Eosinophilic Ulcer of the Oral Cavity, Approach, And Differential Diagnosis
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1. Introduction
Benign ulcerations of the oral mucosa may have a similar appearance to malignant lesions [1, 2]. There are several conditions, both local and systemic, that can manifest as oral ulcers, and that can correspond, on many occasions, to both infectious and autoimmune causes. Probable etiology can often be determined by a complete medical history and a careful physical examination. However, on several occasions, an exhaustive diagnostic study will be necessary, counting on a range of diagnostic suspicions.

Eosinophilic Ulcer of the oral cavity is an infrequent, self-limited clinical and histopathological entity, benign in nature and of little known etiology that can mainly affect adults and has a predilection for the lingual region [3]. The pathogenic mechanisms involved in the development of this entity remain poorly understood [3]. However, local trauma is considered the most reported predisposing factor [3]. Clinically, Eosinophilic Ulcer of the oral cavity usually manifests as a solitary, fast-growing ulcer with raised indurated margins, most frequently located on the lateral surface of the tongue [3]. Other less common locations are the palatal and gingival mucosa and the floor of the mouth [3]. The diagnosis of Eosinophilic Ulcer is difficult and requires a correct differential diagnosis, since different entities may share both the clinical and histopathological results [2].
The objective of this work is to report a case of recurrent Eosinophilic Ulcer of the oral cavity, located at the lingual region, in a female patient with a history of other ulcerative lesions in the oropharynx and larynx; and whose study and approach required the performance of multiple biopsies to achieve the diagnosis, after which an adequate remission of the disease was achieved. Furthermore, we consider it appropriate to discuss the differential diagnosis of ulcerative lesions of the oral mucosa to adequately guide the etiological study.

2. Clinical Case
We present a 54-year-old patient, native of Philippines, without toxic habits, without a history of previous trauma to the tongue or oral cavity, with a medical-surgical history of an ulcerative lesion in the left tonsil in 2015, whose pathological study was normal; another ulcerative lesion on the soft palate, whose pathological study was nonspecific; an extended total epiglottectomy in 2018 due to the presence of an epiglottic ulcer on its laryngeal face with extension to both arytenoepiglottic folds, whose pathological anatomy result revealed the presence of inflammatory ulcerative tissue, negative for malignancy and HPV.
In July 2020, as a result of a painful oral lesion, she attended the Otorhinolaryngology Service of our hospital, where the oral examination revealed an irregular ulcerative lesion, painful to the touch, with whitish margins, approximately 2.5 cm of greater diameter, located at the level of the right lateral border of the tongue, with an evolution of several months (Figure 1). We proceeded to make a first biopsy, whose anatomopathological result showed the...
presence of ulcerative tissue with the predominance of an acute inflammatory infiltrate and absence of malignancy. After the first biopsy, the ulcerative lesion persisted and increased in size, so in November 2020, the patient returns to the emergency department, reporting growth of the ulcerative lesion on the right lateral lingual border, characterized by being exophytic, irregular, painful, with a rapid and progressive size increase compared to the initial lesion. A new biopsy was taken, with the result of a squamous epithelium fragment with the presence of acantholytic intraepidermal cleavage, suggestive of Pemphigus type lesion; sample in which it was suggested to broaden the analysis and study to achieve the diagnosis.

Figure 1: Initial presentation image of the lesion on the right lateral border of the tongue

Given the inconclusive results, in January 2021, a third biopsy of the lingual lesion was performed, which revealed an ulcerative lesion with granulation tissue, with a polymorphic inflammatory infiltrate with the presence of eosinophils and that was extended to the deeper structures (Figure 2). Furthermore, a broad immunohistochemically panel was carried out, ruling out the possibility that it was a lymphoproliferative disease or a spirochete, leishmania or EBV infection. Similarly, the sample was also negative for HSV, mycobacteria, fungi, and malignancy. Regarding general laboratory blood tests, all parameters were within normality.

Figure 2: Pathological anatomy study of the lesion on the right lateral border of the tongue, which contains granulation tissue, with a polymorphic inflammatory rich in eosinophils

Treatment was started with oral corticosteroids in a descending regimen with a partial initial response. In February 2021, a fourth perilesional biopsy was taken to carry out an immunofluorescence study. The pathological anatomy result showed the presence of an inflammatory infiltrate with eosinophils, with the absence of neo-plastic infiltration and a direct immunofluorescence study that was negative for all immunoglobulins and C3.

At this point, an idiopathic lingual Eosinophilic Ulcer vs. a Horton Disease were suspected. However, given the presentation pattern and the pathochrony, Horton Disease was reasonably ruled out. The Patient continued with oral corticosteroid treatment.

During the subsequent follow-up, it was only possible to verify the postoperative changes with the practical resolution of the ulcerative lesion, without observing recurrence of the lesion after a follow-up time of 5 months (Figure 3). In June 2021, she received the last oral dose of corticosteroids.

Figure 3: Image showing the resolution of the initial ulcerative lesion, note the postoperative changes of the multiple biopsies

3. Discussion

Eosinophilic Ulcer of the tongue or Traumatic Ulcerative Granuloma with Stromal Eosinophilia (TUGSE) is an infrequent clinical and histopathological entity, benign in nature and with an unclear etiopathogenesis [4, 5]. Presents two age peaks, appearing during the first 2 years and then in the fifth decade of life [6]. It does not usually present a clear distinction by sex or an established recurrence rate [7].

It usually presents as a lesion with a subacute-chronic clinical course, with indurated edges and a fibrin base, with a variable size [8]. More than 50% of the lesions are located at the tongue, on the back or lateral edges, but they can occur anywhere on the oral mucosa. It usually has a rapid growth, developing in days to weeks [9, 10] Despite spontaneous regression, healing can take weeks and even months [7, 11], as in our case. It is important to emphasize that some authors propose a traumatic or stress trigger as the etiology of Eosinophilic Ulcer, while others refer to reactivation of viral processes as the etiology of the disease [7].

Histopathological diagnosis is essential, characterized by a polymorphic infiltrate, rich in eosinophils, which affects the superficial
mucosa and the muscular layer. We speak of defective eosinophils with low levels of cytokines, the same ones that intervene in tissue repair, such as Transforming Growth Factor Beta (TGF B) [5].

In recent years, the presence of CD30 + lymphocytes have been found in lesional infiltrates, then Eosinophilic Ulcer of the oral mucosa has been related to lymphoproliferative entities such as Anaplastic Large Cell Lymphoma and Lymphomatoid Papulosis, which also present CD30+ acquired immunity cells [7, 12].

Within the differential diagnosis of Lingual Eosinophilic Ulcer there are entities that can manifest as oral ulcers and that must be ruled out due to their aggressive nature and the need for specific treatments. These include: Squamous Cell Carcinoma, Pemphigus, Temporal Arteritis or Horton Disease; also infectious entities such as Leishmaniasis, Primary Syphilis or Epstein Barr Virus infection, among others [13, 14]. To emphasize in some, Squamous Cell Carcinoma has clear risk factors such as exposure to tobacco, alcohol, or the presence of Human Papillomavirus (HPV); Temporal Arteritis occurs mainly in elderly patients, presenting fever, asthenia, weight loss and headache. Syphilitic chancre can be found in the oral cavity in up to 4% of patients, observing a clean, painless ulcer, accompanied in most cases by regional lymphadenopathy. Other rarer causes may be iatrogenic or due to medications [13]. All these entities will be differentiated mainly by particular histopathological findings in the context of a medical history that will help to direct the diagnosis.

Traumatic Ulcerative Granuloma with Stromal Eosinophilia usually resolves on its own in most cases. It is curious to see how patients after the performance of an incisional biopsy tend to heal quickly their lesions, suggesting that the biopsy itself can regulate the healing process. Symptomatic management should be the mainstay in the treatment of these patients. A soft diet can be recommended avoiding spicy foods; associated with topical or oral analgesics, as well as an assessment by a dental professional if dental pathologies are evidenced or suspected.

The use of oral corticosteroids is discussed, considering as an advantage the reduction in the healing window [7, 15].

4. Conclusions

Eosinophilic Ulcer is a painful, reactive entity that mainly affects the tongue in adults, and can clinically mimic squamous cell carcinoma or other benign conditions [7].

References