Oral Manifestations of Immunologically Mediated Diseases

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KEYWORDS

• Oral • Mucosa • Swelling • Ulcer • Erythema • Stomatitis • Inflammation

KEY POINTS

- Oral mucosal swelling, ulceration or red-white lesions may be caused by an aberrant immune response.
- Clinical history is important to identify any trigger for the aberrant immune response; removal of the trigger will lead to resolution of the mucosal lesion.
- Clinical investigations may be needed to determine if the oral lesions are associated with extraoral lesions, which may indicate an underlying systemic disease.
- Incisional biopsy is useful for diagnosis of some conditions, whereas other conditions are diagnosed by clinical history and appearance.
- Symptomatic treatment may be provided if no known trigger or causative factor can be found.

Introduction

Immune-mediated conditions represent a spectrum of diseases characterized by an individual's immune system mounting an aberrant attack leading to tissue damage. In this article, we address immune-mediated conditions in which an inappropriate inflammatory reaction results in oral mucosal diseases that range from swelling to ulceration to red/white lesions. The inciting factor for the immune reaction is often difficult or impossible to identify. We highlight the clinical history and appearance of each condition and describe the role of laboratory tests and biopsy in diagnosis. The management of these conditions varies and may include removal of any demonstrable trigger, topical steroid, and other immunosuppressive agents. Conditions that present with self-limited oral lesions only require supportive care. In those conditions where oral lesions are associated with extraoral lesions, timely investigations are important to detect and treat systemic manifestations of disease.

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Swellings

Orofacial granulomatosis

Description

- Characterized by persistent swelling of one or both lips and/or intraoral swelling; biopsy shows inflammation with noncaseating granulomas.
- The etiology and pathogenesis are not fully understood; there may be multiple pathogenetic pathways leading to a common set of clinical manifestations.
- Patients who are known to have Crohn's disease or sarcoidosis may rarely develop orofacial swelling with clinical and histologic features nearly identical to orofacial granulomatosis (OFG); it is a matter of debate whether such patients should be classified as having OFG.
- OFG presenting in childhood is associated with an increased probability of Crohn's disease, although the signs and symptoms of Crohn's disease may only appear after an interval of several years.
- A minority of OFG have been shown to be associated with allergy to food, food preservatives and flavoring agents and oral hygiene products; both type I (immediate, IgE-mediated) hypersensitivity and type IV (delayed, cell-mediated) hypersensitivity have been shown to be associated with OFG.
- The remainder of OFG cases are idiopathic with no associated gastrointestinal tract abnormality and no identifiable allergen.

Prevalence

- OFG is an uncommon condition, but the exact prevalence has not been determined.
- Median age at onset is between 15 and 30 years of age in the majority of case series.

- Males and females are almost equally affected.
- Firm swelling of one or both lips is seen in more than 90% of cases; upper and lower lips are equally likely to be affected (Fig. 1A); the swelling varies in severity and may be symmetric or affect one side more than the other (Fig. 2A).
- Lip swelling may be associated with perioral erythema, angular cheilitis, and vertical fissures of the lip.
- The swelling is usually painless, although severe swelling with scaling and fissuring of the mucosa may cause discomfort.
- Lip swelling accompanied by fissured tongue and facial paralysis is known as Melkersson—Rosenthal syndrome.
- Intraoral lesions include diffuse or segmental swelling of the attached gingiva (see Fig. 1B), cobblestone appearance of the buccal mucosa, linear ulceration and swelling of the buccal vestibule (see Fig. 2B), and swelling of the anterior floor of mouth over Wharton's ducts.
- Clinical and laboratory investigations are required to determine if there is an underlying systemic disease (Table 1) or a local cause (Table 2).
- Patients with Crohn's disease who have orofacial lesions along with intestinal lesions ("oral Crohn's disease") may present clinically similar to OFG patients, but are more likely to have involvement of the mandibular buccal sulcus (Fig. 3A,B); it has also been shown that patients with OFG who have ulcers and swelling of the buccal sulcus are more likely to have concurrent Crohn's disease upon investigation than OFG patients with predominantly lip swelling.

Histopathology

- Edema in the lamina propria, chronic inflammatory infiltrate with nonnecrotizing granulomas consisting of epithelioid macrophages, and lymphocytes, often with multinucleated giant cells.
- Nonnecrotizing granulomas may be absent in the biopsy because of sampling problems or fluctuations in the disease process; a repeat biopsy of deeper tissues may be helpful to demonstrate the granulomatous inflammation.
- Special stains are negative for the presence of acid-fast bacilli and fungal organisms.
- No detectable foreign bodies by conventional or polarized light examination.

Diagnosis

- Based on clinical presentation and biopsy findings.
- Clinically, the lip swelling of OFG can be distinguished from that of angioedema because the latter condition has a rapid onset and resolves after 24 to 72 hours.
- Biopsy to demonstrate nonnecrotizing granulomas is useful to support the diagnosis of OFG.
- Clinical and laboratory investigations are required to determine if there is an underlying systemic disease or an allergy (see Tables 1 and 2).

Treatment

- Investigate for an underlying systemic disease (eg, Crohn's disease); the orofacial lesions should resolve upon treatment of the systemic disease.
- Treatment of odontogenic infections may lead to resolution of OFG.
- Perform cutaneous patch tests and urticarial tests if allergy is suspected; avoid exposure to allergens, for example, by instituting an elimination diet for patients who are found to have an associated allergy.
- Intralesional injections of triamcinolone acetonide are effective in the majority of patients in reducing lip and oral mucosal swelling; the injections are given every 2 to 4 weeks, typically for 4 to 6 months.
- Topical corticosteroids or calcineurin inhibitors (tacrolimus, pimecrolimus) may be used as an adjunct to intralesional injections of corticosteroid.
- Immunosuppressants such as azathioprine, or tumor necrosis factor-α inhibitors such as infliximab may be used in severe cases.
- Pediatric patients (age $<$ 16 years) with OFG but no gastrointestinal disease should be monitored for signs and symptoms of Crohn's disease, because a number of

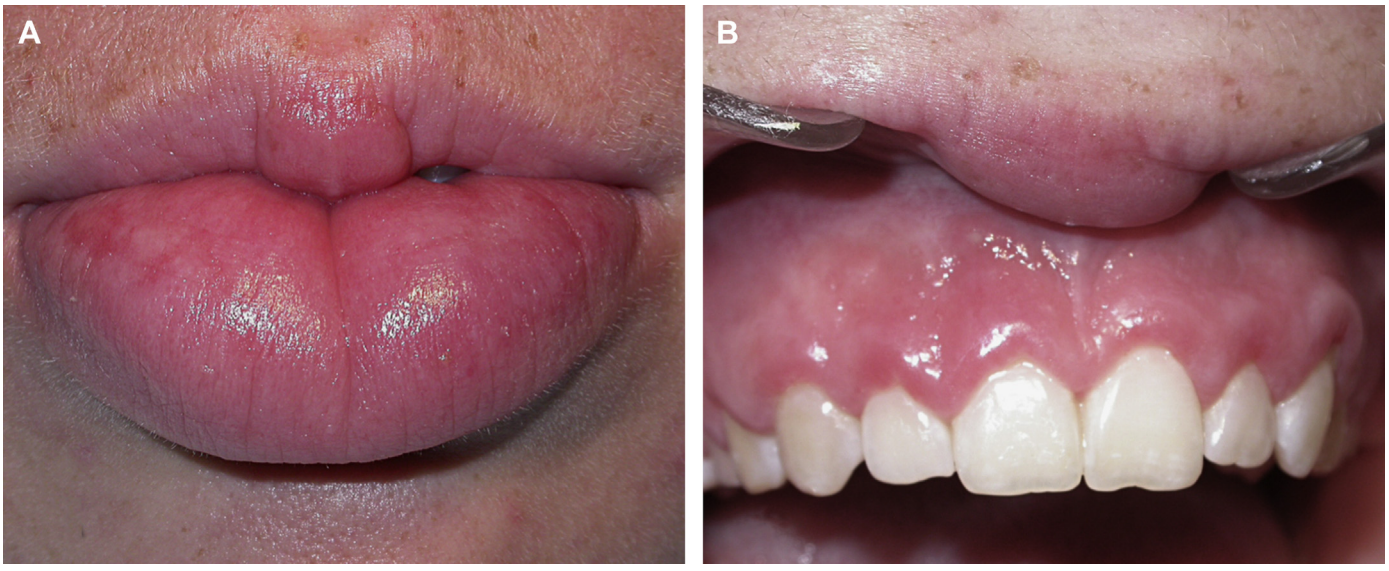

Fig. 1 (*A*) Diffuse, firm swelling of the lower lip and less extensive swelling of the upper lip in a 22 year-old female. The patient had a surgical reduction of the lower lip 7 years earlier but the swelling has slowly recurred. Biopsy showed nonnecrotizing granulomatous inflammation, consistent with a diagnosis of orofacial granulomatosis. (*B*) Same patient as *A*, showing diffuse swelling and erythema of the maxillary labial gingiva. Similar changes were noted in the mandibular anterior gingiva.