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REVIEW ARTICLE

Allergic and immunologic response of the oral mucosa: An overview

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Abstract

Allergic and immunologic diseases very often manifest oral lesions in their earliest stages, an early diagnosis, which may be spurred by a dental examination, is a key for improved outcomes. After systemic diagnosis, oral lesions benefit from special care by dentists in alliance with the medical team. This review aims to highlight the most relevant allergic and immunologic conditions of the oral cavity, their pathogenesis, and their pathognomonic diagnostic features, which will navigate the clinicians to arrive at a prompt diagnosis and subsequent management.

Introduction

An allergy is defined as an altered or changed response of the immune system to foreign proteins. The term "allergy" was conceived by Clemens von Pirquet in 1906. Allergens are foreign substances that initiate allergic reactions. They enter the body by inhalation, swallowing, injection, contact with the skin, oral mucosa, and eye.[1]

The oral cavity is subjected to a wide spectrum of antigenic agents-foodstuffs, microorganisms, cosmetics, drugs, dental materials including restorative materials, toothpaste. Despite high oral bacterial colonization and periodic allergen contact, acute allergic and immunologic reactions are rare because the immune resistance outweighs the allergen attack. Moreover, the antigen presenting cells, such as dendritic cells and different subsets of T-cells, serve as key players in oral mucosal tolerance induction.[2,3]

However, there is evidence of oral allergic reactions that proved fatal. Allergic reactions may manifest as a localized vesicle or a papule, patch, ulceration, or swelling. Thus, onus lies on clinician, based on advances in the understanding of disease pathogenesis, to give an early and accurate diagnosis to prevent further complications. Further research and the emergence of immunotherapeutics will help to ameliorate these diseases.[2]

Working Classification of Allergic and Immunologic Diseases of Oral Cavity[4-7]

Allergic diseases

Localized:
- Contact stomatitis
- Contact dermatitis and cinnamon flavoring
- Perioral dermatitis (PD).

Generalized:
- Drug allergy
- Latex allergy
- Lichenoid reaction
- Angioedema.

Immunologic disease

Localized:
- Recurrent aphthous stomatitis (RAS)

- Midline lethal granuloma (MLG).

Generalized:

- Behcet's disease
- Reiter's syndrome
- Sarcoidosis
- Wegener's granulomatosis (WG)
- Uveoparotid fever.

Mechanisms of allergy [Figure 1]

Immunoglobulin E (IgE)-mediated allergy

Allergic conditions occur when individuals produce increased amounts of the allergic antibody IgE, which binds to specific receptors on mast cells. When the cell-associated IgE comes in contact with an explicit allergen across which it is directed, the IgE molecules become "cross-linked" to that allergen. This activates the mast cell and chemical inflammatory mediators, such as histamine and leukotrienes, are released. Histamine causes acute symptoms of allergy such as itching, rash, and tissue swelling. Leukotrienes have a more prolonged course of action, causing narrowing of airways and swelling which leads to severe systemic manifestations.[1,3]

Non-IgE-mediated allergy

Some allergic conditions are not dependent on IgE. They involve an abnormal immune response to a wide range of external environmental agents. These conditions are known as non-atopic (non-IgE-mediated). The mechanisms of non-atopic disease are less understood but may involve different subsets of immune cells known as T-helper-1 (Th1) cells.[1,3]

RAS

The name "aphthous" emerged from the Greek word "aphthae" which means ulceration.[5] RAS, also known as canker sores, is one of the most common painful mucosal conditions affecting the oral cavity. RAS shows 20% prevalence in the general population. The peak age of onset is during early childhood, with a propensity to diminish in frequency and severity with age. The pathogenesis of aphthous ulcers is related to dysfunctions of the immune system.[9] The causative agent could be an endogenous or an exogenous antigen. They have a non-specific etiology, such as stress, trauma, and food allergies. Three different forms of aphthous ulcers have been identified - minor, major, and herpetiform. These present as multiple, recurrent, small, rounded, or oval ulcers, with circumscribed margins, having yellow or gray floors, encompassed by an erythematous halo.[6,9,10]

Minor aphthous ulcers are 0.5-1 cm in size. They heal spontaneously in 7-10 days without scar formation. Major aphthous ulcers are larger in size (>1 cm) and are painful. They persist for 6-10 weeks and heal with scar formation. Herpetiform aphthous ulcers present as recurrent crops of small ulcers. They heal spontaneously in 10-14 days without scar formation.[6,7] These ulcers are not preceded by vesicles and characteristically appear on the buccal mucosa, floor of the mouth, tongue, and soft palate. Rarely do these lesions occur on keratinized mucosa-like hard palate and attached gingiva, providing an important clinical sign for the differentiation of aphthous ulcers from herpetic ulcers.[6,10]

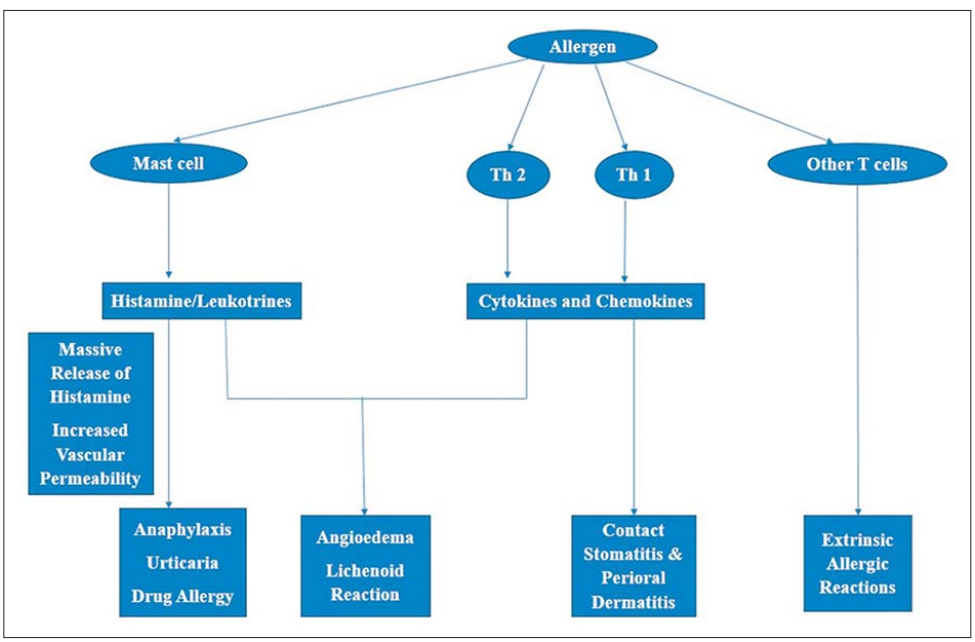

Figure 1: Flowchart representing the mechanisms of allergic reactions[1,3,8]

Key features facilitating diagnosis[5,7,9,10]
- Located in non-keratinized oral mucosa
- Not preceded by vesicle formation which differentiates them from herpetic ulcers
- Histopathology shows presence of Anitschkow cells, consisting of cells with elongated nuclei containing linear bars of chromatin extending toward the nuclear membrane
- Indirect immunofluorescence shows binding of immunoglobulin M and immunoglobulin G antibodies to the spinous layer of the epithelium
- Serum of aphthous ulcer patients shows elevated levels of gamma globulin.

Behcet's disease

Behcet's disease is a persistent inflammatory disorder where recurrent oral aphthae is a consistent feature. It was first described by Turkish dermatologist Hûlusi Behçet in 1937. Its exact pathogenesis remains unknown. It has been postulated that the disease may be prompted by environmental factors, such as infection, pollution, and in genetic susceptible patients. Studies have shown that human leukocyte antigen (HLA)-B 51 (more than 60% of patients) is associated with Behçet's disease. It consists of a triad of recurrent oral aphthous ulcers, genital ulcers, and ocular lesions. Relapsing polychondritis (e.g., auricular cartilage and nasal cartilage) in association with Behcet's stigmata has been designated as the Mouth and Genital Ulcers with Inflamed Cartilage syndrome [Table 1].[6,11,12]

Key features facilitating the diagnosis[6,11,12]
- Presence of recurrent oral aphthae is imperative for a diagnosis of Behcet's disease
- Apart from recurrent oral aphthae, presence of any two minor criteria is mandatory
- Patients with Behcet's disease manifested with hypergammaglobulinemia, eosinophilia and elevated erythrocyte sedimentation rate
- Platelet rosette formation around the neutrophils is a key diagnostic factor during the acute phase of the disease.

Reiter's syndrome

Reiter's syndrome was first described by Hans Reiter in 1917. Currently, it is stated as a secondary syndrome to microbial infections such as *Chlamydia*, Yersinia, *Campylobacter*, *Salmonella,* and *Shigella*. Pleuropneumonia-like organisms have also been implicated in the etiopathogenesis of Reiter's syndrome.[5] Genetic predisposition, with high association of HLA-B27 histocompatibility, is associated with this entity.[14,15] The onset of Reiter's syndrome is acute, with the simultaneous appearance of mucocutaneous lesions in the oral cavity along with urethritis, bilateral conjunctivitis, and oligoarthritis affecting large and small joints of lower limbs. Other features include fever, weight loss, vasomotor abnormalities in the feet, and skin lesions consisting of faint macules, vesicles, and pustules on the hands and feet. Oral lesions have been described as relatively painless aphthous-type ulcers occurring almost anywhere in the mouth. Tongue lesions simulate geographic tongue in appearance.[6,7]

Table 1: Diagnostic criteria for Behcet's disease[6,13]

Major criteria	Recurrent aphthous ulcers and genital lesions
Minor criteria	1. Arthritis or arthralgia
	2. Eye lesions
	3. Skin lesions (erythema-nodosum such as folliculitis)
	4. Positive pathergy test
	5. Family history
	6. CNS symptoms
	7. Gastrointestinal symptoms
	8. Vascular lesions

CNS: Central nervous system

Key features facilitating diagnosis[5,6,15]
- History of enteric or sexually transmitted infections
- Combination of mucocutaneous oral lesions, urethritis, conjunctivitis, and peripheral joint dysfunction.

Oral lichenoid reaction

OLR represents a common end point to extrinsic agents (drugs, allergens), altered self-antigens, or superantigens.[5,6] It can be considered a separate entity or an exacerbation of already existing oral lichen planus by intake of medication or presence of dental material. The mechanism of development of lichenoid reaction remains unknown. A series of triggering factors, such as dental restorative materials, graft-versus-host disease, flavoring agents, and tobacco chewing, is implicated in the causation of lichenoid reactions. Keratinocyte antigen expression induced by systemic drugs, mechanical trauma (Koebner phenomenon), and microbial infection have been implicated in the pathogenesis of lichenoid reaction. CD8+ cytotoxic T-cells may trigger apoptosis of keratinocytes through activation of the cells by an antigen coupled with major-histocompatibility-complex class I on basal keratinocytes. Pain is the most prevalent symptom. Oral manifestations such as metallic taste or dry mouth can also be observed [Table 2].[16-18]

Key features facilitating diagnosis[6,16-18]
- Unilateral or bilateral lesions
- Direct topographic relationship to the suspected etiologic agent
- Spontaneous remission of the lesion upon withdrawal of offending material.

Contact stomatitis

It is a type of allergic reaction characterized by a lesion in the oral mucous membrane after repeated contact with the offending agent.[6,7] These causative agents are chemical in nature (haptens) and require union with proteins to become effective. This process occurs with help of intraepithelial dendritic cells which converts the hapten into a competent antigen and presents it to T-lymphocytes for sensitization and production of

Table 2: Comparison of clinical and histopathological oral lichen planus and oral lichenoid reaction[16,19]

Features	Oral lichen planus	Oral lichenoid reaction
Clinical features	1. Presence of bilateral, more or less symmetrical lesions 2. Presence of a lacelike network of slightly raised gray-white lines (reticular pattern) 3. No evidence of any etiologic agent	1. Presence of unilateral or bilateral lesions 2. Presence of a lace-like network of slightly raised gray-white lines (reticular pattern) 3. Evidence of an etiologic agent Lesions resolve on withdrawal of etiologic agent
Histopathological features	1. Presence of a well-defined band like zone of cellular infiltration that is confined to the superficial part of the connective tissue, consisting mainly of lymphocytes 2. Signs of liquefaction degeneration in the basal cell layer 3. Absence of epithelial dysplasia	1. Presence of a well-defined band like zone of cellular infiltration that is confined to the superficial part of the connective tissue, consisting of lymphocytes and eosinophils 2. Liquefaction degeneration of the basal cell layer 3. No evidence of epithelial dysplasia

IgE. Following antigenic re-exposure, local lymphocytes secrete chemical mediators of inflammation that produce the clinical and histologic changes characteristic of this process. Numerous allergens, varying from simple chemical elements to complex organic substances, are implicated with the pathogenesis of this disease. There is a well-recognized group of materials which cause the oral lesion, and for this reason, they are of special interest to the dentist. They can be classified as dental/cosmetic preparations such as dentifrices and mouthwashes; dental materials such as nickel and acrylic; dental therapeutic agents such as alcohol, phenol, and antibiotics. It manifests as an itching or burning sensation at the site of contact followed by erythema and vesicle formation.[20-22]

Key features facilitating diagnosis[6,20-22]

- Biopsy reveals intercellular edema of epithelium along with vesicle formation
- History of a chronic allergen associated with the entity
- Discontinuance of the allergen causes remission of symptoms.

Sarcoidosis

Sarcoidosis is a multifactorial disease of unknown origin first reported by Jonathan Hutchinson in 1875. It is characterized by the formation of uniform, discrete, non-caseating granuloma. Boeck coined "sarcoidosis" which stems from the Greek words "sark" (meaning flesh) and "oid" (meaning like) and refers to the flesh-like tumors first observed on the skin of affected patients.[5,23] A positive association with HLA-A1, HLA-B8, and HLA-DR3 has been identified as a putative genetic background in the pathogenesis of sarcoidosis. Infectious agents (mycobacterium, propionibacteria, Epstein-Barr virus, and human herpes virus-8), environmental factors (dust, clay, pollen mold, and silica), and occupational exposure are potential etiological agents. Th1 lymphocytes play a primary role in granuloma formation as a result of deposition of poorly soluble antigenic material in the tissue. Cutaneous lesions, present in approximately 25-35% of patients with sarcoidosis, may be the only distinct manifestation of the disease.[7] Involvement of lymph nodes or salivary glands is manifested by bumpy enlargement. Hepatomegaly and splenomegaly may occur, owing to the presence of the disease in the liver and spleen. In the oral cavity, the disease manifests on the lips, palate, and buccal mucosa. Lesions on the lips appear as small, papules, or plaques, resembling herpetic lesions. Lesions appear as bleb-like, comprising of clear yellowish fluid, or as solid nodules on the palate and buccal mucosa. They may produce diffuse destruction of the bone.[23-27]

Key features facilitating diagnosis[24-26]

- Appearance of asteroid bodies in indirect immunofluorescence
- An intracutaneous test (Kveim-Siltzbach test), using a suspension of known sarcoidal tissue, confirms diagnosis.

PD

PD and light-sensitive seborrheic are synonyms for chronic papulopustular facial dermatitis.[6] It is an inflammatory orofacial skin disorder commonly affecting women, first described by Frumess and Lewis in 1957. Its etiology remains unknown. Overzealous use of topical steroids and cosmetics often precedes manifestation of the disease. Use of inhaled steroid sprays into the nose and mouth can also precipitate PD. Physical factors such as UV light, heat, and wind worsen PD. Investigators believe the infections may arise from fusiform spirilla bacteria, *Candida* species, and *Demodex folliculorum*. Hormonal factors are suspected because premenstrual deterioration has been observed. The disease presents with follicular reddish papules, papulovesicles, and papulopustules in the perioral region. Predominantly affected sites are the perioral area around the lips, nasolabial fold, and lateral portions of lower eyelids. A frequent feature of PD is a border of normal skin separating lesional skin from the lips.[7,28,29]

Key features facilitating diagnosis[6,28,29]

- Histopathological examination reveals early papular lesions with eczematous changes consisting of parakeratosis and mild acanthosis
- History of prolonged usage of corticosteroids or overzealous use of cosmetics is a marker for diagnosis
- Disappearance of symptoms upon removal of the offending agent.

WG

WG, first described by Friedrich Wegener in 1936, is a chronic relapsing granulomatous disease.[30] It involves the oral cavity,

vascular, renal, and respiratory systems. WG can occur at any age although majority of cases are seen in the fourth and fifth decades of life with a slight male predilection.[30-32] Its exact etiology remains unknown. Investigators believe the disease is caused by an atypical immune reaction to a non-specific infection or a hypersensitivity reaction to an unknown antigen. Inflammation in WG is due to the formation of antineutrophil cytoplasmic antibody (ANCA). ANCA-mediated vasculitis involves the interaction of polymorphonuclear neutrophils and endothelial cells via cell adhesion molecule interactions.[33] Classically, WG comprises a triad of vascular, lung, and kidney infection. Involvement of the oral cavity occurs with considerable frequency. Gingival involvement is the most common and characteristic manifestation and is termed strawberry gingivitis. The inflammatory process begins in the interdental papilla and spreads to the periodontium leading to bone loss and tooth mobility. Ulceration of palate is a frequent feature followed by extension of the disease to the nose, resulting in destruction of the nasal septum.[6,32,33]

Key features facilitating diagnosis[6,7,32,33]

- Triad of vascular, lung, and kidney infection with frequent involvement of oral cavity
- Demonstration of ANCA in the blood of the patient confirms the diagnosis
- Oral biopsy shows pseudoepitheliomatous hyperplasia with subepithelial abscess formation.

MLG

MLG, first described by McBride in 1897, is characterized by an idiopathic progressive destruction of face, palate, nose, paranasal sinuses, and pharynx.[7] Its exact etiology is unknown. Due to the presence of intense granulomatous inflammation, it was thought to be a localized hypersensitivity phenomenon with tissue destruction. Both bacteria and Epstein-Barr virus infection are implicated in the pathogenesis of MLG. Currently, it is regarded as a localized form of angiocentric immunoproliferative lesions, characterized by massive necrosis. This is the pathological hallmark of MLG. It begins as a superficial ulceration of the palate or nasal septum, often preceded by a feeling of stuffiness in the nose, clinically resembling carcinoma. The ulceration spreads from palate to the nasal cavity and thence outside. Palatal, nasal, and malar bones may become involved, undergoing necrosis, and sequestration. The patient may exhibit purulent discharge from eyes and nose; perforating sinus tracts may develop, and much of the soft tissue of the face may slough away, leaving a direct opening into the nasopharynx and oral cavity. Histopathological examination reveals extensive necrosis with inflammatory cell infiltration and formation of new capillaries. The lesional process invades and destroys normal tissue in the area. Necrosis is often present in areas of the lesion, secondary to infiltration of the blood vessels by the lesional cells.[34-37]

Key features facilitating diagnosis[34-37]

- Locally destructive, ulcerative lesions in the midline with no systemic involvement
- Necrosis, non-specific inflammation with the absence of malignant epithelial cells.

Angioedema

Angioedema, also known as Quincke's disease, is an acute edema of the mucosa or skin, characterized by an irregularly shaped swelling, which manifests itself episodically.[38] Certain allergens trigger the hypersensitivity reaction by binding to IgE, which causes release of histamine and other vasoactive substances in mast cells. Among medications, non-steroidal anti-inflammatory drugs, antibiotics, and antiepileptics frequently induce angioedema. It affects women more frequently than men. Typical sites involved are lips, eyelid, genitals, and distal parts of extremities. The affected skin becomes pale, sometimes slightly red. The swelling reaches its peak in several hours and dwindles. The whole process lasts between 8 and 72 h [Table 3].[39-41]

Key features facilitating diagnosis[38,41]

- Thorough history of the patient is essential to define potential triggering factors
- Radioallergosorbent test is a blood test used to extract the exact allergen for the cause
- Scarification test (scratching test) performed on the volar side of the forearm demonstrates hypersensitivity to various allergens.

Uveoparotid fever

Uveoparotid fever, also called uveoparotitis and Heerfordt's syndrome, is a rare clinical condition, first described by Heerfordt in 1909. Its definite cause is unknown.[5] A combination of environmental agents and a genetic predisposition is hypothesized in the pathogenesis of this disease. *Mycobacterium* and *Propionibacterium* species have been suggested as environmental agents, though the evidence is inconclusive. It is characterized by bilateral parotitis, uveitis, and mild fever, enlargement of lymph nodes and occasional cerebrospinal palsies. A patchy erythema of

Table 3: Forms of angioedema[39]

Form of angioedema	Characteristics
Hereditary angioedema (1-2%)	Autosomally dominant inherited genetic mutation affecting C1 INH protein or clotting factor XII
ACE inhibitor-induced angioedema (30%)	Delayed onset (days to months after the first use of ACE inhibitor)
Idiopathic angioedema (38%)	Cause of angioedema is unknown; usually relapsing and occurring with urticaria
Acute allergic angioedema (30%)	Allergen-induced (e.g., food, drugs, radiologic contrast media, and latex gloves)

ACE: Angiotensin-converting enzyme

the skin has been reported in the early course of the disease. The most common eye lesion is uveitis, but keratitis, conjunctivitis, and corneal herpes have also been noted.[42,43]

Key features facilitating diagnosis[7,42,43]

- Triad of fever, bilateral parotitis, and uveitis
- Clinical history plays a key role in diagnosis.

Latex allergy

Natural latex is a product of the rubber tree, *Hevia brasiliensis*. The use of natural rubber latex gloves serves as a barrier and prevents transmission of infectious diseases including HIV and viral hepatitis. Dental surgeons, dental students, patients, and other health-care providers are at risk of latex allergy. Development of latex allergy depends on the quantity of the latex protein present on the latex material. The range of allergen protein varies between 220 and 12000 units (AU/ml of allergen), based on the latex brand. The following are mechanisms by which patients at risk can be sensitized:

- Intake of airborne latex allergen
- Oral mucosal contact with latex protein.

Contact urticaria is the most frequent manifestation and may be the only presentation preceding systemic manifestations. Skin rash and bronchospasm can occur subsequently. Latex is considered to be an occupational allergen and can cause occupational asthma in the people involved with the regular use of latex.[44-46]

Key features facilitating diagnosis[44-46]

- Diagnosis is based on thorough history and clinical suspicion
- Definitive diagnosis can be obtained through skin test and determination of antigen-specific IgE levels in the patient's blood.

Conclusion

Allergic and immunologic diseases are common in the head and neck region. Oral manifestations are encountered with greater frequency and are often the first clinical signs of these diseases. Dentists play a key role in recognizing the oral signs and symptoms and are instrumental in timely diagnosis and therapeutic intervention.[2] As some of these diseases have higher rates of morbidity and mortality, it is necessary to obtain an early diagnosis and refer the patient for further medical care. To aid in this process, an in-depth knowledge of these diseases helps in early recognition and facilitates a positive therapeutic outcome and disease prognosis. Optimal management of these conditions requires a multidisciplinary medical team consisting of physicians, dermatologists, dentists, and ophthalmologists.[2,47]

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