ORAL MUCOSA AND SKIN REACTIONS RELATED TO AMALGAM

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Abstract—Documented cases of oral mucosa and skin affections related to amalgam restorations are rare, although the exact incidence is unknown. Lesions of the oral mucosa may be due to specific immunologic or non-specific toxic reactions toward products generated from restorations. The immunologic reaction most probably involved in mucosal affections related to amalgam is the delayed or cell-mediated (type IV) reaction. Such reactions are seen in contact allergy, and the term “contact lesions of the oral mucosa” has been used. There is a much lower tendency of sensitization through mucous membranes than through skin, and it is questionable whether mercury released from amalgam restorations is able to sensitize a patient.

A chronic toxic reaction may be established due to repeated or constant influence to toxic agents in low concentrations over long periods. Such reactions are most frequently localized to the contact zone with the toxic agent. Chronic toxic reactions may possibly be seen in areas of the oral mucosa in direct contact with amalgam fillings. Since the clinical features of these lesions do not differ from those of lesions due to contact hypersensitivity, the diagnosis is obtained by exclusion based on a negative patch test.

The purpose of this presentation is to review available documentation on affections of oral mucosa and skin related to amalgam restorations. However, it is important to keep in mind that the reactions described are not restricted to amalgam, but may occur adjacent to virtually any dental restorative material.

Lesions related to amalgam fillings which have recently been reviewed (Holmstrup, 1991) may be leukoplakia- or lichen planus-like whitish or reddish, sometimes ulcerative, but usually without symptoms (Bolewska et al., 1990a). The lesions have previously been denoted as electrogalvanic or galvanic lesions or as lesions related to dental restorations (Bánoczy et al., 1979; Axell et al., 1984), but since neither clinical nor experimental studies have supported the hypothesis of a relationship between electrogalvanic currents and oral mucosal affections, the terms “electrogalvanic” or “galvanic” lesions are confusing and should be avoided (Knychalska-Karwan, 1966; Phillips et al., 1968).

Lesions of the oral mucosa caused by dental restorations, which is the main topic of the present review, are due to specific immunologic or non-specific toxic reactions to products generated from restorations.

HYPERSENSITIVITY REACTIONS OF THE ORAL MUCOSA

The immunologic basis for lesions caused by products from restorations is contact allergy or Type IV hypersensitivity, which is a manifestation of an excessive immune response to an antigen, leading to tissue damage, but whereas contact allergic reactions of the skin are common, such reactions in the oral mucosa are rare (Merritt, 1986).

There seems, however, to be a great discrepancy in the reported incidence of hypersensitivity reactions inherent with the use of amalgam restorations. Djerassi and Berova (1969) reported that about 16% exhibited a positive reaction to the epicutaneous test performed with amalgam and its compounds.

A questionnaire study pertinent to allergy possibly caused by dental materials indicated that nearly half of the dentists had seen or diagnosed an allergy associated with dental treatment. About 10% of the lesions could be ascribed to reactions associated with amalgams (Franz, 1982). A study of hypersensitivity reactions to dental materials in a referred group of patients showed that 12 (7.9%) of 152 patients subjected to epicutaneous tests had positive skin reactions to mercury salts; 5 of the 12 had oral mucosal changes (Stenman and Bergman, 1989). This corresponds to 3.3% of the referred patients. The epicutaneous test was carried out by use of a standard test series of dental materials applied on the skin as described by Fregert (1981). Kallus and Mjöör (1991), in a recently published study of the incidence of adverse effects of dental materials, found that lichenoid reactions in the oral mucosa adjacent to amalgam restorations occurred more often than other long-term side-effects of dental materials. A review
of reports on mercurial hypersensitivity from mercury exposure in dentistry has been given by Bauer and First (1982), but not all case presentations were supported by relevant tests.

Two of the essential problems in the diagnosis of hypersensitivity reactions are to prove that the reaction is indeed due to a hypersensitivity reaction and to identify the antigen causing that reaction. Hypersensitivity reactions due to corrosion products of amalgam restorations seldom occur. They seem to be related to mercury in almost all cases.

It is not fully understood why some patients react and others do not, and why patients react in some instances and not in others. It is well-recognized, although the reasons for it are not understood, that there is a lower tendency for sensitization through mucous membranes than through skin. Furthermore, it is uncertain whether mercury released from amalgam restorations is able to sensitize a patient. Most probably, other sources of mercury contact are more common causes of sensitization, examples being mercury-containing wound disinfectants and mercury preservatives in vaccines.

In order for a contact allergic reaction to be established, metal ions which are leached from amalgam have to penetrate the epithelial lining, bind with host proteins, and stimulate the immune system by interaction with macrophages and lymphocytes.

So far, information pertinent to mucosal diffusion of corrosion products of dental alloys seems to be scarce (Brune, 1986). An increased mercury content has been observed in gingival biopsies from areas in close contact with amalgam (Fräden et al., 1974). Moreover, accumulations of mercury have been found in lysosomes of macrophages and fibroblasts of submucous connective tissue of contact lesions. However, mercury has also been identified in normal mucosa and in oral lichen planus lesions with or without any relationship to amalgam (Bolewiska et al., 1990b). Therefore, it appears that mercury is taken up by damaged oral mucosa, but under certain, as present unknown, conditions, mercury may also be taken up by the intact oral mucosa without causing clinical or histopathologic changes.

A recent study demonstrated a different response of lichenoid mucosal lesions dependent on the extent of the lesions. Those lesions, which were confined to the area of contact with amalgam, denoted contact lesions, showed total or almost total disappearance without recurrence after replacement of the restorations; whereas lesions exceeding the contact zone showed only minor changes (Bolewiska et al., 1990a). Patients with contact lesions showed a positive skin test to 0.05% mercury chloride in 52% of cases, whereas the corresponding figure among patients with lesions exceeding the contact area was 5%. These findings indicate a different etiology for the two types of lesions, and it was proposed that lesions exceeding the contact zone are lichen planus lesions; whereas the others may be due to Type IV hypersensitivity or, in some instances, to toxic reactions to mercury.

Patients with signs of hypersensitivity reactions should be evaluated by a specialist in allergology or dermatology. These specialists may perform an epicutaneous test, which is a useful technique for documentation of Type IV hypersensitivity (Fregert, 1981). A positive skin reaction is frequently taken as proof that the patient is allergic to those antigens causing the positive reactions. However, a positive patch test is not proof that the patient's current lesion is caused by the antigen. The next step is usually to avoid the allergen. If the lesion subsides, it is taken as suggestive evidence that the antigen was the cause. The final step may be to reintroduce the allergen and observe if the lesion recurs. However, it is rarely possible for such a full test regime to be completed.

No internationally approved patch test kit has been developed to test hypersensitivity to substances from dental restorations. Hensten-Pettersen and Holland (1985) have composed a standard series of allergens for use in epicutaneous tests to elucidate possible contact allergy to amalgam (Table). The standard series takes into account that mercury from amalgam restorations may be in the form of metal, as organic substances, and as inorganic salts. Few patients respond to all three forms.

Mercury is a problematic test allergen owing to its irritant properties. A recently published study identified 5% amalgam, 1% ammoniated mercury, and 0.05% thiomerisol as suitable screening allergens for detection of mercury sensitization. The metals, together with mercury in dental amalgam, are of almost no allergological significance (von Mayenburg et al., 1991). Distinction of the rare cases of allergy, in accordance with strict allergological criteria, from other forms of amalgam intolerance is necessary at all events. Further multi-center investigations, especially with regard to the clinical significance of the test reactions, should be called for. One of the major problems is assessment of the relevance of skin tests in the elucidation of oral mucosal allergy. The complex formation between a metal ion and a host substance is the immunologic reaction required. Due to possible site specificity of the host protein, which combines with the metal to form the complete allergen, a skin test may not mimic the mucosal reaction.

For a hypersensitivity reaction of the oral mucosa to be obtained, a test concentration has to be from five to 12 times higher than that needed to develop a skin reaction (Lüders, 1987). The reasons why a higher antigen concentration is

| TABLE |
| STANDARD SERIES FOR EPICUTANEOUS TEST TO ELUCIDATE CONTACT HYPERSENSITIVITY TO AMALGAM |
| Substance | Test Concentration |
| Mercury | 0.5% in petrolatum |
| Mercuric nitrate | 0.05% in water |
| Mercuric chloride | 0.1% in water |
| Phenylmercuric aceta | 0.1% in alcohol |
| Merthiolate | 0.1% in petrolatum |
| Silver nitrate | 2% in water |
| Copper sulfate | 5% in water |
| Stannous chloride | 5% in alcohol |

From Hensten-Pettersen and Holland (1985).
needed are unknown, but one modifying consequence of the high concentration needed may be false-positive registration due to a toxic reaction.

Hensten-Pettersen and Holland (1985) list the basis for requiring allergologic examination of dental patients:

- the presence of oral mucosal lesions as lichen planus and stomatitis resistant to treatment; and

- clear, anatomic relationship between an oral mucosal lesion and the suspected dental restorative material.

The authors emphasize that such uncharacteristic oral phenomena as smarting pain, burning sensations, diffuse pain, battery sensation, and metallic or other taste sensations are not indicative of the need for allergologic examination. This attitude is supported by studies of patients with orofacial complaints in which no difference in patch test reactions was found between patients and controls (Axell et al., 1983; Yontchev et al., 1986). Clinically relevant contact allergies are also rare in patients with burning mouth syndrome (Lindmaier and Lindemayr, 1989), and patch testing is not indicated (Baürl and Schönberger, 1986). Likewise, distant symptoms, such as headache or paresthesia, are not indications for patch testing (Hensten-Pettersen and Holland, 1985).

Lichen planus is one of the most common oral mucosal disorders (Axell, 1976). It has an unknown cause and shows various clinical manifestations, including papules, reticular patterns, erythema, plaque-like changes, and bullae (Thorn et al., 1988).

It has been proposed that hypersensitivity to mercury from corroding amalgam fillings plays an important part in the etiology of oral lichen planus (Hensten-Pettersen and Holland, 1985). Such a hypothesis has been supported by studies demonstrating hypersensitivity to mercury among 16-62% of patients with oral lichen planus (Finne et al., 1982; Eversole and Ringer, 1984; Lundström, 1984; Mobacken et al., 1984; James et al., 1987), whereas mercury hypersensitivity in the general population has been found in 1-4% (Magnusson et al., 1968).

One explanation may be that the clinical and histopathologic changes of lichen planus lesions resemble those of Type IV hypersensitivity reactions, and consequently, it may be difficult, or even impossible, to distinguish between a contact lesion due to Type IV mercury hypersensitivity and one due to oral lichen planus. Furthermore, the presence of lichen planus affections of the oral mucosa may well render the host more susceptible to mercury hypersensitivity, due to increased penetration of the affected oral mucosa by allergens. The latter possibility was not supported by our findings in a group of patients with lichen planus exceeding the contact area with amalgam. Only 5% had a positive skin reaction (Bolewksa et al., 1990a).

Another cause of lesions related to dental restorations may be immunologic or toxic reactions to plaque accumulations on the surfaces of the restorations. Although this phenomenon has received little attention, lesions due to plaque accumulation on restorations are important in differential diagnosis and should always be kept in mind. Such lesions may disappear after improved oral hygiene—supported, for instance, by chlorhexidine mouthrinses. A change in oral lichen planus lesions as the result of amalgam fillings being replaced with resin composite, porcelain-fused-to-metal, or other materials has been observed in some cases by the author and has also been reported (Hensten-Pettersen, 1984; Lind et al., 1986). However, it is important to exclude plaque accumulations on restorations as an etiologic factor before replacing fillings with alternative materials. Plaque reduction may also have surprising effects on mucosal lesions of lichen planus (Holmstrup et al., 1990). The reason why some oral lichen planus affections changes their clinical appearance after replacement of fillings is probably due to changes of the surface microbiology of the restorations.

**GENERALIZED HYPERSENSITIVITY REACTIONS**

Generalized symptoms caused by Type IV mercury hypersensitivity reactions are extremely rare (White and Smith, 1984). They include eczema and urticaria occurring on the face and limbs, predominantly on the flexural aspects (Juhlin and Öman, 1968; Thomson and Russell, 1970). These can occur concurrently with symptoms manifested in the mouth (Fernström et al., 1962). In some cases, the patient presents a personal or family history of past allergies to various sources, including mercury (Bauer and First, 1982).

White and Smith (1984) were able to find only 28 case reports in the dental and dermatological literature of individuals with rashes attributed to dental restorations. More than half of these had been sensitized previously by a local application to the skin and not by the restorations. It is likely, therefore, that the incidence of sensitization by mercury in amalgam is low. This observation was further substantiated in a study which was unable to demonstrate any significant difference in patch test reactions to mercury in individuals with and without amalgam fillings (Sprengler, 1958; Götz and Fortmann, 1959).

Mercury vapor liberated during insertion of new amalgam fillings and during removal of old ones may give rise to the development of mercury exanthema in highly sensitized individuals. A series of 15 patients has been reported with generalized rash, mostly appearing one or two days after the breaking of a clinical thermometer or during dental treatment (Nakayama et al., 1983). The patients had similar skin manifestations, i.e., diffuse symmetrical erythema, predominantly on major flexural areas. Most of the patients had a previous history of contact dermatitis to mercurochrome. They were found, by being subjected to patch testing, to have contact allergy to several mercurials. The clinical findings indicated that the patients had developed systemic Type IV hypersensitivity due to inhalation of mercury vapor, but the primary induction was to compounds as mercurochrome.

From the cases reported as mercurial hypersensitivity, the lesions are usually self-limiting and subside after two to three weeks, even without the removal of the allergen. Most likely, this is because of a decrease in mercury release to a level not able to maintain the hypersensitivity reaction (Frykholm, 1957). Some authors suggest antihistamine therapy during treatment for relief of symptoms and, in sensitized individuals, as a prophylactic pre-medicament to reduce the patients’ post-
operative discomfort (Wright, 1971; White and Brandt, 1976). In situations in which symptoms do not resolve, removal of offending fillings and restorations with non-mercurial dental materials may still be indicated. The use of rubber dam, water spray, and high-speed evacuation can minimize tissue contact with the sensitizer. This procedure is especially important, because the time of exposure is more closely related to insertion or removal of amalgam restorations than to existing fillings in the mouth (Bauer and First, 1982).

Occupational contact with amalgam compounds appears to play a much more significant role in mercury sensitization than do amalgam restorations. White and Brandt (1976) showed that positive patch tests to mercuric chloride increased in the mouth (Bauer and First, 1982). Because the time of exposure is more closely related to insertion or removal of amalgam restorations with non-mercurial dental materials, they may still be indicated. The use of rubber dam, water spray, and high-speed evacuation can minimize tissue contact with the sensitizer. This procedure is especially important, because the time of exposure is more closely related to insertion or removal of amalgam restorations than to existing fillings in the mouth (Bauer and First, 1982).

Occupational contact with amalgam compounds appears to play a much more significant role in mercury sensitization than do amalgam restorations. White and Brandt (1976) showed that positive patch tests to mercuric chloride increased in dental students from 2% among freshmen to 10.8% among seniors. None of the students suffered from symptoms due to mercury sensitivity.

It has been found that patients with epidermal hypersensitivity to mercury, producing clinical symptoms of dermatitis, seldom present lesions of the oral mucosa related to dental amalgam (Gaul, 1966). This observation was considered to be due to the epidermal specificity of the antigen formed by mercury and protein, i.e., the specific protein being present only in the epidermis. Another possible explanation is the higher concentration needed for a reaction to be obtained in oral mucosa than in skin.

**TOXIC REACTIONS**

A chronic toxic reaction may be established due to repeated or constant influence of toxic agents in low concentrations over long periods. Such reactions are most frequently localized to the contact zone with the toxic agent (Hensten-Pettersen and Holland, 1985). Chronic toxic reactions may be seen in areas of the oral mucosa in direct contact with amalgam fillings. Since the clinical features of these lesions do not differ from those of lesions due to contact hypersensitivity, the diagnosis is obtained by exclusion based on a negative patch test. Differential diagnosis is difficult, because a negative skin test may reflect a possible site-specific mucosal contact allergy.

Little is known about toxic reactions of the oral mucosa to dental restorative materials, including amalgam. A pronounced cytotoxic effect of dental amalgam on monolayer cultures of human epithelial cells has been reported (Leirskar, 1974). However, the amounts of silver, mercury, copper, and tin in media from cultures were below those found to be toxic to the cells, and the author suggests that the release of zinc ions might be of major importance for the cytotoxicity of silver amalgam. This has been confirmed in another in vitro study demonstrating the higher cytotoxicity of zinc-containing amalgam than of other amalgams (Kaga et al., 1988). The cytotoxicity of amalgam decreased with aging time, possibly due to the combined effects of surface oxidation and further amalgamation.

**CONCLUSIONS**

Lesions of the oral mucosa caused by amalgam restorations are rare. They may be due to Type IV contact hypersensitivity or to toxic reactions. The lesions—which are reddish, whitish, or sometimes ulcerated—are characterized by a clear anatomic relationship to the fillings. It is important that improved oral hygiene exclude plaque accumulations on the surfaces of the fillings as a possible etiologic factor. Further, differential diagnostic considerations include lichen planus and leukoplakia.

Patients with signs of hypersensitivity reactions should be evaluated by a specialist in allergology or dermatology. These specialists may perform an epicutaneous test to elucidate possible contact allergy to amalgam. Hypersensitivity reactions to amalgam seem to be related to mercury in almost all cases.

The basis for requiring allergologic examination of patients suspected of contact hypersensitivity to amalgam is the presence of whitish or reddish, sometimes ulcerative, oral mucosal lesions with a clear anatomic relation to amalgam fillings. Replacement of such restorations with resin composite, porcelain-fused-to-metal, or other materials, in most cases results in total, or almost total, disappearance of the mucosal lesions. Generalized symptoms caused by Type IV mercury hypersensitivity are extremely rare, and the incidence of sensitization by mercury in amalgam is low.

The clinical features of lesions due to toxic reactions from amalgam restorations do not differ from those of lesions due to contact hypersensitivity, and the diagnosis is obtained by exclusion based on a negative patch test. Further research is needed with respect to (a) relevant test allergens and methods to elucidate mucosal contact allergy; (b) penetration of the oral mucosa by products from restorative materials; and (c) toxic reactions of the oral mucosa from restorative materials.

**REFERENCES**


