Oral epithelioid hemangioendothelioma

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Abstract

Epithelioid hemangioendothelioma (HE) is an intermediate malignant potential vascular neoplasm with uncertain clinical behavior, wide variations in microscopic findings, and prognosis. According to the World Health Organization (2002) classification, epithelioid HE has been considered under malignant tumors which rarely metastasize. The epithelioid variant, the most aggressive one, has similar gender predilection and sporadic occurrence in children. The patients usually present with an asymptomatic oral mass whereas few cases may report with the painful bleeding lesion. We attempt to present a case in an adolescent male with previously never described biological behavior, diverse histopathological features, and immunohistochemistry findings.

Keywords: Angiosarcoma, immunohistochemical, vascular

Introduction

The term hemangioendothelioma (HE) was proposed by Borrmann as early as 1899 with Weiss and Enzinger documented first case in 1982.[1] The first case of epithelioid HE in the oral cavity was reported by Ellis and Kratochvil in 1986.[2] Epithelioid HE is an uncommon angiocentric vascular neoplasm characterized by proliferation of endothelial cells around the vascular lumen. It is an extremely rare neoplasm affecting one in 10 lakh people and only 0.01% of the cancer population.[3] Slightly above 30 cases of intraoral epithelioid HE have been reported in literature to date.[4] Its biologic behavior, clinically and histologically, falls between hemangioma and angiosarcoma.[5] They are reported in both genders in the age range of 20–40 years with rare occurrence in childhood.[6] It is a slow growing tumor with an unpredictable behavior and tendency to metastasize. It usually develops in soft tissues and internal organs such as lungs, liver, bone, musculoskeletal system and rarely involves head and neck, intestines, lymph node, stomach, nervous system, pleura, and skin.[3] We present here an extremely interesting previously unreported behavior of epithelioid HE in a teenage male with immunohistochemical analysis.

Case Report

A 16-year-old male was presented with a history of growth in the upper right back teeth region for 8 days. The growth was sudden in onset and was gradually increasing in size. The patient reported minimum discomfort with a bleeding episode from the growth following toothbrush trauma for 1 day. The family, dental, medical, and surgical history was unremarkable. On general physical examination, mild pallor was detected in conjunctivae and nailbeds. Extraoral examination revealed a solitary diffuse swelling on right middle one-third of the face with no secondary changes in the overlying skin [Figure 1a]. There was no evidence of regional or distant lymphadenopathy. On intraoral inspection, a solitary well-defined sessile, proliferative, 3.5 cm × 3 cm, roughly oval growth obliterating the buccal vestibule completely was noted arising from the buccal marginal, interdental, and attached gingivae of maxillary right first and second molars. The surface of the growth appeared irregular and nonlobulated. The color of the growth was white with interspersed dark red areas and blood clots over the surface. There was evidence of pus discharge and bleeding from the growth. Palpation revealed a mildly tender, soft to firm, bleeding friable growth [Figure 1b].

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A provisional diagnosis of pyogenic granuloma was considered. Peripheral giant cell granuloma, solitary fibrous tumor, hemangioendothelioma, angiosarcoma, amelanotic melanoma, and metastatic lesion were kept in the differential diagnosis. Intraoral periapical radiograph of maxillary right first and second molars showed a homogeneous soft tissue density extending from maxillary right first molar to maxillary right second molar with no evidence of calcifications. Orthopantomograph also revealed similar findings with intact maxillary sinus floor [Figure 2a and b]. Routine blood investigations revealed mild anemic status. Incisional biopsy was performed from the lesion for which histopathological diagnosis of pyogenic granuloma was given. After incisional biopsy, the growth rapidly increased in size within 10 days to reach 6 cm × 4 cm in dimension [Figure 1c and d]. Considering pyogenic granuloma as the suspected diagnosis, excisional biopsy of the lesion was performed under general anesthesia. On excisional biopsy microscopy sections, ulcerated epithelium with underlying connective tissue showed complex branching vascular channels lined by plump endothelial cells. Surrounding tissues showed spindle cells with areas of hemorrhages and necrosis [Figure 3a, b, and c]. Immunoreactivity was positive for vimentin, CD31, CD34, and KI-67 marker [Figure 4a, b, c, and d]. CD107 was reportedly negative. Hence, a final diagnosis of epithelioid HE was made. Thorough physical examination was undertaken to evaluate metastatic status. Fortunately, there was no evidence of local or distant metastasis and the patient was recurrence-free 5 years postsurgery.

Figure 1: (a) Extraoral frontal profile of the patient before incisional biopsy. (b) Intraoral view of lesion before incisional biopsy. (c) Extraoral frontal profile of the patient after incisional biopsy. (d) Intraoral view of lesion after incisional biopsy

Figure 2: (a) Intraoral periapical radiograph of the region of interest. (b) Orthopantomograph showing intact maxillary sinus floor

Figure 3: (a) H and E, ×20 stained section showing surface stratified squamous epithelium. (b) H and E, ×10 stained section showing proliferating blood vessels and endothelial cells. (c) H and E, ×20 stained section showing spindle cells in the stroma

Figure 4: (a) Positive immunoreactivity for vimentin. (b) Positive immunoreactivity for CD31. (c) Positive immunoreactivity for CD34. (d) Positive immunoreactivity for KI-67
Discussion

HE is an exceedingly rare vascular tumor with an intermediate malignant potential with a tendency to recur and metastasize. There are many histological variants of HE such as epithelioid, retiform, kaposiform, Dabska tumor (papillary intralymphatic angioendothelioma), sarcoma-like/pseudomyogenous, composite, infantile hepatic, cutaneous, endovascular papillary, histiocytic, mammary, polymorphous, pulmonary, and spindle cell varieties. Epithelioid variant is among the most common types.[3]

Epithelioid HE is also referred to as a low grade epithelioid angiosarcoma. Its cytogenetics is not well-documented, as yet: T(1; 3)(p36.3; q25) and a small supernumerary marker chromosome involving 22q11 have been outlined in the literature.[3]

Oral epithelioid HE clinically mimick as benign reactive lesions such as pyogenic granuloma, chronic periodontal disease, acute necrotizing gingivitis, and peripheral giant cell granuloma with a good number of cases presenting with a bleeding friable soft tissue mass. Similar findings were appreciated in our case also. Our differential diagnosis included peripheral giant cell granuloma, solitary fibrous tumor, angiosarcoma, amelanotic melanoma, and metastatic lesion. Peripheral giant cell granuloma is noticeably a more purplish growth. Solitary fibrous tumor is firmer to palpation as compared to vascular tumors due to the presence of abundant fibrous component. Amelanotic melanoma and angiosarcomas are reportedly aggressive lesions with prevalence in sixth and seventh decades of life. An overview of eight cases of maxillary HE reported until the date has been summarized [Table 1]. Accordingly, maxillary HE can have varied clinical presentation with color ranging from pink to purple, with or without ulceration, pedunculated or sessile or growth or swelling and high chances of recurrence.

The unusual behavior of rapid increase in the size of this neoplasm was first time evident in the present case; thus, enhancing the possibility that any invasive procedure can stimulate the growth of the tumor tissues tremendously.

Table 1: Maxillary epithelioid HE reported till date

| Authors            | Clinical features                                      | Age/sex | IHC analysis                                      | Follow-up               |
|--------------------|--------------------------------------------------------|---------|--------------------------------------------------|-------------------------|
| Ellis and Kratochvil (1986) | Swelling, pink, tooth mobility, 4 years               | 13/female | Factor VIII-Rag+                                | Recurrence free post 6 years |
| Marrogi et al. (1991) | Erythematous lesion, 1.5 cm                            | 45/male | -                                                | Recurrence post 3 and 6 months |
| Ramer et al. (2001) | Swelling, 3.5 cm                                       | 32/male | VIII-Rag+, CD34+                                | Recurrence post 6 months |
| Kubota et al. (2004) | Painless gingival swelling, 6 months                  | 50/female | Vimentin+, VIII-Rag+, CD34+                      | Recurrence free post 9 years |
| Chi et al. (2005)  | Purple swelling, 0.6 cm                                | 28/female | CD31+, Fli-1+CD34+, CD68-                       | Recurrence free post 8 months |
| Sun et al. (2007)  | Ulcerated swelling, 3.0 cm, 3 months, bone destruction, tooth mobility | 12/male | CD34+, factor VIII-Rag+, Vimentin+, SMA+, AE-1/AE-3+ | Recurrence free post 6 months |
| Mohtasham et al. (2008) | Ulcerated reddish swelling, asymptomatic, 1.0 cm, 6 months | 9/male | CD31+, CD34+                                    | Recurrence post 1 year |
| Sreenivasan et al. | Sessile pink growth, 5 months                          | 48/male | Vimentin+, CD34+                                | Recurrence free post 1 year |

HE: Hemangioendothelioma; IHC: Immunohistochemistry

Table 2: Immunohistochemical markers and their significance in diagnosing HE

| Markers | Signify                                      | Positivity | Expression in HE                  |
|---------|----------------------------------------------|------------|-----------------------------------|
| Vimentin | Mesenchymal origin (high sensitivity and low specificity) | Sarcomas, melanomas, vascular tumors | Positive |
| CD 31, CD34 | Vascular phenotype                          | Hemangioma, hemangioendothelioma | Positive |
| VIII-Rag+ | Vascular phenotype                          | Not positive in epithelioid sarcoma and angiosarcoma | Positive |
| S-100, CD107 | Melanocytic origin                         | Melanoma | Negative |
| SMA     | Myofibroblastic origin                      | Muscular tumors | May be focal positivity in myopericytic cells |
| AE-1/AE-3 | Cytokeratins-epithelial markers              | Mainly carcinomas | Negative |
| CD68    | Origin from cells of the macrophage lineage | Malignant histiocytosis, histiocytic lymphoma Gaucher’s disease | Negative |
| EMA or CD227 | Glandular or ductal epithelial cells origin | Adenocarcinomas | Negative |
| Ki-67   | Cellular proliferation                      | Prostrate and breast carcinomas | May be positive |

HE: Hemangioendothelioma
secondary to increased neovascularization, fibrosis, and epithelialization. To the best of our knowledge, this is first such case in the literature.

Histopathologically, the intraoral epithelioid HE shows spindle cells predominantly as compared to HE in other body parts.[7] More commonly, cellular atypia is insignificant with low mitotic activity and lack of necrosis. However, conspicuous atypia with high mitotic rate and necrosis may be also evident in a limited number of cases. The abundance of spindle cells, cellular atypia, and necrosis in our case may be suggestive of more aggressive clinical course but not of tumor prognosis.[8] The histopathological differential diagnosis should be melanoma, epithelioid angiosarcoma, epithelioid sarcoma, metastatic carcinoma, and adenocarcinoma.

The significance of immunohistochemical analysis in the diagnosis of epithelioid HE cannot be belittled. The immunohistochemical markers which should be run to diagnose HE and rule out other similar histopathological tumors with their interpretation have been listed [Table 2]. The mesenchymal origin of tumor in the present case was confirmed by vimentin positivity. The vascular phenotype of this tumor was demonstrated by endothelial markers such as CD31 and CD34. Ki-67 positivity denoted the increased cellular proliferation within the neoplasm, but its functional significance is yet unclear.[9]

Wide surgical excision is recommended for HE due to the tendency toward local recurrence, distant metastasis, and malignant potential.[10] Though literature suggests the high rate of recurrence for HE in maxillary gingiva; no recurrence was evident in our case even after 5 years.

**Conclusion**

The authors suggest that differential diagnosis for common reactive lesions of the oral cavity with a friable soft to firm consistency should include vascular tumors such as HE. Histopathologically, epithelioid HE diagnosis should be considered for oral lesions having epithelioid cells with or without cellular atypia, low to high mitotic activity, little or no necrosis, and abundance of spindle cells. The vascular phenotype of this neoplasm should be substantiated by appropriate immunohistochemical analysis. The patients should be kept under follow-up for prolonged periods as the lesion has a tendency toward relapse.

**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.

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