Eosinophilic Ulcer of the Oral Mucosa

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ABSTRACT

Eosinophilic ulcer of the oral mucosa (EUOM) is a benign, rare, self-limiting, and asymptomatic lesion that shows spontaneous regression. Its etiopathogenesis remains still unclear, but trauma seems to play a central role in the occurrence of this lesion. Clinically, this lesion manifests as an isolated long standing ulcer predominantly located on the tongue, demonstrating a raised & indurated border with white or yellowish base, clinically mimicking as squamous cell carcinoma. Microscopically, it is characterized by an inflammatory infiltrate rich in eosinophils. Since these lesions show spontaneous cure, treatment becomes unnecessary, but in certain cases, cure is obtained by excision of the ulcer during biopsy.

KEYWORDS: Eosinophilic granuloma, eosinophilic ulcer, oral mucosa, tongue, trauma, traumatic ulcer

INTRODUCTION

Eosinophilic ulcer of the oral mucosa (EUOM), also known as Traumatic eosinophilic granuloma or traumatic ulcerative granuloma with eosinophilic stroma (TUGSE), is considered a rare and reactive lesion with a benign clinical course. It is uncommon, self-limiting lesion, of an inflammatory nature preferentially found on the lateral and ventral surface of the tongue, but can also occur on the lip, palate, mucobuccal fold and gingiva.[1] Despite the fact that the pathogenesis of EUOM is indeterminate, an essential role has been ascribed to trauma.

CASE REPORT

A 68-year-old male referred from a private clinic with a lesion on the left buccal mucosa and vestibule, which was rapidly developing for about 1 month. After clinical examination an ulcer was found in relation to grossly decayed 37. It manifested elevated and indurated margins and yellowish, necrotic bottom. The patient history was unremarkable. Under local anaesthesia tooth 37 was extracted along with excisional biopsy of the lesion was done and the specimen was submitted for histopathological examination with a provisional of squamous cell carcinoma. On gross examination, three pieces of soft tissue were seen (Fig. 1). On histologic examination, ulcerated parakeratinized stratified squamous epithelium is seen with necrotic bottom. The margins of the ulcer presented hyperplastic epithelium with bottom border blurred by the dense inflammatory infiltrate (Fig 2). Under the necrotic tissue there was a dense, polymorphic, inflammatory infiltrate rich in lymphocytes and numerous eosinophils (Fig 3). The atypical large mononuclear cells with abundant cytoplasm, irregular nuclear contours, fine chromatin and small nucleoli were scattered within the eosinophil rich inflammatory infiltrate (Fig 4).

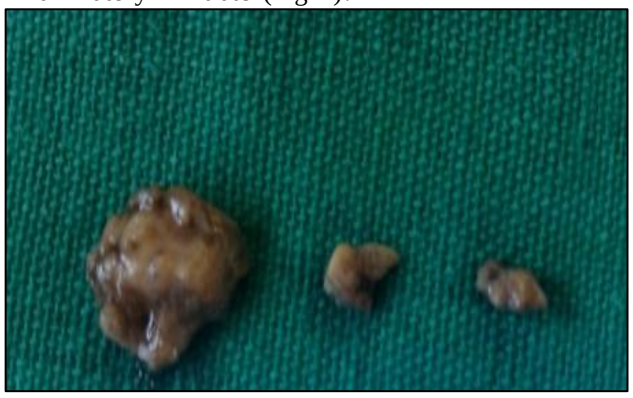

Figure 1: Gross picture showing three pieces of soft tissue

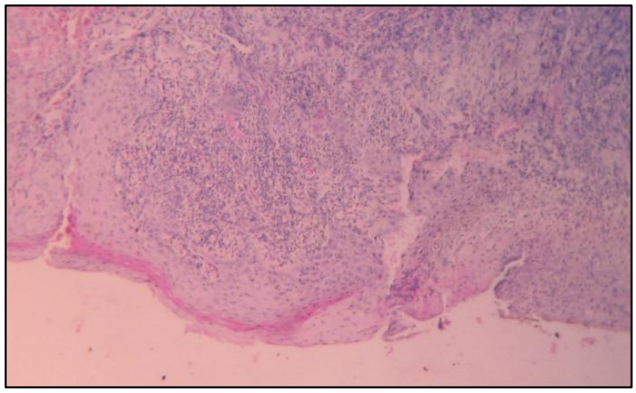

Figure 2: 4X- Ulcerated parakeratinized stratified squamous epithelium is seen with necrotic bottom. The margins of the ulcer presented hyperplastic epithelium with bottom border blurred by the dense inflammatory infiltrate.

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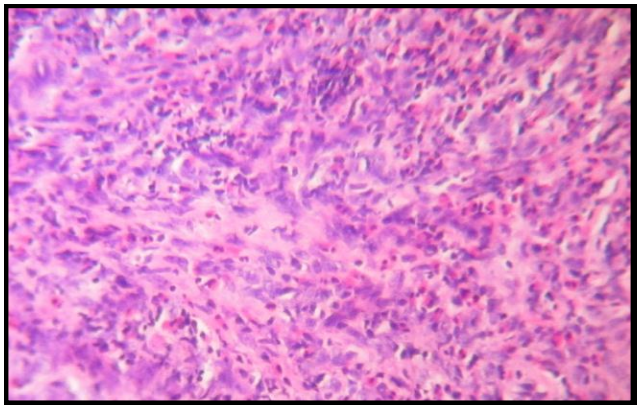

Figure 3: 10X- Under the necrotic tissue there was a dense, polymorphic, inflammatory infiltrate rich in lymphocytes and numerous eosinophils

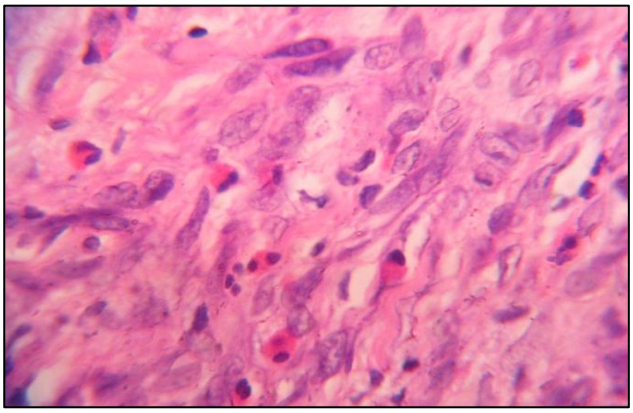

Figure 4: 100X- Atypical large mononuclear cells (long arrow) with abundant cytoplasm, irregular nuclear contours, fine chromatin and small nucleoli were scattered within the inflammatory infiltrate rich in eosinophils (short arrow).

DISCUSSION

Eosinophilic ulcer of the oral mucosa (EUOM) or traumatic ulcerative granuloma with eosinophilic stroma (TUGSE) was initially depicted in adults by Popoff in 1956.[1] In late 1960s this lesion was included within the spectrum of granuloma facialeand a few authors proposed the term, ulcerated granuloma eosinophilicum diutinum of the tongue' (Hjorting-Hansen and Schmidt, 1961).Later Shapiro and Juhlin, 1970 proposed this lesion as a distinct entity.

Since then, different names such as TGSE (Elzay, 1983; Hirshberg et al, 2006); traumatic eosinophilic granuloma of the tongue (Ficarra et al, 1997; Alobeid et al, 2004) and eosinophilic ulcer on the tongue, or the oral mucosa (El- Mofty et al, 1993; Mezei et al, 1995; Velez et al, 1997; Garcia et al, 2002) has been used to describe this lesion leading to further confusion.

Etiopathogenesis: The pathogenic mechanisms implicated in the development of EUOM are poorly understood and only a limited number of studies have been specifically designed to elucidate the origin of this condition.[1]

Role of trauma: The common suggested **pathogenesis** of' this lesion is ulceration resulting from some form of trauma, which permits the ingress of microorganisms, toxins, or foreign protein into the connective tissue.These substances in the predisposed persons induce a severe inflammatory response resulting from an exaggerated mast cell-eosinophil reaction similar to that observed in the pathogenesis of bronchial asthma.[2]

Role of eosinophils: According to Elzay, the increased numbers of mast cells suggested that interactions between mast cells and eosinophils might play a pathogenic role. Due to exaggerated mast cell-eosinophil reaction the mast cells degranulate, resulting in the release of mediators, which cause inflammation and also attract eosinophils which are a component of the immune system by the release of eosinophil chemotactic factor of anaphylaxis.[3] Eosinophils in general act as defensive elements of mucosal surfaces that respond not only to antigens but also to parasites, chemicals, and trauma. In contrast to neutrophil leukocytes, eosinophil leukocytes defend the host from macroorganisms rather than microorganisms, such as antigens and foreign bodies. Eosinophil leukocytes appear to have "lytic" potential, due to their cationic major basic proteins which causes cell and tissue destruction.[4] In contrast to their cytolytic action, eosinophil leukocytes participate in tissue remodeling. This peculiarity allows eosinophil leukocytes to concentrate in a tissue exposed to injury.[5]

Also eosinophils release aryl sulfates, which inhibit slow reacting substance of anaphylaxis and histamine (harmful mediators). Eosinophils further suppress basophils and mast cell degranulation and inhibit the release of other mediators of inflammation by mast cells. Eosinophils also produce a major basic protein, which causes cell and tissue destruction.[2]

Despite that, eosinophils produce a wide spectrum of other cytokines, like TNF, which enhances tissue damage and keep the inflammatory response unfinished.[6]

Recent studies have shown that eosinophils may also interact with fibroblasts and endothelial cells (Munitz and Levi-Schaffer, 2004). Their interaction with fibroblasts may result in a contribution towards wound healing via the synthesis of transforming growth factor (TGF) α and β, as demonstrated in a study using a mice wound-healing model (Wong et al, 1993). A lack of significant synthesis of transforming growth factors, by eosinophils has been demonstrated in traumatic ulcerative granuloma with stromal eosinophilia. This phenomenon may explain the frequent delayed healing observed in these lesions (Elovic et al, 1996).[6]

Role of cell mediated immunity: Although trauma seems to be important, other factors might be involved in the pathogenesis of this lesion. Immunohistochemical study by El-Mofty et al.(1993) revealed numerous T-cell specific antigen-presenting cells and concluded that cell-mediated immunity might play an important role in the pathogenesis. They suggested that recurrent trauma leads to, alteration of tissue antigens or introduces microbial products into the tissues; either event could incite a local immune reaction. Activated T lymphocytes produce numerous lymphokines which include IL-1, IL-5 and

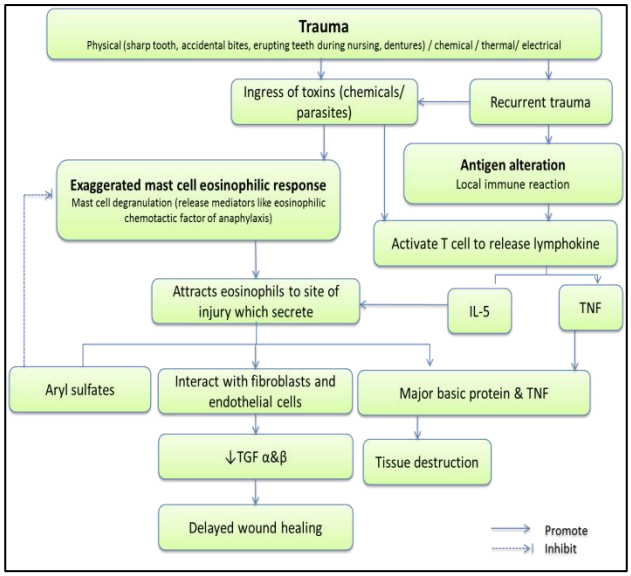

Figure 5: Summary of pathogenesis of EUOM

TNF which act as eosinophil-chemotactic agents. IL-5 is essential for the maturation of eosinophils and is also involved in the differentiation of mast cells. Thus the release of IL-5 might recruit mast cells in these lesions. Degeneration and necrosis of muscle, epithelial and endothelial cells might be caused by either degeneration of cytotoxic T-cells or by the toxic products of eosinophils.[7]

Clinically, all age groups, from one week to 92 years of age (mean age is 44 years) are affected, with a slight male predilection (Male: Female ratio is 1.6:1).[8] Predilection for men (5.25:1), mean age of 39 years, has been reported by Sklavounou and Laskaris. El-Mofty et al[7] observed a discrete predilection for women who frequently present asymptomatic lesions. EUOM preferentially found on the lateral and ventral surface of the tongue (47% reported by El-Mofty et al & 64% reported by Elzay et al), but can also occur on the lip, palate, mucobuccal fold and gingiva and manifests clinically as an ulcerated/ nodular-ulcerated lesion with raised and indurated borders, progresses rapidly, and commonly persists due to delayed healing for many days or months. The lesions are asymptomatic or extremely painful. Schmitt-Koppler et al. described it as an ulcer with erythematous edge and central base displaying white or yellowish removable fibrinopurulent membrane with no lymphadenopathy. The lesions occur in an isolated manner, are non-recurring, and can persist for 1 week to 8 months.[8] In addition, Ficarra et al. and Vélez et al reported cases of recurrent lesions, whereas Chung et al observed the simultaneous presence of multiple lesions.

Clinically, it mimics oral squamous cell carcinoma and microscopically, lymphoid neoplasm or Langerhans's cell disease. The clinical features of eosinophilic ulcer of the oral mucosa lead to wide differential diagnoses shown in (Table 1).

Histopathologically ulcerated, stratified squamous epithelium with hyperplastic epithelium on ulceration margins overlying a connective tissue stroma with dense Eosinophil-rich mixed polymorphic inflammatory infiltrate containing small T & B lymphocytes, macrophages and neutrophils is seen.[9]

Table 1: Clinical differential diagnoses for eosinophilic ulcer of theoral mucosa

Malignancies:	Squamous cell carcinoma Lymphoma Histiocytosis X Salivary gland tumours
Infections:	Tuberculosis Syphilis Herpes Deep fungal infections: Histoplasmosis
Autoimmune diseases:	Discoid lupus erythematosus Wegener's granulomatosis
Traumatic ulcer	
Major apthous ulcers	

Proliferating endothelial cell within granulation tissue and atypical-looking histiocytes with large size, containing variable amounts of cytoplasm, large nucleus with irregular nuclear contour, single prominent nucleoli and sometimes mitotic figures are seen involving the superficial mucosa and the deeper muscle layer. The origin of these mononuclear cells is debated suggesting their origin to be Histiocytic cells/ Dendritic cell marker/ Myofibroblastic cells/ Activated lymphoid cells (CD30, CD3, CD4 and CD8- T cells).[1]

Histopathological DD:Spectrum of conditions usually manifesting themselves as a single lesion can be considered in the differential diagnosis. When a patient presents a single and isolated oral ulcer in a given site, a differential diagnosis shouldalways include: chronic trauma, neoplasms like oral squamous cell carcinoma, haematological neoplasms and salivary gland malignancies (mucoepidermoid and adenoid cystic carcinoma), although unusual causes, such as tuberculosis, necrotizing sialometaplasia and syphilis couldalso be considered.[10] Solitary ulcers persisting for more than 2 weeks after treatment without signs of evident healing must be taken seriously and a biopsy ismandatory.

Prognosis & Treatment:Wait-and-see approach as spontaneous healing usually occurs within 1 month, but may rarely take as long as 8 months. Vélez et al [5] reported that EUOM disappears without treatment. Antibiotics, topical, intralesional and/or systemic corticosteroids, have been tried in longstanding cases. The effect of corticosteroids is debatable as El-Mofty et al. stated steroids to be effective due to proposed cell-mediated immunity in pathogenesis, contrary to these findings Segura and Pujol et al.[11] reported no response to steroid therapy and also since deep fungal infection is one of the differentials, steroid therapy is not an option. An incisional biopsy is often required for definitive diagnosis when no evidence of spontaneous healing is observed at 1-month follow up. Recurrence has been reported rarely.[12] Curettage, cryosurgery is also helpful, but surgical excision is the most commonly cited treatment procedure among the different therapies used. Elena et al.

proposed that surgical intervention may reactivate the healing response by stimulating local repair and growth factors which favour healing.

CONCLUSION

Traumatic granuloma is a benign reaction of the oral mucosa with trauma as the contributing factor. Recognition is important because it often mimics oral cancer. In most of the cases, the lesions heal spontaneously so there is no need for more radical surgery. Clinical, histopathological and follow-up data are crucial to achieve a correct diagnosis in the difficult and uncommon cases and to avoid possible overtreatment.

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