Innovations

Inflammatory lesion clinically masquerading as malignant lesion

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Abstract: *Oral ulceration is one of the most common lesion encountered in clinical practice which is of a multifactorial etiology. The ulcer is an entity which is a cause of concern for both the patient and the physician. The ulcers may be solitary or multiple. When the ulcers are multiple, they are usually chronic and benign. But when the ulcers are solitary, they may be acute or chronic. TUGSE is a rare, benign ulcerative lesion of the oral mucosa commonly affecting the tongue. TUGSE presents itself as a solitary asymptomatic or painful ulcer with rapid onset and has rolled out self-limiting borders. This paper presents a case series of TUGSE with varied presentations which mimicked malignancy, the diagnostic protocol and management strategies which resulted in complete resolution of lesion. In this paper all the three ulcers are found in the lateral border of the tongue. All the three patients responded well to the treatment with topical medications of 0.3% triamcinolone acetonide, topical chlorhexidine gluconate gel, and betnesol mouth rinse twice daily for one week.TUGSE clinically mimics malignant ulcers in clinical presentation and is often reported to a primary care physician or dentist. The presentation of the ulcer by itself causes cancerphobia to the patient. But still there remains a few unanswered questions pertaining to the etiology of the ulcers.*

Keywords: 1.*TUGSE, 2.Inflammatory ulcers, 3.Eosinophilic ulcers, 4.Malignancy*

Introduction:

Oral ulceration which is of multifactorial etiology is commonly encountered in clinical practice. An ulcer is often a sign of concern for both the patient and physician. The ulcers may be solitary or multiple. When the ulcers are multiple, they are usually chronic and benign. But when the ulcers are solitary, they may be acute or chronic. A chronic solitary ulcer is a cause of concern as it triggers the cancerphobia in the patients [1]. A rare ulcer referred to as Traumatic ulcerative granuloma with stromal eosinophilia (TUGSE), if present mimics a chronic non healing ulcer or malignant ulcer.

TUGSE is a rare, benign ulcerative lesion of the oral mucosa commonly affecting the tongue [2]. TUGSE presents itself as a solitary asymptomatic or painful ulcer with rapid onset and has rolled out self-limiting borders [3]. The exact etiology is obscure, traumatic irritation to the oral mucosa is reported to cause ulcers in 50% of individuals. TUGSE is referred to as eosinophilic ulcer, eosinophilic granuloma of soft tissue, ulcerative eosinophilic granuloma, or eosinophilic - cumdiutinum [4].A similar condition when noticed in children under two years of age is termed as Riga-Fede disease. These children have the habit of breastfeeding or suckling with a precocious eruption of teeth suggesting a traumatic etiology [5]. The histopathological feature of this rare presentation is the presence of dense, polymorphic inflammatory eosinophils and lymphocytes without any dysplasia [6].The lymphocyte accumulation is CD30+ lymphocytes, suggesting that TUGSE may be considered a lymphoproliferative disorder [6]. In a few cases there has also been a monoclonality of the lymphocytes increasing the weightage of the abundant presence of eosinophils causing degeneration of the epithelium by its cytokine network [7]. The lack of synthesis of TGF - α, and β causes delayed wound healing [3]. The clinical presentation of this lesion being histologically benign, and self-healing, supportive management with watchful neglect is the ideal management strategy raises suspicion of malignancy to any clinician.

This paper presents a case series of TUGSE with varied presentations which mimicked malignancy, the diagnostic protocol and management strategies which resulted in complete resolution of lesion.

Clinical presentation:

Case 1:

A 19-year-old male presented with ulceration on his left side of the tongue of one-year duration. History revealed difficulty in chewing food on the affected side and the presence of a burning sensation on the consumption of hot and spicy food. He is a routine consumer of smokeless tobacco with areca nut and pan, with the habit of using 4-5 packets of pan and placement of the same on the left buccal mucosa. The patient also reports occasional smoking and alcohol consumption. Clinical examination revealed a solitary irregular ulcer measuring about 2cmx1.5cm seen on the left lateral border of the tongue with raised and everted margin. Indentation marks of tooth cusps were seen along the ulcer border. [Figure 1]. There was depapillation and blanching of the tongue on the ulcerated side. On palpation, the ulcer was tender with an indurated base. Mucosal changes were seen on the right and left buccal mucosa with fibrosis along with reduced mouth opening suggestive of oral submucous fibrosis. These clinical findings suggest a possible traumatic ulcer, Oral Submucous Fibrosis (OSMF) turning into malignancy, and primary tongue carcinoma.Initially, coronoplasty of the adjacent cuspal tips was done, and an incisional biopsy from the tongue was performed. [Figure 1]

Case 2:

A 61-year-old female reported with the chief complaint of the presence of ulcer on the left border of the tongue for the past few weeks. History revealed difficulty in chewing for the past days, with trauma from sharp cuspal tips impinging on ulcer and causing pain. The patients' personal history revealed no tobacco usage.Intra orally*, an* oval-shaped ulcer was seen on the left lateral border of the tongue, measuring about 2x2cm. The ulcer had undermined margins and a pseudomembranous base and surrounding erythematous halo. The ulcer showed mild induration tenderness with no secondary changes on palpation. Submandibular lymph nodes of the left side were enlarged and tender. The patient experienced mild dysphagia. The clinical features were suggestive of an ulcer with traumatic origin or possible chronic ulcer with malignant changes due to irritation of the sharp teeth. The source of irritation left mandibular second premolar, and first molars were extracted under local anesthesia along with an incisional biopsy from the ulcer on the left lateral border [Figure 2].

Case 3:

A 50-year-oldmale presented with a painful ulcer on the left lateral tongue of 3 weeks. The patient's history revealed ulceration seen on his left lateral border of tongue for the past ten days with pain in speaking and swallowing. On clinical examination, two irregular-shaped ulcers measuring about 3.5cmx2.5cm and 0.5x1cm respectively were seen on the left lateral border of the tongue with a sloping edge, floor covered with necrotic tissue, and surrounding erythema. On removing the necrotic slough, the underlying deep muscle tissue was exposed. The ulcer was non-tender, and no secondary changes were seen. The patient has no systemic comorbidities. This clinical picture would possibly suggest the ulcer of possibly being traumatic in nature or necrotizing sialometaplasia, infectious etiology or possibly malignant ulcer. Sharp cusps of the tooth in the ulcer region were rounded, and an incisional biopsy was done [Figure 3].

Figure 1. Case 1 shows an ulcer with proliferative margins in the left lateral border of the tongue (pre and post healing)

Figure 2 Case 2 - A solitary ulcer on the left lateral border of the tongue (pre and post healing)

Figure 3: Case 3 Multiple ulcers on the left lateral border of the tongue (pre and post healing)

Histopathological findings:

The histopathological features in all the 3 cases revealed mixed inflammatory cells infiltrate, which consisted of predominantly plasma cells, lymphocytes, macrophages, and neutrophils intermixed with eosinophils. These cells were seen extending into the skeletal muscle causing degeneration suggestive of Traumatic ulcerative granuloma with stromal eosinophilia (TUGSE) [Figure 4,5]

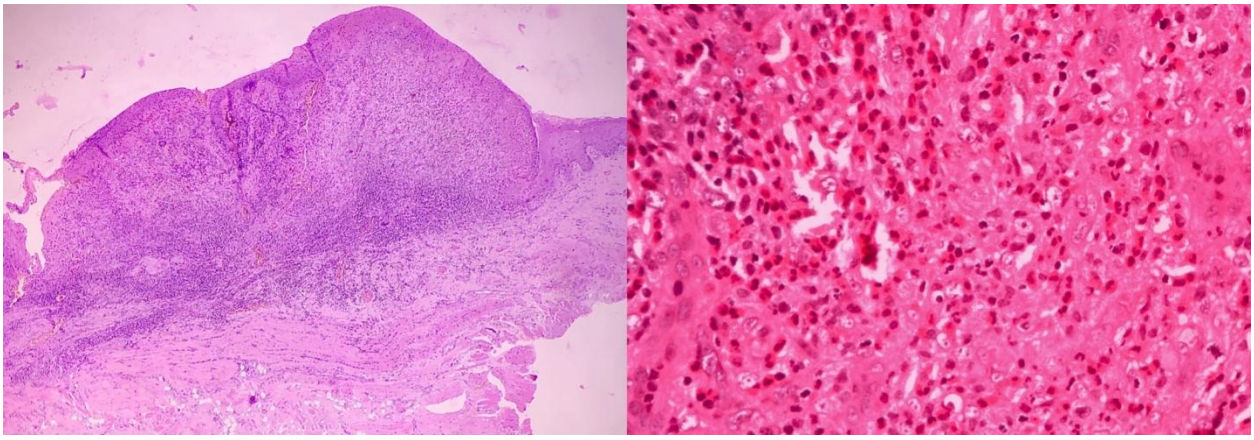

Figure 4: Histopathological images in 10x and 40x magnification

Treatment:

We eliminated the primary traumatic factor in all the presented cases as part of the treatment protocol. The patient was started on topical medications of 0.3% triamcinolone acetonide, topical chlorhexidine gluconate gel, and betnesol mouth rinse twice daily for one week. When the patients were reviewed after a four-week duration, a complete resolution of the ulcer was noted in all the cases. [Figure 2].

Discussion:

TUGSE is a rare, reactive but self-limiting lesion with an unclear etiology initially reported in children by Riga and Fede in 1881 and 1890. respectively, and in adults by Popoff in 1956. In children, the lesion was called Cardarelli aphthae, sublingual ulcer, sublingual granuloma or Riga Fede lesion [4]. There have been several oral lesions with the presence of eosinophils viz: eosinophilic lymphoid granuloma(kimura's disease), eosinophilic fasciitis, eosinophilic granuloma (histiocytosis X). The histomorphology and the clinical presentation of Rige-Fede disease was different from the other lesions by the presence of non-osseous involvement, solitary ulcerations, absence of sheets of eosinophils, the term of TUGSE is used [8]. There are two significant peaks in the incidence, with the first being in the first two years of life and the second in the fifth- seventh decade of life[9]. Our case series had a presentation in different age groups. The etiology of this lesion has been highly debated with viral, toxic agents and accidental bites being the most common. However, in an animal study model using rats, an ulcer with similar histomorphologic features has been established in rats [10,11]. Hence it is believed that trauma seems to be the most common cause and the occurrence of the lesion in sites of frequent trauma has further made us accept the fact. However stromal eosinophilia, which is one of the key features of TUGSE is not a common feature of all traumatic ulcers. One of the probable reasons is that the migration of mast cells into the lesion at an earlier stage causes the release of eosinophil chemotactic factor which attracts a flux of eosinophils to the lesional site. And in a study, it has been demonstrated that there is a marginal rise of mast cells in TUGSE lesions [8]. So even though the role of

trauma seems to be the most plausible reason for the occurrence of this lesion, the pathogenesis is markedly different from that of other lesions of traumatic origin.

The most common site of occurrence is the tongue, floor of the mouth, palate, and gingiva [10] but all cases presented with a lesion on the left lateral tongue. Clinically the ulcer persists with an elevated margin, fibrinous floor, and erythematous halo, which proliferates and mimics a malignancy. The duration of these ulcers is from weeks to months, and healing is delayed unless the traumatic cause is removed. The clinical presentation of the ulcer may also be mimicking a tuberculous lesion or a deep fungal lesion [11].

Delayed healing of these ulcers is associated with a lack of secretion of TGF-α and β by eosinophils [12]. The ulcer inflicted due to trauma causes inflammation resulting in myositis that can deeply penetrate the tissues if left untreated. The ulceration extends into the submucosa, deep muscle fibers, and salivary glands. Bhaskar and Lilly et al. coined "traumatic granuloma" [4,14]. Histopathologically, TUGSE lesions are present with abundant inflammatory cells infiltrated with lymphocytes, eosinophils, and single nucleolus infiltrating the underlying muscle bundles [14]. Immunohistochemistry analysis has shown positive CD30, reported first by Ficarra et al [14] CD30 are markers expressed when B and T cells are activated in lymphoproliferative disorders [15,16]. This classical clinical picture of TUGSE makes a clinician make a clinical diagnosis of malignancy in the initial visit[17,18]. However, on histopathological examination, if the ulcer does not show the presence of any dysplastic cells but only shows the presence of inflammatory cells, then a diagnosis of TUGSE is made, the patient is treated with corticosteroids, antiseptics, and elimination of local irritants [19,20].

The role of steroids is understandable given the abundance of eosinophils in an established lesion, the usage of immunosuppressants could reduce the inflammatory cells. However, in a small series of cases, there has been a recurrence of the lesion in 40% of cases when steroids were used in their management [21]. Except for that observation none of the other studies have reported on any recurrence of the lesion [17,19,20]. In our case series all the patients were treated with corticosteroids, recurrences were not observed in any of the patients. There have been few case reports suggesting local excision and cryotherapy for the management of the lesion. But none of these case reports have made any mention about the recurrence of the lesion [22,23]

To broadly summarize the features of TUGSE trauma seems to be the most common cause of this ulcer given the site of occurrence and the lack of definitive role of viral or toxic agents with a peak prevalence in two decades. Role of the mast cells in the pathogenesis process in the initial stages is hypothesized but till date there has not been much research activity to detect the mast cell or therapeutic role of antihistamines in its management. It also mimics a lymphoproliferative disease giving the features of malignancy. There have also been numerous inflammatory mediators implicated for the delayed healing of the lesion. There are no standardized treatment protocols due to the limited number of cases being reported from selected regions of the world.

Conclusion:

TUGSE clinically mimics malignant ulcers in clinical presentation and is often reported to a primary care physician or dentist. The presentation of the ulcer by itself causes cancerphobia to the patient. A careful history, clinical examination, and biopsy are essential to confirm the diagnosis. A correct diagnosis and initiating most appropriate biopsy-results in resolution of the lesion. Nevertheless, there are still a lot of

unanswered questions about the exact etiology and probable pathogenic mechanisms which when understood can lead to an easier diagnosis and the usage of alternate drugs in its management.

Conflicts of interest :
There is no conflict of interest regarding the publication of this article.

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