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Eosinophilic Ulcer: Report of Four Clinical Cases

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ABSTRACT

Unique histopathological type of chronic traumatic ulceration of the oral mucosa is the chronic inflammatory process with ulceration and eosinophilia, which may exhibit a pseudo invasive deep inflammatory reaction and regresses slowly. Interestingly, many of these lesions resolve after an incisional biopsy. The aim of this paper is to report four clinical cases of eosinophilic ulcers, with emphasis on an appropriate diagnosis by biopsy. In the four cases reported, an incisional biopsy was chosen because the lesions presented clinical characteristics of a probable squamous cell carcinoma, which was discarded after the surgical procedure and histopathological analysis. The performance of biopsy in cases of eosinophilic ulcer is essential for a correct diagnosis since the lesion resembles malignancies and other conditions.

Keywords: *Eosinophilic Ulcer, Diagnosis, Biopsy, Squamous Cell Carcinoma*

Introduction

Eosinophilic ulcer (EU), also known as traumatic eosinophilic granuloma, traumatic ulcerative granuloma with eosinophilic stroma (Dhanrajani and Cropley, 2015; Gonçales *et al*., 2007), or ulcerative eosinophilic granuloma (Dhanrajani and Cropley, 2015), is a chronic, benign, rare, and self-limiting lesion of the oral mucosa of unknown etiology (Didona *et al*., 2015).

Clinically, it occurs as an ulcer with a white, keratotic border, usually on the lateral tongue, present for weeks, with or without pain, and raising the suspicion of malignancy, traumatic ulcerations, fungal and bacterial infections. It is worth noting that any site with underlying muscle may be involved

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and that synchronous or metachronous bilateral lesions may occur. (Bortoluzzi *et al*., 2012; Regezi *et al*., 2017; Woo, 2017).

Traumatic ulcerative granuloma is secondary to deep penetrating inflammation involving the underlying skeletal muscle and is most often associated with trauma but can also be seen in chronic traumatic ulcerative conditions such as aphthous ulcers (Shen *et al*., 2015; Woo, 2017).

The histopathological findings are characteristic and consist of mixed inflammatory infiltrates rich in eosinophils, involving the superficial mucosa and the deeper muscle layer, accompanied by a population of large mononuclear cells of controversial origin (Bortoluzzi *et al*., 2012; Dhanrajani and Cropley, 2015; INCA, 2022; Woo, 2017).

Usually lesions can heal after biopsy, otherwise topical steroids, intralesional steroid injections, or complete excisions are indicated for management. Recurrence is common, especially if the patient has a flaccid or enlarged tongue, for example, older patients who wear lower complete dentures or who have lost teeth in the posterior jaw (Shen *et al*., 2015; Woo, 2017).

The aim of this paper is to report four cases of EU, highlighting the importance of an adequate diagnosis by biopsy, due to its similarity with other lesions, including malignant ones.

Clinical Case Reports

Case 1

A 61-year-old white male patient presented to the Army Service of Oral Medicine (OCEx) complaining of a painful ulcer of approximately 3 cm, present for approximately three weeks, on the lateral border of the tongue on the right side. The patient's past pathological history includes a stroke eight years ago and the removal of a skin carcinoma. On clinical examination, no palpable lymph nodes were detected. Intraoral examination revealed the presence of root remnants and dental calculus (Fig. 1A and Table 1). The patient reported being a drinker for 30 years. Due to the patient's history and the characteristics of the lesion, the probable clinical diagnosis was squamous cell carcinoma, and an incisional biopsy was performed. The final diagnosis obtained was EU, and the tooth edge that caused the local trauma was smoothed (Fig. 2A). The patient was instructed to rinse with 0.12% chlorhexidine twice a day for 15 days, and topical Triamcinolone Acetonide three times a day (Shen *et al*., 2015; Woo, 2017). After 15 days, a significant improvement in clinical appearance was observed. After one month of follow-up, the lesion was completely healed.

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Case 2

A 57-year-old white female patient came to the Army's Oral Medicine Service (OCEx) with a crusted, itchy and painful lesion on her upper lip that had been there for two months (Fig. 1B and Table 1). She reported using cephalexin, acyclovir (orally and as an ointment), mupirocin, and boric acid dissolve in water, with no evidence of improvement. During her medical history, the patient revealed that she had been a smoker for 20 years, smoking one pack a day, and having quit a year ago. The diagnostic hypothesis was squamous cell carcinoma, and an incisional biopsy was performed. Histopathological analysis revealed an ulcer with granulation tissue formation and inflammatory infiltrate composed of lymphocytes, plasma cells and numerous eosinophils extending to the deeper layers, compatible with the diagnosis of EU (Fig. 2B).

Case 3

A 38-year-old white female patient was referred to the Army Oral Medicine Service (OCEx) with an ulcerated lesion on the right lower labial mucosa, measuring approximately 2.5 cm, with an erythematous halo and necrotic surface, which had been present for two weeks (Fig 1C and Table 1). The patient reported having bitten his lip a few days before the lesion appeared and had taken topical Triamcinolone Acetonide for one week. An incisional biopsy was performed in. two sites, with the diagnostic hypothesis of EU, which was confirmed by the histopathological report (Fig. 2C).

Case 4

A 68-year-old white male patient sought the Army Oral Medicine Service (OCEx) complaining of a tongue lesion that appeared after trauma, with evolution of about 10 days. Clinically, it was observed a painful ulcer with precise limits, irregular contours, elevated edges, were present on the tongue dorsum (Fig. 1D and Table 1). According to these clinical features, the main diagnostic hypotheses were traumatic ulcer and squamous cell carcinoma. After the incisional biopsy, the final diagnosis obtained was EU (Fig. 2D).

A summary of the characteristics of the four cases of eosinophilic ulcer is shown in Table 1.

Table 1: Summary of the characteristics of the four cases of the EU.

Cases	Gender	Age	Site of the EU	Smokers	Drinkers	Trauma	Pain
Case 1	Male	61	Lateral border of tongue	No	Yes	No	Yes
Case 2	Female	57	Upper lip	Yes	No	Yes	Yes
Case 3	Female	38	Mucosa of lower lip	No	No	Yes	No
Case 4	Male	68	Dorsum of tongue	No	No	Yes	Yes

Figure 1: Clinical features: Eosinophilic ulcers on lateral border of tongue (A); upper lip (B); mucosa of lower lip (C); and dorsum of tongue (D).

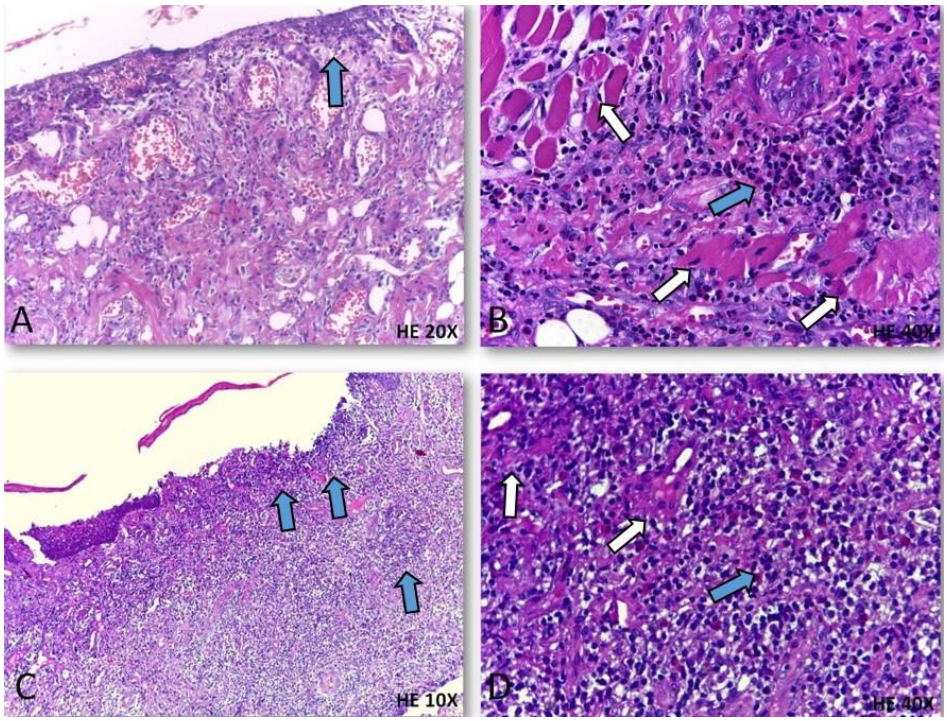

Figure 2: Histopathological characteristics: Mixed, intense, reactive inflammatory infiltrate, rich in eosinophils (blue arrows), which extends deeply involving the superficial mucosa, the submucosa, and the deeper muscle layer, with degeneration of muscle fibers and necrosis (white arrows) (A, B, C). The vascular connective tissue may be hyperplastic (A, D).

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Discussion

EU was first described in adults by Popoff in 1956 and recognized as an independent entity in 1970 by Shapiro and Juhlin (Fonseca *et al*., 2013). However, a similar condition, restricted to the infant population, had already been clinically described by Riga (1881) and microscopically by Fede (1890) (Fonseca *et al*., 2013; Gonçales *et al*., 2007; Vélez *et al*., 1997), and was later accepted as a spectrum of EU in adults (Fonseca *et al*., 2013).

Different terms have been used in the literature to describe this entity, including eosinophilic ulcerated granuloma of the tongue, traumatic granuloma of the tongue, eosinophilic granuloma of the tongue, ulcerative eosinophilic granuloma of the tongue, traumatic ulcerative granuloma with eosinophilic stroma, or simply eosinophilic ulcer (EU) (Fonseca *et al*., 2013; Gonçales *et al*., 2007; Vélez *et al*., 1997).

EU is considered a reactive, benign, self-limiting disease of poorly understood pathogenesis. Many etiologic hypotheses have been proposed, emphasizing mainly trauma (Damevska *et al*., 2014). Most authors suggest that the lesions are caused by accidental biting or repetitive trauma against sharp, misaligned or fractured teeth (Shen *et al*., 2015; Neville *et al*., 2016; Woo, 2017).

The high incidence of injury to the tongue, which is easily exposed to trauma by chewing, and the history of traumatic injury in approximately one-third to one-half of the cases, argue in favor of this hypothesis (Didona *et al*., 2015; Vélez *et al*., 1997). In the present study, three of the four reported cases were associated with trauma.

On the other hand, the frequency of injuries to the oral mucosa is much higher than the prevalence of EU, and the occurrence of multiple lesions also weakens the theory of traumatic origin (Damevska *et al*., 2014; Gonçales *et al*., 2007). Therefore, it is likely that although trauma is important, other factors are involved in the pathogenesis of this entity (Gonçales *et al*., 2007; Vélez *et al*., 1997). Studies suggest that trauma may act only as an adjuvant factor, allowing other agents to enter the oral mucosa, although so far none have been identified (Fonseca *et al*., 2013; Song *et al*., 2011).

EU generally shows the equal distribution between men and women, involving especially those in the 5th and 7th decades of life (Fonseca *et al*., 2013). However, in some studies, men were preferentially affected, with two prevalence peaks being observed: (1) in the first decade of life and (2) around the 4th, 5th, 6th or 7th decade (Gonçales *et al*., 2007; Vélez *et al*., 1997). In other reports, women were slightly more affected, comprising both children and the elderly (Dhanrajani and Cropley, 2015; Didona *et al*.,

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2015; Gonçales *et al*., 2007; Vélez *et al*., 1997). In this study, there was no sex predilection, involving one patient at the end of the 3rd decade and the others between the 5th and 6th decades of life.

Clinically, an ulcer with hardened and elevated margins is observed, with a white or yellowish base, an erythematous periphery and a surface covered by a fibrinous membrane (Damevska *et al*., 2014; Song *et al*., 2011). Pain or tenderness may be present in about 30% of cases (Didona *et al*., 2015). Although the tongue is the most common location, the lips, the buccal mucosa, the palate, the gums, the floor of the mouth and the retromolar region can also be affected (Damevska *et al*., 2014; Didona *et al*., 2015; Neville *et al*., 2016; Vélez *et al*., 1997; Woo, 2017). A solitary painful ulcer is the main clinical presentation of this entity, as in the four cases reported. However, cases with multiple lesions, although rare, have been described (Damevska *et al*., 2014; Fonseca *et al*., 2013; Regezi *et al*., 2017).

The histopathological findings consist of a mixed, intense, reactive inflammatory infiltrate, rich in eosinophils, which extends deeply involving the superficial mucosa, the submucosa, and the deeper muscle layer, with degeneration of muscle fibers and necrosis (Dhanrajani and Cropley, 2015; Didona *et al*., 2015; Fonseca *et al*., 2013; Gonçales *et al*., 2007; Vélez *et al*., 1997). In addition, the vascular connective tissue at the bottom of the ulcer may become hyperplastic, causing superficial elevation (Neville *et al*., 2016; Woo, 2017). In some cases, there is epithelial hyperplasia with atypia that may mimic a malignancy, although in a long-standing ulcer it is more likely that the atypia is reactive in nature (Dhanrajani and Cropley, 2015; Regezi *et al*., 2017).

Depending on the affected site and its clinical presentation, EU may present a variety of differential diagnoses, including malignant neoplasms such as squamous cell carcinoma and non-Hodgkin's lymphoma, viral infections such as those caused by herpes simplex virus or Epstein-Barr virus, deep fungal infections, bacterial infections such as tertiary syphilis, autoimmune diseases, and reactive proliferative processes (Dhanrajani and Cropley, 2015; Didona *et al*., 2015; Fonseca *et al*., 2013; Gonçales *et al*., 2007). Clinical and histopathological features, together with special staining techniques for microorganisms and immunohistochemical markers, should help distinguish such conditions (Dhanrajani and Cropley. 2015).

Various therapeutic options have been described for EU, including topical, intralesional and/or systemic corticosteroids, curettage, antibiotics, cryosurgery and surgical excision (Bortoluzzi *et al*., 2012; Damevska *et al*., 2014; Song *et al*., 2011). However, the benign behavior of the lesion predicts spontaneous remission before therapeutic approaches are needed. Spontaneous healing usually occurs within one month but can take up to eight months (Didona *et al*., 2015). The EU often heals spontaneously

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after diagnostic biopsy, and the reason for such behavior may be reactivation of the healing response after surgical intervention (Bortoluzzi *et al*., 2012; Damevska *et al*., 2014; Didona *et al*., 2015; Neville *et al*., 2016).

Recurrences are not common, although some authors advocate surgical excision to achieve complete resolution (Fonseca *et al*., 2013; Regezi *et al*., 2017). Although the EU is benign in nature, clinical follow-up is mandatory in all cases (Didona *et al*., 2015; INCA, 2022).

Conclusion

The proper diagnosis of EU by biopsy is extremely necessary, since the lesion can mimic malignant lesions, especially squamous cell carcinoma, fungal, bacterial, or even autoimmune diseases. Similarly, due to the benign and self-limiting nature of EU, in most cases the lesion will heal after biopsy without the need for further treatment or more aggressive surgical intervention.

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