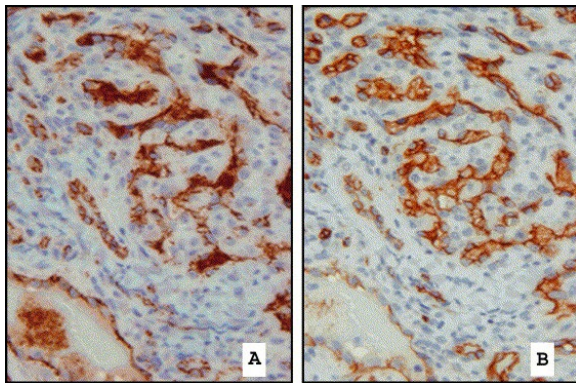
Fig 4. **A,** CD31 and **B,** CD34 mark the endothelium of the numerous vascular channels within the tumor (×100 image scale).
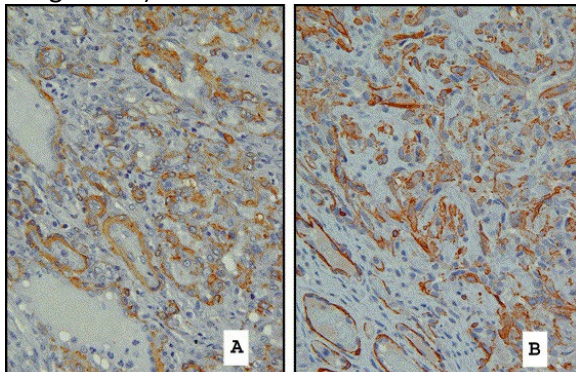
Fig 5. Vascular myopericytes express α-smooth muscle actin **(A)** and muscle specific actin (HHF 35) **(B)** (×200 image scale).
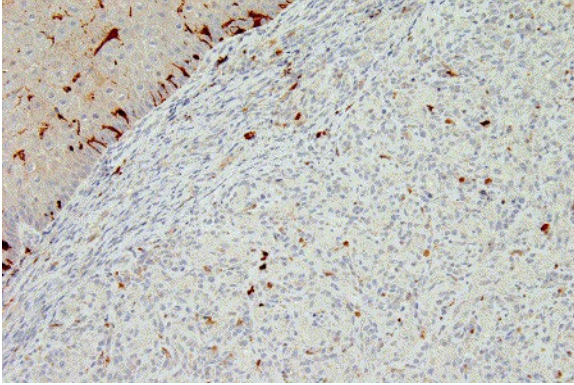

Fig 6. Intraepithelial Langerhans cells and stromal dendritic cells strongly express S100 protein reactivity. The S100 reactive cells comprised less than 10% of the lesional cells (×100 image scale).
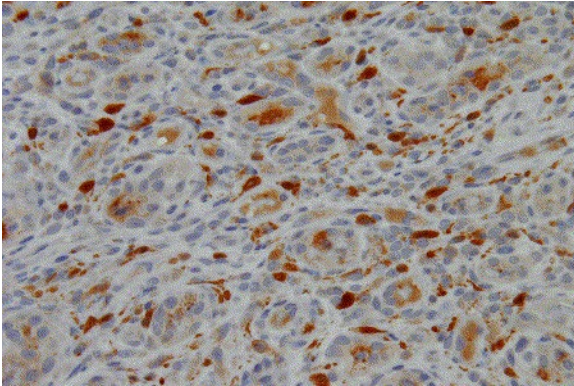

Fig 7. Epithelioid histiocytes express weak to moderate cytoplasmic reactivity to factor XIIIa while strong nuclear and cytoplasmic expression by stromal non-Langerhanian dendrocytes is noted (×200 image scale).

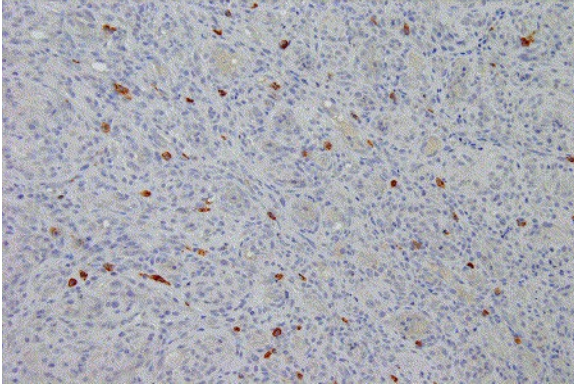Fig 8. CD 117[+] mast cell population among the lesional tissue (×100 image scale).

Management

The lesion was managed by surgical scalpel excision, and healing of the sutured wound was uneventful. The patient is currently free of residual or recurrent disease.

Discussion

In 1989, Jones et al[1] extended our understanding of fibrohistiocytic lesions by describing the epithelioid cell histiocytoma, a neoplasm with a unique admixture of cells speculated to be derived from the dermal microvascular unit.[2] Although dermal dendritic subunits are distributed throughout

most collagenous tissues including the oral cavity,[2, 14] to date there have been no reports of ECHs in the oral cavity. Notably, the clinical presentation, light microscopic features, and immunohistochemical staining profile of this current ventral tongue tumor compare favorably with the features previously reported in cutaneous ECHs.[1, 2, 3, 4, 5, 6, 7]

Dermal dendritic subunits, which contain CD34+ fibroblasts and FXIIIa+ histiocytes serve as key players in tissue remodeling and wound healing.[2] The putative histogenesis of the ECH entails activation of a subset of "sentinel" resident dermal (or submucosal) CD34+ primitive dendrocytes, which subsequently act to recruit FXIIIa histiocytic dendrocytes and mast cells. Notably, the ECH lesional histiocytes manifest a stromal assembly (FXIIIa) phenotype in contrast to a phagocytic (CD68+) phenotype. While not categorized as lesional cells per se, mast cells contribute to ECH progression by release of potent proangiogenic cytokines and tumor necrosis factor α, which subsequently increases expression of transglutaminase XIIIa by dermal dendritic histiocytes.[2] The end result is the juxtracrine mediated activation of 2 dermal dendritic cell populations, ie, fibroblastic and histiocytic cells in conjunction with abundant neovascularization. It has been suggested that CD34 expression by interstitial fibroblasts is lost as they differentiate towards procollagen forming fibroblasts.[2] The absence of CD34 expression by lesional cells with a distribution proximate to the collagenous stroma suggests a similar transition in this case.

The ECH presents as a solitary, exophytic, connective tissue nodule that ranges in size from 0.3-2.0 cm, and varies in duration from 1 month[7] to 18 years.[3] Sites primarily affected are the skin over the lower limbs followed by the upper extremities.[1, 3, 6, 7, 9] Other cutaneous regions have included the neck[4, 5]; back[6]; anus, eyelid, and canthus[3]; face[6, 7]; and abdomen.[3, 7] The tumor has been diagnosed in almost all decades of life (Table I) with the youngest patient being 7 years old[3] and the oldest being 84 years old (our case), which would average the age at 45.5 years. Although in their initial report of 19 cases, Jones et al[1] described a slight female predilection, an overall male-to-female ratio of 1.5:1 is noted (Table I).

Clinically, the epithelioid cell histiocytoma has a symmetrical outline and may be red, blue, or black in color, depending on the degree of vascularity, extravasation of red cells, and formation of hemosiderin pigment. Therefore, it may resemble a pyogenic granuloma or a nodular nevomelanocytic proliferation. Upon microscopic examination, the epithelioid histiocytes and vague fascicles of spindle cells are suggestive of other lesions including benign fibrous histiocytoma, epithelioid spitz nevus, atypical xanthogranuloma, juvenile xanthogranuloma, reticulohistiocytoma, and epithelioid hemangioma.[1, 4, 6, 9]

In contrast to melanocytic lesions, the ECH lacks junctional melanocytic hyperplasia, nesting of nevocytes in theques, and downward maturation of epithelioid cells.[3, 4, 13] Less than 10% S100 positive cells are present in the ECH and their distribution is scattered to patchy.[1, 4, 6, 7, 13, 15] Care should be used in interpreting these S100 positive cells as they represent stromal dendritic cells rather than nevomelanocytic cells. The nevocytes in melanocytic nevi are completely negative for factor XIIIa as well as CD68.[7, 15] As compared to the epithelioid cell histiocytoma, the epithelioid spitz nevi are less well circumscribed with the epithelioid cells being separated by thick bundles of collagen.[7, 9]

Histopathologically, the pyogenic granuloma (lobular capillary hemangioma) may display a collarette of epithelium surrounding lobules of angiomatous tissue. However, the CD31+/CD34+ capillaries[16, 17] with

prominent protuberant endothelial cell nuclei in each angiomatous lobule appear to branch and arborize from a central feeder vessel.[7] The pyogenic granuloma, however, lacks the epithelioid cells and factor XIIIa-positive dendrocytes are scarce.[14, 18] In addition, inflammation is a much more prominent feature in pyogenic granuloma.

The ECH is considered by some to be a variant of the benign fibrous histiocytoma (BFH).[1, 2, 3, 6, 7] However, the BFH arises in a deeper location and is poorly circumscribed. It also demonstrates a storiform pattern of arrangement of cells with thicker bundles of collagen. Lipid-laden and hemosiderin-laden macrophages, giant cells, and inflammatory cells may also be seen in the BFH. In contrast, the ECH contains a prominent epithelioid cell component admixed with numerous vascular channels. Furthermore, due to its deeper origin, the BFH rarely demonstrates a polypoidal clinical appearance.[9, 13] While the BFH is categorized as a reactive fibrohistiocytic lesion, the ECH is considered a benign dermal dendrocytic tumor. Due to its distinguishing microscopic features and probable different histogenesis, it appears prudent to classify the ECH as a unique entity.

The reticulohistiocytoma differs from the epithelioid cell histiocytoma by demonstrating the presence of inflammatory cells including eosinophils with variation in the morphology of the histiocytes and multinucleate giant cells.[1] The giant cells may be as large as 100 μm with a periodic acid Schiff stain positive (PAS+) glassy eosinophilic cytoplasm. The nucleus is eccentrically located like a ganglion cell. A prominent lymphocytic and conventional histiocytic (CD68+) infiltrate may also be seen.[3, 7, 9, 13]

The atypical fibroxanthomas have polypoidal architecture like the epithelioid cell histiocytoma. Atypical fibroxanthomas, however, also demonstrate cellular pleomorphism, bizarre nuclear morphology, and presence of numerous mitotic figures; features which are not observed in the ECH.[1, 4, 7, 9]

Juvenile xanthogranulomas are characterized by the presence of a prominent foam cell compartment, Touton type, and other giant cells in addition to inflammatory cells and eosinophils.[9] Like the epithelioid cell histiocytoma, histiocytes within the juvenile xanthogranuloma may be positive for factor XIIIa. In the event of FXIIIa positivity, concurrent expression of the macrophage antibody HAM-56 by the juvenile xanthogranuloma cells facilitates diagnosis. Notably, HAM-56 is only expressed in 2% to 5% of cells of the epithelioid cell histiocytoma.[7, 9]

The epithelioid hemangioma is another diagnostic consideration that must be differentiated from the ECH.[9] The epithelioid hemangioma also known as angiolymphoid hyperplasia with eosinophilia or histiocytoid hemangioma typically shows a circumscribed symmetrical growth around a muscular artery. The growth is characterized by a prominent proliferation of small, capillary-sized vessels lined by plump, epithelioid endothelial cells. Lumen formation may be lacking. A moderate to severe infiltration of lymphocytes and eosinophils accompanies this vascular proliferation.[9, 10]

The ECH is a unique but lesser-known vasoformative proliferation of epithelioid and dendritic histiocytes. Diagnosis should be based on both clinical and microscopic features. Clinically, the lesion is exophytic, pigmented, polypoidal, and may have a history of recent growth. Microscopically, the ECH contains 3 primary cell populations, ie, epithelioid histiocytes, dermal dendrocytes, and mast cells, which are contained in a richly vascularized connective tissue. In many respects, the ECH resembles a variety of other reactive and neoplastic lesions from which it must be distinguished. Differential

diagnostic considerations for the ECH include the pyogenic granuloma, benign fibrous histiocytoma, atypical and juvenile xanthogranulomas, nevomelanocytic lesions, and epithelioid hemangiomas. As discussed previously, although the ECH is classified as a neoplasm, many lesional features, such as the dermal dendritic subunit activation, imply a reactive process. Accordingly, conservative local excision is curative, and the prognosis is excellent.

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