Eosinophilic ulcer of the oral mucosa (EUOM) is an uncommon self-limited oral condition that clinically manifests as a solitary ulceration with elevated indurate borders affecting the tongue, buccal mucosa or lip. Microscopically, it is characterized by a polymorphic inflammatory infiltrate with a prominent polymorphonuclear eosinophilic component extending deep into the submucosa, underlying muscle and salivary glands. Large mononuclear cells probably corresponding to histiocytes, myofibroblasts or activated lymphoid cells are also frequently observed. The exact pathogenetic mechanisms implicated in the development of EUOM are poorly understood; however, the possibility that trauma may play a role in its development has been often postulated. Since its original description, the possibility that EUOM could be either considered an individualized disorder or a non-specific reactive pattern secondary to several stimuli has been discussed. EUOM may show some overlapping features with some entities such as atypical histiocytic granuloma, mucosal angiolymphoid hyperplasia with eosinophilia, and Kimura disease. The clinical and histopathological features and the differential diagnosis of EUOM are reviewed and its existence as a distinct disease discussed.

**Keywords:** eosinophilic ulcer; oral mucosa; traumatic granuloma; stromal eosinophilia; CD30-positive lymphoproliferative disorders

**Introduction**

Eosinophilic ulcer of the oral mucosa (EUOM) is an uncommon self-limited oral condition mostly appearing on the tongue. Several terms have been used to describe this process, such as traumatic granuloma of the tongue, eosinophilic ulcer of the tongue or traumatic granuloma with stromal eosinophilia (TGSE). Clinically, it usually manifests as a persistent oral ulcer, which clinically may give rise to a broad differential diagnosis with several infectious, tumoral and autoimmune conditions (Table 1).

Histologically, in some cases typical features such as dense polymorphic inflammatory infiltrate with abundant eosinophils extending into the underlying muscle may lead to the diagnosis; however, in other cases, the presence of large atypical cells intermixed with the inflammatory infiltrate may be difficult to interpret and special immunohistochemical stains and molecular studies will be required. Further studies such as microbiological cultures and serological tests can also be performed. As there is no specific hallmark of the disease, the diagnosis of EUOM has to be an exclusive one. In this article, we review clinical and histopathological features and differential diagnosis of EUOM and discuss its existence as a distinct disease.

**History**

Eosinophilic ulcer of the oral mucosa was first described in adults by Popoff in 1956. First reports in the 1960s included this process within the spectrum of granuloma faciale and some authors proposed the term ‘ulcerated granuloma eosinophilicum diutinum of the tongue’ (Hjorting-Hansen and Schmidt, 1961). In 1970, this lesion was proposed as a distinct entity by Shapiro (Shapiro and Juhlin, 1970). Since then, different names such as TGSE (Elzay, 1983; Hirshberg et al, 2006); traumatic eosinophilic granuloma of the tongue (Ficarra et al, 1997; Alobeid et al, 2004) and eosinophilic ulcer of the tongue or the oral mucosa (Doyle et al, 1989; El-Mofty et al, 1993; Mezei et al, 1995; Velez et al, 1997; Garcia et al, 2002) have been used to define this process leading to further confusion.

An apparently different disorder had been previously described in the pediatric age. Riga in 1881 reported an ulcerative lesion in the ventral surface of the anterior tongue or in the vestibular mucosa of lower lip, in children under the age of 2 years, produced by friction
Oral Diseases

Eosinophilic ulcer of oral mucosa
S Segura and RM Pujol

<table>
<thead>
<tr>
<th>Etiopathogenic mechanisms</th>
</tr>
</thead>
</table>

The pathogenic mechanisms implicated in the development of EUOM are poorly understood and only a limited number of studies have been specifically designed to elucidate the origin of this condition.

Several clinical features and epidemiological data seem to suggest that trauma may play a role in the development of this disorder: (i) A traumatic event is recorded in a variable proportion of cases of EUOM ranging from 0 to 100% of the cases (average 39%) (Bhaskar and Lilly, 1964; Elzay, 1983; Doyle et al, 1989; El-Mofty et al, 1993; Garcia et al, 2002; Hirshberg et al, 2006); (ii) the lesions are frequently located on the tongue where traumatisms are frequent, and (iii) two peaks of age incidence have been identified in EUOM, one peak during the first 2 years of life, in the context of nursing and teething, and another among the sixth and seventh decade, when missing and malposed teeth, as well as dental appliances and dentures may be more common. In 1964, Bhaskar and Lilly (1964) reported the development of lesions similar to EUOM after experimentally producing repeated injuries to the tongue. However, these results were not confirmed by von Domarus et al (1980) after performing similar investigations. Other authors have suggested that trauma is only a contributing factor in the development of EUOM and that probably some viral or toxic agents could be implicated (Tang et al, 1981). However, different attempts have failed to demonstrate viral particles and/or ultrastructural dense immune deposits in clear-cut cases of EUOM.

As most traumatic oral ulcers are devoid of eosinophils, several hypotheses have been proposed to explain the prominent eosinophilic infiltrates observed in this lesion. A possible direct pathogenic role of cytokine and chemotactic factors released by eosinophils in the development of EUOM has been hypothesized.

A possible interaction between mast cell, a release eosinophil chemotactic factors and tissue eosinophilia has also been postulated. Elzay histologically compared 41 cases of EUOM with 30 patients with a variety of inflammatory conditions affecting the oral mucosa (control group) and biopsies from normal oral mucosa (Elzay, 1983). In EUOM cases, in addition to stromal eosinophilia, an increase in mast cells (intact and degranulating) was observed. In all control tissues, eosinophils were absent whereas a light to moderate population of mast cells was observed in normal and inflamed oral tissue. An increased number of mast cells in the peripheral underlying connective tissue were also detected by El-Mofty et al (1993). Conversely, Regezi et al (1993) found scarce numbers of mast cells in EUOM infiltrates, although a significant numbers were detected in the normal surrounding tissue (Regezi et al, 1993). Nevertheless, the exact role of mast cells in the pathogenesis of EUOM remains controversial.

A traumatic disruption of the oral mucosa would facilitate the action of a non-identified etiologic factor (microorganisms, toxins or foreign proteins) into the connective tissue. This etiologic factor, in a predisposed subject, could induce an intense inflammatory reaction giving rise to a mast cell-eosinophil reaction similar to that noted in the studies on bronchial asthma. A possible additional role of cytotoxic T cells causing mucosal damage in EUOM has also been suggested. Hirshberg et al, (2006) demonstrated the presence of aggregates of TIA-1 positive cells, a marker of cytotoxic T cells in 12 cases of TGSE (Hirshberg et al, 2006). Recent studies have shown that eosinophils may also interact with fibroblasts and endothelial cells (Munitz and Levi-Schaffer, 2004). Their interaction with fibroblasts may result in a contribution towards wound healing via the synthesis of transforming growth factor (TGF) α and β, as demonstrated in a study using a mice wound-healing model (Wong et al, 1993). A lack of significant synthesis of transforming growth factors by eosinophils has been demonstrated in traumatic ulcerative granuloma with stromal eosinophilia. This phenomenon may explain the frequent delayed healing observed in these lesions (Elovic et al, 1996).
Clinical features

Clinically, EUOM usually manifests as a rapidly developing solitary ulcer, from few millimeters to several centimeters in diameter, with elevated and indurated borders arising in the oral cavity or on the lower lip. The lesion may show a peripheral erythema, a white or yellowish base and fibrinous membrane on the surface (Figure 1). Any mucosal surface can be affected; however, the tongue (lateral and dorsal surfaces) is the most common location, accounting for more than half the patients. The second most frequent locations are the buccal mucosa and mucobuccal fold, but it also can arise (in decreasing order of frequency) on the lips, gingiva, palate, floor of the mouth, and retromolar area.

Pain can be associated with variable proportion of cases (from 17% to 100%) and may cause a significant impairment of food intake. Although EUOM is often a solitary ulcer, multiple or metachronus lesions (new lesions on other oral sites) (Doyle et al., 1989; El-Mofty et al., 1993; Ficarra et al., 1997; Velez et al., 1997; Alobeid et al., 2004; Segura et al., 2006) have also been reported. There is a slight female predominance in most of the series and a peak on incidence between the sixth and seventh decades of life. The ulcers usually regress spontaneously in less than a month, although some of the patients may develop recurrences (Doyle et al., 1989).

In rare instances, persistent lesions lasting several months or even more than a year have been reported (Doyle et al., 1989; Garcia et al., 2002). Table 2 illustrates a review of clinical features of the largest series of EUOM published in the literature (Bhaskar and Lilly, 1964; Elzay, 1983; Doyle et al., 1989; El-Mofty et al., 1993; Regezi et al., 1993; Garcia et al., 2002; Hirshberg et al., 2006).

Atypical clinical forms that manifested as erythematous macules, non-specific erythroplakic or leukoplakic lesions have also been reported. Associated internal disease is uncommon in adults and patients with this condition are otherwise healthy (Mezei et al., 1995). In extremely rare cases, association with enlarged regional lymph nodes has been noted (El-Mofty et al., 1993).

In contrast, a pediatric variant of the EUOM, the so-called Riga-Fede disease, may be the presenting sign of an underlying neurologic disorder, such as congenital autonomic dysfunction with universal pain loss, familial dysautonomia (Riley–Day syndrome) (Axelrod et al., 1983; Rakocz et al., 1987; Eichenfield et al., 1990; Zaenglein et al., 2002) or other disorders characterized by self-mutilation causing similar lesions (Lesch–Nyhan and Gaucher’s disease). In children, the lesions often arise on the ventral surface of the tongue or the lingual frenum along the midline because of contact with the adjacent mandibular incisors during breastfeeding. Onset of the lesions is usually concomitant with the eruption of the primary teeth, principally the lower incisors, beginning at 6–8 months of age. The designation of Riga–Fede disease applies specifically to infants and children younger than 2 years with this disorder.

Histopathology

Microscopically, under an ulcerated mucosa, a poorly formed granulation tissue showing an increased number of capillaries with prominent endothelial cells is usually observed. A dense diffuse submucosal polymorphous inflammatory infiltrate involving occasionally the overlying epithelium is usually noted. This infiltrate tends to extend to the deeper underlying soft tissue, muscle fibers and salivary glands (Figure 2). In a histopathological review of 38 cases of EUOM, El-Mofty et al., (1993) noted that degeneration and loss of muscle fibers were an almost constant finding (El-Mofty et al., 1993). The inflammatory infiltrate is composed of small round lymphocytes, abundant polymorphonuclear eosinophils and other inflammatory cells (neutrophils, plasma cells and histiocytes). Degranulation of eosinophils is commonly noted.

Large mononuclear cells with round to ovoid nuclei, showing occasional nuclear atypia, intermingled in the inflammatory infiltrate are also frequently observed. Some authors (Regezi et al., 1993) pointed out that the population of large mononuclear cells is heterogeneous, with a variable proportion of cells expressing histiocytic (CD68) or dermal dendrocyte (factor XIII) markers, and scattered submucosal S100-positive cells (Regezi et al., 1993). In contrast, El-Mofty et al., (1993) in an immunohistochemical study of a series of nine cases of EUOM, observed that these atypical large cells were positive only for vimentin and lacked expression of all lymphoid and histiocytic markers, suggesting that they may correspond to myofibroblasts (El-Mofty et al., 1993).

Figure 1 A 67-year-old man presenting with a painful ulcer on the lateral side of tongue appeared 4 weeks before consultation. No obvious previous trauma. Clinical features of the lesion showing an ulcer with slightly elevated borders and fibrinous surface.
Table 2  Clinical features of main series of eosinophilic ulcer of the oral mucosa reported in the literature

<table>
<thead>
<tr>
<th>Author (Year of publication)</th>
<th>No. cases</th>
<th>Mean age (range)</th>
<th>Sex (M:F)</th>
<th>Clinical features</th>
<th>Size (mean)</th>
<th>Pain</th>
<th>Localization</th>
<th>Duration</th>
<th>Treatment</th>
<th>Previous trauma (%)</th>
<th>Course (follow up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhaskar and Lilly (1964)</td>
<td>7</td>
<td>37 (20–59)</td>
<td>2.5:1</td>
<td>Ulceration</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Tongue (6), Lip (1), Tongue (10), Buccal mucosa (2), Alveolar mucosa (2), Floor of the month (1)</td>
<td>14–63 days</td>
<td>Surgery (6), Radiation (1), Complete excision (10), Healed after biopsy (3)</td>
<td>None</td>
<td>No recurrence (1–2 years)</td>
</tr>
<tr>
<td>Doyle et al (1989)</td>
<td>15</td>
<td>62 (42–77)</td>
<td>1.1:1</td>
<td>Ulceration (14), Not ulcerated (1), Synchronous lesions (2)</td>
<td>0.3–5 cm (1.8)</td>
<td>Not stated</td>
<td>Tongue (19), Buccal mucosa (8), Vestibule (7), Floor of the mouth (3), Lower lip (1), frenum (1), Gingiva (1), palate (1)</td>
<td>2 weeks–6 months</td>
<td>Complete excision (33), Healed after biopsy (8)</td>
<td>5 cases (30)</td>
<td>No recurrence (3 months–6 years)</td>
</tr>
<tr>
<td>Elzay (1983)</td>
<td>41</td>
<td>58 (14–92)</td>
<td>1:1</td>
<td>Ulceration (27), Indurated lesion (13)</td>
<td>Not stated</td>
<td>17%</td>
<td>Tongue (16), Buccal mucosa and fold (15), Retromolar (3), Palate (1), upper lip (1)</td>
<td>3–120 days</td>
<td>Complete excision (33), Healed after biopsy (8)</td>
<td>21 cases (51)</td>
<td>No recurrence (3 months–6 years)</td>
</tr>
<tr>
<td>El-Mofty et al (1993)</td>
<td>38</td>
<td>57 (6–88)</td>
<td>1:1.5</td>
<td>Ulceration (19), Indurated lesion (16), Red lesion (3)</td>
<td>0.5–6 cm (2.2)</td>
<td>Not stated</td>
<td>Tongue (7), Buccal mucosa (1), Tongue (10), Buccal mucosa (1)</td>
<td>Weeks to months</td>
<td>Not stated</td>
<td>7 cases (18)</td>
<td>2 cases with metachronous lesions</td>
</tr>
<tr>
<td>Regezi et al (1993)</td>
<td>8</td>
<td>59 (10–87)</td>
<td>1:3</td>
<td>Ulceration (7), Nodule (1)</td>
<td>Not stated</td>
<td>50%</td>
<td>Tongue (7), Buccal mucosa (1), Tongue (10), Buccal mucosa (1)</td>
<td>2 weeks–6 months</td>
<td>Not stated</td>
<td>11 (100)</td>
<td>1 case metachronous lesion</td>
</tr>
<tr>
<td>Garcia et al (2002)</td>
<td>11</td>
<td>62 (41–81)</td>
<td>1:1.2</td>
<td>Ulceration with indurate borders (10), Two symmetric ulcers (1)</td>
<td>0.4–2 cm (1.2)</td>
<td>100%</td>
<td>Tongue (7), Buccal mucosa (1), Tongue (10), Buccal mucosa (1)</td>
<td>2 weeks–24 months</td>
<td>Remove traumatic factor</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>Hirshberg et al (2006)</td>
<td>12</td>
<td>49 (14–87)</td>
<td>1:1</td>
<td>Ulceration with rolled-up margins (11), Exophytic mass (1)</td>
<td>Not stated</td>
<td>Mild pain most of cases</td>
<td>Tongue (7), Buccal mucosa, vestibule and floor of the month (5)</td>
<td>Days to 1 year</td>
<td>Complete excision or healed after biopsy</td>
<td>4 (30)</td>
<td>No recurrence</td>
</tr>
</tbody>
</table>
Ficarra et al., (1997) described the first case of EUOM in which a proliferation of CD30 atypical large mononuclear cells was identified suggesting that EUOM could also be related to the spectrum of CD30 positive lymphoproliferative disorders (Ficarra et al., 1997). Several authors have also demonstrated the presence of scattered or even clusters of CD30 positive large atypical cells in EUOM lesions (Alobeid et al., 2004; Hirshberg et al., 2006 Segura et al., 2006; Pilolli et al., 2007). We recently reported an old woman with two metachronic EUOM that exhibited aggregated CD30 positive large atypical cells in both biopsy specimens, but clonality could not be demonstrated in any of the lesions (Segura et al., 2006) (Figure 3). Hirshberg et al., (2006) performed histological, immunohistochemical and molecular studies of 12 cases of EUOM. They found that in seven cases, atypical large cells were present, with five cases of CD30 + cells that were scattered in four of them and presented with aggregates and one case forming small clusters infiltrating the underlying muscle. In the latter case, a monoclonal rearrangement of the TCRγ genes was detected in the oral tissue, but not in the bone marrow biopsy or in peripheral blood specimen (Hirshberg et al., 2006). Occasional reports of patients
presenting skin nodules preceding the development of oral lesions and disclosing in both lesions an identical monoclonal rearrangement of the TCRγ chain gene have been reported (Alobeid et al, 2004). In such instances, the possibility that the observed lesions could correspond to a rare example of lymphomatoid papulosis with oral involvement could not be completely ruled out.

As the presence of large atypical CD30+ cells has been reported in a wide range of infectious, parasitic and inflammatory disorders (Hwong et al, 2001; Cesinaro and Maiorana, 2002; Gallardo et al, 2002; Kim et al, 2002; Cepeda et al, 2003; Moreno-Ramirez et al, 2003; Leinweber et al, 2006), we can speculate that CD30-positive cells observed in EUOM could correspond to an activated T-cell lymphocytic population within the context of a reactive lesion. However, the exact pathogenetic significance of this phenomenon remains elusive.

**Differential diagnosis**

The diagnosis of ulcerative lesions affecting the oral mucosa is usually difficult because different process may share a similar clinical appearance (Table 1). The observation of an EUOM that manifested clinically as a rapidly enlarging oral ulceration with indurated margins could lead to suspect the diagnosis of oral squamous cell carcinoma. However, this diagnosis can be easily excluded after performing a biopsy that will show the bland histopathological picture of EUOM, ruling out malignancy.

The clinical differential diagnosis should also include several infectious disorders, such as primary syphilis (syphilitic chancre) and some granulomatous mycobacterial (oral tuberculosis), fungal (histoplasmosis) or even necrotizing bacterial infections. In primary syphilis, the ulcer is usually painless and a regional enlarged lymph node is present. Histologically, at the base of the ulcer, numerous vessels with prominent endothelial cells are also present, but the inflammatory infiltrate has a predominantly perivascular distribution and is composed of lymphoid cells and many plasma cells. The identification of Treponema pallidum spirochetes in mucosal biopsy specimens either by silver-impregnation staining techniques (Warthin–Starry stain) or immunohistochemically in addition to serologic tests may permit to establish the diagnosis. In oral tuberculosis, the observation of a necrotizing granulomatous inflammation is a constant feature. Special stains for mycobacteria may confirm the diagnosis, as well as available molecular studies by PCR for the detection of Mycobacterium tuberculosis and mycobacterial cultures. Oral ulcers observed in disseminated histoplasmosis differ histologically from EUOM by the presence of areas of tissue necrosis in combination with a granulomatous inflammatory infiltrate with occasional multinucleated giant cells. Small spores surrounded by a clear space can be identified within histiocytes and giant cells with H&E stains, being more obvious with PAS or Grocott Methenamine–Silver stain. A necrotizing bacterial infection can be easily excluded by histopathological study, Gram stain and microbiological cultures.

Other clinical differential diagnoses are Wegener’s granulomatosis, sarcoidosis and discoid lupus erythematosus (DLE). DLE may present as chronic ulcers on the oral mucosa. Lesions are usually multiple and recurrent and concomitant skin lesions may also be present. Histological features of mucosal DLE lesions show hyperkeratosis, alternating epithelial hyperplasia and atrophy, disturbed epithelial maturation with reactive cytological atypia, vacular degeneration of the basal layer, and a predominantly lymphocytic dermal infiltrate, which may be focal, interstitial, perivascular or band-like. In difficult cases, direct immunofluorescence studies may be helpful.

Langerhans’ cell histiocytosis (eosinophilic granuloma) is frequently included in the differential diagnosis of EUOM. When mandibular or maxillary bone involvement is present, local pain and occasional gingival swelling and hyperplastic gingival proliferation mimicking a periodontal disease can be observed (Eckardt and Schulze, 2003). Histologically, it is characterized by the presence of a polymorphous infiltrate with abundant eosinophils and proliferation of Langerhans’ cells that characteristicly exhibit an atypical reniform nucleus and are S-100 and CD1a-positive.

Histologically, EOUM may overlap with other entities such as atypical histiocytic granuloma (AHG), angiolymphoid hyperplasia with eosinophilia (ALHE) and Kimura disease. It is not clear if these represent individualized entities or variants of one common spectrum of disorders.

Atypical histiocytic granuloma is a controversial entity that manifests as a benign self-limited ulcer often developing on the gingiva. Histologically, it is characterized by a polymorphous submucosal infiltrate with lymphohistiocytic cells and eosinophils. In contrast to EUOM, the infiltrate is more superficial and rarely extends to the underlying muscle. Occasional large atypical cells are also noted showing ultrastructural (presence of lisosomes) (Eversole et al, 1985) and immunohistochemical (CD68+ expression) histiocytic cells (Regezi et al, 1993). These cells exhibit mild to moderate pleomorphism and mitotic activity (Eversole et al, 1985). In our opinion, as pointed out by other authors (Hirshberg et al, 2006), these lesions are clinically and histologically indistinguishable from EUOM and probably correspond to a superficial variant of this disorder.

Mucosal involvement is a rare phenomenon in ALHE. When present, it often manifests as a solitary asymptomatic nodule, although erythematous macules, plaques, ulcers or even tumors have been also described (Bartralot et al, 1996). Oral lesions tend to develop on the upper lip, but the buccal mucosa, palate and tongue may also be affected. Histologically, the observation of an inflammatory infiltrate with abundant eosinophils and a marked vascular proliferation with bizarrely shaped blood vessels is usually noted. A lymphoid component is also present and may show a tendency to form lymphoid follicles or aggregates (Bartralot et al,
1996; Razquin et al, 1991). Recent studies have demonstrated a monoclonal T-cell population in some cases of ALHE suggesting that in some cases, it could also represent a low-grade T-cell lymphoproliferative disorder (Kempf et al, 2002) more than a reactive vascular disorder as had been previously hypothesized (Peters et al, 1986).

Kimura disease is a chronic inflammatory process of unknown origin. It is mainly observed in oriental subjects and it clinically manifests as the association of deep dermal or subcutaneous nodules or tumors, enlarged lymph nodes and peripheral eosinophilia. Involvement of the oral mucosa that manifested as ulcerated nodules (mainly on the hard palate) has rarely been reported (Terakado et al, 2002; Ray et al, 2003). Histologically, it is characterized by a prominent infiltrate of lymphoid cells and eosinophils, displaying a marked component of germinal centers, but lacking atypical large cells. Most authors believe that Kimura disease has to be differentiated from ALHE (Chun and Ji, 1992). Some authors have postulated that when these lesions are observed in oral mucosa, they might represent a particular subset of EUOM (Alobeid et al, 2004).

The occasional observation in EOUM of large atypical lymphoid cells may raise the histopathological differential diagnosis with some malignant lymphoproliferative disorders. Oral lymphomas are rare, accounting for 2–5% of all oral malignancies. Most of the oral lymphomas are of B cell lineage (98%), and a majority of them (58%) correspond to diffuse large B-cell lymphomas. Swelling, ulceration, and radiographic destruction of bone are the most frequent clinical signs in oral lymphomas (Kemp et al, 2007).

As in some cases of EUOM, clusters (Ficarra et al, 1997; Alobeid et al, 2004; Hirshberg et al, 2006; Segura et al, 2007) or scattered (Alobeid et al, 2004; Hirshberg et al, 2006; Pilolli et al, 2007) CD30+ large atypical cells have been observed, the differential diagnosis should also include the group of CD30+ primary cutaneous lymphoproliferative disorders. In most of the cases exhibiting scattered CD30-positive cells, molecular studies could not demonstrate a clonal rearrangement of the TCRγ genes, whereas in cases exhibiting aggregates of those cells, T-cell clonality could be found (Alobeid et al, 2004; Hirshberg et al, 2006).

CD30+ primary cutaneous lymphoproliferative disorders clinically manifest as a chronic, recurrent, self-healing papulo-nodular eruption [lymphomatoid papulosis (LyP)] or as a solitary, firm, large and often ulcerated nodule [anaplastic large T-cell lymphoma (ALCL)] and share the expression of CD30 antigen as a common phenotypic hallmark (clusters of CD30+ cells in LyP and more than 75% in ALCL) (Willemze et al, 2005). The lesions of both disorders are usually limited to the skin, but some examples of both ALCL and LyP involving the oral mucosa have been reported (Rosenberg et al, 1996; Kato et al, 1998; Savarrio et al, 1999; Sciubba et al, 2000; Pujol et al, 2005).

Oral involvement in LyP is an exceedingly rare phenomenon and usually manifests as ulcerated nodules or papules with central necrosis on the tongue or buccal commissure, always associated with the characteristic cutaneous lesions. Probably, EUOM should be added to the list of reactive inflammatory disorders and neoplastic diseases, which can mimic LyP, such as arthropod bite reaction, verruca vulgaris, scabies, gold acupunctural reaction, molluscum contagiosum and herpes virus infection, among others (Hwong et al, 2001; Cesinaro and Maiorana, 2002; Gallardo et al, 2002; Kim et al, 2002; Cepeda et al, 2003; Moreno-Ramirez et al, 2003; Leinweber et al, 2006). However, in LyP CD30+ cells are found in clusters and their number is usually higher than that observed in EUOM.

The definite diagnosis of LyP should always be established on the basis of the clinical, histopathological, phenotypic and molecular features.

Isolated reports of oral benign lesions mimicking lymphomas (‘oral pseudolymphoma’) have also been published, including cases showing features resembling EUOM, AHG or LyP, but without fulfilling the typical diagnostic features of these disorders. (del Rio et al, 1997).

**Treatment**

Eosinophilic ulcer of the oral mucosa is generally a self-limiting disorder that tends to resolve spontaneously in a few weeks. Once malignancy is excluded by biopsy or eventual complementary studies, the better approach is to wait and see, and in many instances, no treatment is necessary. The etiologic identification and avoidance of a possible persistent mucosal traumatism are mandatory (extraction or restoration of the causative teeth, change or repair of the prosthesis). In cases of painful lesions, topical or oral analgesics can be prescribed.

Many different therapeutic approaches for EUOM have been reported in the literature. The most frequently performed therapy is surgical excision. This approach seems especially indicated in cases with persistent lesions. No further local recurrences are usually noted after excision; however, development of new lesions in other mucosal sites may occur. Topical steroids in cream or mouthwashes can be also prescribed, despite there being no conclusive evidence of its efficacy. Other therapeutic modalities include intralesional or oral corticosteroids (Mezei et al, 1995), topical antibiotics, curettage, and criotherapy (Shapiro and Juhlin, 1970). In isolated and selected cases, radiotherapy has also been advocated (Bhaskar and Lilly, 1964).

**Conclusions**

Eosinophilic ulcer of the oral mucosa is a rare ill-defined condition, mostly reported in oral medicine and poorly referred in dermatologic literature. It probably corresponds to a heterogeneous entity, which includes several groups of disorders. The etiology is unknown, although a local traumatic event has been often incriminated.

Eosinophilic ulcer of the oral mucosa is characterized by rapidly growing ulcers with indurate borders that
outline a wide clinical differential diagnosis. This condition is characteristically self-healing and has a benign course. Although in adults it is not associated with underlying disease, its presence in infants (the so-called Riga–Fede disease) should exclude a neurological disease.

Histology is characterized by a prominent eosinophilic infiltrate. The significance and etiopathogenesis of this phenomenon are not well understood. The second histological hallmark is the presence of variable numbers of large cells, showing occasionally cellular atypia. These cells have been demonstrated to correspond either to histiocytic cells, myofibroblastic cells or activated lymphoid cells.

The occasional observation of large CD30+ cells seems to be related to a reactive pattern of activated T or B lymphocytes simulating a lymphoproliferative disorder as has been described in several reactive conditions. However, there is a subset of cases of EUOM that exhibit aggregates of CD30+ cells in addition to a monoclonal rearrangement of TCRγ gene. These lesions may be better classified within the spectrum of CD30-positive disorders.

Eosinophilic ulcer of the oral mucosa cannot be considered currently a distinct entity and may be best regarded as a reactive pattern of unclear etiology.

Acknowledgement

We thank the Department of Dermatology from Hospital Clinic, Barcelona, for lending us the clinical and histological images from Figure 3.

Author contributions

Manuscript concept and design: Sonia Segura; drafting of the manuscript: Sonia Segura; critical revision of the manuscript: Ramon M Pujol.

References


Eosinophilic ulcer of oral mucosa
S Segura and RM Pujol

295


