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REVIEW

Traumatic Ulcerative Granuloma with Stromal Eosinophilia: From Reactive Process to Low Grade CD30 + lymphoproliferative Disorder

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Abstract

Purpose of Review Traumatic ulcerative granuloma with stromal eosinophilia (TUGSE) is a rare, benign ulcerative lesion of the oral mucosa that exists in both adult and infantile (Riga-Fede) forms. This review examines TUGSE by exploring its clinical presentation, pathogenesis, histopathological features, and treatment approaches. It briefly discusses oral CD30+ T-cell lymphoproliferative disorders (TLPDs) and their potential relation with TUGSE lesions.

Recent Findings While traditionally considered reactive in nature, some recent evidence suggests TUGSE may share features with CD30+ T-cell lymphoproliferative disorders (TLPDs), potentially representing a spectrum of lesions and thereby complicating diagnosis and treatment approaches. Although some TUGSE cases demonstrate CD30 positivity and monoclonality of the T-cell receptor gamma (TCRγ) chain gene, no cases have progressed to widespread or systemic lymphoma. The rarely reported CD30+ TLPDs of the oral cavity appear to share features with their cutaneous counterparts, demonstrating indolent biologic behavior and excellent prognosis, with complete or partial regression frequently occurring after incisional biopsy.

Summary TUGSE presents as a slow-healing ulcer with raised borders and induration, commonly affecting the tongue and potentially mimicking squamous cell carcinoma. While trauma appears to be an important factor, the exact pathogenesis remains unclear. Histopathologically, lesions show ulceration with polymorphous infiltrate rich in eosinophils extending into the submucosa, with characteristic muscle fiber degeneration and variable presence of atypical mononuclear cells. The condition generally follows a self-limiting course with excellent prognosis, responding well to conservative management. Aggressive treatment and extensive follow-up may be unnecessary even for CD30+ cases with monoclonal TCRγ chain genes. Further research is needed to clarify the relationship between oral CD30+ TLPDs and TUGSE.

Key Points

- Traumatic ulcerative granuloma with stromal eosinophilia (TUGSE) is a rare, self-limiting ulcerative lesion that clinically mimics oral cavity squamous cell carcinoma and requires a biopsy for definitive diagnosis.
- Histologically characterized by polymorphous inflammation rich in eosinophils that extends deeply into surrounding tissues with a variable number of atypical mononuclear cells.
- TUGSE may exist along a complex spectrum with CD30 + T-cell lymphoproliferative disorders, as some cases show CD30 positivity of atypical mononuclear cells and monoclonality of the T-cell receptor gamma (TCRγ) chain gene.
- CD30 positivity and T-cell clonality findings require clinical contextual interpretation as they occur in both benign and malignant conditions.

Keywords Traumatic ulcerative granuloma with stromal eosinophilia · Eosinophilic ulcer of the oral mucosa · Traumatic granuloma of the tongue · Atypical histiocytic granuloma · Eosinophilic ulcer · CD30 + lymphoproliferative disorder

Introduction

Traumatic ulcerative granuloma with stromal eosinophilia (TUGSE), also known as eosinophilic ulcer, atypical histiocytic granuloma, and traumatic granuloma, is a rare

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benign ulcerative lesion of the oral mucosa [1]. It was first described in adults by Popoff in 1956 and was recognized as a distinct entity in 1970 by Shapiro and Juhlin [1, 2]. A similar condition was previously described in infants, clinically by Riga in 1881 and microscopically by Fede in 1890, and is now known as Riga-Fede disease [1]. These two conditions are now recognized as existing along a spectrum with an infantile and adult form. TUGSEs are generally considered to be reactive lesions; however, they may contain atypical mononuclear CD30+cells and a monoclonal rearrangement of the T-cell receptor gamma (TCRγ) chain gene, similar to those found in primary cutaneous lymphoproliferative disorders [3]. Therefore, it has been suggested that TUGSE may be part of the spectrum that includes the oral counterparts of primary cutaneous CD30+T-cell lymphoproliferative disorders (TLPDs) [4]. This review will provide a thorough investigation of TUGSE and a brief overview of CD30+lymphoproliferative disorders reported in the oral cavity.

Traumatic Ulcerative Granuloma with Stromal Eosinophilia

Clinical Presentation

TUGSE is a benign lesion that typically presents in adults as a slow-healing ulceration of the lateral or ventral tongue, which is characterized by elevated and indurated borders (32.8% of cases) [1, 4]. These lesions can present as a rapidly developing ulcer with peripheral erythema, a white or yellowish base, and a fibrinous membrane, with dimensions ranging from a few millimeters to several centimeters in diameter [5]. In infants (younger than 1 year), Riga-Fede lesions commonly present on the dorsal or ventral tongue as a result of trauma from rubbing against erupting primary incisors during suckling [6, 7]. It can less commonly arise on the labial mucosa, lingual frenum, and mandibular gingiva. Riga-Fede has a significant male predilection (male to female ratio, 16:3) [6]. The adult form of TUGSE demonstrates a slight male predominance (male to female ratio, 1.3:1) and presents over a wide age range (35–84 years; mean, 58 years). In adults, the most common location is the tongue, particularly the dorsum and lateral borders, with other sites including the hard and soft palate, floor of the mouth, gingiva, and lip [1]. TUGSE lesions have also been reported to develop at the site of a previous surgical excision of oral squamous cell carcinoma in 3 cases [4]. TUGSE typically presents as a solitary ulceration; however, synchronous or metachronous ulcerations have been documented [1]. Pain is a frequently reported symptom. There is wide variability in healing times, ranging from 1 week to 2 years [1, 4]. In extremely rare cases, association with enlarged regional lymph nodes has been noted [7].

Clinical Differential Diagnoses

Due to their elevated or rolled borders and slow-healing times, TUGSE lesions have a broad clinical differential diagnosis including squamous cell carcinoma, deep fungal infections (e.g., histoplasmosis), necrotizing bacterial infections (e.g., tuberculosis), syphilis, and granulomatous disorders (e.g., granulomatosis with polyangiitis) [4, 5]. Riga-Fede disease may be the presenting sign of an underlying developmental or neurologic condition, including familial insensitivity to pain, familial dysautonomia, and other disorders characterized by self-injury, such as Lesch-Nyhan and Gaucher diseases (Fig. 1) [8].

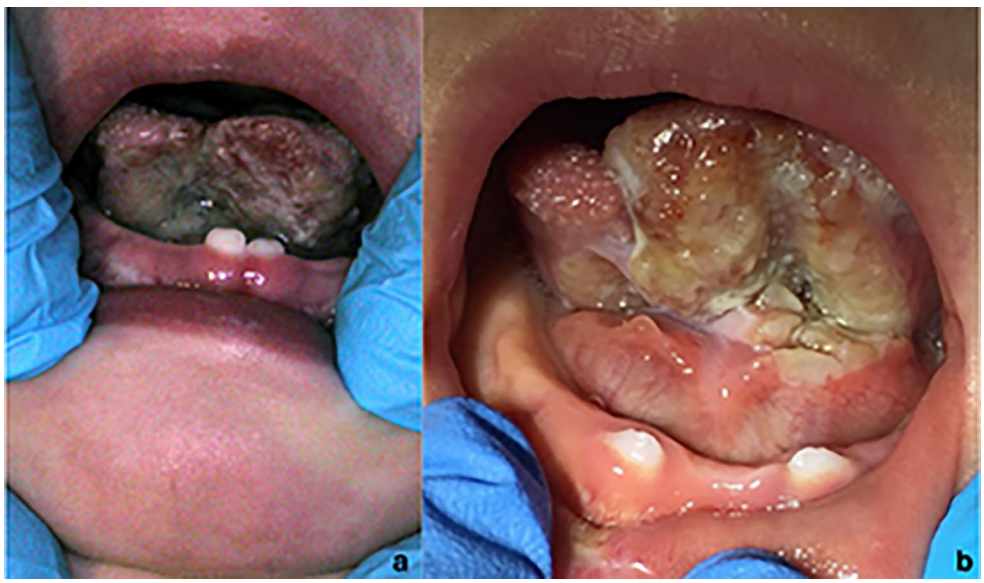

Fig. 1 Riga-Fede disease in an infant with Lesch-Nyan syndrome. **A** Patient is 7 months old with eruption of the deciduous central mandibular incisors and Riga-Fede disease of the ventral tongue. **B** The central incisors were subsequently removed. Patient at 10 months with eruption of mandibular deciduous central incisors and Riga-Fede disease of the ventral tongue

Pathogenesis

Although trauma is assumed to be an important etiologic factor, the exact pathogenesis of TUGSE remains obscure, and most reported lesions lack clinical evidence of a traumatic origin [4, 7]. Furthermore, unlike TUGSE, most traumatic ulcers are devoid of eosinophils. Several hypotheses have been proposed to explain the prominent eosinophilic infiltrate in TUGSE lesions [5]. An older theory postulates that TUGSE begins when an ulceration from trauma allows the ingress of microorganisms, toxins, or foreign material into the connective tissue, which then, in predisposed individuals, induces an adverse inflammatory process through an exaggerated mast cell and eosinophil reaction similar to that observed in studies of bronchial asthma [6]. An increased number of mast cells in the peripheral underlying connective tissue was reported by El-Mofty et al.; however, Regezi et al. found scarce mast cells in TUGSE infiltrates and significant numbers in the surrounding normal tissue [7, 9]. Therefore, the exact role of mast cells in the pathogenesis of TUGSE remains controversial.

Further research, combined with the clinical observation that topical and systemic corticosteroid therapy provides effective treatment, suggests that cell-mediated immunity plays a significant role in the pathogenesis of TUGSE. El-Mofty et al. demonstrated that while the absolute numbers of each cell type in the inflammatory infiltrate of TUGSE lesions vary considerably, their relative proportions remain similar [7]. Additionally, they noted an inverse relationship between the number of large mononuclear cells and other inflammatory cells, with infiltrating T lymphocytes being consistently more prevalent than B cells, and T-cell-specific antigen-presenting cells (APCs) outnumbering non-APC macrophages [7]. Cytotoxic T cells may cause mucosal damage in TUGSE lesions, as suggested by Hirshberg et al.'s. finding of cell aggregates expressing TIA-1, a cytotoxic T cell marker [10]. More recently, the delayed healing times of TUGSE lesions has been linked to the lack of transforming growth factor-alpha (TGF-α) and transforming growth factor-beta (TGF-β) production by eosinophils in TUGSE [11].

Histopathological Features

Histopathologically, TUGSE lesions demonstrate a superficial fibrinopurulent membrane, some with associated bacterial aggregates (15.8% of cases) covering the ulcerated focus [1]. The base of the ulcer consists of abundant granulation tissue with a polymorphous dense infiltrate of neutrophils, lymphocytes, macrophages, plasma cells, and eosinophils that extends deep into the submucosa and adjacent areas, and occasionally involves the overlying epithelium (Fig. 2) [4, 5]. The inflammatory infiltrate penetrates between muscle fibers, creating what is colloquially referred to as a "checkerboard" pattern, along with infiltration into minor salivary glands. Muscle degeneration and focal areas of necrosis (15.8% of cases) frequently accompany this infiltrate [1, 7]. The eosinophilic infiltrate in TUGSE characteristically surrounds the deeply situated muscle fibers and demonstrates either a scattered or clustered pattern, with its density varying among cases, often depending on the stage of the ulcer [1, 4]. A study of TUGSE in a Taiwanese population described the degree of eosinophilic infiltrate as mild in 38.2% of cases, moderate in 29.4%, and severe in 29.4% [4].

TUGSE lesions may contain a secondary cell population of mitotically active large mononuclear atypical cells with round or ovoid pale-staining nuclei with small nucleoli and

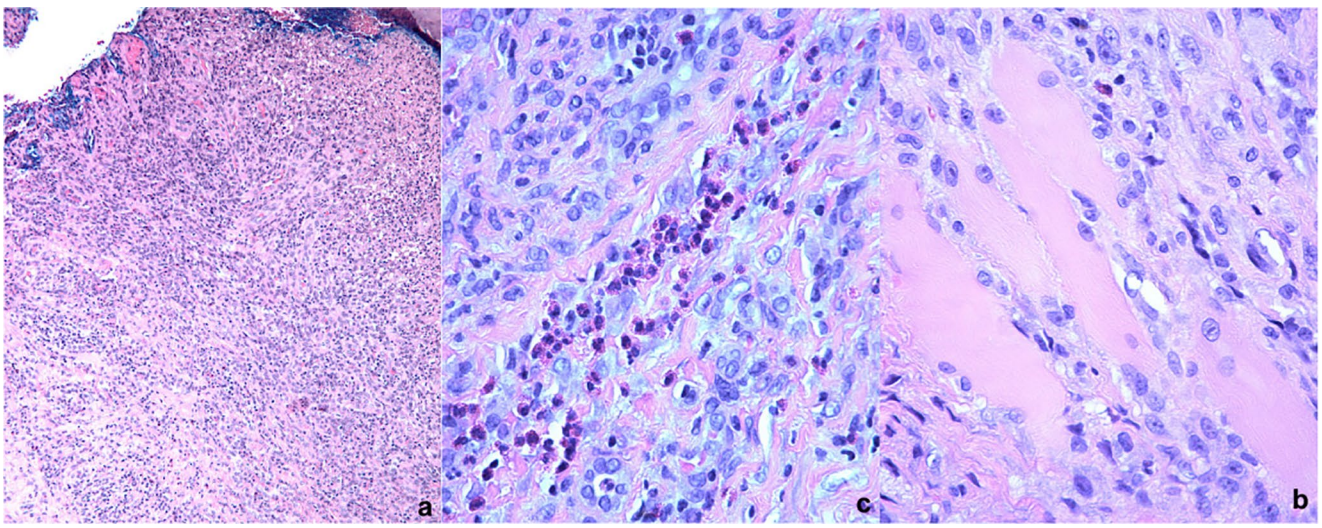

Fig. 2 Traumatic ulcerative granuloma with stromal eosinophilia: **A** Dense polymorphous infiltrate, **B** rich foci of eosinophils, **C** infiltrate surrounding muscle bundles, scarce eosinophils

indistinct cell borders [1, 7]. This cell type, which is often interpreted as histiocytic, complicates the histologic evaluation and has occasionally led to an erroneous diagnosis of a lymphohistiocytic malignancy [7]. In advanced lesions, the cellular infiltrate is predominantly composed of eosinophils and these large atypical mononuclear cells.

The vascularity at the center of the TUGSE lesion is sparse, while numerous capillaries and endothelial cells are present at the periphery [7]. The term "granuloma" in the context of TUGSE does not describe a specific granulomatous process such as that seen in tuberculosis. However, through common usage, granuloma can also refer to a mass composed of granulation tissue, as in TUGSE. Although alternative names have been suggested (e.g., eosinophilic ulcer), TUGSE remains deeply entrenched in the literature, and most pathologists recognize the entity by this designation.

Histologic Differential Diagnoses

The presence of eosinophils at the base of an ulcer is not sufficient to make the diagnosis of TUGSE, as this can be a nonspecific finding observed in aphthous and traumatic ulcers. The histologic differential diagnosis includes angiolymphoid hyperplasia with eosinophilia (ALHE), Epstein-Barr virus (EBV) mucocutaneous ulcers, and diffuse large B-cell lymphoma.

ALHE is a benign vascular neoplasm that primarily affects the skin and rarely involves the oral mucosa [12]. It is clinically characterized by nodular (rather than ulcerated) lesions with bizarrely shaped vascular structures lined by endothelial cells with large, round, vesicular nuclei and eosinophilic cytoplasm, that protrude into the lumina. An inflammatory infiltrate of lymphocytes, eosinophils, plasma cells, histiocytes, and mast cells surrounds the vessels [12]. ALHE does not contain large atypical lymphoid cells; however, clonally rearranged T-cell receptor (TCR) genes have been detected (5/7 cases) [13, 14]. This suggests that ALHE, or a subset of ALHE cases harboring a clonal T-cell population, may represent a TLPD of benign or low-grade malignant nature [13]. This implies the possibility of a relationship between the eosinophil-rich CD30+TLPDs and ALHE [14].

EBV-mucocutaneous ulcer is a lymphoproliferative disorder with a polymorphous lymphoid infiltrate including EBV-positive atypical large B-cells and/or Hodgkin-Reed-Sternberg-like cells [15]. The atypical large B cells and Hodgkin-Reed-Sternberg-like cells are EBV-positive, express B-cell markers, and are frequently CD30 positive, but rarely express CD15. The ulcerative lesions typically involve mucosal and cutaneous sites in patients with immune deficiency/dysregulation [15].

Oral lymphomas are rare, mostly of B cell lineage (98%), with the majority corresponding to diffuse large B-cell lymphoma [16]. Histologically, there is a diffuse proliferation of large lymphoid cells effacing tissue architecture with expression of B cell markers such as CD19, CD20, and PAX5. Additionally, EBV may be positive in some cases. The most frequent clinical signs of oral lymphomas include swelling, ulceration, and radiographic destruction of bone [16].

Immunohistochemical Features

Although some cases of TUGSE are histologically straightforward, others presenting with large, atypical cells intermixed with the inflammatory infiltrate may be difficult to interpret, requiring immunohistochemical and molecular studies to establish a diagnosis [5].

TUGSE has been shown to consistently (100% of cases) have a strong to moderate expression of CD3, a T-lymphocyte marker, and a moderate to weak expression of both CD8 and granzyme B. In contrast myeloperoxidase shows a more inconsistent strong reactivity (42.1% of cases). When positive, myeloperoxidase is detected in the ulcerative areas, due to abundant neutrophils, and in the deeper regions of the lesions, primarily associated with eosinophils [1]. Within the polymorphous infiltrate there is weak staining for CD20 (scare B-cells), CD68 (plasma cells, and AA1 (mast cells) [1].

CD30, a transmembrane protein of the tumor necrosis/nerve factor receptor family, has been identified in varying proportions of cell infiltrates across different TUGSE cases [3]. While strong and homogeneous CD30 expression characterizes multiple hematologic disorders (e.g., classical Hodgkin's lymphoma, anaplastic large cell lymphomas, primary cutaneous CD30+TLPDs), it can also be present in 71% of common neoplastic skin disorders (e.g., insect bites, stasis ulcers) [17, 18]. Fonseca et al. demonstrated a nonspecific staining pattern of CD30+with positivity of large atypical and small lymphoid cells in 70% of TUGSE cases evaluated (26/37) [1].

The origin of the large atypical mononuclear cells that are present in variable numbers in TUGSE lesions remains debatable, as various authors have reported contradictory immunohistochemical features. Some studies have shown these large mononuclear cells to be heterogeneous, with a variable proportion expressing histiocytic (CD68) or dermal dendrocytic (Factor XIII) markers, and occasional S100 positivity [9]. In contrast, another immunohistochemical study of 9 TUGSE cases demonstrated these atypical large cells to only express vimentin, suggesting a myofibroblastic origin [7]. Ficarra et al. first described a TUGSE case with CD30+atypical large mononuclear cells, while Alobeid et

al. later demonstrated that these cells also expressed the protein detected by β-F1 and pan-T-cell markers (CD2, CD3, and CD5), suggesting that they could be of T-cell origin [14, 19]. Abdel-Naser et al. reported the expression of Epstein-Barr virus (EBV)-encoded latent membrane protein 1 in these CD30+large mononuclear cells [20].

Several authors have demonstrated the presence of scattered or clustered CD30+large, atypical cells in TUGSE, including Alobeid et al. who identified 3 cases of TUGSE lesions with CD30+atypical mononuclear cells [14]. In their review of 12 TUGSE cases, Hirshberg et al. reported 7 cases with large atypical mononuclear cells; in 5 of these cases (5/12 cases, 42%), the atypical mononuclear cells were CD30+, with a scattered distribution in 4 cases, and small infiltrating clusters in 1 case. Salisbury et al. identified strong CD30+staining of large, atypical mononuclear cells in 8 cases (8/37 cases, 22%), and focal staining in 18 cases (18/37 cases, 49%) [3]. Hirshberg et al. demonstrated that anaplastic lymphoma kinase (ALK), a marker associated with large cell CD30+lymphoma, was negative in all cases, supporting the reactive nature of TUGSE [10].

Spectratyping Analysis

Using polymerase chain reaction (PCR) analysis for the TCRγ chain gene, some investigators found atypical TUGSE lesions containing CD30+atypical, mononuclear cells to have a monoclonal rearrangement of the TCRγ chain gene [3, 10, 14]. The molecular evidence of T-cell clonality within TUGSE raises the possibility that a subset of these lesions could be classified as low-grade CD30+TLPDs [3]. However, T-cell clonality has been described in various benign and reactive conditions and its presence does not necessarily indicate a T-cell malignancy [21, 22]. In the 3 cases reported by Alobeid et al., the atypical mononuclear CD30+cells demonstrated monoclonality of the TCRγ chain gene [14]. Additionally, one patient presented with skin nodules that preceded the oral lesions, where both the oral and cutaneous specimens had an identical monoclonal rearrangement of the TCRγ chain gene [14]. Among the 5 TUGSE cases with CD30+atypical mononuclear cells reported by Hirshberg et al., the single case showing the CD30+cells infiltrating in small clusters demonstrated monoclonal rearrangement of the TCRγ chain gene [10]. However, the lesion healed without recurrence and no new lesions arose during two years of follow-up [10]. Of the 37 TUGSE cases evaluated by Salisbury et al., 7 cases (7/37, 19%) demonstrated monoclonal rearrangements of the TCRγ chain gene, 22 (22/37, 59%) demonstrated polyclonal rearrangements, and 8 (8/37, 22%) did not contain adequate DNA for PCR analysis [3]. When correlated to the CD30+staining of the atypical mononuclear cells, strong positive staining was identified in 1 case (1/7, 14%) of the TUGSE lesions with monoclonal TCRγ gene rearrangement; focal positive staining was identified in 4 (4/7, 57%) of the monoclonal lesions, and negative staining was observed in 2 (2/7, 29%) of the monoclonal lesions [3]. Salisbury et al. concluded that without morphologic and/or clinical evidence of lymphoma, T-cell clonality and/or CD30 positivity in TUGSE lesions is not indicative of malignancy and should be interpreted with caution [3]. Setti et al. reported a controversial case of a self-healing lesion of the tongue with a clonal-T cell proliferation and CD30-immunohistochemical profile, similar to the two cases previously described by Hirshberg et al. [3, 23].

The presence of T-cell monoclonality does not necessarily indicate a T-cell malignancy, as it has been detected in various benign and reactive conditions [21, 22]. Therefore, the detection of a dominant clone of a T-cell population alone is insufficient to diagnose a T-cell lymphoma. In situations of diagnostic doubt, it is strongly recommended to carefully search for other features characteristic of lymphoma, such as an abundant atypical cell infiltrate, significant mitotic activity, and vascular infiltration. In some cases, the diagnosis of low-grade lymphoma can be difficult to make based solely on histologic and immunohistochemical findings, and is only recognized retrospectively, when the lesion recurs several times, spreads to other areas, or develops more pronounced malignant microscopic features [23]. It has been suggested to reserve CD30 staining of TUGSE lesions, along with testing for TCRγ rearrangement, for rare cases with abundant atypical mononuclear cells that require immunoprofiling [24].

Treatment and Prognosis

TUGSE is a self-limiting lesion, and aggressive surgical treatment is typically not required, although a biopsy can stimulate regression and healing. Additionally, a soft diet and application of corticosteroid or nonsteroidal anti-inflammatory drug ointments, or intralesional steroid injections, cryosurgery, and curettage are other treatment modalities for patients with TUGSE lesions [4]. The reported treatment modalities for Riga-Fede disease vary considerably and include smoothing or extraction of the associated teeth, weaning of the infant, and performing either an incisional or excisional biopsy [6]. There is no reported recurrence for either the infantile or adult form of TUGSE.

Within the small number of TUGSE case reports that demonstrated monoclonal rearrangement of the TCRγ chain genes, some of the included cases should not be regarded as TUGSE. Alobeid et al. included 2 cases that were primarily diagnosed as peripheral T-cell lymphoma morphologically and by molecular markers, and one case diagnosed as lymphomatoid papulosis without any eosinophilia, although the

cases demonstrated favorable behavior with follow-up that included complete resolution for one, and a local recurrence 13 years later [14, 24]. There are no cases in the literature of widespread or systemic lymphoma developing in a patient following the diagnosis of a TUGSE with a monoclonal pattern for the TCRγ gene. Therefore, the previously recommended treatment for CD30+TUGSE lesions of complete excision with surgical free margins, and a lifetime of close follow-up for detection of relapses and lymphoma transformation may be exaggerated [3, 10, 14].

T-cell Lymphoproliferative Disorders

The research on TUGSE with findings of CD30+atypical mononuclear cells and monoclonal rearrangement of the TCRγ chain has led to the investigation of TLPDs in the oral cavity. Since there appears to be a spectrum with TUGSE one end and oral TLPDs on the other, it is important to briefly discuss the recent research findings on oral TLPDs, which are being guided by the better- known cutaneous CD30+TLPDs. Therefore, understanding primary cutaneous CD30+TLPDS is crucial as oral variants share significant similarities with these better-characterized lesions.

Primary cutaneous CD30+TLPDs, the second most common subgroup of cutaneous T-cell lymphomas after mycosis fungoides, represent a heterogeneous group of lymphoid neoplasms including lymphomatoid papulosis, anaplastic large cell lymphoma, and borderline lesions [25, 26]. Lymphomatoid papulosis manifests as self-healing recurrent papulonodular skin lesions with atypical CD30+T-cells and excellent prognosis; while primary cutaneous anaplastic large cell lymphoma has ~90% 10-year survival [27]. Mucosal CD30+TLPDs share features with cutaneous counterparts and require clinical staging to differentiate primary from secondary types, with primary cases resembling cutaneous rather than systemic disease. While no standardized mucosal classification exists, most oral cases are diagnosed as anaplastic large cell lymphoma [28–30]. The diagnosis of oral cavity CD30+TLPDs is as challenging as that of cutaneous lesions, especially in the absence of additional clinical (staging) information [25].

Clinical, Histological, Molecular, Immunohistochemical Features

Primary oral CD30+TLPDs, including anaplastic large cell lymphoma, are rarely reported [29–35]. Eight documented cases of oral mucosal CD30+TLPDs showed spontaneous regression without therapy [14, 25, 29, 31, 35, 36]. These lesions affected mostly females (female to male ratio, 5:3), aged 36–89 years (mean 62), predominantly on the tongue (4/8 cases, 50%), followed by buccal mucosa (2/8 cases, 25%), and soft palate (1/8, 12.5%); one case specified only "oral cavity." All cases lacked systemic involvement, with 7/8 patients showing complete spontaneous resolution without recurrence during follow-up (mean: 17.6 months, range: 11–70) [25]. Monoclonality of the TCRγ chain gene was identified in 3/6 cases (50%) with available molecular studies [14, 25, 36]. Prokopis et al. examined 4 regressing cases of oral CD30+TLPDs where lesional cells strongly expressed CD30 and CD3, with variable positivity for CD2, CD5, and CD7 (Fig. 3) [25]. The T-cell rich stroma contained mixed CD4+and CD8+cells. All cases were negative for ALK and EBER ISH. CD68 identified scattered

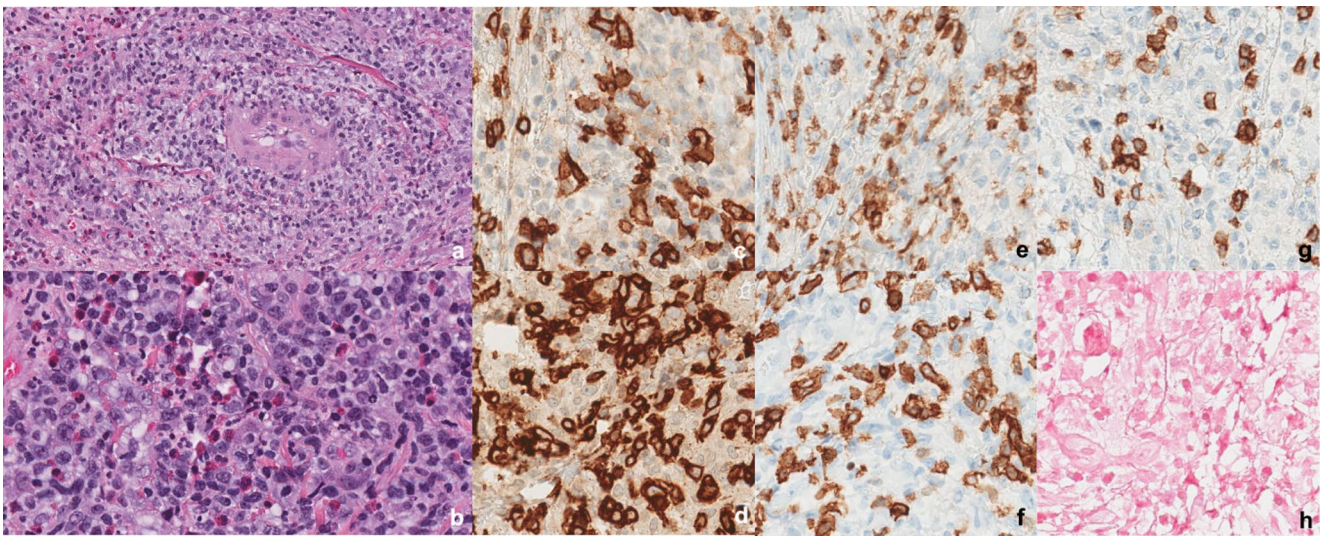

Fig. 3 Histological characteristics and immunophenotypic properties of oral self-healing CD30+T-cell lymphoproliferative disorders: **A**-**B** Angiocentric growth of atypical lymphoid population, dense infiltrate of lymphocytes, eosinophils, **C** lesional cells are strong and diffusely positive for CD30, **D** CD3, **E** variable immunoreactivity for CD2, **F** CD5, **G** CD7. **H** Lesional cells are negative for EBER. *Images courtesy of Dr. Ioannis Koutlas and Dr. Prokopios Argyris (University of Minnesota School of Dentistry, Minneapolis, MN)*

histiocytes, while CD56 marked clusters of stromal but not lesional cells [25].

The etiology of CD30+oral mucosal and cutaneous TLPDs remains unknown. One case report documented an oral CD30+TLPD in a patient on methotrexate for rheumatoid arthritis [37]. As an immunosuppressant, methotrexate can predispose patients to developing TLPDs. Fingolimod, a sphingosine-1-phosphate receptor modulator, has been associated with primary cutaneous CD30+TLPDs; however, no cases of Fingolimod-induced CD30+TLPDs limited to the oral cavity have been reported [25, 38]. Understanding the spectrum of mucosal CD30+TLPDs is critical to avoid possible overtreatment resulting from misdiagnosis of overt T-cell lymphoma. Oral CD30+TLPDs share prognostic features with their cutaneous counterpart, typically showing indolent biologic behavior and excellent prognosis with complete or partial regression after incisional biopsy [25, 29, 31, 36].

Conclusion

The relationship between TUGSE and CD30+TLPDs may represent a complex heterogenous diagnostic spectrum requiring careful clinicopathologic correlation. While the majority of TUGSE cases appear to be reactive in nature, the presence of CD30+atypical mononuclear cells and monoclonal T-cell receptor has raised questions about potential overlap with lymphoproliferative disorders. The current evidence indicates that these findings alone are insufficient to diagnose a malignancy as documented cases with CD30+positivity and monoclonality have exhibited favorable outcomes without progression to systemic disease. Therefore, care must be taken not to over-diagnose cases of TUGSE with atypical CD30+cells and monoclonality of the TCRγ chain as lymphoma. Given these observations, aggressive treatments and extended follow-up regimens may be unnecessary for TUGSE cases exhibiting CD30+and TCRγ chain monoclonality. The majority of TUGSE cases do not contain CD30+atypical mononuclear cells and reserved application of immunohistochemical and molecular studies for cases with abundant atypical mononuclear cells is recommended to avoid overdiagnosis and treatment.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Ethical Approval No identifiable patient information included in this manuscript.

Competing Interests The authors declare no competing interests.

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