Drug-Induced Oral Complications

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KEYWORDS

• Drug-induced • Adverse reaction • Oral complications • Angioedema • Erythema multiforme • Gingival hyperplasia • Biologics • Antitumor necrosis factor

KEY POINTS

- Because of an aging population and rapid development of new medications, dentistry and medicine will likely face a significant increase in patients with drug related reactions.
- Patient history and physical examination are the most essential components of diagnosing drug-induced oral complications.
- Although treatment options vary depending on clinical diagnosis, a multidisciplinary approach is often required.

Drug-induced oral complications

According to US Census Bureau, the projected population aged 65 and over in 2050 will almost double the estimated projection in 2012.[1] As a result of this aging population, emerging medicine, and the rapid development of new medications, dentistry and medicine will likely face a significant increase in patients with drug-related reactions. Several common drug-induced oral complications are discussed in this article. When patients with possible drug-induced oral complications present, thorough medication and social histories are mandatory, including prescription medication, over-the-counter medication, dietary habit, and oral and cosmetic products.

This article focuses on drug-induced complications that directly affect oral mucosa. Hard tissue involvement such as medication-related osteonecrosis of the jaw (MRONJ) and neurologic involvement such as taste alteration or burning mouth syndrome (BMS) are not discussed in this article. Moreover, the complications discussed in this article are due to idiosyncratic reactions. Therefore, exaggerated reactions of expected pharmacologic actions such as excessive bleeding associated with anticoagulant medications are not discussed in this article.

Drug-induced angioedema

Brief description

Angioedema is a diffuse edematous swelling of the subcutaneous and submucosal connective tissue that may affect anywhere in the body, often manifests in the head and neck, and may lead to life-threatening airway obstruction.[2,3]

There are numerous medications that can cause angioedema including NSAIDs (nonsteroidal anti-inflammatory drugs) and antibiotics that are commonly used in dental settings. Many of these are immunoglobulin E (IgE)-mediated hypersensitivities that lead to mast cell degradation.[3,4]

Another common medication that has unique causal mechanism for angioedema is ACEI (angiotensin-converting enzyme inhibitor). It is caused by the inhibition of enzymatic breakdown of tissue bradykinin, causing bradykinin levels to increase.[4] It can occur rapidly or on delayed bases even years after introduction of an ACEI.[4]

Incidence, predilection

Prevalence rates of NSAID-induced angioedema range from 0.1% to 0.3%, which is partly because of the large size of the exposed (at risk) population.[5]

ACEI-associated angioedema affects up to 2% of patients using this medication class and is responsible for 30% of cases presenting to emergency departments.[6]

A recent large epidemiologic study showed an association between ACEI-related angioedema and patients older 65 years, seasonal allergies, a history of drug rash, sensitization to certain food components, and pollen season, but failed to show female predilection or association with smoking that was previously suggested.[7]

Clinical features

Angioedema is characterized by the relatively rapid onset of soft, nontender tissue swelling (Fig. 1). Most common sites are face, hands, feet, and trunk.[8] Although pain is unusual, itching is common.[3,4]

Differential diagnosis

By far, the most essential component required for the diagnosis is history and physical examination. The diagnosis of

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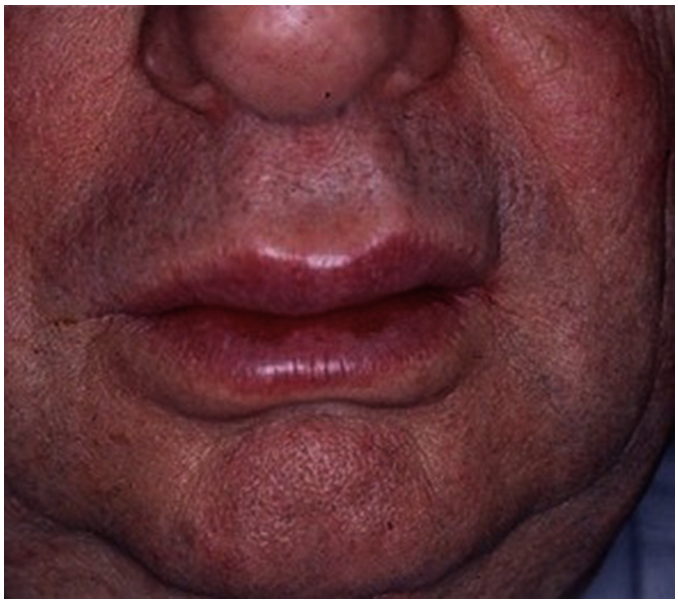

Fig. 1 Angioedema of the lips. (*Courtesy of* Dr John D. McDowell, Department of Diagnostics and Biological Sciences, University of Colorado School of Dental Medicine, Aurora, CO.)

drug-induced angioedema is often made based upon the patient's clinical presentation in conjunction with the history.[3,4] There are no unique histopathologic features of drug-induced angioedema. Dietary diaries and antigenic testing may be indicated when a patient is exposed to possible multiple antigens.[3,4] Complement tests (C1-INH) may be indicated if relations to antigenic exposure cannot be determined.[3,4,6]

Treatment considerations

The primary approach for managing drug-induced angioedema is discontinuation of the offending medication and supportive measures for airway protection.[3,6,9] For IgE-mediated drug-induced angioedema, antihistamines and corticosteroids may be effective.[3,6] For ACEI-Induced angioedema, antihistamines and corticosteroids are often ineffective, because these do not target the underlying mechanism of the ACEI-induced angioedema. Fresh frozen plasma (FFP), C1 inhibitor, Ecallantide, and Icatibant have been reported to be effective treatments in several cases.[9,10] However, there are no definitive data to prove this efficacy.[9,10]

Erythema multiforme

Brief description

Erythema multiforme (EM) represents a group of acute immune-mediated disorders that can affect the skin and mucous membranes.[11] Historically, EM has been classified into 2 groups, EM major (EMM) or EM minor (EMm). Numerous reported cases of EM manifesting in oral mucosa without skin lesion have resulted in a third group being named oral EM by several authors.[11–13] Previously, HSV (herpes simplex virus) was suggested to be the most common cause.[14] However, a recent large case series in oral EM, the largest in the last 2 decades, suggests that medications may be the leading trigger of EM.[11]

Essentially any medication or even food additives can cause EM. Most commonly reported causative medications include NSAIDs and antibiotics.[11–16] Yet, the list of the medications associated with the induction of EM continues to expand and includes new categories of drugs such as biologics.[11,16] It has been also reported that drug-induced EM typically affects oral mucosa.[11–13] Therefore, oral health care providers may face drug-induced EM more than EM triggered by other causes regardless of the commonality.

Incidence, predilection

Current literature regarding the epidemiology of EM remains scarce and controversial, largely due to a lack of universal diagnostic criteria and possible under-reporting of mild cases.[11] There is no gender predilection.[11–15] EM frequently affects young adults, but the age of reported cases ranges widely, from infancy to 80 plus years of age.[11–15,17] The oral cavity is the most frequently involved mucosal site, with a frequency that is varied, ranging from 25% to more than 70%.[3,11–18]

Clinical features

Oral manifestations may be varied, ranging from diffuse oral erythema to multifocal superficial ulcerations. Vesicles/bullae may be present at the initial stage of the disease.[3,11,18] Any area of the mouth may be involved, with the lip, labial mucosa, buccal mucosa, tongue, floor of the mouth, and soft palate being the most common sites.[3,11]

The oral mucosal ulcerations are usually irregular and large with necrotic tissue tags (Fig. 2). In most cases, lip lesions are observed that show hemorrhagic crusting of the lips (Fig. 3). Oral lesions may be an initial manifestation of EM before skin involvement.[11–13] The pain from oral lesions may compromise daily functions such as speech, eating, and fluid intake.

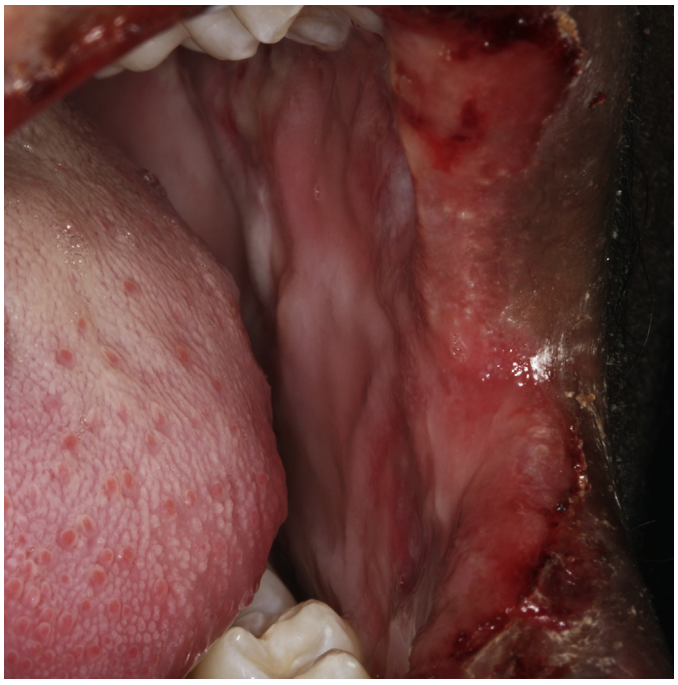

Fig. 2 EM affecting buccal mucosa, lips, and labial mucosa.