Epithelioid Haemangioma – A Diagnostic Dilemma

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Authors’ contributions

This work was carried out in collaboration between all authors. Authors DAT, NR, RSR and TR studied the case and evaluated. Authors DAT and NR designed the case study, and wrote the first draft of the manuscript. All authors managed the literature searches, and author MR managed histopathology report. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Epithelioid haemangioma (EH), synonymously termed as angiolymphoid hyperplasia with eosinophilia, is a rare lesion whose etiopathogenesis is unclear. Clinically it manifests as solitary or multiple nodules in the skin and subcutaneous tissues of the head and neck region. It can also arise in the deep tissues such as muscle, bone and lymphnode. Intra oral involvement is less common and very few cases have been reported in the literature. Common intra oral sites include lip followed by buccal mucosa and tongue. Epithelioid Haemangioma affecting alveolar mucosa is very rare. We report one such case of epithelioid hemangioma of size 4x4 cm on lower right alveolar mucosa in 38 year old female patient.

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1. INTRODUCTION

Epithelioid haemangioma (EH) is a rare benign vascular lesion that is characterized by proliferation of vascular structures that are lined by histiocytoid or epithelioid cells accompanied by an inflammatory infiltrate comprising lymphocytes, plasma cells and eosinophils. It was first reported as Angio lymphoid hyperplasia with eosinophilia by Wells and Whimster [1]. Enzinger and Weiss coined the term epithelioid haemangioma to describe an unusual benign vascular proliferation, probably a tumor [2]. The lesions may be solitary or multiple that vary in clinical appearance from intradermal papules to subcutaneous nodules on the skin of head (face, ear, scalp) and neck region [1,3]. Lesions mostly show muscular, bone and salivary gland involvement. Intra oral involvement is uncommon and only few cases have been reported in the literature. We hereby report a rare case of the same entity.

2. PRESENTATION OF THE CASE

A 38 year old female patient reported to the Department of Oral Medicine, Oral diagnosis and Radiology, with a chief compliant of painful swelling in the lower right back teeth region since one month. Upon evaluation, patient reports of no history of trauma and that the swelling was persistent since one and half year with gradual increase in its size from its onset. The observed swelling was associated with pain and causing difficulty in chewing. The Swelling showed a drastic change in its size which tends to increase for the past one month.

This condition does not seem to have affected other family members and history of no known allergies as reported by the patient.

General physical examination showed the patient to be conscious and well oriented. Clinical examination of the patient revealed gross facial asymmetry on right lower one third of the face. Right submandibular lymphnodes were palpable and tender. Further intraoral examination revealed a nontender, firm growth measuring approximately of size 4 x 4 cm on the alveolar mucosa of 46, 47 teeth region. The surface of the growth was nodular, erythematous and interspersed with tiny bleeding points. The teeth in relation to growth and adjacent to it was displaced buccally (Figs. 1 and 2).

Diascopy was performed and the lesion showed no blanching on pressure. Based on the history and in correlation with the aforementioned clinical findings, a provisional diagnosis of a reactive lesion of the alveolar mucosa in the 46 and 47 teeth region was made.

Peripheral giant cell granuloma, Pyogenic granuloma, Squamous cell carcinoma and Salivary gland neoplasm were considered in differential diagnosis.

Patient was then subjected to blood and radiographic investigations. All the routine blood investigations were performed and all the blood parameters found to be within the normal range (Differential and eosinophil count were within normal range). Upon orthopantomograph examination, no obvious underlying bony trabecular changes were evident except for the change in bony architecture at the lesional site with the alveolar crest receding inferiorly when compared with the contralateral side. Displacement of 46, 47 teeth were observed (Fig. 3).

An incisional biopsy was performed from the site of the lesion. The histopathologic report of the specimen revealed numerous proliferating blood capillaries engorged with red blood cells. The endothelial cells in the dilated blood capillaries were arranged in the form of tomb stone (Fig. 4). Owing to the histopathological features and correlated with clinical and radiological finding a final diagnosis of epithelioid haemangioma was made.

In the present case scenario the lesion tends to be of much larger size. So, CT angiography was made to enhance the probable arterial feeder which is a main component streamlined to the larger size of the lesion. CT angiography suggested that the probable predominant arterial feeder from the facial branch (Fig. 5).

3. DISCUSSION

Ever since their documentation in the literature, the vascular anomalies pertaining to head and neck region have confused clinicians over the years owing to their distinctive features (Table 1).
A number of vascular benign lesions with specific and distinctive histologic features were described in the literature. Epithelioid haemangioma (EH) is one amongst them which is unusual but distinctive vascular lesion. Different synonyms for this specific lesion as reported in the literature includes inflammatory angiomatous nodule, pseudo or atypical pyogenic granuloma, histocytoid haemangioma. EH is witnessed more often among Asians and Caucasians [4] and reported to occur commonly among patients aged 20-50 years. The observed mean onset of age for this typical lesion is 33 years which is similar in accordance with the present case. This specific condition is slightly more prevalent in females, though a male predominance has been noted in Asian population [5].

Approximately 85% of the lesions occur on the skin and subcutaneous tissues of head and neck; most common frequent sites to be involved are ear, forehead or scalp [4] and also involves other sites such as the vulva, colon, orbit, parapharyngeal space and oral mucosa [3]. Occurrence of this lesion in oral mucosa is a rare presentation, nevertheless if present it manifests as dome shaped lesion with papules or nodules and the sites most commonly represent this lesion in the oral cavity includes lip, followed by buccal mucosa, tongue and alveolar mucosa [4-8]. The presenting lesions may be erythematous to brown with surface erosions or crustations. In 20% of cases, the lesions are associated with lymphadenopathy and eosinophilia [7]. In the present case the lesion demonstrates an erythematous surface with few tiny bleeding points on the alveolar mucosa which is associated with lymphadenopathy.

The central dogma of the lesion is that it is a benign tumor whose pathogenesis still remains obscure. The reported literature suggests that it may be a result of unusual reactive process secondary to an artery or vein damage following traumatic insults or hormonal imbalance [9]. Olsen and Helwig found arteriovenous shunts in 42% cases of epithelioid haemangioma and referred it as a possible cause of this typical lesion [10]. Fetsch et al. [11] found that in 63% of cases, a medium sized artery or vein was associated with the lesion as identified in the present case where facial artery was involved. Studies still suggest EH to be a hypersensitivity response based on eosinophilia in some patients [3]. In the present case the subject represented with normal range of eosinophil count ruling out this possibility. Few researchers propose that renin stimulates the proliferation of vessels through angiotensin H, and that raised serum levels of renin, eosinophilic cationic protein and interleukin 5 in AngioLymphoid Hyperplasia with eosinophilia (ALHE) closely related to a chain of inflammatory reactions [12].

Due to varied clinical presentation Kaposi sarcoma, Squamous cell carcinoma, Haemangioma should be considered in differential diagnosis.

Histopathological picture of epithelioid haemangioma shows prominent proliferation of vessels lined by plump “epithelioid” endothelial cells with abundant eosinophilic cytoplasm and central oval nucleus. The distinctive endothelial cells have been described as having cobblestone appearance. The stroma of the tumor is formed by fibromyxoid tissue with inflammatory cells that surround the vessels. The inflammatory cell infiltrate is composed of eosinophils, plasma cells, lymphocytes, macrophages and mast cells [13,14]. Occasionally an infiltrate is devoid of eosinophils. Immunohistochemical analysis reveals a positive reaction of epithelioid haemangioma for Vimentin and factor VIII related antigen. It exhibits a negative reaction for other markers such as cytokeratin, EMA, S-100, desmin and smooth muscle actin [8].

Figs. 1 and 2. Intra oral swelling observed in the tooth region of 46, 47
Fig. 3. Orthopantomograph showing bone loss of 4-5 mm from the alveolar crest with the displacement of tooth in relation to region of 46, 47.

Fig. 4. H & E stained tissue showed endothelial cells in the dilated blood capillaries proliferating into the lumen in the form of tomb stone. (Magnification × 100x)

The histological differential diagnosis also includes other epithelioid vascular tumors and non-vascular soft tissue tumors showing epithelioid characteristics including epithelioid angiosarcoma, epithelioid haemangioma, hobnail haemangiomia and epithelioid angiomatous nodule. Epithelioid angiosarcoma of oral mucosa is rare and present as an infiltrative destructive growth pattern and composed of markedly pleomorphic cells and numerous abnormal mitosis [13]. Oral epithelioid haemangioendothelioma is composed of mildly pleomorphic epithelioid endothelial cells and intravascular lumens with a hyalinised or myxoid stroma. The other histopathological features of haemangioendothelioma are cellular atypia, mitosis and presence of necrosis [9]. Hobnail Haemangioma is extremely rare in oral mucosa and characterized by well-defined dilated vascular channels lined by prominent “hobnailled endothelial cells” [15]. Cutaneous epithelioid angiomatous nodule is recent entity of vascular proliferation with distinct morphological spectrum. The lesions are usually confined to dermis with only infrequent extension into superficial subcutaneous tissue and rarely in submucosa [7]. Other microscopically similar soft tissue tumors such as epithelioid neurofibroma, epithelioid schwannoma, epithelioid fibrosarcoma may be considered but the histological appearance is sufficiently distinctive to allow differentiation [8].

It is important to distinguish epithelioid haemangioma (EH) from Kimura’s disease (KD). Recent studies indicate that the two diseases are different entities [8]. Clinically KD tends to form as deep seated nodules accompanied by lymphadenopathy, peripheral eosinophilia and elevated serum IgE. In contrast, EH appears superficial, red to brown papules or nodules with or without lymphadenopathy and is less frequently accompanied by peripheral eosinophilia. Histologically KD is characterized by the presence of well formed lymphoid follicles with germinal centres and marked infiltration of eosinophils but plump epithelial endothelial cells are not present. Histopathologically, epithelioid haemangioma is considered to be an endothelial cell origin, while Kimuras disease is as a result of inflammatory process [4, 18].
Table 1. Variants of the vascular lesions [16,17]

| Vascular neoplasms                        | Site of involvement                                                                 | Clinical features                                                                 |
|------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| 1. Infantile haemangioma                 | Midline glabella (nasal bridge), low-back, and facial hemangiomas                    | Typically present between 2 weeks and 2 months of life. Single or multiple, may involve one or many organ systems and may be focal or regional |
| 2. Congenital haemangioma (Non involuting congenital haemangioma) | Solitary and present on the head, near a joint.                                    | NICH, which present at birth demonstrate proportional limbs growth without regression RICH, which present at birth and regress completely within 2 years. |
| 3. Kaposiform haemangioendothelioma       | Retroperitoneum, skin, head and neck region, mediastinum, deeper soft tissues of the trunk and extremities | Occurs in infancy and in first decade. Present as abdominal mass ascites, jaundice. Cutaneous lesions as violaceous plaques. |
| 4. Epithelioid Haemangioendotheliomas     | Superficial or deep soft tissue of the extremities. One half to two thirds originate from vessel. | Painful nodule in superficial or deep soft Associated symptoms of oedema or thrombophlebitis. |
| 5. Composite haemangioendotheliomas       | Distal extremities, hands and feet                                                 | Common in adults especially history of lymphoedema, Long standing reddish blue nodule. |
| 6. Retiform haemangioendotheliomas (Hobnail haemangioendothelioma) | Skin and subcutaneous tissue, Distal extremities, Particularly the lower limb       | Common in young adults, Red/bluish nodule less than 3 cm. |
| 7. Angiosarcoma                           | Deep muscles of the lower extremities, arms, trunk and head and neck.               | Common in older age, majority of them are cutaneous tumors associated with lymphoedema Associated symptoms coagulopathy, anaemia, persistent haematoma, or bruising ability. |
| 8. Acquired vascular tumors (ie, pyogenic granuloma or Lobular capillary haemangioma) | Typical location -Cheek, eyelids and extremities. It also occurs on lips, oral mucosa, tongue and nasal cavity. | Lesion usually has a pedunculated shape with stalk |

Table 2. Various treatment modalities for haemangiomas based upon their clinical presentation [16,17,19]

| Mechanism of action | Mode of use | Type of haemangiomas | Adverse effects |
|---------------------|-------------|----------------------|-----------------|
| Imiquimod           | Immunomodifier | Topical application, for a cycle of 3 to 5 months | Small and intermediate-sized hemangiomas | Hyperpigmentation |
| Laser therapy Neodymium: yttrium-aluminum-garnet (Nd:YAG) laser of 1064nm | Selective destruction of the blood vessels and photoacoagulation of the targeted vessels while keeping the overlying skin intact | Simplicity of use, which can be repeated at an interval of 2 to 4 weeks | Superficial proliferating hemangiomas | Tissue necrosis and scarring |
| First line of Pharmacotherapy | Mechanism of action | Mode of use | Type of haemangiomas | Adverse effects |
|-------------------------------|---------------------|-------------|----------------------|-----------------|
| Oral prednisolone             | Steroids tend to sensitize the vascular bed to vasoconstricting agents. Inhibits the angiogenesis | 3.0–5.0 mg/kg Every other morning for 6 to 8 weeks. Dosage is tapered after that for 2 or 3 weeks. 1 to 2 mg/kg of body weight at monthly intervals | Mixed hemangiomas, proliferative hemangiomas, and hemangiomas that affect vital organs or are life threatening. Localized hemangiomas, such as orbital or parotid lesions | Cushingoid appearance Blindness and eyelid necrosis are the major complications |
| Intrallesional Triamcinolone  |                     |             |                      |                 |

| Second line of pharmacotherapy | Mechanism of action | Mode of use | Type of haemangiomas | Adverse effects |
|--------------------------------|---------------------|-------------|----------------------|-----------------|
| Pingyangmycin Hydrochloride    | High sclerosing effect on vascularendothelium | Pingyangmycin Hydrochloride (8mg/syringe) is dissolved with 2% lidocaine and dexamethasone (5 mg/1 ml) | Cutaneous hemangiomas Proliferative hemangiomas | Anaphylactic shock |
| Bleomycin A5                   |                     |             |                      |                 |

| Vincristine                    | It inhibits the capillary network formation. Inhibits endothelial cell growth and migration | Dosage is 0.5 to 1.0mg/kg intravenously once a week over 6 weeks | Haemangiomas unresponsive to steroids or rebound after steroids | Nausea, vomiting Diarrhea, Peripheral neuropathy |

| Sclerosing agents             | Produce endothelial damage that results in permanent endofibrosis and clinical obliteration of the vessel | Hypertonic saline solution Detergent solutions includes Sodium morrhuate, ethanolamine oleate, Sodium tetradecyl sulfate - 0.25% to 0.50% Polidocanol. 0.5%, 1%, 2%, and 3% Alcohol 90-100% |                      | Post injection pain Anaphylaxis reaction Burning sensation. |

| Propranolol (Nonselective β-adrenergic antagonist) | Regulation of vascular growth factors and hemodynamic cytokines. | Newer treatment regimen. 2-3 mg/kg separated into two or three-times-a-day regimens | Currently used for problematic Haemangiomas that would have received either surgical or some other systemic therapy to prevent untoward side effects | Exacerbation of gastroesophageal reflux due to beta-receptor blockade at the lower esophageal sphincter |
Once the diagnosis is confirmed, surgical resection with conservative margins is the treatment of choice. Other treatment modalities include corticosteroid therapy, cytotoxic chemotherapy, and cryosurgery and laser therapy as an adjuvant therapy in recurrent cases. (Table 2 above) Recurrence is common (33-50%) when lesion is inadequately excised [3]. Park Y et al. [4], Granizo M et al. [3] reported epithelioid haemangioma of the tongue, where no recurrence is seen after surgical excision.

4. CONCLUSION

Epithelioid haemangioma pose a diagnostic dilemma among the lesions occurring in the oral cavity. The present case report suggests that epithelioid haemangioma should be considered in the differential diagnosis of peripheral oral lesion especially among elderly females. Owing to size of the lesion, use of advanced diagnostic imaging such as CT angiography should be performed for arriving at a proper diagnosis and aid in formulating a better treatment plan.

CONSENT

All authors declare that written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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