Delayed and immediate hypersensitivity reactions associated with the use of amalgam

B.McGivern,[1] M.Pemberton,[2] E.D. Theaker,[2] J.A.G.Buchanan,[3] and M.H.Thornhill,[4]

Hypersensitivity to the constituents of dental amalgam is uncommon. When it occurs it typically manifests itself as a lichenoid reaction involving a delayed, type IV, cell-mediated hypersensitivity response. Rarely, a more acute and generalised response can occur involving both the oral mucosa and skin. We describe two cases that illustrate the presentation and management of these two types of reaction.

In brief

- Despite the widespread use of dental amalgam as a restorative material, hypersensitivity reactions to amalgam are relatively uncommon.
- When hypersensitivity reactions occur, they most commonly take the form of delayed lichenoid reactions affecting oral mucosa in direct contact with amalgam fillings.
- Much more rarely a more acute generalised mucocutaneous response can occur.
- Dental practitioners should be aware of the possibility of such hypersensitivity reactions so that they may institute appropriate management.

There is an increasing awareness that materials routinely used in dentistry can give rise to hypersensitivity reactions in both sensitised patients and members of the dental team. Well-recognised allergenic substances encountered in the dental environment include local anaesthetic agents,[1] antibiotics,[2] restorative materials[3] and latex.[4] Hypersensitivity to mercury associated with amalgam restorations may also occur and present in one of two different ways. Most commonly it presents as an oral lichenoid reaction affecting oral mucosa in direct contact with an amalgam restoration and represents a delayed, type IV, cell mediated immune response to mercury or one of the other constituents of the dental amalgam. Much more rarely an acute more generalised or systemic reaction can occur.[5–7] In both cases the diagnosis may not be immediately obvious. To illustrate these different responses and their management, we present 2 cases here.

Case 1

A 50 year old man was referred to the Department of Oral Medicine by his general dental practitioner for investigation of possible lichen planus (LP). He complained of soreness affecting the left buccal mucosa and right side of his tongue that was made worse by consuming spicy foods and acidic drinks. He had first noticed symptoms 12 months before presentation and they had become progressively worse with time. His medical history was unremarkable, he was taking no medication and had no known allergies. Intra-oral examination revealed a heavily restored dentition with asymmetrically distributed white striated and red, atrophic lesions affecting the left buccal mucosa and right and left lateral borders of the tongue. The lesions were in direct contact with the buccal and palatal surfaces of an old corroding amalgam restoration in ⌊7 (Fig. 1) and the lingual surface of an amalgam restoration in 6⌋.

Given the close association of the lesions with the amalgam restorations, a provisional diagnosis of a lichenoid reaction to amalgam was made and the patient was patch tested using the European Standard and Dental Materials Series (Trolab Biodiagnostics Ltd, Worcestershire, UK) patch test allergens. A strongly positive response to mercury (Trolab allergen E0602, 1% ammoniated mercury in petrolatum) and a slightly weaker response to amalgam (Trolab allergen E2509, 5% amalgam in petrolatum) were obtained after 72 hours (Fig. 2). These results were conveyed to the patient's dentist who placed a bonded porcelain crown over ⌊7 ensuring complete coverage of the amalgam core. The smaller amalgam restoration in the lower right 6⌋ was replaced with glass ionomer cement. Other amalgam restorations not in contact with the oral mucosa were left alone. Within 2 months of replacement of these restorations the patient was

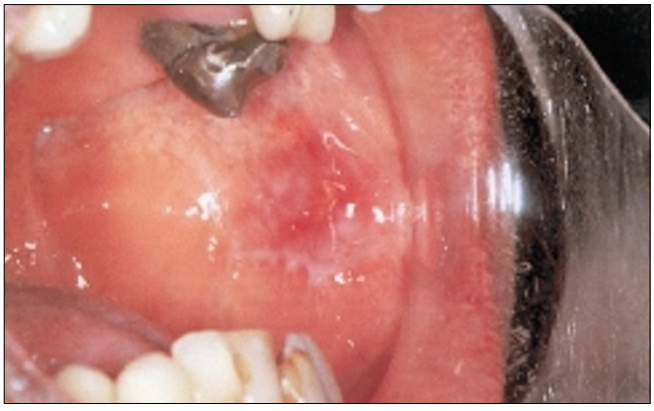

Fig. 1 Buccal lichenoid reaction to a large amalgam restoration of ⌊7 (case 1).

[1]Senior House Officer, [2]Clinical Lecturer in Oral Medicine, Clinical Academic Group of Oral Medicine and Dental Diagnostic Science, The University Dental Hospital of Manchester, Higher Cambridge Street, Manchester M15 6FH, [3]Clinical Lecturer in Oral Medicine, Department of Oral Medicine, [4]Professor of Clinical Oral Science, The Oral Disease Research Centre, St. Bartholomew's and the Royal London School of Medicine and Dentistry, Turner Street, London E1 2AD
Correspondence to Professor M. H. Thornhill.
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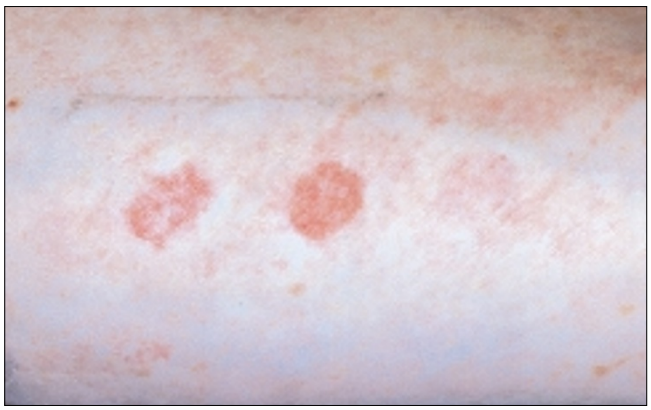

Fig. 2 A strong positive skin patch test response to ammoniated mercury and a weaker response to amalgam after 72 hours exposure (case 1).

asymptomatic and at follow-up 12 months later the lichenoid lesions had completely resolved (Fig. 3).

Case 2

A 57 year old woman was referred to the Department of Oral Medicine by her general dental practitioner for investigation of episodes of intra-oral blistering and a facial rash provoked by dental treatment. At her last visit to the dentist an amalgam restoration in a tooth on the left side of her mouth had been repaired with a small amount of amalgam without the need for local anaesthetic. The procedure was atraumatic but within three hours bullae had developed on the oral mucosa adjacent to the tooth and a pruritic rash had developed on the left side of her face extending into her scalp and neck.

On direct questioning the woman gave a long history of recurrent episodes of urticarial rash affecting the skin of her face, scalp and neck precipitated by restorative dental treatment. Within three hours of the visit the patient would notice an itchy sensation affecting the skin of the face, neck and on one occasion her scalp. This was rapidly followed by the development of an urticarial rash consisting of numerous pinhead-sized wheals and erythema normally confined to the side on which the restorative procedure had been carried out. The reaction was fully established within 12 hours and would resolve over 2–3 days and be completely gone within one week. In general the reactions had become progressively worse and the intraoral signs and symptoms were a relatively new feature. To date the patient had not noticed any difficulty breathing or any other systemic manifestations.

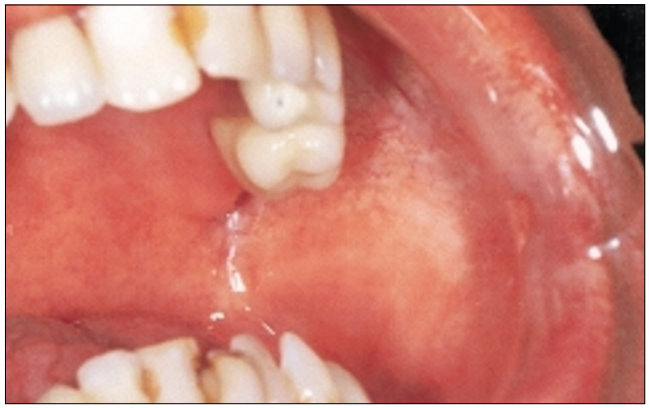

Fig. 3 Resolution of the lichenoid reaction following crowning of ⌊7 (case 1).

Routine dental examination alone did not elicit a reaction and for some years the patient had thought that she might be 'allergic' to local anaesthetic but had not informed her dentist. The patient gave a history of allergy to penicillin, fish and strawberries but there was no personal or family history of eczema or asthma. The patient was taking no medication and there was no history suggestive of exposure to mercury other than from amalgam restorations. Whilst the reaction could have been consistent with a local anaesthetic or latex allergy, no local anaesthetic had been given on this occasion and it transpired that the patient's dentist did not wear gloves for routine dental procedures.

Patch testing to various allergens including the European Standard Series, the Dental Material Series (Trolab Biodiagnostics) and various brands of latex glove was performed. The patient was reviewed after 2, 24 and 72 hours. She reported itching soon after application of the test allergens and after 2 hours slight erythema was noted at the ammoniated mercury test site. On examination at 24 hours there was a very strong positive reaction to ammoniated mercury with vesiculation, spreading erythema and oedema. All other allergens were negative (Fig. 4). The mercury patch was left off and the others re-applied. The response to ammoniated mercury was only slightly reduced in intensity at 72 hours with no response to any of the other materials tested.

These results were consistent with an acute hypersensitivity response to mercury. The patient and her dental and medical practitioners were advised that alternative restorative materials should be used in future. Furthermore, they were advised that should the removal of any existing amalgam restoration be required, then it should be performed under rubber dam with high speed suction to reduce exposure to any free mercury that might be released.

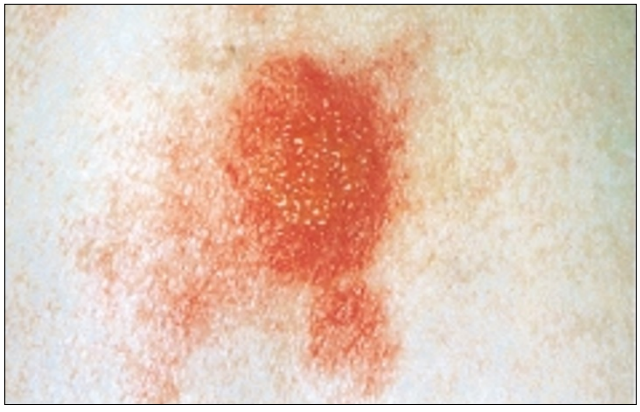

Fig. 4 Strong positive skin patch test response, with vesiculation, spreading erythema and oedema, following 24 hours exposure to ammoniated mercury in case 2.

Discussion

In spite of the widespread use of amalgam as a posterior restorative material, reported

Table 1 Characteristics of hypersensitivity reactions associated with amalgam restorations

	Chronic lichenoid reactions	Acute reaction to mercury
Onset	Gradual—may be several years after amalgam was inserted.	Within hours of insertion or removal of a filling.
Location	Buccal or lingual mucosa in intimate contact with the amalgam filling.	Typically skin of face and neck. May be even more generalised. Only 1 in 7 have intra oral features.
Clinical appearance	Resembles lichen planus but not usually bilateral and symmetrical.	Erythematous, pruritic, urticarial skin rash. Intraorally, erythematous, vesiculobullous eruption. Rarely, facial oedema or difficulty breathing.
Duration	Prolonged—lasts as long as the mucosa remains in contact with the filling.	Resolves spontaneously within a few days
Patch test response to mercury	Usually positive by 72 hours.	Positive within 24 hours and often within 2-4 hours. Reaction may spread to surrounding tissues or become generalised.
Response to amalgam removal	Resolution within 12 months	May provoke a reaction. Should be performed with rubber dam and high volume suction to reduce exposure to released mercury.

cases of hypersensitivity to amalgam are relatively infrequent. By far the most common type is the delayed oral lichenoid reaction (OLR).[6,8] Essentially this involves a cell-mediated, type IV hypersensitivity response to a constituent of the amalgam restoration and as such is the oral equivalent of skin allergic contact dermatitis. Most often the allergen is mercury but occasionally the response is to one of the other components of amalgam alloy such as copper, tin or zinc. The lesions of OLR are similar to those of LP. However, they can be distinguished from the lesions of LP by their close relationship with amalgam restorations, and their tendency to be localised and asymmetrically distributed.[9] In contrast the lesions of classical LP tend to be more widespread, bilateral and symmetrical in distribution. As with LP, OLRs may have reticular, plaque-like, atrophic and erosive components (Table 1). A positive patch test to mercury or another component of amalgam may help to confirm the diagnosis. Final confirmation, however, may have to await resolution of the lesion following removal of the offending amalgam restoration.

OLRs may also occur in response to a number of other allergens including drugs such as antimalarials, antihypertensive agents, oral hypoglycaemics and non steroidal anti-inflammatory agents,[10] as well as palladium-based crowns[11] and composite resins.[12] It is, therefore, not surprising that reports of mercury sensitivity on patch-testing in OLR have varied between 12–62%.[3] Patients in whom the OLR is intimately associated with an amalgam restoration are much more likely to have a positive mercury sensitivity response[3] than those with more extensive or non contacting lesions.[13] Similarly, the reported benefit of replacing amalgam restorations in patients with LP or OLRs has been variable[14] but has been most effective in those patients with OLR lesions in direct contact with amalgam fillings. Bratel *et al.*[15] demonstrated improvement in 95% of such patients treated. The time course of resolution is also variable. Ibbotson *et al.*[14] found that the lesions resolved in 16 out of 17 patients with patch test positive OLR to amalgam within 12 months of replacement, with a mean time of 2 months. Providing that there is no amalgam in physical contact with the mucosa there is no need to replace all the amalgam restorations in the mouth and, as in case 1, amalgam can even be left *in situ* as a core for a crown.

It is not known why particular individuals should develop lichenoid reactions to amalgam. Many patients have had amalgam restorations in their mouths without problems for many years before becoming sensitised. Once sensitised they then consistently develop lesions wherever amalgam is in prolonged contact with the mucosa.

To become sensitised, patients require prior exposure to the antigen. In the case of mercury this commonly occurs through exposure to dental amalgam but may also involve other sources of mercury notably disinfectants, cosmetics, dyes, foods and vaccine preservatives.[7] Sensitising allergens are usually highly reactive molecules of relatively low molecular weight (<1 kDa) which bind covalently to skin or tissue proteins prior to becoming immunogenic. In the case of mercury it is believed that sensitised mercury specific T cells react with, and damage, basal keratinocytes within the epithelium that present mercury-peptide complexes, or mercury alone, bound to MHC molecules on their surface.[7] Skin patch testing is a useful way of identifying the allergen responsible for such cell mediated, delayed, type IV hypersensitivity responses and typically results in a positive response after 72–96 hours. Although it is a relatively straightforward procedure, it needs to be performed at a specialist dermatology, allergy or oral medicine centre for correct interpretation.

More acute and generalised hypersensitivity reactions to the components of amalgam are far less common. In a recent review, Veron *et al.*[16] found that of 41 cases of amalgam allergy with systemic features reported between 1905–1986, 37 were due to mercury hypersensitivity. Of the remainder, 2 were due to copper and 2 due to silver. In contrast to the more delayed amalgam-associated OLRs, inhalation or absorption of mercury vapour leads to the development of a cutaneous, erythematous, urticarial rash affecting the face and limbs, usually on their flexural aspect.[17] Often, as in case 2, the rash is on the same side of the body as the dental intervention. Acute oral manifestations of exposure to mercury or amalgam are much less common than cutaneous lesions[18,19] and may present as a burning sensation associated with the formation of vesicles which rupture to leave areas of erosion.[19] Frykholm[20] found that only one in seven patients with mercury allergy developed oral signs and symptoms whereas all had a cutaneous reaction. Reports have often been imprecise on the time course of the reaction but they tend to occur relatively rapidly in comparison to OLRs, usually within hours[21–26] of placement or removal of an amalgam filling. As with patient 2 these reactions are usually self-limiting and completely resolve over a period of a few days,[25] presumably as the release of free mercury from the amalgam restoration diminishes.

The precise nature of these acute allergic responses is not clear. However, the rapid onset, urticarial rash and more widespread

nature of the response, suggest that a type I hypersensitivity response may be involved. Type I immediate hypersensitivity reactions tend to occur rapidly and are caused by antigen binding to, and cross linking, allergen specific IgE or IgG_4 on the surface of mast cells. This causes the mast cells to degranulate releasing histamine and other acute inflammatory mediators. If localised, this results in an urticarial rash and other local changes. However, if more severe, the effects may be more widespread with oedema, tachycardia and respiratory difficulty.

Skin patch testing is not designed for investigating type I hypersensitivity responses, although reactions within the first 24 hours of applying skin patch test allergens may occur in sensitised individuals. Normally, type I hypersensitivity responses are detected using the in-vitro radioallergosorbent test (RAST) for antigen-specific IgE antibodies or by skin prick testing. However, the small size of the mercury molecule, the lack of its conjugate and its toxicity, precludes performing these assays and to our knowledge no center currently offers a RAST for mercury. This makes it difficult to confirm that acute reponses to mercury in amalgam are the result of a type I hypersensitivity response. Indeed, it is possible that some cases, particularly those that are very localised or have a more prolonged time course, represent a mixed or more acute type IV response. In general, however, the clinical features help to clearly distinguish between acute responses to mercury and chronic lichenoid reactions (Table 1).

Since lesions associated with acute hypersensitivity reactions to mercury are generally self-limiting and resolve after a few days, existing sound amalgam restorations may be left *in situ*. However, alternative materials should be used for new restorations. When removal of amalgam restorations is necessary, it should be performed using rubber dam, water-spray, and high-volume suction to minimise exposure to any mercury that may be liberated.[17,27] Antihistamine cover may also be beneficial during amalgam removal in those where the response is thought to be due to type I hypersensitivity.

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