

Contact allergy to dental restorative materials in patients with oral lichenoid lesions

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118 patients with oral lichenoid lesions (OLL) topographically related to dental fillings were patch tested (PT) to reveal contact allergy to restorative materials. 80 (67.8%) patients displayed positive PT reactions to metals of dental filling materials: 76 reactions were found to various mercury compounds, 4 to sodium aurothiosulphate, 3 to stannic chloride and 2 to silver nitrate. The positive patch test reactions appeared more commonly in patients with restricted contact lesions (85.1%, type-1 lesions) as compared to patients with lesions exceeding to the adjacent areas (38.6%, type-2 lesions). The replacement of dental fillings was carried out in 62/80 PT-positive and 15/38 PT-negative patients. 28 out of 62 (45.2%) PT-positive and 3/15 (20%) PT-negative patients showed complete healing of OLL after a mean follow-up time of 16 months. Complete healing occurred in 29/54 (54.0%) type-1 and 2/23 (8.7%) type-2 lesions. Topographical relation between the lesion and the filling material (restricted versus exceeding the contact area) indicated association of OLL lesion and the filling material, which could be further confirmed by patch testing in the majority of patients. The patch test series should include mercuric chloride (0.1%), mercury (0.5%) and mercury ammonium chloride (1.0%), each in pet.

Key words: oral lichenoid lesions; contact allergy; mercury; dental amalgam; patch testing; amalgam removal; follow-up; tin; gold. © Munksgaard, 1997.

Accepted for publication 11 November 1996

The significance of contact allergy to mercurial compounds in the etiology of oral lichen planus (OLP) has been a matter of debate (1-3). Recently, a high rate of allergic reactions also to gold and palladium salts, found in routinely patch tested patients, has give rise to concern as to possible sensitization through the oral mucosa (4-5). On the other hand, suitability of skin patch testing to identify oral allergic reactions has been questioned, since delayed-hypersensitivity reactions are well-documented in the skin, but in the oral mucosa are difficult to classify (6-8). Bolewska et al. (2) and Warvfinke & Larsson (9) have suggested that direct contact between oral mucosa and dental fillings is crucial for eliciting an adverse reaction in the oral cavity. However, if the allergens are dissolved and spread in saliva, mucosal lesions may exceed the contact areas. Hypersensitivity reactions may be combined with cytotoxicity, infection or trauma caused by roughened and corroded fillings, which modify the clinical and histological features of the lesions (10). Mercury has shown to be able to penetrate both the clinically healthy and

compromised mucosa, but little is known as to how mercury or other metallic haptens released from dental fillings are capable of sensitizing in vivo (11-12). Furthermore, other factors like medication, alimentation, tumor antigens, and autoantigens can stimulate cell-mediated immune responses with clinical and histopathological features similar to OLP (13).

In the present study, the clinical features of oral lichenoid lesions (OLL) and the relevance of positive patch test results to compounds of dental filling materials was studied with regard to regression of oral lesions after the replacement of dental fillings.

Patients and Methods

Patients

118 patients (102 women, age range: 19-71 years, mean: 49.6 years; and 16 men, age range: 29-74 years, mean 50.4 years) referred for diagnosis and treatment of oral lichenoid lesions (OLL) to the Departments of Dermatology and Oral Diseases,

University Central Hospital of Turku, Finland, during 1989–1995, were enrolled in the study. Only patients with OLL present for more than 6 months and topographically related to the dental fillings were included. Oral lesions were classified as: type-1 lesions: lesions restricted to the contact area of the fillings; type-2 lesions: lesions exceeding the contact area of the fillings. All lesions were diagnosed histopathologically using the classification of Östman et al. (19).

All patients underwent a thorough dermatological examination. Systemic diseases and drugs used by the patients were recorded. The serological screening included blood cell count, anti-gliadin, anti-nuclear, anti-epithelial (intercellular substance and basement membrane zone antibodies), anti-reticulin and anti-cow milk antibodies, and circulating immune complexes. In the case of suspicion of systemic disease, the patient was referred for consultation to a specialist in internal medicine.

Patch tests

The patients were patch tested with the European standard series and a series of dental materials (Chemotechnique, Malmö, Sweden). The dental series was supplemented with mercuric chloride 0.1%, stannic chloride 2.5%, benzoic acid 5%, thimerosal 0.1%, silver nitrate 1.0%, palladium chloride 1.0%, tin 5%, zinc 2.5%, mercury ammonium chloride 1% (each in petrolatum (pet.)) and amalgam powder as such and 20 % pet. The tests were applied using Finn Chamber[®] aluminium cups (Epitest, Hyrylä, Finland) on Scanpor[®] tape (Norgeplaster, Norway) and occluded for 2 days before interpretation by an experienced dermatologist at 4 days. Erythematous, papular and indurated patches were regarded as positive. Plain erythema and reactions with mercuric chloride alone were confirmed with a dilution series. The patch tests applied have been found reliable in detecting allergic reactions in a previous study of patients with diverse oral symptoms (15).

Replacement of dental fillings

After the patch tests, complete replacement of the dental fillings was suggested to all PT-positive patients and PT-negative patients with type-1 lesions. Partial replacement of the fillings, i.e. replacement of all fillings of the teeth on the side of the jaw where the most severe lesions were located, was suggested to PT-negative patients with type-2 lesions. Replacement was carried out by the patient's own dentist.

Clinical appearance, size and location of oral lesions were registered with photographs before re-

moval and at each follow-up appointment. The follow-up examinations were carried out 2, 6 and 12 months after treatment and then annually. The minimum follow-up time was 6 months (mean 16 months). The effect of the replacement of dental fillings on oral lesions was graded as: grade 1: complete healing; grade 2: regression of lesion (>50% of the area) and change to a less severe clinical form (no ulceration or erythema and disappearance of symptoms); grade 3: change to a less severe clinical form without regression of the size; grade 4: no improvement.

Statistical analysis

The differences between the groups were tested by repeated measured analysis of variance using statistical analysis system package, version 6.10 (SAS Institute, Cary, NC, USA), χ^2 test and the Fisher exact test.

Results

Patch tests

Positive patch test reactions in 118 patients with oral lichenoid lesions are presented in Table 1. 80 (67.8%) patients were found positive to metal compounds included in their dental appliances. 62 patients reacted to more than 1 and 14 to 1 mercury compound (mercuric chloride 10, metallic mercury 3, amalgam powder 1). 1 mercury positive-patient also reacted to silver nitrate. 3 patients were positive to stannic chloride and one to silver nitrate only. In addition, 11 patients were patch-test-positive to sodium aurothiosulphate. 4 of these had dental gold alloy restorations. No positive reactions to acrylates were seen, but 3 patients had a positive reaction to formaldehyde.

Medical findings in patients

24 out of 80 PT-positive and 12 out of 38 PT-negative patients had a history of systemic disease or use of medication. The following systemic factors were recorded: use of antihypertensive drugs or non-steroidal anti-inflammatory analgesics (18.8% of PT-positive and 5.0% PT-negative patients), generalized lichen planus (10.0% PT-positive, 13.2% PT-negative), rheumatoid arthritis (11.3% PT-positive, 10.5% PT-negative) and diabetes mellitus (5.0% PT-positive and 5.3% PT-negative).

Increased levels of antinuclear antibodies were found in 8 patients (6 PT-positive and 2 PT-negative), circulating immune complexes in 19 patients (12 PT-positive and 7 PT-negative) and anti-epithelial antibodies to basement zone in 1 PT-positive patient. 1 of the PT-negative patients was diag-

Table 1. The number of positive reactions to various metal salts used in patch tests in 118 patients with oral lichenoid lesions related to dental restorative materials

Positive patch tests to various metal salts			Positive patch tests to mercury compounds		
	<i>n</i>	(%)		<i>n</i>	(%)
<i>Metal salts related to dental amalgam</i>					
mercury compounds	76	64.4	mercuric chloride	67	88.2
stannic chloride	3	2.5	metallic mercury	50	65.8
silver nitrate	2	1.7	mercury ammonium chloride ^{a)}	36	85.7
			phenyl mercuric acetate	35	46.0
			thimerosal	34	44.7
			amalgam powder	15	19.7
<i>Other metal salts</i>					
nickel sulfate	17	14.4			
sodium aurothiosulfate	11	9.3			
cobalt chloride	4	3.4			
palladium chloride	2	1.7			
potassium dicyanoaurate	2	1.7			
potassium dichromate	1	0.8			
aluminium chloride	1	0.8			

^{a)} 1% mercury ammonium chloride was included in the test series of 42 patients.

nosed as having discoid lupus erythematosus during the follow-up.

Oral lesions

Buccal mucosa and lateral border of the tongue were the most frequently affected sites in both patient groups (Table 2). 50 out of 64 (78.1%) patients with lesions both on buccal mucosa and tongue were PT-positive. Lesions were bilateral in all PT-positive patients and in 87.2% of PT-negative patients. Type-1 lesions were significantly more common in PT-positive than PT-negative patients ($p=0.001$). In the former group, type-2 lesions were found in 9/24 patients with a systemic disease and in 8/56 healthy patients. The corresponding figures for PT-negative patients were 9/12 and 18/

26, respectively. All but 1 patient with generalized LP had type-2 lesions.

Histopathological findings

Tissue specimens of all patients were available for histopathological examination. Oral lesions of 80 PT-positive patients were designated histologically as follows: lichen planus 24 (30%), lichenoid reaction 25 (31.3%), benign hyperkeratosis 8 (10.0%), and nonspecific ulceration 23 (28.7%). The corresponding figures for 38 PT-negative patients were 16 (42.1%), 6 (15.8%), 9 (23.7%), and 7 (18.4%), respectively. Eosinophil granulocytes were detected within the inflammatory infiltrate in 24 (30.0%) and 8 (21.1%) specimens taken from PT-positive and negative patients, respectively. Candida hyphae were observed in PAS stained histological sections of 6 (5.1%) specimens. No evidence of dysplastic changes were seen in any specimen.

Healing of oral lesions

18 out of 80 PT-positive and 23 out of 38 PT-negative patients refused replacement. 9 of these patients (4 PT-positive and 5 PT-negative) took part in the follow-up. Their oral lesions persisted unchanged. In all, total or partial replacement was carried out in 77 patients (Table 3). Complete healing of oral lesions (Grade 1) was achieved in 28/62 (45.2%) PT-positive and 3/15 (20.0%) PT-negative patients ($p=0.143$). 29 out of 54 (54.0%) type-1 and 2/23 (8.7%) type-2 lesions showed complete regression ($p<0.0001$). Complete healing was not seen in any of 6 type-2 lesions in PT-negative patients. Patients with lesions on both buccal mucosa

Table 2. Location of lesions in 118 patch-tested (PT) patients with oral lichenoid lesions topographically related to dental fillings

Location of oral lesions	Patients	
	PT-positive (80) <i>n</i> (%)	PT-negative (38) <i>n</i> (%)
buccal mucosa	80 (100.0)	36 (94.7)
margin of tongue	69 (86.3)	25 (65.8)
gingiva	26 (32.5)	16 (42.1)
lip	4 (5.0)	3 (7.9)
palate	4 (5.0)	1 (2.6)
base of mouth	1 (1.2)	0
<i>Relation to dental fillings</i>		
type-1: lesions restricted to contact area of dental fillings	63 (78.8)	11 (28.9)
type-2: lesions exceeding the contact area of dental fillings	17 (21.2)	27 (71.1)

Table 3. Resolution of oral lichenoid lesions after the replacement of dental fillings in 74 patients with and without positive patch test reactions to metals included in dental amalgam

Patch test results	No. patients			Healing of oral lesions ^{a)}			
	Total	Replacement of dental fillings		Grade 1	Grade 2	Grade 3	Grade 4
positive	62	56	6	28 (45.2%)	22 (35.5%)	5 (8.1%)	7 (11.3%)
negative	15	6	9	3 (20.0%)	7 (46.7%)	2 (13.3%)	3 (20.0%)

^{a)} Grade 1: complete healing. Grade 2: regression in size and change to a less severe clinical form. Grade 3: change to a less severe clinical form. Grade 4: no improvement.

and tongue showed a greater tendency to heal than those with lesions in other locations ($p < 0.0001$).

Oral lesions healed completely in 1 patient with cutaneous LP and type-1 lesions while the replacement had no effect on skin or oral lesions in the other 12 patients with generalized LP and type-2 lesions. 3 PT-positive patients with raised levels of anti-nuclear antibodies showed complete healing, 1 remarkable resolution, 1 had no improvement and 1 did not participate in the follow-up. The patient with anti-epithelial antibodies (basement membrane zone) did not benefit from amalgam removal.

Discussion

In this study, which comprises patients with OLL lesions in contact with dental fillings, 67.8 % were positive on patch testing. This number of positive patients is one of the highest ever reported (2–3). It is probably due to the selection of patients and the patch test series used. The patch test series applied to identify patients allergic to mercury have varied from study to study (16–19).

In our study, patch testing was carried out with various mercury compounds, including mercury chloride. Mercury chloride has been regarded as highly irritant when used in aqueous solution, because of the formation of HCl (20). However, we have previously tested 91 unselected patients with OLL and burning mouth syndrome, using mercuric chloride in petrolatum. In that series, the preparation was not found to be irritant, but was positive particularly in patients with OLL and amalgam lesions in close contact, suggesting sensitization to mercury salts (15). Typically, many patients reacted simultaneously to several mercury compounds, as also in our present study, favouring true sensitization.

Ammoniated mercury has commonly been used in patch testing to detect allergy to mercury compounds (7, 17). In our series, 42/76 mercury-positive patients were also tested with 1 % mercury ammonium chloride. From these 42 patients, 36 became positive and 6 remained negative. 5 of the

6 were followed up and, after amalgam removal, remarkable resolution of lesions was seen in all, with complete resolution in 4 patients. Thus, if the test had been carried out with ammoniated mercury only, these patients would have been missed. Bolewska et al. (2) used 0.05 % mercuric chloride for patch testing and found positive reactions in 52 % of patients. Handley et al. (17), using various mercury compounds, suggested a combination of both metallic and ammoniated mercury compounds to obtain more reliable results. According to our experience, patch testing for mercury allergy should include all 3 compounds, metallic mercury, ammoniated mercury and mercuric chloride.

Association of positive patch test reactions with etiology of OLL has been questioned. Skoglund et al. (7) observed no difference in the healing rate of PT-positive and negative OLL patients after amalgam removal. In the present study, complete healing was observed in 45.2% of PT-positive as compared to 20% of PT-negative patients after replacement.

Contact lesions located on the buccal mucosa and lateral border of the tongue seem to be the major indication for patch testing and suspicion of possible dental-material-related side-effect. When patients with type-1 lesions were patch tested, 78.8% were positive. Furthermore, 44/47 of these patients healed completely or remarkably after removal of amalgam fillings. Improvement was usually noted 2 to 4 weeks after replacement, favouring contact allergy. Among patients with type-1 lesions, 15 were PT-negative, 3 of these clearing completely after amalgam removal. This may suggest that testing was not sensitive enough, or that other factors, such as chronic irritation caused by strongly corroded rough fillings, local toxicity or microbes, are also important in the etiology (1, 21). 3 of the type-1 OLL were persistent despite positive PT findings and topographical association. The possibility of mucosal antigen retention and continuous exposure, as demonstrated in skin, remains (22).

Among the PT-positive group, type-2 lesions, often with oral lesions on the gingiva, palate, floor of mouth or lips, were more common in patients with cutaneous lichen planus or other systemic diseases. Consequently, these lesions may also represent a different immunologic response and diverse etiopathology. However, several of these patients obtained at least some relief of their symptoms after replacement. These patients may have become sensitized secondarily, due to increased antigen penetration through diseased oral mucosa.

Reports of contact allergy to silver, copper or tin released from silver amalgams are rare and the possibility of irritant reactions is difficult to exclude (1). In the present study, 5 positive reactions to these salts were found. The oral lesions of 1 patient with a positive patch test reaction to tin healed completely after replacement of fillings. In the other patients, the lesions remained unchanged, suggesting an irritant explanation for these lesions.

A relatively high proportion of patients has been shown to be positive to gold on patch testing (4, 23). On the other hand, opinions on the clinical significance of this finding are controversial. Recent reports indicate that sensitivity to gold is subclinical, rarely causing oral lesions (24). In the present study, only 1 patient with a positive reaction to a gold salt was followed up. Her lesions healed completely after amalgam removal. Allergic reactions to acrylates, well-known occupational sensitizers, are mostly related to handling of unpolymerized materials by dental personnel (25). This study did not find allergic PT reactions to components of dental composites.

Removal of amalgam fillings in OLL patients has also been carried out without any histological or allergological examinations (26). In our opinion, amalgam replacement is such a time-consuming and expensive therapy that proper diagnosis is a prerequisite. Although allergic reactions cannot be diagnosed on the basis of histopathological examination, a biopsy is recommended to rule out other diseases with oral mucosal manifestations. It appears that PT results, combined with the localization of the lesions and topographical relation to dental fillings, are the best prognostic markers of the benefit to be obtained from amalgam replacement.

References

- Holmstrup P. Reactions of oral mucosa related to silver amalgam: a review. *J Oral Pathol Med* 1991; 20: 1-7.
- Bolewska J, Hansen H J, Holmstrup P, Pindborg J J, Stangstrup M. Oral mucosal lesions related to silver amalgam restorations. *Oral Surg Oral Med Oral Pathol* 1990; 70: 55-58.
- Finne K, Göransson K, Wickler L. Oral lichen planus and contact allergy to mercury. *Int J Surg* 1982; 11: 236-9.
- Laeijendecker R, Van Joost Th. Oral manifestations of gold allergy. *J Am Acad Dermatol* 1994; 30: 205-209.
- Arber W, Holub H, Strohal R, Slavicek R. Palladium in dental alloys. The dermatologists responsibility to warn? *Contact Dermatitis* 1993; 28: 163-165.
- Hietanen J, Pihlman K, Förström L, Linder E, Reunala T. No evidence of hypersensitivity to dental restorative metals in oral lichen planus. *Scand J Dent Res* 1987; 95: 320-327.
- Skoglund A. Value of epicutaneous patch testing in patients with oral, mucosal lesions of lichenoid character. *Scand J Dent Res* 1994; 102: 216-222.
- Platt J L, Grant B W, Eddy A A, Michael A F. Immune cell populations in cutaneous delayed-type hypersensitivity. *J Exp Med* 1983; 158: 1227-1242.
- Warvänge G, Larsson Å. Spontaneous lymphocytic infiltrates of oral mucosa in HgCl₂ induced autoimmunity of BN rats: phenotypic characteristics and contact hypersensitivity to Hg. *Reg Immunol* 1990; 3: 88-96.
- Hensten-Petersen A, Jacobsen N. Toxic effects of dental materials. *Int Dent J* 1991; 5: 265-273.
- Eneström S, Hultman P. Does amalgam affect the immune system? A controversial issue. *Int Arch Allergy Immunol* 1995; 106: 180-203.
- Bolewska J, Holmstrup P, Møller B, Kenrad B, Danscher G. Amalgam-associated mercury accumulations in normal oral mucosa, oral mucosal lesions of lichen planus and contact lesions associated with amalgam. *J Oral Pathol Med* 1990; 19: 39-42.
- Eversole L R. Oral mucosal Diseases. In: Millard H D, Mason D K (eds): *Second World Workshop on Oral medicine*. Ann Arbor, Michigan: Continuing Dental Education, School of Dentistry, University of Michigan, 1993: 41-56.
- Östman P-O, Anneroth G, Skoglund A. Oral lichen planus lesions in contact with amalgam fillings: a clinical, histologic and immunohistochemical study. *Scand J Dent Res* 1994; 102: 172-179.
- Laine J, Kalimo K, Forssell H, Happonen R-P. Resolution of oral lichenoid lesions after replacement of amalgam restorations in patients allergic to mercury compounds. *Br J Dermatol* 1992; 126: 10-15.
- Fischer A A. The misuse of the patch test to determine 'hypersensitivity' to mercury amalgam dental fillings. *Cutis* 1985; 35: 110-117.
- Handley J, Todd D, Burrows D. Mercury allergy in a contact dermatitis clinic in Northern Ireland. *Contact Dermatitis* 1993; 29: 258-261.
- Nordling K, Lidén S. Patch test reactions to metal salts in patients with oral mucosal lesions associated with amalgam restorations. *Contact Dermatitis* 1992; 27: 157-160.
- Pang B, Freeman S. Oral lichenoid lesions caused by allergy to mercury in amalgam fillings. *Contact Dermatitis* 1995; 33: 423-427.
- Kubo Y, Nonaka S, Yoshida H. False positive reaction to patch testing with aqueous mercuric chloride in an aluminum Finn Chamber. *Contact Dermatitis* 1992; 26: 136.
- Holmstrup P, Schiotz A W, Westergaard J. Effect of plaque control on gingival lichen planus. *Oral Surg Oral Med Oral Pathol* 1990; 69: 585-590.
- Bowyer A. Epidermal reactions and prolonged dermal reactions to patch testing with gold salts. *Acta Dermatovenereologica* 1967; 47: 9-14.
- Bruze M, Edman B, Björkner B, Möller H. Clinical relevance of contact allergy to gold sodium thiosulfate. *J Am Acad Dermatol* 1994; 31: 579-583.
- Räsänen L, Kalimo K, Laine J, Vainio O, Kotiranta J, Pe-

- sola I. Contact allergy to gold in dental patients. *Br J Dermatol* 1996; 134: 673-677.
25. Kanerva L, Henriks-Eckerman M-L, Estlander T, Jolanki R, Tarvainen K. Occupational allergic contact dermatitis and composition of acrylates in dental bonding systems. *J Eur Acad Derm Venereol* 1994; 3: 157-169.
26. Henriksson E, Mattson U, Håkansson J. Healing of oral lichenoid reactions following removal of amalgam. *J Clin Periodontol* 1995; 22: 287-294.

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