Pathophysiology

In most patients with eosinophilic ulcers, trauma is the etiologic factor, and the apparent source of irritation is easily identified. This mechanism is further supported by findings in rats in which microscopically similar lesions were experimentally induced by chronic mechanical injury.[3] How ever, in a number of studies, patients with multiple synchronous or metachronous lesions at different mucosal sites were identified. The source of the chronic irritation also is not evident in a number of patients; therefore, factors other than trauma may be involved in the pathogenesis of these ulcers. Eosinophilic ulcer has also been reported to occur in association with medication use; therefore, eosinophilic ulcer also may represent an unusual manifestation of a drug reaction.

Several investigators have proposed that eosinophilic ulcers develop as a result of a T-cell–mediated immune response. In certain predisposed individuals, recurrent trauma may lead to the alteration of tissue antigens or ingress of unknown factors (eg, viral particles, toxic microbial products), which result in a hypersensitivity or allergic reaction. However, neither virally altered cells nor viral DNA is identified in biopsy specimens of typical eosinophilic ulcer.

Tissue eosinophilia is not uncommonly associated with T-cell–mediated immune reactions. Activated T lymphocytes produce a variety of lymphokines that are involved in eosinophilic maturation and act as eosinophil-chemotactic factors. Damage and degeneration of mucosal tissues may be due to a proliferation of cytotoxic T cells or toxic products released by degranulating eosinophils. Constituents of eosinophil secretory granules include a number of highly cytotoxic proteins, including eosinophil cationic protein, major basic protein, and eosinophil-derived neurotoxin.

One study demonstrated that, in most eosinophilic ulcer, the synthesis of transforming growth factor-alpha and transforming growth factor-beta is not increased in infiltrating eosinophils.[4] This observation is in contrast to that of the animal wound-healing model, in which eosinophils that express transforming growth factor are typically recruited to healing tissue sites. These findings may help explain the delayed healing that is characteristic of eosinophilic ulcer.

Eosinophilic ulcer, tumorlike eosinophilic granuloma of the skin, and transient eosinophilic nodulomatosis have been suggested to represent a mucocutaneous reaction pattern[5] ; thus, all may share a common pathogenesis

## History

- The most common complaint is that of an asymptomatic or mildly tender, solitary, nonhealing ulcer of variable duration.
- The lesion may be present for as short as 1 week or 12 months or longer.
- Patients with early ulcers often report pain and severe discomfort.
- Patients may have a history of trauma to the affected area.
- Depending on the location of the ulcer, other signs and symptoms may include dysphagia, odynophagia, dysphonia, and dyspnea.
- Occasionally, patients may present with a history of recent weight loss.
- Infants with Riga-Fede disease often experience discomfort while breastfeeding, and they may fail to thrive in the postnatal period.

## Physical

- Clinical appearance
- Eosinophilic ulcer typically presents as an irregular, solitary ulcer with a fibrinous membrane on the surface. A zone of erythema surrounds the ulcer.
- The margins of the lesion are often raised and usually indurated.
- Purulence may be noted emanating from the ulcer.
- Eosinophilic ulcers may be a few millimeters to as large as 7-8 cm in greatest dimension.
- In rare reports, multiple synchronous or metachronous lesions have been identified.
- Occasional ulcers may be macular, whereas others may present as nonspecific erythroplakic or leukoplakic lesions.
- In rare cases, an eosinophilic ulcer may present as an elevated, smooth mass that is free of ulceration; however, biopsy reveals the underlying, characteristic, invasive cellular proliferation. In some of these cases, the overlying epithelium may have regenerated without resolution of the underlying inflammation.

- Mucosal sites
- Any mucosal surface can be affected; however, the tongue is the most common location, accounting for 60% of reported cases. [6]
- The lateral and dorsal surfaces are usually affected because these are the areas most often traumatized.
- Lesions on the ventral surface of the tongue more commonly are observed in infants because of contact with the adjacent mandibular incisors during breastfeeding.
- The dorsal surface of the tongue may also be affected in infants because of irritation associated with maxillary incisors.
- The buccal mucosa and mucobuccal fold are also particularly susceptible to ulceration; lesions in these locations account for 24% of reported cases.

- Eosinophilic ulcers have also been reported (in decreasing order of frequency) on the lips, gingiva, palate, floor of the mouth, and retromolar area.

- In extremely rare cases, cervical lymphadenopathy is reported.

## Causes

- Common causes of oral trauma include the following:
- Self-inflicted injury in which the patient accidentally or deliberately traumatizes the mucosa

- Injury due to sharp-edged teeth or food
- Injury due to neonatal or natal teeth (Riga-Fede disease)
- Toothbrush abrasion
- Injury due to ill-fitting dentures
- Injury due to orthodontic or occlusal appliances
- Iatrogenic injuries (eg, those that occur during dental procedures, such as anesthetic necrosis that occurs during intubation for surgery)
- Injuries due to accidents

- Certain patients may be inherently predisposed to the development of eosinophilic ulcers, although this factor remains controversial.
- The role of drug reactions, if any, is unclear.
- Medical conditions or therapeutic regimens that predispose an individual to immune suppression may also delay healing.

## Procedures

- The clinical presentation and history often suggest the cause and nature of eosinophilic ulcers; however, many cases can resemble ulcerative squamous cell carcinoma. However, if the origin of the lesion is not obvious or if eosinophilic ulcer does not respond to conservative therapy, biopsy under local anesthesia is indicated.
- For small lesions, excisional biopsy may be performed; however, incisional biopsy is recommended for larger ulcers.
- In general, a biopsy specimen of an eroded or ulcerated area should include a portion of the adjacent intact epithelium.

## Histologic Findings

Microscopic sections typically show ulcerated stratified squamous epithelium with underlying granulation tissue characterized by an invasive, dense, mixed cellular infiltrate composed mainly of sheets of large mononuclear cells with pale nuclei and numerous eosinophils. The eosinophils, including many cells that show evidence of degranulation, usually infiltrate deep into the subjacent skeletal muscle, dissecting through and separating the muscle fibers. Degenerating muscle, interfascicular fibrosis, and regenerative myocytes may be identified.

The adjacent surface epithelium may be normal or hyperplastic and occasionally hyperkeratotic. Numerous capillaries, often lined by plump endothelial cells, are usually seen deep to the ulcer. This vascular hyperplasia may lead to surface elevation, which gives the lesion a clinically raised appearance.

Immunohistochemical studies have demonstrated that the large mononuclear cells include 2 phenotypically distinct cell types: CD68-positive histiocytes and factor-XIIIa–positive submucosal dendrocytes in varying ratios. Longer-standing lesions may have more dendrocytes than histiocytes; however, this finding is controversial.

Typically, small T lymphocytes are scattered throughout the connective tissue, and a minority of these cells are of the CD4 phenotype. Usually, B cells are scarce. Neutrophils are often clustered within and near the base of the ulcer; mast cells, occasional plasma cells, and focally scattered S-100–positive histiocytes also are seen. An increased number of dendritic Langerhans cells may be identified in the epithelium immediately adjacent to the ulcer.

Smooth muscle actin and muscle-specific actin tests usually fail to highlight any of the cells in the connective tissue (except endothelial cells). This finding suggests that myofibroblasts are not an integral component of the cellular proliferation.

Although cellular atypia or mitoses are not typical findings, in rare cases, large atypical cells and mitotic figures may be scattered throughout the cellular infiltrate, creating a pseudolymphomatous pattern. These lesions are termed atypical histiocytic granulomas.

Immunohistochemical studies are often necessary to rule out lymphoma. In some cases, these

atypical lesions recur and are subsequently determined to be CD30-positive T-cell non-Hodgkin lymphoma.[7]

The histologic differential diagnosis may include lymphoma, Langerhans cell disease, angiolymphoid hyperplasia with eosinophilia, and Kimura disease. Immunohistochemical studies may be necessary to confirm the diagnosis.

## Medical Care

- Dental-related trauma
- The source of chronic irritation must be eliminated when an eosinophilic ulcer is due to obvious trauma.
- Referral to a dentist is recommended if the lesion is related to a tooth, dental restoration, or appliance.
- Although extraction of the anterior primary teeth is not recommended, this may resolve the ulcerations in Riga-Fede disease. However, if the teeth are stable, they should be retained. In these cases, breastfeeding should be discontinued, or a protective shield should be constructed to prevent any further trauma. These measures are usually sufficient to resolve the condition.

- Treatment modalities
- Palliative care: Nonsteroidal anti-inflammatory drugs (NSAIDs) or topical anesthetics (eg, viscous lidocaine, benzocaine, dyclonine) may be used to provide temporary relief and comfort when the patient eats. A magic mouthwash may also provide symptomatic relief.
- Therapeutic care: Some clinicians suggest that the use of corticosteroids may delay healing; however, a mixture of Orabase and a topical corticosteroid ointment (eg, clobetasol, fluocinonide, triamcinolone) is often effective. Dexamethasone elixir is also effective. Although unnecessary, systemic or intralesional corticosteroids may be used.

## Surgical Care

- As a rule, if the lesion does not resolve or it continues to appear ominous after 2 weeks of treatment, biopsy is warranted.
- After biopsy, rapid healing of the ulcer is often typical, even with large eosinophilic ulcers, and no further treatment is necessary.
- Occasionally, lesions may have to be surgically excised.

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Although unnecessary, treatment with systemic prednisone or intralesional injections of triamcinolone has been successful in some patients.

Dexamethasone elixir and magic mouthwash may also provide relief.