Traumatic Ulcerative Granuloma With Stromal Eosinophilia: A Malignant-Appearing Benign Lesion

Jason N. Butler, DO; Todd T. Kobayashi, MD

PRACTICE **POINTS**

- Immunohistochemical staining of traumatic ulcerative granuloma with stromal eosinophilia (TUGSE) may suggest an underlying lymphoproliferative disorder.
- Early recognition of TUGSE, which often is malignant appearing, is key, with watchful waiting as the mainstay therapy.
- Adjunctive therapy for TUGSE includes prednisolone and oral analgesics.

Traumatic ulcerative granuloma with stromal eosinophilia (TUGSE) is an underreported diagnosis in dermatologic literature. Rapid expansion with an ulcerative clinical appearance often provokes fear of malignancy despite its benign nature. Traumatic ulcerative granuloma with stromal eosinophilia is thought to be a reactive tissue response to trauma, but CD30$^+$ mononuclear cells within a TUGSE lesion suggests the possibility of an underlying lymphoproliferative disorder. This case highlights the clinical and histological features of TUGSE and provides a brief review of the literature addressing this debate. Knowledge of this condition, which uncommonly presents to the practicing dermatologist, is important in providing appropriate patient care and counseling. When correctly identified, unnecessary therapies and emotional stress can be avoided.

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Traumatic ulcerative granuloma with stromal eosinophilia (TUGSE) is an uncommon, benign, self-limited condition that is restricted to the oral mucosa, most commonly seen in the fifth to seventh decades of life.[1-3] The pathogenesis of TUGSE is unknown, but current theory suggests trauma is the instigating factor. The presence of CD30$^+$ mononuclear cells within TUGSE raises the possibility of a CD30$^+$ lymphoproliferative disorder in some cases.[4] However, because CD30$^+$ cells are not uncommon in other benign reactive processes, they may simply represent a reactive phenomenon.[3]

Traumatic ulcerative granuloma with stromal eosinophilia traverses multiple disciplines, including dermatology, oral surgery, dentistry, and pathology, resulting in a diverse nomenclature including traumatic granuloma of the tongue, traumatic eosinophilic granuloma of the oral mucosa, ulcerated granuloma eosinophilicum diutinum, and eosinophilic ulcer of the oral mucosa.[1,4-6] It is important to differentiate eosinophilic granuloma of the oral mucosa from the eosinophilic granuloma that is associated with Langerhans cell histiocytosis. Although both may present with oral ulceration, Langerhans cell–associated eosinophilic granuloma typically develops from underlying bone, whereas eosinophilic granuloma of the oral mucosa (TUGSE) is described as nonosseous.[7,8] Furthermore, the gingiva is the most common oral site in Langerhans cell–associated eosinophilic granuloma, whereas the tongue is most commonly involved in TUGSE.[8] Shapiro and Juhlin[9] clearly distinguished TUGSE from Langerhans cell–associated eosinophilic granuloma in 1970. Histologically, the 2 conditions are completely different.

When ulcerative granulomas develop in the pediatric population, usually in children younger than 2 years, it is termed *Riga-Fede disease.*[10] These children were typically breastfeeding, suckling, or teething, suggesting trauma as a triggering event. In 1961, Hjorting-Hansen and Schmidt[5] described 3 separate lesions similar to Riga-Fede disease

From the San Antonio Uniformed Services Health Education Consortium, Texas. Dr. Butler is from San Antonio Military Medical Center. Dr. Kobayashi is from Wilford Hall Ambulatory Surgical Center.

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Correspondence: Jason N. Butler, DO, 3401 Williamsburg Ln, Texarkana, TX 75503 (jason.n.butler.mil@mail.mil).

in an adult patient. Subsequently, Riga-Fede disease was grouped under TUGSE.[3]

Histologically, TUGSE shows an ulcerated epithelium with a polymorphic inflammatory cell infiltrate that has a large predominance of eosinophils. The infiltrate affects the superficial and deep layers of the muscle tissue and penetrates into the salivary glands. Large atypical mononuclear cells with an ovoid and pale-appearing nucleus often are present. These cells may be mitotically active and stain positively for CD30.[1,4,11] $CD68^+$ macrophages, T lymphocytes, and factor XIIIa–positive dendritic cells commonly are present.[12]

Given the presence of large atypical $CD30^+$ cells in many lesions, the possibility of a $CD30^+$ lymphoproliferative disorder has been postulated by some authors. Indeed, lymphomatoid papulosis (LyP) has been documented to involve the oral mucosa.[2,4]

Case Report

An 81-year-old man presented with a rapidly enlarging, 1.7×1.3-cm, vascular-appearing nodule with a collarette of mucosal epithelium on the left side of the dorsal surface of the tongue of 2 weeks' duration (Figure 1). He denied any history of trauma, tobacco chewing, weight change, fever, or fatigue; however, he did report a 30 pack-year smoking history. There was no other pertinent medical history to include medications or allergies.

The differential diagnosis included pyogenic granuloma, granular cell tumor, squamous cell carcinoma, other neoplasms (eg, oral lymphoma, salivary gland tumors), and a traumatic blood blister from tongue biting. The patient was referred to the oral maxillofacial surgery department for an excisional biopsy, which showed a solitary ulcerated nodule with associated granulation tissue, thrombus, and fibrinoid debris (Figure 2). A surrounding dense mixed inflammatory cell infiltrate composed of lymphocytes, histiocytes, and numerous eosinophils was noted extending through the submucosal tissue and underlying striated muscle fibers (Figure 3). The adjacent mucosal epithelium appeared normal. CD30 staining showed only rare positive cells. These findings were consistent with TUGSE.

Due to the benign nature of TUGSE, the patient was released with symptomatic care and instructed to return for any new growth. The growth spontaneously resolved over 1 month and no recurrence or new lesions were reported 1 year later.

Comment

Despite encompassing multiple disciplines of medicine, TUGSE has minimal exposure in the dermatologic literature. It is an important clinical and histologic diagnosis that will provide reassurance to the patient when accurately identified and reduce potentially harmful treatments.

Clinical Presentation—Typically, TUGSE presents as a painful solitary nodule with a central ulcer and yellow fibrinous base. The margins of the ulcer typically have an indurated and rolled appearance.[1,4] More than 50% of the lesions develop on the tongue, specifically the dorsal or lateral surfaces, but they may present anywhere in the oral mucosa.[7] Traumatic ulcerative granuloma with stromal eosinophilia is a fast-growing lesion, typically developing in days to weeks. Although it spontaneously regresses, the lesion may take weeks or months to resolve. In one case, it resolved 1 year later.[1] Traumatic ulcerative granuloma with stromal eosinophilia has a bimodal age distribution, generally appearing in the first 2 years of life and later in the fifth through seventh decades. The male-to-female predominance is equal.[1,7,11] Reoccurrence is rare, but

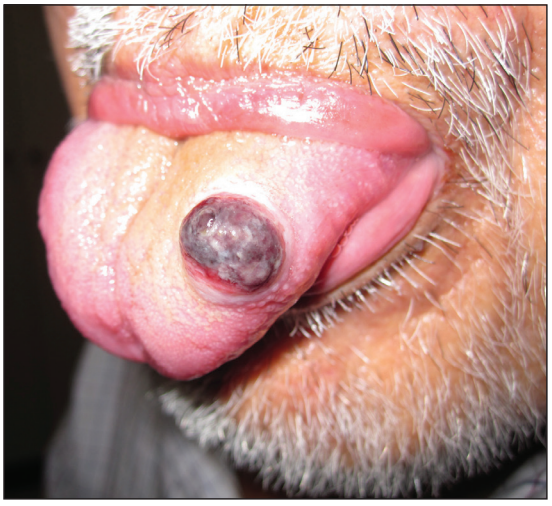

FIGURE 1. Traumatic ulcerative granuloma with stromal eosinophilia consisting of a 1.7×1.3-cm vascular-appearing nodule with a collarette of mucosal epithelium on the left side of the dorsal surface of the tongue.

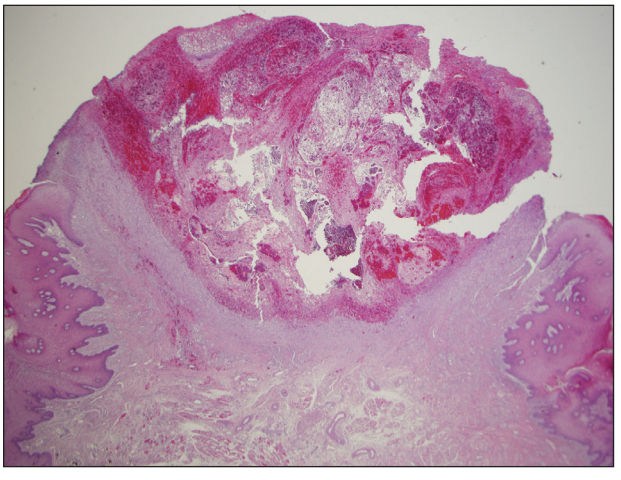

FIGURE 2. Traumatic ulcerative granuloma with stromal eosinophilia histopathology consisting of fibrinoid hemorrhagic necrosis overlying an ulcerated nodule with a collarette of epithelium at the base (H&E, original magnification ×20).

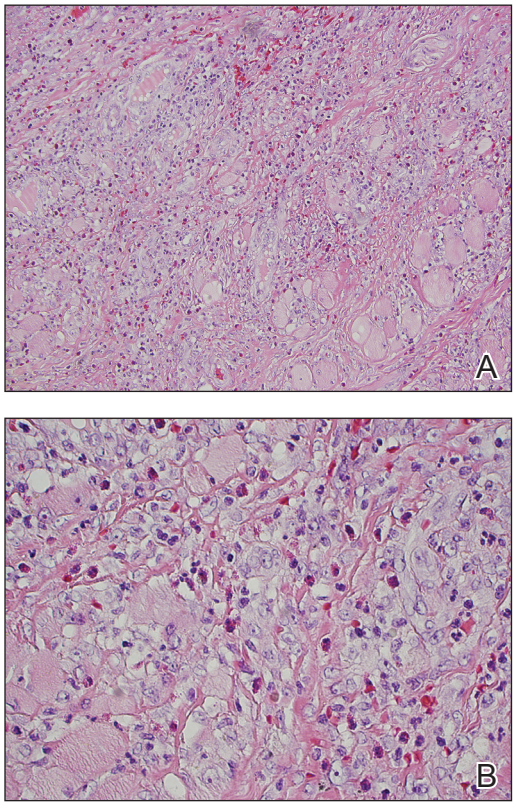

FIGURE 3. Traumatic ulcerative granuloma with stromal eosinophilia histopathology consisting of a mixed inflammatory cell infiltrate composed of lymphocytes, histiocytes, and numerous eosinophils extending through the submucosal tissue and underlying striated muscle fibers (A and B)(H&E, original magnifications ×100 and ×400).

some reports have shown patients with multiple episodes of TUGSE.[13,14]

Differential Diagnosis—The clinical differential diagnosis for TUGSE includes squamous cell carcinoma, pyogenic granuloma, lymphoproliferative disorder, traumatic neuroma, Langerhans cell histiocytosis, granulomatous disorders, and oral lymphoma. Inflammatory disorders such as syphilis, Behçet's disease, herpes, histoplasmosis, Wegener granulomatosis, and others also should be considered.

Immunohistochemistry—Immunohistochemical analysis of TUGSE lesions recently has revealed the presence of $CD30^+$ cells. These cells are associated with cutaneous lymphoproliferative disorders including LyP, anaplastic large cell lymphoma (ALCL), and borderline $CD30^+$ lesions, among others. Systemic diseases with $CD30^+$ cells include mycosis fungoides, other T-cell lymphomas, and Hodgkin lymphoma.[15,16] Once $CD30^+$ cells were recognized, multiple authors began speculating there was a correlation between TUGSE and the $CD30^+$ lymphoproliferative disorders.[1,2,13] Anaplastic large cell lymphoma and LyP of the oral mucosa have been reported in several cases.[17-20] One report described 2 cases of ulcerated $CD30^+$ T-cell non-Hodgkin lymphoma of the oral mucosa, one of which showed eosinophilic infiltrates and was initially thought to be TUGSE. Based on these overlapping clinical and histologic features, the authors hypothesized there was a correlation between oral ALCL, LyP, and TUGSE.[17] In one report, a patient developed multiple TUGSE lesions throughout his life, suggesting a pathologic process similar to LyP. The lesion biopsied showed that 70% of the T cells expressed CD30 (Ki-1) antigen.[13]

Underlying Causes—In support of an underlying immunologic process that augments the growth of these lesions, 2 separate case reports of TUGSE in the presence of human T-lymphotropic virus 1 (HTLV-1) and Epstein-Barr virus have been documented.[2,21] Concurrent presentation of TUGSE and HTLV-1 in one report demonstrated eosinophilia in both the oral lesion and peripheral blood, suggesting an immunologic relationship. Furthermore, the authors postulated that local trauma initiated the development of TUGSE, providing the catalyst for the HTLV-1 carrier to develop peripheral eosinophilia.[21]

In the second case, a 12-year-old boy developed TUGSE in the presence of Epstein-Barr virus.[2] Immunologically, this virus can be reactivated from its latent stage during immunosuppression. Epstein-Barr virus has been implicated in lymphoproliferative diseases of both B- and T-cell origin, including $CD30^+$ ALCL and LyP.[22,23] The authors in this report again hypothesized there was a correlation between lymphoproliferative disorders and TUGSE lesions.[2,24]

Alternatively, TUGSE may simply be a reactive process to trauma or another underlying trigger. It has been speculated that the presence of eosinophils correlates with antigen insertion into the oral mucosa, whereas other ulcers of the oral mucosa are devoid of eosinophils.[1] These antigens may include microorganisms, endogenous degradation products, or foreign proteins.[7,25] Additionally, the presence of $CD30^+$ lymphocytes is not isolated to lymphoproliferative disorders. $CD30^+$ cells have been documented in arthropod bite reactions, atopic dermatitis, drug reactions, molluscum contagiosum, and scabies, among others.[1,26]

Healing and Management—The length of healing in TUGSE ulcers has substantial variability, from days to up to 1 year in an isolated case.[1,24] Sequential expression of transforming growth factor (TGF) α and TGF-β expressed by tissue eosinophils may be underlying factors associated with a quicker healing response as demonstrated by similar ulcers in hamsters.[27] Chronic nonhealing oral ulcers, particularly TUGSE lesions that demonstrated the typical increase in eosinophils in 11 of 12 cases, showed minimal TGF-α or TGF-β expression by eosinophils, perhaps indicating a possible mechanism leading to delayed wound healing in some cases. Interestingly, incisional biopsies often led to rapid wound healing,

suggesting that the biopsy itself allowed for a transition back to the regular wound-healing processes.[28]

Traumatic ulcerative granuloma with stromal eosinophilia spontaneously resolves on its own in most cases; however, because of the concern for malignancy, it has the potential to be overtreated.[26] Symptomatic treatment only is the mainstay of therapy. The patient should be instructed to avoid trauma, and referral to a dental professional is indicated when associated with dentures or other periprosthetic devices. Diet should consist of soft foods while avoiding spicy foods. Topical or oral analgesics may be necessary if substantial pain is associated with the lesion.[2] Oral prednisolone was used in a patient with concurrent HTLV-1 and TUGSE to treat peripheral eosinophilia.[21] The patient's peripheral eosinophils dropped to 1% in 1 day, and the patient's oral lesion began to improve at day 3 and disappeared by day 10. 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.[21,26] 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.[28]

Clinical Recognition—The clinician should be aware of the possibility of a $CD30^+$ lymphoproliferative disorder, which has been associated with TUGSE in some cases, or may simulate TUGSE both clinically and histologically. Further studies are needed to clarify the relationship between these 2 entities. Whether it is a true relationship, simple coincidence, or simply overlapping clinical and histologic features remains to be determined.

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