Review: allergic contact stomatitis

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Allergic contact stomatitis (ACS) is an oral mucosal immunoinflammatory disorder variably characterized clinically by erythematous plaques, vesiculation, ulceration, and/or hyperkeratosis and by pain, burning sensation, or itchiness. ACS is brought about by a T cell−mediated, delayed hypersensitivity immune reaction generated by a second or subsequent contact exposure of an allergen with the oral mucosa, in a genetically susceptible, sensitized subject. Lichenoid contact reaction is a variant of ACS brought about by direct contact with the oral mucosa of certain metals in dental restorations. The features of ACS are neither clinically nor histopathologically specific, so the diagnosis is usually presumptive and can only be confirmed by resolution of the inflammation after withdrawal or removal of the suspected causative allergen. When ACS is suspected but an allergen cannot be identified, patch testing is necessary. In persistent cases, topical corticosteroids are the treatment of choice, but for severe and extensive lesions, systemic corticosteroid and systemic antihistamines may be indicated. In this short review, we highlight the clinical, immunologic, and histopathological features of ACS, and provide some guidelines for diagnosis and management. (Oral Surg Oral Med Oral Pathol Oral Radiol 2017;123:559-565)

Allergic contact stomatitis (ACS) is an immunoinflammatory disorder caused by an antigen-specific T cell−mediated hypersensitivity immune reaction to an exogenous allergen or allergens that are in direct contact with the oral mucosa. Many agents have been reported to induce ACS[1−14] (Table I), and patch testing is often necessary to identify the allergen.[15] However, a positive reaction to a patch test may be merely an indication of immunologic sensitization, and therefore a diagnosis of ACS must be supported by a relevant history and clinical findings.[16] Treatment includes the avoidance or removal of the allergen, and in persistent cases, the use of topical, sublesional, or systemic glucocorticosteroids.[17,18]

ACS occurs in patients who are genetically susceptible to it, but prior exposure to a particular sensitizer is necessary to generate an antigen-specific, T lymphocyte−mediated, delayed hypersensitivity immune response after primary exposure. It takes 12 to 72 hours for ACS to develop after second or subsequent contact exposure.[1,17−19] The mechanisms by which the allergens induce T-cell activation are uncertain. However, it has been suggested that molecules of the exogenous allergens bond covalently to endogenous proteins to form a hapten-peptide complex, which is presented in the regional lymph nodes to naïve T lymphocytes by dedicated antigen-presenting cells, in association with the human leukocyte antigen (HLA) system that encodes the major histocompatibility complex (MHC) proteins. The recognition of these hapten-peptide complexes by T cell receptors (TCRs) is MHC restricted.[17,19−21]

It has been documented that in drug-specific T cell-mediated hypersensitivity immune responses, binding of the particular allergen to a specific HLA molecule brings about molecular alterations to the MHC peptide-binding groove, which in turn induces the activation of T cells.[17,19,21] However, exogenous allergens also directly interact with TCRs or equivalent "immune receptors" on other cells in the microenvironment, contributing to the development of ACS.[17,21]

Once the exogenous allergen has induced the T-cell immune response, a clinical phenotypical reaction, to a major extent, is determined by the particular effector cells, which may be CD4+ T cells, cytotoxic T cells, monocytes/macrophages, eosinophils, or plasma cells, by the collaboration between the activated cells and by the types of chemokines and cytokines secreted into the microenvironment (Figure 1).[17,21]

After a primary episode of allergic contact dermatitis (ACD), recurrent episodes can be induced by systemic exposure to the same or to a chemically closely-related allergenic substance. Such a systemically induced

Statement of Clinical Relevance

The clinical appearance of allergic contact stomatitis (ACS) depends on the nature, potency, and concentration of the allergen, and on the period of exposure. It is accompanied by pain, burning sensation, or itchiness. Resolution occurs after removal or withdrawal of the allergen.

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Table I. Some agents that may induce allergic contact stomatitis

- Medications
  - Mouthwashes: chlorhexidine, Listerine[4]
  - Topical anesthetics,[5] topical glucocorticoids[6]
  - Inhaled budesonide[2]
- Food, spices (particularly cinnamon), candies, chewing gum[7]
- Gloves, rubber dams[8]
- Dental impression material, gingival retraction cords[9]
- Dental restorative metals[10]
- Acrylic denture materials[11]
- Dental implants[12,13]
- Metal orthodontic devices[14]

recurrence may occur not only at the site of the initial contact eruption.[15] However, it is unknown whether systemic exposure to an allergen can play any role in sensitizing the oral mucosa to recurrent allergic contact stomatitis.

This short review focuses on the pathogenesis and clinical aspects of ACS, and provides some practical guidelines for diagnosis and management, with consideration of whether there are significant differences between cases of ACS induced by different allergens, and whether lichenoid tissue reactions should fall within the spectrum of ACS.

ORAL MUCOSAL IMMUNITY

The oral mucosa is constantly exposed to a wide range of foreign agents, some of which might be allergens with the capacity to generate antigen-specific, T cell–mediated, delayed hypersensitivity immune reactions.

The epithelium of the oral mucosa provides the outermost barrier, protecting deeper tissues from physical damage, invasion by microorganisms with their associated antigens and toxins, and penetration of water and water-soluble molecules, including habit-related agents like alcohol and tobacco products.[22] The keratinized epithelium of the masticatory mucosa of the hard palate and gingiva are less permeable and physically tougher than the non-keratinized epithelium of the buccal mucosa, ventrum of tongue, and floor of the mouth.[22]

The epithelium and the underlying lamina propria are endowed with innately immune cells, including antigen-presenting dendritic cells, natural killer cells, and polymorphonuclear leukocytes with their associated cytokines and chemokines. These, together with keratinocyte-derived biological mediators, salivary flow, salivary secretory immunoglobulin A, and gingival crevicular fluid, all contribute biological and physical elements to oral mucosal immunity.[23]

Bearing in mind that so many immune cells and biological mediators that can initiate hypersensitivity immune responses are an integral part of the oral mucosa, and that oral epithelium is a thin, semipermeable structure constantly exposed to exogenous allergens, episodes of ACS are less common than might be expected. The relatively low incidence of ACS[16,24] is probably explained by the constant flow of the saliva in the mouth, which flushes away potential allergens from the epithelium by the physical coating of the oral mucosa by the saliva, which excludes some potentially allergenic exogenous agents from direct contact with the epithelium, and by the abundant blood supply of the oral mucosa that clears the allergens relatively quickly.[24–26]

It is possible that either dysregulation of oral mucosal immunity or some dysfunction in the mechanisms that exclude or limit contact of allergens with the oral mucosa may have the consequence of developing oral mucosal hypersensitivity immune reactions.

MECHANISMS OF IMMUNE RESPONSES IN THE CONTEXT OF ACS

Allergens which can induce T cell-mediated hypersensitivity immune reactions are usually low-molecular-weight substances, and an overt ACS will develop only after repeated exposure to subthreshold concentration of the allergen, because each exposure is insufficient to generate allergic signs and symptoms. It may therefore require weeks or months of repeated exposures before the allergic reaction will occur.[20]

The induction of ACS requires sensitization of a genetically predisposed subject to a specific allergen. The exogenous allergen must gain access both to viable keratinocytes that have the capacity to act as immunocytes and to innate immune cells within the epithelium that can detect those molecular structures of allergens or endogenous molecules termed *danger-associated molecular patterns*. This occurs through their germline-encoded pattern recognition receptors, including Toll-like receptors and the nucleotide-binding oligomerization domain–like receptor family.[20,23,25,27,28] The endogenous danger-associated molecular patterns, including reactive oxygen species, heat-shock proteins, ATP, uric acid, and low-molecular-weight hyaluronic acid, are generated by tissue-damaging factors such as hypoxia, trauma, or toxins, which elicit danger signals.[20,23,27,29]

In a susceptible subject, stimulation of these receptors, singularly or in combination by allergens or by allergen-induced danger signals, may trigger the production of pro-inflammatory cytokines and chemokines including tumor necrosis factor-α (TNF-α) and interleukin 1 β (IL-1 β), which play essential roles in the mobilization of dedicated antigen-presenting cells to the area of the mucosa in contact with the allergen.[27,30] The non-specific inflammatory signals induced by the