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A sudden flare-up of a quiescent oral lichen planus: methylisothiazolinone as the prime suspect?

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Case Report

A 61-year-old woman with a history of asymptomatic oral lichen planus, proven by mucosal biopsy 15 years previously, was referred to us with oral complaints that had occurred in September 2013, shortly after the placement of a new upper dental prosthesis (consisting of a metal frame made of a Vitallium[®] alloy, containing cobalt, chromium, and molybdenum, and acrylate tooth material made of polymerized methyl methacrylate (PMMA); Fig. 1). The prosthesis was used by the patient without any fixative. After a few weeks, the wearing of the prosthesis had resulted in intraoral swelling, vesicles, and small, painful, aphthous ulcers, accompanied by a metallic taste and a dry mouth. Whenever she removed the prosthesis, the complaints settled after several hours, only to recur when she wore the prosthesis again. At the time of presentation, 6 months later, clinical examination showed an inflammatory and lichenoid aspect of the buccal mucosa (Fig. 1), particularly those parts in contact with the prosthesis, that is, the lateral borders of the tongue, the gingiva, and the upper palate. Because of the suspicion of a contact allergy, patch tests were performed with the

Belgian baseline series [including both methylisothiazolinone (MI) 500 ppm aq. and methylchloroisothiazolinone (MCI)/MI 100 ppm aq., and supplemented with MI 2000 ppm aq., MCI/MI 200 ppm aq., benzisothiazolinone (BIT) 500 ppm pet., and octylisothiazolinone (OIT) 1000 ppm pet.], a dental series, an acrylate series (stored refrigerated), and a bakery series, all from Chemotechnique Diagnostics (Vellinge, Sweden), and (ingredients of) her personal dental hygiene products. Readings were performed according to ICDRG guidelines, and showed no reactions at D2, but 1+ reactions at D4 to MCI/MI 100 and 200 ppm aq., and to MI 500 and 2000 ppm aq. (Figs. 2 and 3). There were no reactions to BIT or to OIT, and no late reactions ($\geq$ D7) were observed. Interestingly, the patient had never experienced any dermatitis resulting from skin contact with cosmetics, household detergents, paints, or glues. However, she informed us that she had taken the advice of her dentist to clean her prosthesis twice weekly by soaking it, usually for 15–30 min, but sometimes for up to 1 hr, in a jar filled with water to which a highly concentrated dishwashing liquid [Dreft[®]; Procter & Gamble, Strombeek-Bever, Belgium] had been added. The label of the detergent mentioned the presence of MI, and to verify this a chemical analysis was performed at the Research Group Natural Products and Food – Research and Analysis of Antwerp University. Briefly, 1 g of the detergent was dissolved in 6 ml of methanol and placed for 30 min in an ultrasonic bath. The solution was then quantitatively transferred to a 10.0-ml volumetric flask, and adjusted to volume with methanol. Prior to analysis, the solution was filtered (0.45 μ m). The solution obtained was then analysed by high-performance liquid

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Fig. 1. A dental prosthesis containing cobalt, chromium, molybdenum and polymerized methyl methacrylate producing lichenoid lesions of the palate, gingiva, and lateral borders of the tongue.



Fig. 2. Methylchloroisothiazolinone/methylisothiazolinone 100 and 200 ppm aqua producing 1+ reactions at D4.

chromatography (HPLC) with an ultraviolet (UV) detector. The column used was a GraceSmart RP C18-column (5 μ m; 4.6 $\times$ 250 mm²) (Grace™ Alltech™, Deerfield, IL, USA), the mobile phase consisted of 0.1% (vol/vol) formic acid in water as mobile phase A and 0.1% (vol/vol) formic acid in acetonitrile as mobile phase B (using gradient elution), the flow rate was 1 ml/min, the injected volume was 20 μ l, and the wavelength used for the detection of MI was 274 nm. Comparison with a standard solution of MI (obtained from Santa Cruz Biotechnology®, Santa Cruz, CA, USA) showed that the detergent contained MI, which could be quantified at ~135 ppm (mean of two independent results). No MCI, BIT or OIT was found. A spike experiment (adding known amounts of MI, MCI, BIT and OIT to the sample) confirmed the suitability of the applied method for this sample, resulting in recovery of between 97.3% and 103.1% for the four isothiazolinones. The patient was instructed to stop the cleansing procedure and to thoroughly clean her prosthesis by soaking it in plain water and rinsing it several times before using it again. Also, her dentist recommended the use of an alternative prosthesis-friendly cleaning method (Dentipur® gel; Helago-Pharma GmbH, Erftstadt, Germany). Additionally, the remaining active lichenoid lesions, which showed a waxing and waning course, were treated with a topical betamethasone dipropionate 0.05% mouth paste.

When the patient was contacted again after 2 weeks, she had cleaned the prosthesis three times, which had already enabled her to wear it for a longer period of time during the day, and at a second follow-up at 6 weeks she was again wearing the prosthesis continuously during the day.

Besides inadequate rinsing, possible penetration of MI into the acrylate component of the prosthesis was considered as a possible explanation. In order to verify this hypothesis, the following experiment was performed. Three small pieces of PMMA (~1 cm²) were delivered by the dental technical laboratory that had manufactured the prosthesis: (i) one piece was soaked for 1 hr in 15 ml of water to which two drops (~0.1 ml) of the MI-containing household detergent were added twice weekly for 4 weeks, and after each procedure it was thoroughly rinsed for 2 min; (ii) one piece was treated in the same way, but with MI 500 ppm aq. (Chemotechnique Diagnostics®); and (iii) one piece was treated with only water and served as a control. The patient agreed to be tested with all three pieces of PMMA placed on the upper arm for 48 hr. Readings at D2 and D4, however, remained negative. An additional effort to show the penetration of MI was undertaken by soaking a similar PMMA-based prosthesis in a jar containing 150 ml of water to which two drops of the same detergent were added. After 2 days, it was thoroughly rinsed and cleaned in fresh water by



Fig. 3. Methylisothiazolinone 500 and 2000 ppm aq. producing 1+ reactions at D4.

use of an ultrasonic bath for 5 min. The residual water, concentrated after evaporation, was then analysed with the aforementioned HPLC method, but no MI was found.

Discussion and Conclusion

Dental prostheses can be responsible for oral contact allergy caused by metals or, more rarely, the acrylates used to manufacture them (1). In our case, MI was considered to be the cause of a sudden flare-up of a latent oral lichen planus, owing to its presence in a household detergent that was used to clean a prosthesis. Besides cosmetics and paints, household detergents have been pointed out as important allergen sources of MI, the latter mainly in relation to hand dermatitis (2). As the labelling of household detergents is mandatory, but not always correct (3), and because we did not have any information on the range of use concentrations of MI in the particular dishwashing liquid, we verified its presence and concentration by means of HPLC with UV detection, which actually showed a high content of MI (~135 ppm). Although the use of a household detergent to clean a dental prosthesis might seem erroneous, some dentists advise this, as can also be seen when some commercial dental care websites are consulted(4).

We hypothesize that inadequate rinsing of the prosthesis, with some of the film-forming detergent and MI present therein remaining, might have triggered the reaction in our patient. Alternatively, MI might have penetrated the porous structure of the acrylate component of the prosthesis, possibly even accumulating in it with repeated soaking, as the acrylate part of such dental prostheses, which is usually made of PMMA, is not a solid material, but a porous one, with the degree of porosity depending on several factors (e.g. the amount of residual monomers), which might lead to microorganisms (e.g. *Candida albicans*) being harboured, and also the retention of fluids (5). Interestingly, it was recently reported

that MI might penetrate through natural rubber latex gloves (6), and a similar observation was reported by Fukunaga et al., who described a case in which OIT, the isothiazolinone that is structurally most related to MI, penetrated from the inner gel layer of a mattress, through a middle polyethylene layer, to the outer textile layer, causing contact dermatitis (7). Our attempts to show such penetration of MI into the dental acrylate material were unsuccessful, and several reasons might explain this: (i) we could only test small pieces of acrylate material (~1 cm²), with the absolute MI content being possibly too low to elicit reactions when tested 'as is' on the skin; and (ii) a similar, but not identical, PMMA-based prosthesis was used for the experiment, and there might have been differences with regard to polymerization status and the amount of residual monomers, influencing the degree of porosity of the prosthesis. Further, the duration of soaking of this prosthesis in the MI-based solution of only 2 days might have been too short for enough accumulation of MI inside the prosthesis for the described HPLC method to detect its presence.

Our patient never experienced any hand eczema or other dermatitis after the use of MI-containing or MCI/MI-containing cosmetics or detergents, which, after careful examination of her personal care and household products, consisted only of rinse-off products. Moreover, the patch test reactions in our patient were all of a mild 1+ intensity, and rinse-off cosmetics or detergents containing MI might not, therefore, necessarily produce clinical symptoms in such low-grade sensitized patients, as has also been described for MCI/MI-containing rinse-off products in MCI/MI-allergic patients (8). Alternatively, our patient might represent a case of contact allergy to MI with clinical relevance only at the mucosal level, without contact dermatitis of the skin. It is of note that MI can also be present in sexual lubricants that are used on the anogenital mucosa and cause MI-related genital dermatitis (2).

In conclusion, we report a case in which MI, present in a household detergent used to clean a dental prosthesis, might have caused primary mucosal sensitization, resulting in koebnerization and thus leading to a flare-up of a long-lasting, but hitherto inactive, oral lichen planus. Apart from its toxicity, its allergenic potential makes it clear that the use of MI at the mucosal level should be avoided. In the future, one might focus on the potential

of the isothiazolinones to penetrate solid materials such as rubbers, plastics and, possibly, even acrylates, although the last of these remains to be proven.

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