Traumatic ulcerative granuloma with stromal eosinophilia. A case report and short literature review

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We introduce a case of 53-year-old female with rapidly developing tongue ulceration clinically mimicking squamous cell carcinoma of the oral mucosa. After a microscopic examination traumatic ulcerative granuloma with stromal eosinophilia (TUGSE) was diagnosed. In a short literature review, we characterize this entity, analyse its aetiology and nature. Differential diagnosis is also discussed.

Key words: traumatic ulcerative granuloma with stromal eosinophilia (TUGSE), eosinophilic ulcer.

Introduction

Traumatic ulcerative granuloma with stromal eosinophilia (TUGSE) is considered to be a benign, reactive and self-limiting lesion. It is known under a variety of names including traumatic granuloma of the tongue, eosinophilic ulcer of the oral mucosa, ulcerated granuloma eosinophilicum of the tongue etc. [1]. It can be diagnosed at any age, but most commonly it is found as a rapidly developing lesion in the 5th decade of life. The same entity in infants and neonates is called Riga-Fede disease as it was first clinically described in 1881 by Riga and then histologically in 1890 by Fede [1, 2]. The main theory of TUGSE origin is matched with trauma, however the injury is identified in less than 50% of cases [3]. Clinically TUGSE is manifesting as an ulcer with elevated and indurated margins. It occurs mainly on the dorsal or lateral surface of the tongue, but other areas of the mouth can also be involved, including the buccal mucosa, vestibular mucosa or gingiva. This features along with rather quick development can clinically mimic squamous cell carcinoma. And due to threatening symptoms, it warrants a biopsy or excision [4]. There has been described also a case of TUGSE which was misdiagnosed as a primary syphilitic chancre on clinical grounds without serological confirmation and treated with a high dose benzathine penicillin [1]. The ulceration is causing a mild to severe pain. It persists for several weeks or months and heals without any treatment. Rapid healing after a biopsy or excision has also been reported.

Case report

A 53-year-old female suffering from a lesion on the dorsal surface of the tongue, which was rapidly developing for about 2 weeks, was admitted to the laryngological out-patient clinic. After clinical examination an ulcer was found. It manifested elevated and indurated margins and yellowish, necrotic bottom. The patient history was unremarkable. First, the clinician took a biopsy, but unfortunately it contained only superficially taken squamous epithelium. After discussion and a second clinical opinion, the whole change was excised and sent to our Department without any other data. Surgeons suspected squamous cell carcinoma of the tongue.

The material was fixed in 10% buffered formalin and paraffin-embedded. After sampling and routine processing, 5-µm-thick sections were stained with haematoxylin-eosin.

The change was microscopically manifesting as an ulceration with necrotic bottom (Fig. 1). Under the

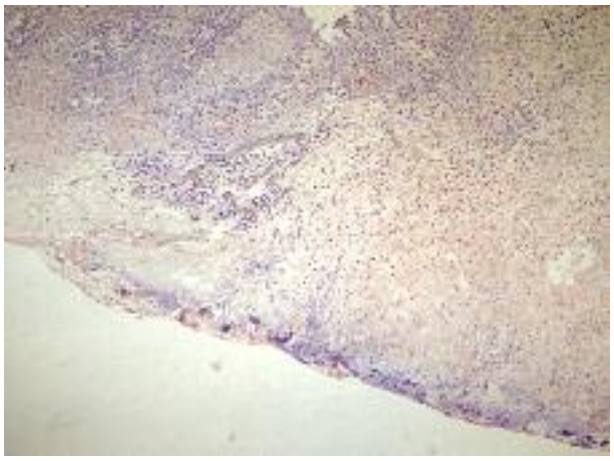

Fig. 1. Ulceration of an oral mucosa with dense inflammatory infiltrate underneath. HE, magnification 4×

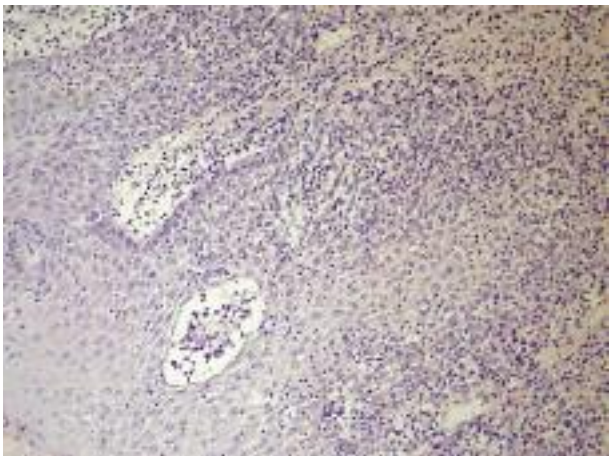

Fig. 2. Dense inflammatory infiltrate consisting of lymphocytes and multiple eosinophils extending deep into the tongue soft tissues. HE, magnification 20×

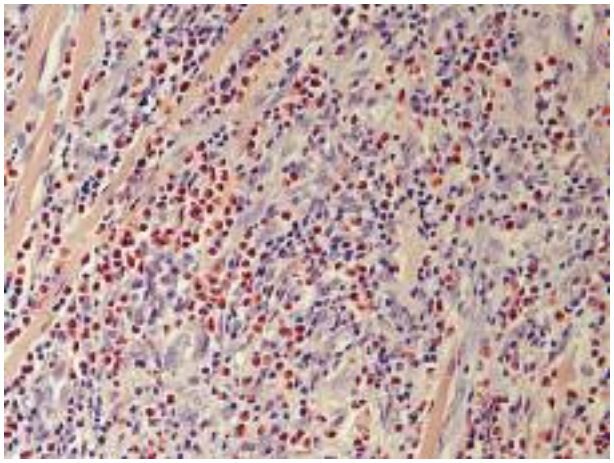

Fig. 3. Large, atypical, mononuclear cells with irregular nuclear margins and small nuclei. HE, magnification 40×

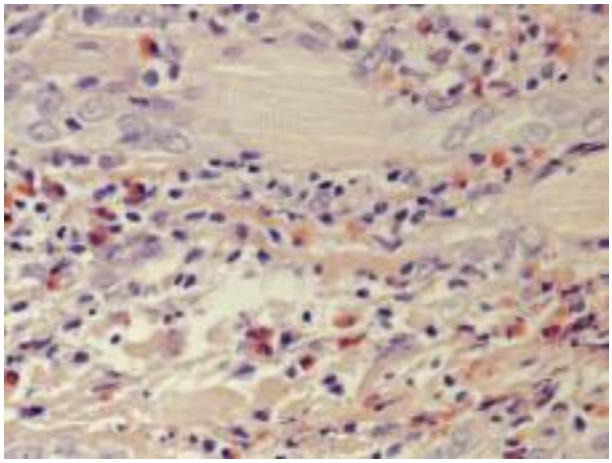

Fig. 4. Hyperplastic tongue epithelium on ulceration margins. HE, magnification 10×

necrotic tissue there was a dense, polymorphic, inflammatory infiltrate rich in lymphocytes and numerous eosinophils. The inflammation involved the superficial mucosa and the deep muscle layer of the tongue (Fig. 2). The atypical large mononuclear cells with abundant cytoplasm, irregular nuclear contours, fine chromatin and small nucleoli were scattered within the inflammatory infiltrate (Fig. 3). The margins of the ulcer presented hyperplastic epithelium with bottom border blurred by the dense inflammatory infiltrate (Fig. 4).

According to microscopic manifestation of the entity, the prior suspicion of squamous cell carcinoma appeared to be incorrect and traumatic ulcerative granuloma with stromal eosinophilia has been diagnosed.

Discussion

The clinical features of the TUGSE in many cases are recognized as suggesting malignancy. However, the further microscopic studies and immunohistochemical features indicate a benign process. Microscopically TUGSE is characterized by dense, polymorphic inflammatory infiltrate extending deep into the underlying muscle and other soft tissues. The dominant cells in the infiltrate are small T and B cells, macrophages. In all reports published up to now, prominent eosinophils are highlighted. The presence of eosinophils in the infiltrate is not completely understood, because most traumatic ulcers in the oral mucosa are devoid of eosinophils. It is suggested that eosinophil infiltrate is a tissue response to mucosal trauma which introduces some unknown antigen into submucosa. Among such usual toxins, microorganisms, endogenous degradation products or foreign proteins are mentioned [4, 5]. The other characteristic features of TUGSE are large, atypical, mononuclear cells with abundant cytoplasm, irregular nuclear contours, small nucleoli and fine chromatin [4].

The trauma was considered to have a major role in aetiology of TUGSE, but obvious trauma could be demonstrated in only 50% of cases. There have been

made some suggestions (especially according to recurrent or multiple traumatic ulcers) that some patients could have a predisposition to develop an eosinophilic ulcer [1]. The delayed self-healing characterizing TUGSE is explained by some authors by the lack of synthesis of TGF by eosinophils in the inflammatory infiltrate. Despite that, eosinophils produce a wide spectrum of other cytokines, such as TNF, which enhances tissue damage and keep the inflammatory response unfinished [5].

The immunohistochemical characteristic of the eosinophilic ulcer has been a matter of debate for several years especially because of the unknown origin of the large, atypical, mononuclear cells. Some authors reported their origin from macrophages (CD68-positive), dendritic cells (Factor XIII-positive) and even some others from myofibroblasts (vimentin-positive) [5]. Then, finally the latest survey reveals that these are CD30-positive cells originating from T lymphocytes [6].

This discovery initiated a new discussion whether the TUGSE is a benign counterpart of primary cutaneous CD30-positive lymphoproliferative disease (CD30+ LPD) or just a reactive and benign lesion or yet another histological simulator of CD30+ LPD.

CD30+ primary cutaneous LPD (25% of all cutaneous T-cell lymphomas) represent a wide spectrum of diseases extending from lymphomatoid papulosis (LyP) to anaplastic large T-cell lymphoma (ALCL). All these aforementioned disorders have been reported in oral mucosa and there have been described a few cases with eosinophilia. All are indolent diseases with a favourable outcome, a frequent spontaneous regression and common large atypical CD30-positive cells [3]. Another argument for the theory of the eosinophilic ulcer being a counterpart of eosinophil-rich CD30+LPD of the oral mucosa has been made according to the presence of atypical CD30+ cells mentioned earlier in three TUGSE cases, in which PCR analysis of monoclonality of the TCR-γ-chain gene was made. On the other hand, the description of occurrence of the skin lesion after healing of the oral ulcer with the same histological features and molecular TCR-γ

Table I. Most common differential diagnosis for TUGSE

Parameter	TUGSE	Squamous cell carcinoma	Atypical histiocytic granuloma	Langerhans cell histiocytosis	Lymphocyte rich CD30+ Lympho-proliferative disorders	Angiolym phomatoid hyperplasia with eosino-philia (ALHE)
location in the oral cavity	often (dorsal or lateral surface of the tongue, buccal mucosa, vestibular mucosa, gingiva)	often (bottom of the oral cavity, lateral side of the tongue, lower lip)	often (mainly gingiva)	less often	rarely	very rarely (mainly in the skin of the head and neck)
macrosco-pically	ulcer with elevated and indurated borders	ulcer with elevated and indurated borders	ulcer with elevated and indurated borders	nodules or ulcerated plaques	nodules or ulceration	rather nodules or plaques than ulcers
age	every age (most commonly in the 5th decade of life)	above 5th decade of life	every age	children from 0 to 15 years old (very rarely adults)	senior age	from 3rd to 7th decade of life (most commonly in 4th decade of life)
histopa-thology	a dense, polymorphic, inflammatory infiltrate rich in lymphocytes and eosinophils involving the deep muscle layer. Presence of atypical large mononuclear cells	sheets of neoplasmatic, atypical cells	like TUGSE (a dense, polymorphic inflammatory infiltrate) but without the deeper soft tissues involvement	infiltrate with Langerhans cells, T lymphocytes and eosinophils	infiltrate of atypical cells with the eosinophilic component involving the oral epithelium and the deep soft tissues	inflammatory infiltration (with eosinophilia but without atypical large mononu-clear cells) accompanied with bizarrely shaped blood vessels
immuno-histoche-mistry	CD30+, CD1a neg	CK+	CD68 neg	CD1a+	CD30+, ALK+	

clonality analysis outcomes were recently published [7]. The opponents of this theory reply that CD30 is a member of TNF/NGF receptor superfamily recognized with Ki-1 monoclonal antibody [6]. This receptor is a transmembrane glycoprotein with extracellular domain commonly expressed on activated B and T cells and as such it is thought to be a nonspecific lymphocyte activation marker [5, 6]. CD30 is a histological marker of CD30+ LPD, Hodgkin and R-S cells. However, it occurs also in many non-neoplastic cutaneous disorders such as atopic dermatitis, adverse drug reaction, scabies, molluscum contagiosum, insects' and spiders' bites [5, 6]. Some authors suggest also that many benign lesions may contain a dominant T-cell clone, for example a clonal TCR-γ gene rearrangement has been observed in acute mononucleosis [4]. However, most TUGSE cases show TCR-γ-chain gene policlonality [4, 5]. According to all these just discussed arguments, TUGSE is thought to be a benign, reactive lesion.

Due to a variety of cells found in inflammatory infiltrate, TUGSE should be also histologically differentiated from atypical histiocytic granuloma, angiolymphomatoid hyperplasia with eosinophilia (ALHE), Langerhans cell histiocytosis and pseudolymphoma. Atypical histiocytic granuloma is clinically and histologically similar to TUGSE, but the ulcer appears mainly on gingival, the polymorphous inflammatory infiltrate rarely involves the underlying muscle and the atypical cells are of the histiocytic type [3]. However, some authors revealed that because of the similarities between TUGSE and atypical histiocytic granuloma, these entities may represent a spectrum of the same disease [8]. ALHE rarely involves the oral mucosa and when it does, it presents as a nodule rather than an ulcer. Inflammatory infiltration with eosinophilia is accompanied with bizarrely shaped blood vessels and there are no atypical monoclonal cells characteristic of TUGSE [3]. Langerhans cell histiocytosis ulceration can be rarely found in oral mucosa, but mostly in children up to 15 years old and the atypical mononuclear cells are of Langerhans cell origin (CD1a-positive with Birbeck granules) [3]. Pseudolymphoma is an inflammatory disease that simulates malignant lymphoma either clinically, histologically or both. A dense histiocytic infiltrate, high mitotic activity and atypical intraepithelial lymphocytes separate this change from TUGSE [9]. The spectrum of most common differential diagnosis is presented in Table I.

Though the literature contains the differential diagnosis for TUGSE, it is far from clear whether diseases mentioned earlier (starting from TUGSE to ALHE) are variants of one main entity or separate disorders [7, 10]. Our case showed that the change described by pathologists simply as a chronic ulceration of oral mucosa could be a part of a wide spectrum of neoplastic and non-neoplastic changes.

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