Hypersensitivity of the oral mucosa: clinics and pathology

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Hypersensitivity reactions of the oral mucosa comprise an array of clinical manifestations. Some of the reactions are difficult to differentiate from toxic reactions. Hypersensitivity reactions of type I, type III, and type IV are well known, although, especially for types I and III, they are rarely encountered. Type-I reactions are most frequently seen related to application of polymers in the oral cavity, such as orthodontic bonding and fissure sealant materials. There may also be systemic manifestations such as urticaria. Type-IV reactions may be seen related to most dental materials used, from amalgam and gold to polymers. These reactions appear as chronic reddening and/or ulceration of the oral mucosa. Lichenoid reactions have histopathological characteristics compatible with type-IV hypersensitivity reactions and are the most prevalent material-adverse reactions seen in the oral cavity. A special variety inside the lips with multiple papules and/or diffuse redness has recently been identified. This lesion comprises a serious treatment challenge. Skin patch tests, applying a series of dental materials in non-toxic concentrations on the skin, have been used to identify sensitization. However, the value of those tests can be questioned. Exacerbation of geographic stomatitis may be another form of hypersensitivity to dental materials. □ *Allergy; dental materials; hypersensitivity; oral mucosa*

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Hypersensitivity reactions of the oral mucosa comprise an array of clinical manifestations, induced by type-IV and, rarely, type-I and type-III hypersensitivity (1). Reactions to drugs, including local anesthetics, and to dental materials, toothpastes, impression materials, latex, and various food components can be seen (1).

For some lesions there is clinical and/or histopathological evidence of immunological mechanisms in their pathogenesis, whereas such evidence is doubtful for others. There is strong evidence for the role of immunological mechanisms in oral lichen planus, whereas for aphthous stomatitis the picture is less clear.

Erythema multiforme

Erythema multiforme (EM) is a disorder with several immunological features. Clinically, EM has been suggested to exist in three forms with increasingly severe involvement of skin and mucosa. The minor form of EM shows skin and/or mucosal lesions, and there may be conjunctival and bullous manifestations. Some forms only occur in the oral region, most often involving the vermilion border. Major or disseminated EM shows a more widespread pattern involving the mucosa of the oral cavity, genitalia, and conjunctiva, in addition to skin lesions. This form has also been labeled Stevens–Johnson syndrome. The most severe form, possibly a separate disorder, is toxic epidermal necrolysis (TEN) (2). The pathogenesis of EM is not fully understood, but there is evidence that circulating immune complexes localized to vascular walls play a central role (3). These complexes may be associated with complement fixation, and vascular wall complement factor-3 deposition has been shown.

Previously, acute adverse reactions to drugs were labeled stomatitis medicamentosa. Probably such reactions comprise a form of erythema multiforme, in which a type-III hypersensitivity reaction, with circulating immune complexes, plays a fundamental role in the pathogenesis. A similar reaction pattern may be valid for erythema multiforme reactions associated with viruses, especially herpes simplex virus (2). In skin biopsy specimens from EM lesions it has been possible to amplify HSV DNA sequences in one third to more than half of the cases (4). Thus, the etiology of EM reactions has been linked to drugs and/or viruses in more than half of the cases. The mortality rate of minor EM is low but may rise to 5%–15% for the major form.

Recurrent aphthous stomatitis

Recurrent aphthous stomatitis (RAS) is probably mediated by immunological mechanisms (5). However, in contrast to lichen planus, aphthous lesions show no specific histopathological features to suggest an underlying immunological response. RAS may present in three forms: minor RAS, major RAS, and herpetiform ulcers. So far, no specific or dominant etiologic factor has been identified for any of these forms. Aphthous-like ulcers are encountered in Behçet syndrome, together with genital ulcers, arthritis of major large joints, cutaneous lesions, and neurologic symptoms. There is some evidence of association between RAS and hematinic deficiencies. Previously alleged

associations between RAS and atopy or exogenous antigens, including gluten, are probably invalid (6).

The immunological mechanisms behind the pathogenesis of RAS are probably cell-mediated rather than humoral (5). Some T-cell fractions, including gamma delta T cells, seem to be increased in patients with active RAS. These cells are thought to be involved in antibody-dependent cell-mediated cytotoxicity, although the antigen is not known (7).

Cross-reactivity between the oral mucosa and oral microorganisms, especially *Streptococcus mitis*, has been considered to play a possible etiologic or pathogenic role. Such reactivity has been shown involving a streptococcal 60- to 65-kDa heat-shock protein (HSP). There seems to be some cross-reactivity between the bacterial 65-kDa HSP and the 60-kDa human mitochondrial HSP (8).

There is only scant evidence that viruses play a decisive role in the etiology or pathogenesis of RAS.

The release of antigen could possibly explain why RAS almost exclusively affects non-keratinized mucosa. Such release could be triggered by, for example, mechanical trauma in non-keratinized mucosa, and keratinization may protect from such release. Smokers have RAS to a considerably lesser extent than non-smokers (9), probably owing to the changed keratinization pattern of the oral mucosa induced by tobacco smoking (10).

Oral lichen planus/lichenoid reactions and immunological reactions associated with dental materials

Most hypersensitivity reactions to dental materials are type-IV or type-IV-related reactions. However, there are a few reports on type-I hypersensitivity reactions too. The latter reactions have been reported after application of polymers such as fissure sealants and orthodontic bonding material (11, 12). They appear as red mucosal lesions with or without ulcerations, in contact with the material or at other locations of the oral mucosa. They may be accompanied by systemic signs and symptoms, such as asthmatic attacks and urticaria of the skin (Fig. 2). The reactions disappear after removal of the materials and do not recur if similar materials are avoided.

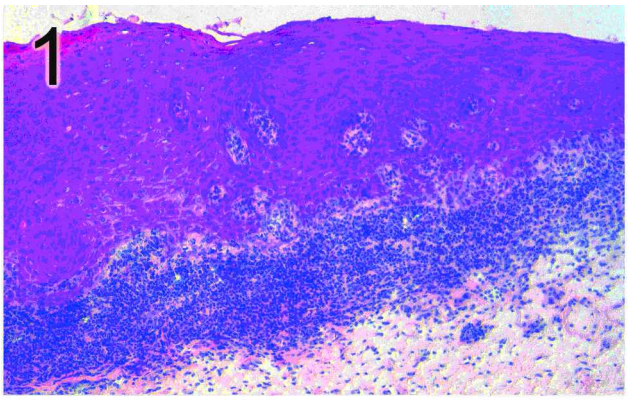
Hypersensitivity type-IV reactions to polymers may also arise, the most prevalent being reactions to acrylic dentures (13). Other possible haptens in acrylic dentures probably play a minor role. Rarely, reactions have also been shown to acrylic fillings, the nature of the reactions supported by positive patch tests (14).

The most prevalent hypersensitivity type-IV-like reactions comprise lichenoid contact lesions. Lichen planus shows all the characteristics of a classical type-IV hypersensitivity reaction, including a band-shaped subepithelial accumulation of T cells and macrophages (5, 15) (Fig. 1). The pathogenesis of lichenoid lesions or reactions seems to be complex and is still not fully understood. The oral lesions show clinical and histopathological characteristics compatible with the disease lichen planus, but they appear only in, or just outside, contact areas with dental restoration materials. Possibly, lichen planus and lichenoid reactions represent a reaction pattern with T-cell-mediated immunologic mechanisms as a common trait. Lichenoid reactions may appear as classical white lesions with Wickham striae, but often erythematous areas are seen. Such red lesions are often accompanied by severe symptoms such as feeling of smarting and soreness. Frequently, they are infected by *Candida* (16), and this probably contributes to such symptoms.

A basic element in the pathogenesis of oral lichen planus (OLP) seems to be an antigenic challenge, inducing cytokine release from keratinocytes and epithelial/connective tissue dendritic cells. After processing in regional lymph nodes, a local T-lymphocyte response is generated, promoted by adhesion of activated lymphocytes to submucosal endothelium, emigration into the connective tissue, and chemotaxis to the epithelial/connective tissue junction. Antigen processing and presentation by dendritic cells to effector CD4 helper/inducer lymphocytes is the basic feature in delayed hypersensitivity, and this process is most probably present in OLP. Antigen may also be presented by keratinocytes, since they can express class-II molecules on their cytoplasmic membranes (2). To what extent, however, this may contribute to the epithelial cell damage observed, or results in other biological reactions, is still unclear.

Another important feature is the homing process that directs the T cells to the site where antigen is presented. Adhesion molecules and chemotactic factors play decisive roles in this context. One important molecule is ICAM 1, expressed by keratinocytes after stimulation by cytokines. ICAM 1 binds to an integrin on the membrane of activated lymphocytes contributing to 'capture' of immunologically active cells in the lower strata of the epithelium. Chemotactic factors including transforming growth factor (TGF)-β1 are secreted by keratinocytes and may contribute to attracting leucocytes from the blood vessels (2). TGF-β1 also has other biological effects,

Fig. 1. Band-shaped subepithelial accumulation of mononuclear cells in a lichenoid reaction.
Fig. 2a. Allergic stomatitis developed some hours after bonding of orthodontic brackets. 2b. Urticaria of skin developed in the patient shown in 2a some hours after bonding.
Fig. 3. Exacerbation of lichenoid reaction in contact with porcelain-fused-to-metal restorations.
Fig. 4. Lichenoid reaction inside the upper lip in contact with composite material.
Fig. 5a. Geographic lesion developed in contact with a recently made amalgam crown. 5b. Histologic picture of geographic lesion in the buccal mucosa.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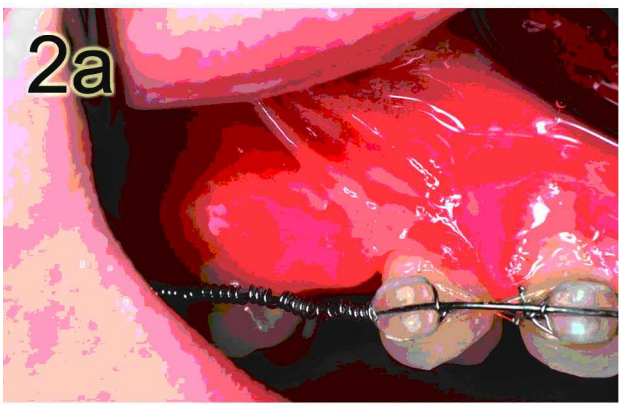
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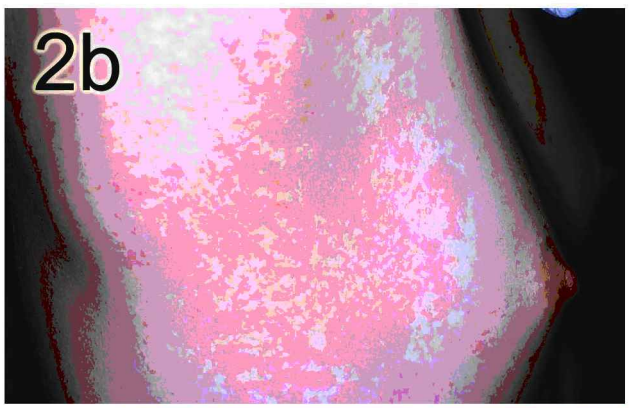
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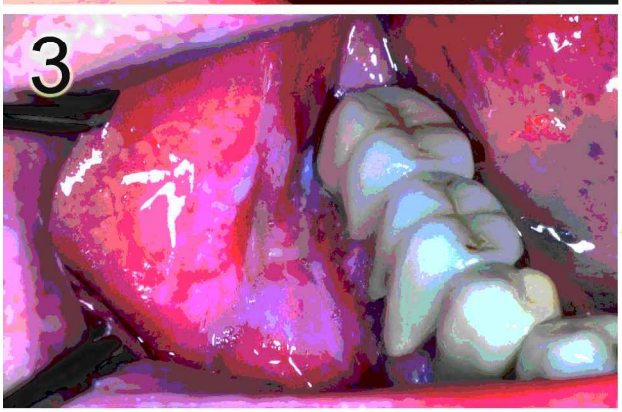
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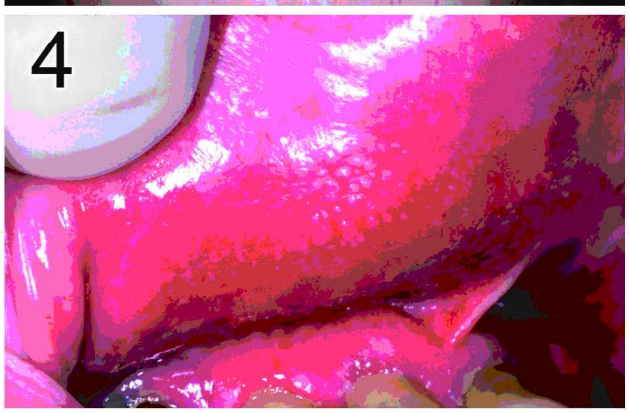
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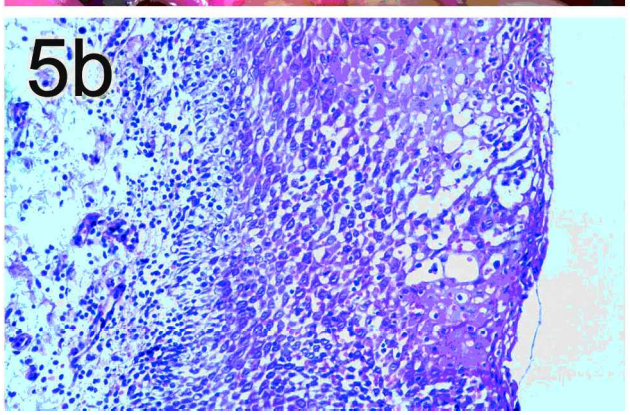
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including an effect on cell turnover that may possibly contribute to the epithelial atrophy often seen in OLP (17).

Lichenoid reactions are most often directed towards amalgam fillings and then most presumably to mercury (18). Gold and palladium may also be involved in oral mucosal hypersensitivity reactions (19). Metal haptens may link to epithelial proteins and be presented to T cells by dendritic cells and keratinocytes. Release of heat-shock proteins could also be involved in the pathogenetic process. Expression of HSP60 has been found in the basal epithelial cells in OLP (20). Such proteins could possibly be released by mere mechanical factors. This could partly explain why therapeutic attempts to remove amalgam fillings induce alleviation of lichenoid reactions, irrespective whether hypersensitivity to mercury is present or not (21). HSP could also be involved in pathogenesis of the remarkable exacerbations of lichenoid reactions sometimes seen in contact with porcelain-fused-to-metal restorations (22) (Fig. 3). Such exacerbations can be seen after removal of amalgams and disappear after replacement with gold or with ceramic restorations. It is unclear whether any of the metals included in the alloys of the porcelain-fused-to-metal restorations play a classic antigenic immunological role or not.

A rare and sometimes extremely painful lichenoid reaction is seen inside the lips, especially the upper lip. The clinical picture is most frequently one of papular OLP with multiple papules. It may also show up as a more diffuse red lichenoid area. This lesion is often seen in contact with composite fillings, but the possibility of a contributing eliciting traumatic factor cannot be excluded (23) (Fig. 4).

An interesting aspect of lichen planus, and probably also of lichenoid reactions, is the involvement of psychological factors in its pathology. Patients with lichen planus or lichenoid reactions may have exacerbation of their lesions during periods of stress, anxiety, or depression (24). Stress modulation of immunological reactions has been recognized (25) and may be a basis for fruitful approaches for better understanding of the pathogenesis of lichen planus and lichenoid reactions and also for treatment approaches.

Geographic lesions

Geographic lesions, not located on the tongue, have been reported to occur with a prevalence of 0.05% (26). In rare cases such lesions and geographic tongue lesions have shown exacerbations in association with application of dental materials, including amalgam fillings, gold restorations, and orthodontic appliances (12) (Fig. 5). They appear as classical geographic lesions with red areas surrounded by whitish or yellowish serpiginous lines. However, they may well appear as just red, diffusely outlined areas. The clinical diagnosis may then be a challenge. However, a biopsy is of valuable diagnostic guidance: geographic lesions show no characteristics of classical hypersensitivity but rather of psoriasiform lesions including intraepithelial accumulations of polymorphonuclear leukocytes, sometimes forming intraepithelial abscesses. The pathogenesis of the exacerbation of geographic lesions is not as yet understood.

In summary, oral immunological reactions comprise an array of manifestations. Knowledge of their pathogenesis is steadily increasing but is for many conditions still poorly understood.

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