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Traumatic Ulcerative Granuloma with Stromal Eosinophilia In Oral Mucosa: A literature review

A Project Submitted to

The College of Dentistry, University of Baghdad, Department of Oral Diagnosis

In Partial Fulfillment for the Bachelor of Dental Surgery

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Certification of the Supervisor

I certify that this project entitled **" Traumatic Ulcerative Granuloma with Stromal Eosinophilia In Oral Mucosa: A Literature Review"** was prepared by fifth year student **Borooj Luay Mahdi** under my supervision at the College of Dentistry / University of Baghdad in partial fulfillment of the graduation requirements for the bachelor degree in dentistry.

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Dedication

To my dear parents, sisters and brother for their support and encouragement.

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Abbreviation	Phrase
TUGSE	Traumatic ulcerative granuloma with stromal eosinophilia
HE	hematoxylin and eosin stain
CTOM	Chronic trauma of the oral mucosa
OSCC	oral squamous cell carcinoma
ALHE	Angiolymphoid Hyperplasia with Eosinophilia
HTLV-1	Human T-cell leukemia virus type 1

Introduction

Oral ulceration is a common report encountered by the oral physician, and a solitary ulcer of long duration especially when it is asymptomatic and occurs in middle aged and elderly patients is always under suspicion for oral squamous cell carcinoma,Chronic trauma of the oral mucosa (CTOM) due to repeated mechanical irritation from an intraoral injury agent has been debated as an oral potentially malignant disorder contributing to oral carcinogenesis and needs to be evaluated ruling out other associated contributing factors like tissue abuse habits and oral hygiene**(Banerjee, Abhishek, et al.2021).**

Traumatic ulcerative granuloma with stromal eosinophilia is an uncommon lesion characterized by solitary ulceraon of the oral mucosa. Riga first defined this lesion clinically in 1881, and Fede first described it histologically in 1890. Shapiro and Juhlin recognised it as a disnctenty in 1970, but it was only in 1983 that Elzy coined the word TUGSE. Since TUGSE is not widely recorded in the literature, the exact frequency is uncertain, but it is thought to be fairly frequent. Men and women are affected almost equally, with a slight female predominance. It can be reported at any age, but it is most frequently discovered in the fifith decade of life.(**Keshwar, Shashi, et al. 2021).** TUGSE presents as a single ulcer which may be asymptomatic or associated with pain with the dorsum or the tip of the tongue being the most common site. The importance of this rare lesion lies in the fact that it is often misdiagnosed as oral carcinoma or specific infections like tuberculosis, primary syphilis or Epstein-Barr virus ulcer. Biopsy is mandatory and exhibits typical histological findings diffuse polymorphic inflammatory infiltrate, predominately consisting of histiocytes, activated and predominantly T-lymphocytes, and of eosinophils with the lesion extending deep into the submucosa, deeper muscle fibres and even the salivary glands**(Chandra, Sunira, et al. 2014).**

TUGSE is also called by other names including eosinophilic granuloma, eosinophilic ulcer, Riga Fede disease (in infants and children) and atypical histiocytic granuloma**(Chavan, S. S., & Reddy, P. 2013).**

The aetiopathogenesis of TUGSE is debatable but a localised traumatic cause is a significant predisposing factor , though it may be absent in half of the cases. Eosinophils are known to regulate local inflammatory and immune responses; hence, their presence is associated with inflammation and infection and their abundance in this lesion indicates an associated inflammatory component. **(Hirshberg, Abraham, et al. 2006)**.The pathogenesis of TUGSE is uncertain; however, trauma induced ulceraon, allows microorganisms, toxins, and foreign parcles to enter the surrounding tissue. The mast cell-eosinophil reacon, which recruits eosinophils cause more damage by exacerbang inflammaon locally, is one of 8 the considered pathogenesis of the lesion(**Sivapathasundharam, B., & Lavanya, S. 2005).**

Chapter one

Review of literature

Review of Literature

1.Review of Literature

1.1Oral Ulcer

Ulcer is a break in epithelial continuity of the mucous membrane, disintegration and necrosis of epithelial tissue with penetration into the epithelial-connective tissue border, with its base at a deep level in the submucosa, or even within muscle or periosteum. Ulceration is the most common lesion of oral mucosa and is the manifestation for many local and systemic disorders **(Scully, 2013).**

Generally speaking, the morphology of the ulcerative lesion including its shape, size, border and base characteristics, as well as the presence or absence of a pseudomembrane and/or peripheral component, provide important and sometimes definitive clues to the diagnosis. Equally important to the accurate description of the morphologic features of ulcerative lesions is the assessment of their number (single or multiple), onset and duration (acute or chronic), and potential for recurrence (recurrent or non-recurrent). Although overlapping features among ulcerative lesions of widely variable etiology and significance are expected, the combination of a thorough history, careful clinical examination, and appropriate laboratory investigations, including biopsy, will afford a definitive diagnosis **(Neville et al., 2015)**

Traumatic ulcers, either accidental (e.g. tongue biting) or less often factitious in origin, are among the most commonly encountered oral ulcers. Identification and removal of the traumatic stimulus should induce complete healing in no more than 2 weeks. Failure of the lesion to heal after elimination of suspected traumatic (or other reactive) causes should always necessitate a proper re-evaluation of the case and biopsy to confirm diagnosis. Nevertheless, persistent oral ulcerations of traumatic etiology have been described as traumatic ulcerative granulomas with stromal eosinophilia (TUGSE); the persistence of these lesions along with their atypical clinical features (e.g. indurated hard borders) raises the possibility of malignancy and dictates the need for biopsy **(Nikitakis, 2005).**

1.2 Traumatic ulcerative granuloma with stromal eosinophilia (TUGSE)

1.2.1 History

The first seed in the discovery of this lesion was dispersed by **Popoff (1956),** who reported one case of an ulcerative lesion in the gingiva of the maxillary incisors under the term "eosinophilic granuloma", but he gave insufficient information to justify his diagnosis. Thereafter, **Hjorting-Hansen and Schmidt (1961)** described an ulcerated lesion of the tongue with tissue eosinophilia that healed spontaneously; they termed it as "ulcerated granuloma eosinophilicum diutinum of the tongue".

Subsequently, further studies and reports concentrating on this issue had been conducted. In a study of 7 human oral ulcerative lesions along with studying the effect of administration of single and multiple physical traumas to tongues of albino rats, **Bhashkar and Lilly (1964)** described the histogenesis and natural history of a lesion of the oral mucosa that was characterized by histiocytic and fibroblastic proliferation with presence of prominent eosinophilic infiltration. It was concluded that the lesions under discussion in their study were essentially reactive, and resulted from trauma; if a name should be attached to these lesions at all, the term "traumatic granuloma of the tongue" appeared most appropriate since that term signified the traumatic origin of the lesions as well as its reactive nature

Justification for utilizing such term was given. "Traumatic", since these lesions were frequently associated with a history of trauma. "Ulcerative", as it was presented clinically as an oral ulcer. "Granuloma", this term might be objected to describe such lesions, since the term (granuloma) had been used to denote a specific granulomatous process, as in tuberculosis; nevertheless, such term might be defined as a tumefaction composed of granulation tissue; furthermore, the term (granuloma) had been frequently applied to TUGSE lesions and was deeply established in the literature, as a result, it was reserved in describing TUGSE lesions. "With", having. "Stromal", referred to underlying stromal tissue (connective tissue). "Eosinophilia", denoted to increased number of eosinophils in the stromal/connective tissue **(Elzay, 1983).**

Lastly but not least, an unusual indurated submucosal mass on the dorsal surface of the tongue of a medically compromised 62-year-old woman had been reported under the term “oral traumatic granuloma ”. Microscopically, sections consisted of dense inflammatory infiltrate with eosinophils extending into the underlying muscle with relatively few histiocytes and macrophages without evidence of atypical cells **(Joseph and BairavaSundaram, 2010).**

In general, TUGSE traversed multiple disciplines including pathology, dermatology, surgery, and dentistry, resulting in a diverse nomenclature. It is important to differentiate TUGSE from other oral pathological conditions **(Butler and Kobayashi, 2017).**

1.2.2 Clinical Appearance

These lesions show a male gender predilection with an age range of 41–60 years. The lesions generally heal following biopsy. TUGSE is entirely a histologic entity and is incidentally diagnosed when lesions associated with chronic truma of the oral mucosa (CTOM) are biopsied suspecting malignancy**(Banerjee, Abhishek, et al.2021).**

UGSE appears as an ulcer with elevated and indurated margins with a yellowish fibrinous base and rapid growth of the lesion could lead to over diagnosis of this lesion as oral squamous cell carcinoma (OSCC) **(Segura, S., et al. 2006)**

Clinical appearance of TUGSE mimics malignancies such as squamous cell carcinoma, lymphoma, and salivary gland tumours, making differential diagnosis difficult. Even the histopathological differential diagnosis may include many lesions marked by infiltraon of eosinophil within the connective tissue; such as Langerhans cell disease, Angiolymphoid Hyperplasia with Eosinophilia (ALHE), Kimura disease, some forms of lymphomas, allergic reactions, and parasitic diseases.**(Goncales, Eduardo Sanches, et al. 2007), (Cepeda, Laura T., et al. 2003)**

These lesions are almost ulcerated but some have been described as submucosal masses. It is usually manifested as a single ulcer varying in size from a few millimetres to more than 6 cm in 2 diameter, with an average size of 2 cm .

Purulence may be present, and the ulcer with a base of white fibrinous necroc debris. The margins of the ulcer are frequently elevated and indurated, and in the early stages the circumambient mucosa has an inflammatory red halo. In older lesions, the peripheral erythema is often absent. The symptoms range from slightly tender to excruciangly painful lesion. Ulcers can last for weeks or months, and in some cases, years. Clinical diagnosis alone of TUGSE is challenging, so histopathology with clinical correlation is the must to confirm the diagnosis. **(Keshwar, Shashi, et al. 2021)**

TUGSE may be asymptomatic or associated with mild to severe pain. The margins of the ulcer typically have an indurated and rolled appearance with the surrounding mucosa demonstrates an inflammatory red halo in the early stages. The peripheral erythema is often lacking in older lesions. More than 50% of the lesions develop on the tongue, specifically the dorsal or lateral surfaces, **(Fig 1.1)**which seems reasonable since tongue movement makes it more vulnerable to trauma, but they may present elsewhere in the oral mucosa such as lips, gingiva, palate, vestibular mucosa, retromolar area and floor of the mouth. TUGSE is a fast growing lesion, typically developing in days to weeks. Although it often spontaneously regresses, the lesion may take weeks or months to resolve (up to one year). TUGSE exhibits an exuberant pseudo invasive inflammatory reaction that is slow to heal **(Neville et al., 2016; Richardson, 2016; Sharma et al., 2016; Butler and Kobayashi, 2017).**

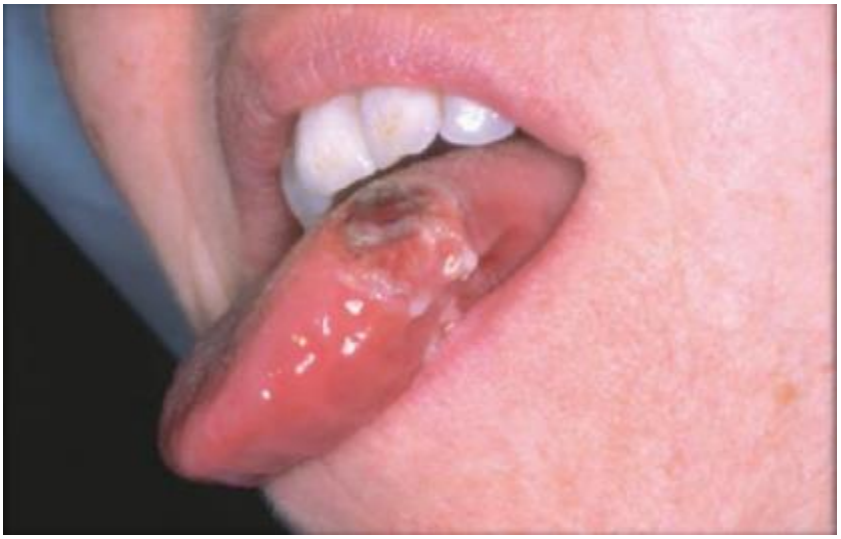

Figure (1.1): Clinical presentation Of TUGSE on the lateral surface of the tongue as a solitary ulcer with slightly elevated margins. Image courtesy of **Bouquot et al. (2009)**

1.2.3 Pathogenesis

Among all etiological factors, mucosal trauma (accidental bites, prosthetic dentures, repeated thrusting against sharp, misplaced or fractured teeth, root stumps) appeared to be the major instigating factor of this lesion. **Bhaskar and Lilly (1964)** had experimentally induced ulcerative lesions with similar eosinophilic characteristics by inflicting repetitive local trauma to the tongue of rats, noting that crush injury to tongue muscle initiated a granulation response with tissue eosinophilia; nevertheless, the failure of other studies to reproduce these results suggested that trauma, per se, might not represent a major etiological factor for TUGSE development **(von Domarus et al., 1980).** In a different point of view, it was assumed that if trauma was the sole cause, this lesion would be more common. Trauma had been proposed as only a contributing factor in the development of TUGSE; a break in the epithelial barrier could lead to viral or toxic agents entering the underlying tissue to cause an inflammatory response resulting in tissue damage **(Tang et al., 1981).**

It was suggested that interactions between increased numbers mast cells and eosinophils might play a pathogenic role. Due to exaggerated mast celleosinophil reaction, the mast cells degranulate, resulting in release of mediators, which cause inflammation and also attract eosinophils by the release of eosinophil chemotactic factor of anaphylaxis. Consequently, any form of trauma may permit the ingress of microorganisms, toxins, or foreign protein into the connective tissue. These substances, in predisposed persons, might induce an adverse inflammatory process resulted from such an exaggerated mast cell-eosinophil reaction that subsequently resulted in TUGSE development, similar to that noted in bronchial asthma. **(Elzay, 1983).**

Thereafter, it was conceivable that, in susceptible patients, recurrent trauma might lead to an alteration in tissue antigens or introduce microbial products into that tissue, initiating a local immune reaction which resulted in the development of TUGSE **(Velez et al., 1997).**

However, traumatic etiology had been reported by many other authors. Definite history of trauma caused by a sharp denture was present **(Jayalakshmy et al., 2017).** Events of trauma to the oral mucosa may result in TUGSE development, especially in the tongue, buccal mucosa, gingiva and floor of mouth, since these are common sites for trauma from mastication, iatrogenic events, and idiopathic causes **(Richardson, 2016).** Strikingly, TUGSE could develop in reaction to the trauma caused by mini implants without the protection provided by a denture base when the lingual vestibule is too shallow and the attached mucosa is sparse around implants **(dos Reis et al., 2014**). Khat chewing, as a mechanical and chemical form of trauma, has been stated as an etiological factor for TUGSE in tongue **(Hullah et al., 2014).** Furthermore, trauma induced by prolonged tracheal intubation recorded as an unusual cause of TUGSE in tongue **(Sabharwal et al., 2014)**. Moreover, TUGSE was described as a unique type of chronic traumatic ulceration of the oral mucosa with distinctive histopathological features **(Neville et al., 2015).**

1.2.4 Histopathology

Histopathologically the lesion showed squamous mucosa with hyperplastic changes and ulceration covered with abundant purulent exudate .Granulation tissue showed proliferating capillaries with prominent endothelial cells and a dense polymorphous infiltrate comprising of many eosinophils and histiocytes.There was no evidence of malignancy or dysplasia. Inflammatory infiltrate was extending down to involve the skeletal muscle and mucous salivary glands.**(fig1.2)** (**Mehta, S. S., & Muthusamy, R. K. 2020).**

The Inflammatory infiltrate was composed primarily of small, round lymphocytes, granulocytes, and abundant eosinophils, large atypical cells could be identified in clusters or scattered as single cells; the large cells had irregular nuclear contours, fine chromatin, small nucleoli, and abundant cytoplasm, mitotic figures were observed in several of the large cells. Proliferating endothelial cells and blood vessels were distributed throughout the lesion**(Hirshberg, Abraham, et al. 2006)**.

1.2.5 Differential Diagnosis

The clinical differential diagnosis of ulcerative lesions of the tongue, in particular, includes traumatic ulcers, infections such as syphilis, and tumors like squamous cell carcinoma, lymphoma, and rarely metastasis. (**Marszałek, A., & Neska-Długosz, I. (2011).** Eosinophilic ulcer of oral mucosa has to be differentiated from eosinophil rich disorders like Angiolymphoid hyperplasia with eosinophilia, Kimura's disease, Langerhans cell Histiocytosis, contact allergy, drug reactions, and Immunobullous disorders.In Angiolymphoid hyperplasia with eosinophilia, mucosal involvement is rare. The lesions show pronounced vascular proliferation with plump endothelial cells and lymphoid follicles .Kimura's disease is a chronic inflammatory disorder with rare oral mucosal involvement, lack of histiocytic infiltrate despite having prominent inflammatory infiltrate, and eosinophilic folliculolysis of germinal centers. (**Segura, S., & Pujol, R. M. 2008).**

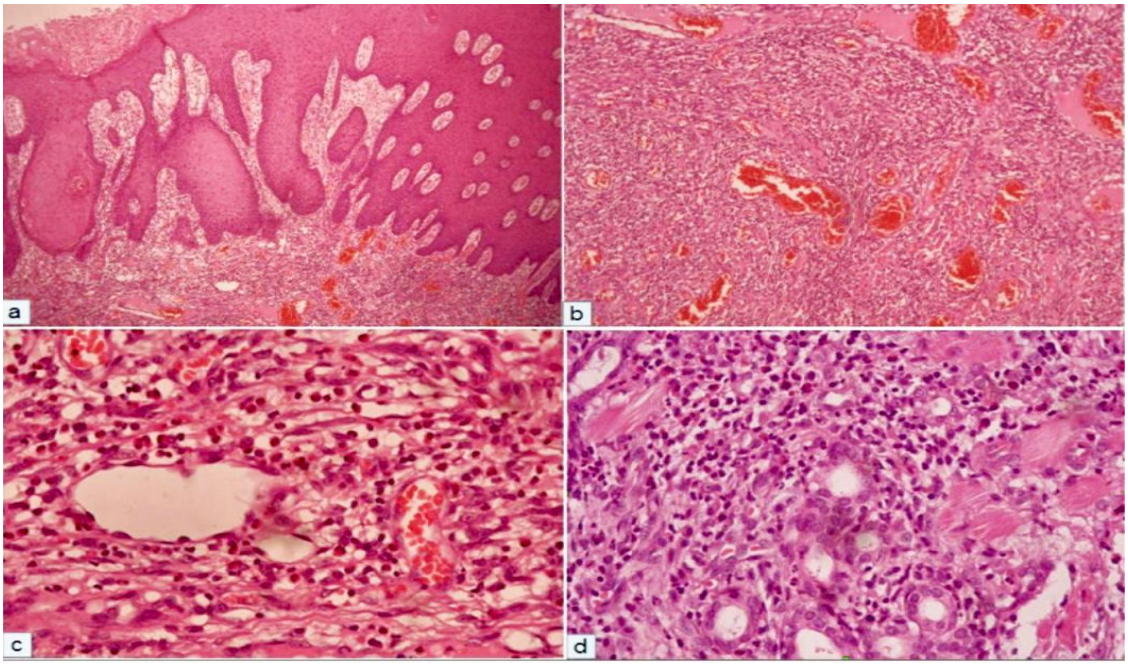

Figure (1.2): Hyperplastic epidermis adjacent to the ulcer with inflammatory infiltrate in the stroma (HE stain; X100). 1b: Stroma with dense polymorphous inflammatory cell infiltrate and many vessels (HE stain; X100). 1c: High power image showing polymorphous infiltrate rich in eosinophils (HE stain; X400). 1d: High power image showing dense polymorphous infiltrate infiltrating between skeletal muscle fibers and salivary gland lobule(**Mehta, S. S., & Muthusamy, R. K. 2020).**

The presence of eosinophils is not completely understood because most traumatic oral ulcers are devoid of eosinophils. It has been suggested that eosinophils represent a tissue reaction to some unknown antigen introduced via mucosal breakdown following trauma.` Mucosal degeneration so characteristic of TUGSE may be attributed to proliferation of cytotoxic T cells or toxic products released by degranulating eosinophils. Aggregates of T-cell intracytoplasmic antigen 1+ cells, a marker of cytolytic T cells, were found in large **(Hirshberg, Abraham, et al. 2006).**

1.2.6 Immunohistochemistry

The immunohistochemical characteristic of TUGSE has been a matter of debate due to the unidentified origin of the large, atypical mononuclear cells. Authors have suggested their origin in macrophages (CD68 positive cells), dendritic cells (factor XIIIa positive cells), and myofibroblasts (vimentin positive cells). Yet these large, atypical mononuclear cells (often CD30 positive) most likely originate from T-lymphocytes, as they often express T-cell markers or/and cytotoxic markers, and often display clonal T-cell receptor gene rearrangements, They might play a role in the reparative phase of the lesion**(Bentiez, Benito, et al. 2019).**

In 1997, **Ficarra et al.(1997)** for the first time described a case of TEG, in which CD30-positive cells in an ulcerated lesion could be evidenced. Subsequently, other reports revealed CD30-positive eosinophilic ulcers.CD30-positive large atypical cells can be observed in TUGSE lesions in a scattered or clustered manner [**(Hirshberg, Abraham, et al. 2006)**, **(Segura, S., et al. 2006).**

Therefore, these lesions were considered the oral counterpart of the spectrum of primary cutaneous CD30-positive LPDs by some authors. CD30 is commonly expressed on activated B- and T-cells and is a useful histological marker for a spectrum of LPDs, including Hodgkin lymphoma. Yet many non-neoplastic cutaneous disorders, such as atopic dermatitis, drug reactions, molluscum contagiosum, and scabies, can contain CD30 positive cells.The CD30 positivity of some TUGSE lesions is most probably a sign of an unspecific Tand/or B-cell activation,also eosinophilic ulcer of the oral mucosa to be a nonspecific locotypic reaction rather than a distinct entity **(Bentiez, Benito, et al. 2019).**

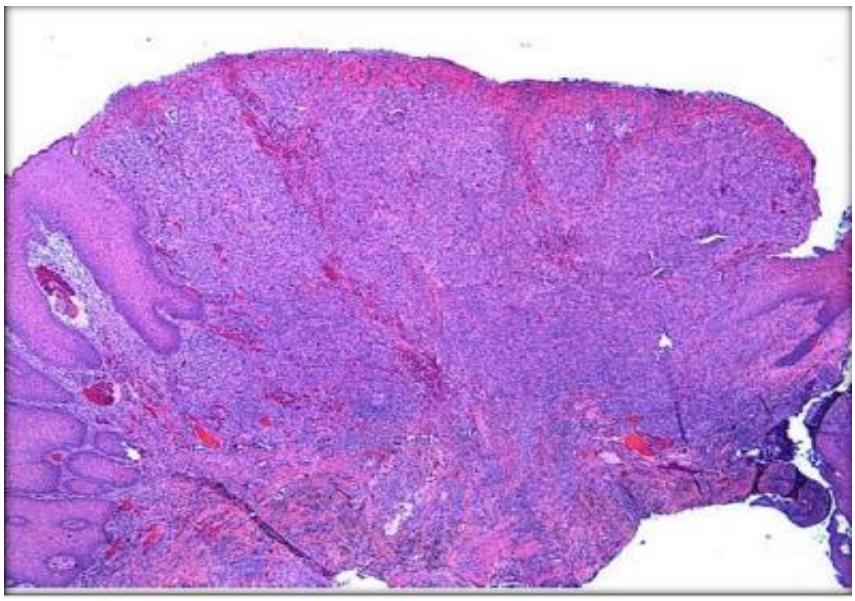

Figure (1.3): Primary CD30-positive TLPD of the tongue. Extensive surface ulceration with a deeply infiltrative lesion composed of mixed inflammation supporting large atypical lymphoid cells (X20). Image courtesy of **Müller (2017)**

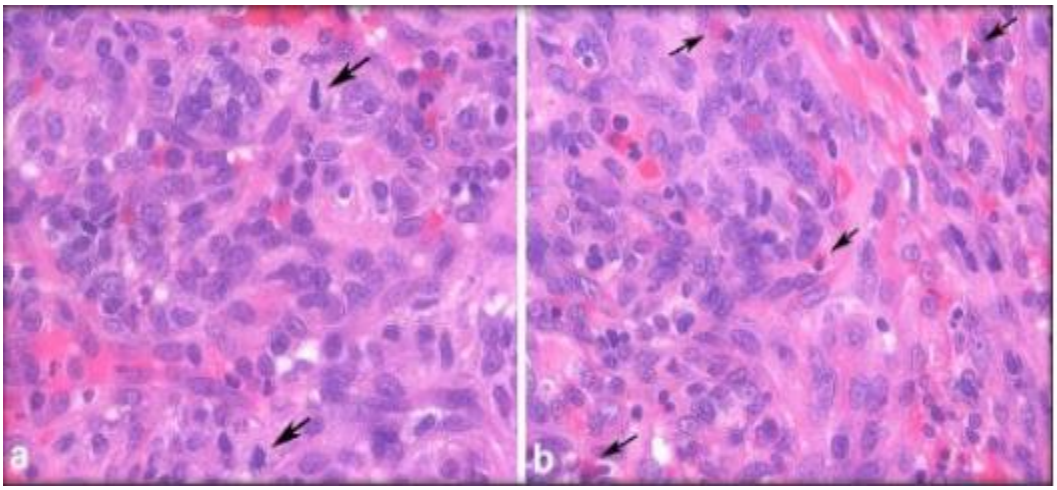

Figure (1.4): Primary CD30+ TLPD (a) Large, atypical lymphoid cells that are mitotically active (arrows) (X400); (b) Numerous scattered eosinophils (arrows) with a mixed inflammatory background (X400). Image courtesy of **Müller (2017)**

1.2.7 Treatment and prognosis

The delayed healing in TUGSE ulcers has substantial variability from days to up to 1 year in an isolated **case (Hirshberg et al., 2006).** Chronic non-healing oral ulcers, particularly TUGSE, showed minimal TGF-α or TGF-β expression by eosinophils, perhaps indicating a possible mechanism leading to delayed wound healing related to these factors. Interestingly, incisional biopsy often led to rapid wound healing, suggesting that the biopsy itself allowed for a transition back to the regular wound-healing processes **(Elovic et al., 1996).** TUGSE spontaneously resolves on its own in most cases; however, because of the concern for malignancy, it has the potential to be over treated **(Marszalek and Neska-Dlugosz, 2011).**

Symptomatic treatment only is the mainstay of therapy **(Butler and Kobayashi, 2017).** The patient should be instructed to avoid trauma, and referral to a dental professional is indicated when associated with dentures or other prosthetic devices. Diet should consist of soft food while avoiding spicy food. Topical or oral analgesics may be necessary if substantial pain is associated with the lesion **(Abdel-Naser et al., 2011).**

Oral prednisolone was used in a patient with concurrent Human T-cell leukemia virus type 1 (HTLV-1) and TUGSE to treat peripheral eosinophilia. Although TUGSE may spontaneously resolve within a 10-day period without steroids, it may be a reasonable treatment to improve healing time in an otherwise healthy individual **(Yamazaki et al., 2012).** If there is concern for malignancy, the patient should have the lesion biopsied to provide reassurance and for the added benefit of a transition to normal healing response and decreased healing time **(Elovic et al., 1996).**

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