Case Report

Hemangioendothelioma of palate: A case report with review of literature

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Abstract

Hemangioendothelioma commonly occurs in the superficial or deep soft tissue of the extremities, lungs, liver, bone and lymph nodes, with oral cavity being a rare location. It is usually benign but can show variable grades of malignancy. According to the histological presentation, hemangioendothelioma has been classified as epithelioid, Kaposiform, hobnail (Dabska-Retiform), epithelioid sarcoma like and composite. We present a case of ulcerated swelling of palate clinically diagnosed as pyogenic granuloma which presented a diagnostically challenging histological picture. We discuss the differential diagnoses obtained from various oral pathologists and general pathologists and substantiate the diagnosis of hemangioendothelioma based on its clinical behavior, histological features and immunohistochemical findings. In addition, we attempt to highlight the diagnostic dilemma that such cases can pose to the attending pathologists.

Keywords: Hemangioendothelioma, oral cavity, palate, vascular tumors

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INTRODUCTION

Hemangioendothelioma is a vascular tumor of intermediate grade between hemangioma and angiosarcoma, characterized by proliferating neoplastic endothelial cells. The tumor cells may form small intracellular lumen, which may be seen as clear spaces, or vacuoles, that distort (or blister) the cell. Lesions that arise from vessels may expand the vessel, usually preserving its architecture and extend centrifugally from the lumen to the soft tissue. Hemangioendothelioma has good prognosis and is treated surgically and/or by chemotherapy/radiation. Hemangioendothelioma is capable of local recurrence and metastasis albeit at a lower rate as compared to malignant neoplasm. Clinically, it can mimic reactive lesions such as pyogenic granuloma, chronic periodontal disease and peripheral giant cell granuloma. The patients usually present with an ulcerated soft-tissue mass that may resemble friable granulation tissue.[1] The submandibular region, gingiva and alveolar mucosa are the most common intraoral sites with hard palate being an uncommon one.[2] Only <12 cases of hemangioendothelioma affecting the palate have been reported, as per Google and PubMed search.

CASE HISTORY

A 46-year-old male patient presented with a soft ulcerated swelling in the posterior aspect of left side hard palate, of approximate size 2 cm × 2 cm × 2 cm of 1 month duration. The patient noted a slight increase in size of the lesion. There were two incidents of spontaneous bleeding from

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the swelling, during this period. History revealed a similar lesion at the same site about 2 months before the current presentation which he had reported to a private hospital, where it was excised. The histopathologic report presented stated a diagnosis of pyogenic granuloma. His systemic examination was unremarkable.

On intraoral examination, swelling was noted as sessile, with an ulcerated, friable surface. On palpation, there was associated bleeding. Lesion was nonindurated. No lymph nodes of the neck region were palpable. There were no other relevant clinical findings. A complete blood count was done, and all values were within normal range. Radiographic imaging ruled out erosion of the underlying bone.

Based on the present clinical findings and the previous histopathology report, the attending clinician arrived at a diagnostic conclusion of pyogenic granuloma. No computed tomography scans or other auxiliary imaging techniques were sought to determine the extension of the lesion. A surgeon performed an excision biopsy under local anesthesia.

Histopathologic examination of excised specimen revealed diffuse and lobulated collections of round to oval cells [Figure 1] with a round, vesicular and occasionally indented nucleus. The cells formed small intracellular lumens which appeared as vacuoles and clear spaces, giving them a "blistered appearance" [Figure 2]. Mitoses, pleomorphism and necrosis were absent. An area of spindling of cells was also noted [Figure 3]. The cells were surrounded by a moderately collagenous fibrous connective tissue with dilated blood vessels. The overlying stratified squamous epithelium was focally ulcerated and necrotic, with juxtaposed chronic inflammatory cell infiltrate, predominantly lymphocytes. A differential diagnosis of capillary lobular hemangioma and hemangioendothelioma was made.

The slide was circulated among two oral pathologists and seven general pathologists (all selected individuals are qualified and reputed in their expertise) of higher centers. Among the general pathologists, two gave a definite diagnosis of hemangioendothelioma, while three others gave a broader diagnosis of a tumor of vascular origin, advising an immunohistochemical analysis. The two remaining general pathologists provided a detailed description of the slide awaiting immunohistochemistry analysis. The oral pathologists gave a differential diagnosis of capillary lobular hemangioma, hemangioendothelioma and pyogenic granuloma with immunohistochemical analysis to aid in a definitive diagnosis. This brings to light the absence of a consensus in the histopathologic

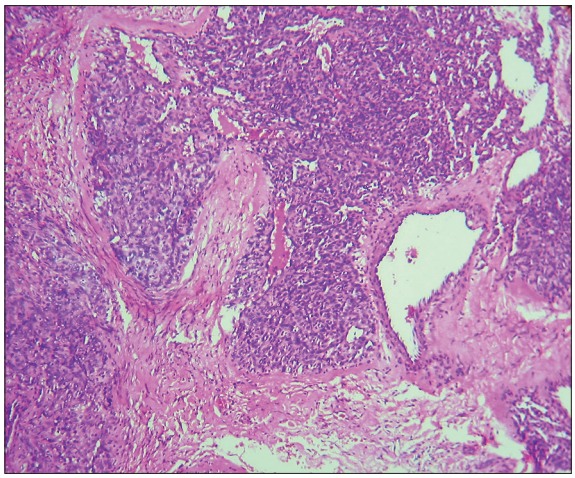

Figure 1: Low-power view showing tumor cells arranged in lobular pattern and proximity to adjacent blood vessel (H&E, ×10)

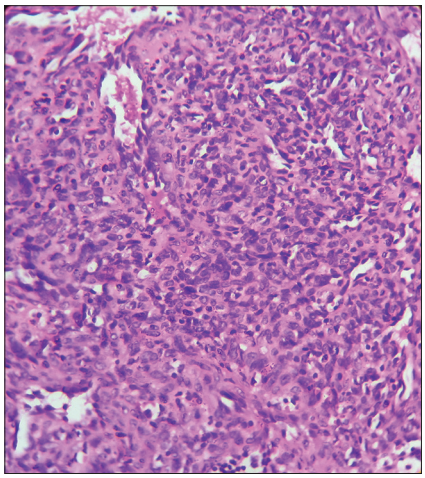

Figure 2: High-power view showing blistering of cells and primitive lumen formation at areas (H&E, ×40)

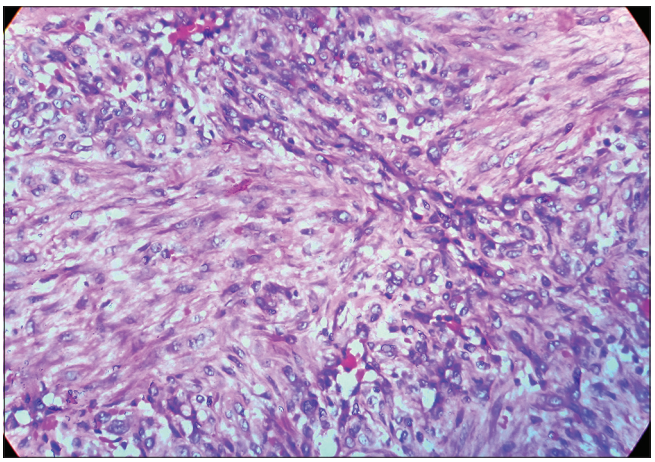

Figure 3: High-power view showing diffuse arrangement of tumor cells with occasional areas of spindling and pseudosarcomatous change (H&E, ×40)

diagnosis among the attending pathologists in this case with an atypical presentation.

Considering all opinions, the differential diagnosis now encompassed capillary lobular hemangioma, pyogenic granuloma, hemangioendothelioma and granulomatous inflammation with possible foreign body etiology. Although palate is a common site of trauma, with chances of foreign bodies such as fish bones to get lodged in, the absence of giant cells and nonretrieval of any foreign body excluded the probability of a granulomatous reaction to foreign body. The diagnosis of lobular capillary hemangioma was also less likely due to the restriction of the characteristic lobular arrangement to a small area of the section. The high degree of cellularity with blistering of the round cells and the presence of erythrocytes entrapped in lumen made the diagnosis of hemangioendothelioma a probable one.

A Gomori's methenamine-silver stain for fungal organism was done, which was negative, following which immunohistochemical studies were done. A positive reaction to cluster of differentiation 31 (CD31) and CD34 was noted [Figure 4], confirming the vascular origin of the lesion. A final diagnosis of hemangioendothelioma of intermediate grade, with areas of necrosis and pseudosarcomatous change, was arrived upon. A clear-cut subcategorization was not possible in this case due to its unusual presentation. The margin of the resected specimen was not free of the tumor and hence the patient was subjected to a second surgery for wider excision [Figure 5]. A reticulin stain was also done [Figure 6]. Since the oral counterpart of hemangioendothelioma has an unpredictive course, the patient has been kept on regular follow-up for the past 1 year which has been uneventful.

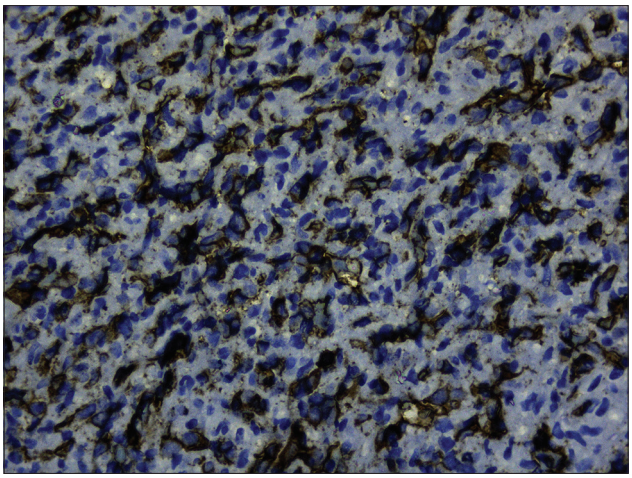

Figure 4: High-power view showing positivity to CD34 antigen (×40)

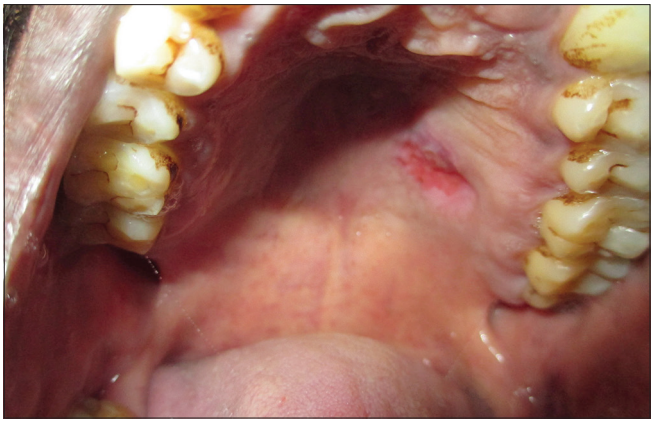

Figure 5: Postoperative view, after excision biopsy. The lesion was incompletely excised hence had to be reexcised

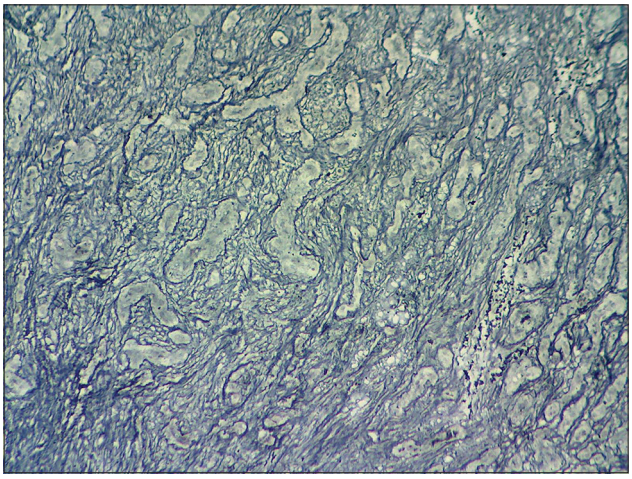

Figure 6: Low-power view reticulin stain (×10)

DISCUSSION

The term hemangioendothelioma was originally given by Mallory in 1908, to include all proliferations that he considered as of originating from endothelial cells of blood vessels.[3] Hemangioendothelioma is characterized by endothelial cell proliferation around a vascular lumen. It is considered as a vascular neoplasm with an intermediate-to-low-grade malignant potential. Clinical and histological behavior places it intermediate between hemangioma and conventional angiosarcoma. Enzinger and Weiss have categorized hemangioendothelioma into epithelioid, Kaposiform, hobnail, composite and epithelioid sarcoma-like hemangioendothelioma.[4] Hemangioendothelioma is characterized by a slow-growing pattern, with potential for destruction of underlying bone, local recurrence and even metastasis. It usually occurs in soft tissue and internal organs, head and neck being an uncommon site.[5] In oral cavity, the lesion has been encountered in gingiva, tongue, maxilla, buccal mucosa and palate.[6] Hemangioendothelioma of oral cavity is rare, with reported cases of the epithelioid variant being only around 30, while the Kaposiform variant numbers

to about 14 reported cases.[1] The other variants are still fewer in number.[7-9]

Many cases of hemangioendothelioma of oral cavity have been clinically diagnosed as benign lesions such as pyogenic granuloma, fibroma, peripheral giant cell granuloma, peripheral ossifying fibroma, inflammatory fibrous hyperplasia and necrotizing ulcerative gingivitis.[10] Since hemangioendothelioma has shown the potential to recur and metastasize, the clinical diagnosis of benign lesion has a large impact on treatment provided initially. Often, an incomplete removal may result in recurrence and would require a further wider excision surgery.

In majority of the cases, the patient is asymptomatic, only a small fraction of the affected cases complain of pain. Our patient did not complain of any associated pain. According to literature, radiographic features in about 25% of cases showed resorption of underlying bone.[10] The asymptomatic nature of lesion and a slow-growth rate may well play a role in slow destruction of the underlying bone. No apparent radiographic changes were evident in our case.

Predicting the biological behavior of hemangioendothelioma is a difficult task, the epithelioid type being the most aggressive one with highest tendency to metastasize to distant sites and recur locally. Literature reveals a recurrence rate of 13% and metastasis of about 30% in case of epithelioid hemangioendothelioma.[11] However, the reticular type is frequently associated with lymph node involvement. Due to the rarity of the lesion in oral cavity, there is still a lack of agreement on terminology and definite criteria for diagnosis. The histopathological picture is not definite for predicting the biologic nature; however, some authors believe that the presence of high grade of cellular atypia, increased number of mitotic figures,[12] spindling of tumor cells, metaplastic bone formation and areas of focal necrosis can point toward a more aggressive behavior. The lesion reported here did not reveal much cellular atypia or mitotic figures; however, spindling of cells was noted at areas.

The intraoral epithelioid hemangioendothelioma, according to literature, presents with size ranging from 0.2 cm to 7.0 cm, with a mean of 1.7 cm.[10] The size of lesion noted clinically was well within the range mentioned above. In terms of histological picture, however, our case did not present the typical features of hemangioendothelioma. This case presented with greater cellularity and lesser lumen formation. The arrangements of the tumor cells also varied at areas. The cells were arranged as lobules, in a diffuse pattern, as sheets and a few small cords. The tumor cells were oval and round with one suspicious area of hobnail pattern. The cells also underwent a spindling area. The closest categorization of our case would be polymorphous type, which is characterized by wide microscopic patterns, including solid, primitive vascular and angiomatous components.

Since the surgeon had performed an excision biopsy, a cytological study was not conducted in our case. Literature reveals the characteristic cytological picture of epithelioid hemangioendothelioma to be composed of small-sized clusters and scattered cells with occasional acinar or glandular arrangement. The tumor cells reveal remarkable atypia with intranuclear inclusion bodies and grooved nucleus. A "physaliform pattern," that is, a nucleus characterized by the presence of multiple pale, round-oval hypochromatic areas, has also been suggested as a diagnostic clue.[13]

Special stain for reticulin can be used to highlight the fibrous component surrounding individual tumor cells, which can help in ascertaining the vascular origin of the tumor cells. The difficult histological picture in some cases necessitates immunohistochemical studies. Literature review shows that the cells of hemangioendothelioma show positivity to CD34, CD31 and von Willebrand factor. In our case, positive reaction to both CD34 and CD31 were present. Epithelioid hemangioendothelioma shows positivity to *Ulex europaeus* antigen also. The cytoplasmic lumen formation in the "blistering" cells can be confirmed by factor VIII positivity. Podophyllin, lymphatic vessel endothelial receptor 1 and prospero homeobox 1, when positive, signal a lymphatic line of differentiation.[14]

The cells of epithelioid variant of hemangioendothelioma may contain large amount of intermediate filaments and there might be a positive reaction to cytokeratins 7 and 18 and with smooth muscle actin . Hence, one should be careful not to misdiagnose such cases as oral squamous cell carcinoma. In such cases, where there is cytokeratin positivity to differentiate from squamous cell carcinoma, mucin staining, *U. europaeus* and factor VIII can also be of use.[15]

Immunohistochemical studies with proliferating cell nuclear antigen (PCNA) and vascular endothelial growth factor (VEGF) have been used by Uehara *et al*. to understand the biological nature of hemangioendothelioma.[8] The PCNA labeling index (LI) was calculated as the percentage of the PCNA-positive cells in 1000 tumor cells counted from randomly selected four fields viewed under magnification of ×400. VEGF is a dimeric polypeptide growth factor, and its mitogenic activity is specific for

vascular endothelial cells. The intense expression of VEGF and high PCNA-LI may indicate an aggressive proliferative activity and metastatic behavior.[8] Similar attempts to profile the biological character and aggressiveness have also been attempted using other proliferating markers such as Ki67.

Hemangioendothelioma has been conventionally treated with nonmorbid wide local excisions for operable sites. Studies revealed a 10-year survival rate of about 92% with wide local excision of the lesion. Long-term effectiveness of radiation therapy as a treatment modality has also been been studied, with promising results in patients who have been treated with radiation therapy alone and when instituted postoperatively. Chemotherapy has been proven successful in six refractory cases of Kaposiform hemangioendothelioma, with sirolimus an mTOR inhibitor.

To summarize, the present lesion was a recurring palatal swelling that clinically mimicked a benign reactive lesion. The histological picture showed varied morphological pattern, high cellularity and only few areas of lumen formation compounding the histological diagnosis of the lesion. The slides were circulated within various pathologists and differential diagnosis obtained ranged from fungal infection to angiomatous lesion. Immunohistochemical studies were resorted to and the vascular origin confirmed. Correlating the clinical, histological and immunohistochemical studies, a diagnosis of hemangioendothelioma was reached upon. The summary of immunohistochemical assessment of various subtypes of hemangioendothelioma is shown in Table 1.[9-15]

CONCLUSION

From the case presented above and literature analyzed, one can conclude that hemangioendothelioma of oral cavity is a rarity and often is clinically misdiagnosed as a benign reactive lesion, necessitating a histological diagnosis. The histological picture is still controversial, posing diagnostic challenges at times due to lack of definite criteria for diagnosis. Prompt immunohistochemical analysis to confirm, followed by surgical treatment, should be mandatory in cases of oral hemangioendothelioma to reduce chance of local recurrence and metastasis. Further, this case is a proof that, at times, a consensus in diagnosis may not be reached by various pathologists, in times of unusual presentations.

Table 1: Immunohistochemical markers for assessing various subtypes of hemangioendothelioma

Hemangioendothelioma subtype	Immunohistochemical markers
Epithelioid	*Ulex europaeus* antigen
Kaposiform	Lymphatic markers (PROX1, LYVE1 and podoplanin)
Dabska and retiform	von Willebrand factor and lymphatic markers corresponding to a mixture of B (CD20+) and T (CD3+) cells
Composite	CD34 negativity in most cases with some cases having SMA positivity in stromal cells and PROX1 positivity
Epithelioid sarcoma like	CD31, FLI-1, cytokeratin and INI1 positivity negative for CD34

PROX1: Prospero homeobox 1, LYVE1: Lymphatic vessel endothelial receptor 1, CD20: Cluster of differentiation 20, CD3: Cluster of differentiation 3, CD34: Cluster of differentiation 34, SMA: Smooth muscle actin, CD31: Cluster of differentiation 31, FLI-1: Friend leukemia integration 1 transcription factor, INI1: INI gene product

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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.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Manjunatha BS, Kumar GS, Vandana R. Intraoral epithelioid hemangioendothelioma: An intermediate vascular tumor – A case report. Dent Res J (Isfahan) 2009;6:99-102.
2. Mohtasham N, Kharrazi AA, Jamshidi S, Jafarzadeh H. Epithelioid hemangioendothelioma of the oral cavity: A case report. J Oral Sci 2008;50:219-23.
3. Requena L, Kutzner H. Hemangioendothelioma. Semin Diagn Pathol 2013;30:29-44.
4. Goldblum JR, Folpe AL, Weiss SW. Hemangioendothelioma: Vascular tumors of intermediate malignancy. In: De Francesco K, editor. Enzinger and Weiss's Soft Tissue Tumors. 6th ed. Philadelphia: Elsevier Saunders; 2014. p. 681-702.
5. Gupta SC, Tewarson SL, Malhotra M. Haemangioendothelioma of paranasal sinuses with intracranial extension. Indian J Otolaryngol Head Neck Surg 2006;58:196-8.
6. Sawair FA, Cheng J, Yamazaki M, Al-Eryani K, Khraisat A, Ono Y, *et al*. Epithelioid hemangioendothelioma of the tongue: A report of solitary and multiple lesions in two young children. Oral Med Pathol 2008;13:15-20.

7. Fasolis M, Iaquinta C, Montesco MC, Garzino-Demo P, Tosco P, Tanteri G, *et al*. Composite hemangioendothelioma of the oral cavity: Case report and review of the literature. Head Neck 2008;30:974-9.
8. Uehara M, Shibahara K, Fujita S, Tobita T, Ohba S, Fujisawa A, *et al*. Epithelioid hemangioendothelioma of tongue: A case report with immunohistochemical studies. Oral Oncol Extra 2006;42:101-4.
9. Tosios KI, Gouveris I, Sklavounou A, Koutlas IG. Spindle cell hemangioma (hemangioendothelioma) of the head and neck: Case report of an unusual (or underdiagnosed) tumor. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;105:216-21.
10. Gordón-Núñez MA, Silva eM, Lopes MF, de Oliveira-Neto SF, Maia AP, Galvão HC, *et al*. Intraoral epithelioid hemangioendothelioma: A case report and review of the literature. Med Oral Patol Oral Cir Bucal 2010;15:e340-6.
11. Yoruk O, Erdem H, Mutlu V, Erdogan F, Altas E, Kantarci M, *et al*. Epithelioid hemangioendothelioma of the submandibular gland. Auris Nasus Larynx 2008;35:157-9.
12. Basavannaiah S, Deogaonkar S, Shinde V, Gore C. Hemangioendothelioma of oral cavity and oropharynx: A rare neoplasm. Indian J Oral Sci 2014;5:35-8.
13. Kurisu Y, Tsuji M, Kuwabara H, Shibayama Y. Characteristic cytologic findings of epithelioid hemangioendothelioma: A case report and review of literature. Diagn Cytopathol 2011;39:124-7.
14. Naqvi J, Ordonez NG, Luna MA, Williams MD, Weber RS, El-Naggar AK, *et al*. Epithelioid hemangioendothelioma of the head and neck: Role of podoplanin in the differential diagnosis. Head Neck Pathol 2008;2:25-30.
15. Cheng YS, Kessler H, Rees TD, Philofsky D, Pontikas A. Gingival swelling in a 13-year-old girl with multiple recurrences. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103:85-91.