

The prevalence of contact hypersensitivity in patients with oral lichen planus

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Abstract

Introduction: Oral lichen planus (OLP) is a chronic autoimmune inflammatory disease with an unknown aetiology and a higher prevalence in women. Oral lichenoid lesions both clinically and histologically resemble oral lichen planus and are often associated with contact allergy to dental materials.

Aim: To investigate the prevalence of delayed hypersensitivity reactions in patients with OLP and to identify the most common allergens that may exacerbate the disease.

Material and methods: Twenty patients diagnosed with OLP and undergoing treatment in the Gerodontology and Oral Pathology Department of the Poznan University of Medical Sciences were enrolled in the study. The subjects underwent a detailed oral examination consisting of anamnesis and a clinical evaluation by a qualified dentist, while an assessment of the skin and skin appendages was carried out by a dermatologist. Patch testing was performed using the Polish Baseline Series and Dental Screening Series.

Results: Fifty percent of the examined patients displayed positive patch test reactions. A total of 18 allergic reactions were revealed, but only four appeared during the first test. The most common allergens were found to be nickel, gold, and a fragrance mix. Only 1 patient had a positive reaction to more than three allergens.

Conclusions: There seems to be a high contact reaction rate in patients with oral lichen planus, which is not related to contact with synthetic dental materials. However, further investigations on a larger population with the introduction of additional tests administered 7 days after exposure are required to confirm the effects of delayed hypersensitivity reactions on patients with OLP exacerbation.

Key words: oral lichen planus, hypersensitivity, patch tests, oral pathology, contact dermatitis, allergens.

Introduction

Lichen planus (LP) is a chronic autoimmune inflammatory disease affecting the skin, nails, scalp, genital and oral mucosa. Oral lichen planus (OLP) affects up to 2.2% of the population, mostly middle-aged people, with a higher prevalence in women. Up to 60% of patients with cutaneous LP develop oral lesions, but only about 15% of patients with OLP present skin involvement [1–3]. The disease aetiology remains unknown; however, T-cell triggered apoptosis of oral epithelium basal cell keratinocytes is involved in the pathogenesis [1, 4]. Numerous factors such as stress, dental materials, infectious agents (e.g., hepatitis C virus), drugs, autoimmunity, diabetes mellitus and hypertension have been suggested as triggers for the lesions [2, 4, 5].

Oral manifestations of LP may present as papular, reticular, erosive, atrophic bullous lesions or plaque-like lesions usually involving bilaterally buccal, lingual and gingival mucosa [3, 5]. As no causative treatment of OLP is available, the management of the disease includes the elimination of predisposing factors, the use of topical corticosteroids, immunomodulators, retinoids, and the application of laser therapy [1, 3, 5, 6].

Oral lichenoid lesions (OLL) clinically and histologically resemble OLP but have identifiable aetiology and appear unilaterally. The most common factors associated with OLL are exposures to dental materials (especially amalgam), drugs (non-steroidal anti-inflammatory drugs and angiotensin-converting enzyme inhibitors) and graft-versus-host disease (GVHD) [5, 7–9]. OLL triggered by direct contact

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with restorative materials is considered to be a delayed contact hypersensitivity reaction (type IV according to Gell and Coombs' classification). To distinguish OLP from OLL, skin patch testing may be used as an additional tool in the diagnosis of atypical and treatment-resistant OLP [10–12].

Patch testing (PT) is a standard procedure used to diagnose contact allergy resulting from type IV hypersensitivity. It was first introduced at the end of the 19th century and Josef Jadassohn as well as Bruno Bloch are considered as pioneers, hence the reference to PT as the Jadassohn-Bloch technique. PT is performed by applying potential allergens under occlusion on the skin under standardized conditions. Test substances are prepared in various suitable vehicles such as petrolatum, water, hydrophilic gel, or solvents. The patch tests are applied to the upper back of the patient for 48 h. The reactions are checked initially after 48 and then within 72–96 h. According to the recommendations of the European Society of Contact Dermatitis, PT should be performed in patients presenting with contact dermatitis (including dermatitis related to occupation), but also mucous membrane eruptions in which delayed-type hypersensitivity is suspected [13].

Aim

This study was designed to investigate the prevalence of delayed hypersensitivity reactions in patients with OLP and identify the most common allergens that may exacerbate the disease.

Material and methods

Twenty patients diagnosed with OLP and undergoing treatment in the Gerodontology and Oral Pathology Department of the Poznan University of Medical Sciences were enrolled in this study. Subjects were referred to the above Department by their dentists or general practitioners when they presented with white non-removable lesions or/and burning mouth sensation. Patients with lesions which were

due to contact with amalgam restorations, and who did not sign the informed consent form were excluded.

A detailed oral examination consisting of anamnesis and clinical evaluation was performed on all recruited subjects. The patients' history included age, gender, subjective complaints related to the oral cavity, dental hygiene habits, addictions, and use of prosthetic appliances. Oral cavity examinations were performed in artificial light with a dental mirror by a qualified dental specialist. All patients underwent skin examination performed by a dermatologist in the Dermatology Department of the Poznan University of Medical Sciences. PT included the Polish Baseline Series and Dental Screening Series, the list of test substances is presented in Tables 1–3. PT were performed by applying haptens into Finn Chambers which were then mounted onto the normal skin of the back for 48 h. The PT reading was performed after 48 and 72 h, in accordance with the International Contact Dermatitis Research Group recommendations (Tables 1–3).

Results

The study group comprised 18 women and two men with an average age of 63 years (range: 42–88, SD 11.53 years). The mean duration of the disease was 3 years and 9 months (range: 0.5–21 years). Eight (40%) patients presented reticular OLP, an equal number of patients suffered from atrophic/erosive OLP, in 3 (15%) cases, the co-occurrence of atrophic/erosive and desquamative gingivitis was noticed, and only 1 woman had a plaque-like type OLP. Fourteen (70%) subjects used denture appliances, and only 2 (10%) smoked tobacco. Thirteen (65%) patients reported subjective complaints such as burning sensation and pain. Half of the population presented positive reactions to the patch tests. A total of 18 contact sensitization reactions were confirmed in 10 female patients. Table 4 shows the distribution of positive PT reactions according to the clinical type of OLP (Figure 1).

Table 1. Test substances used in the Polish Baseline Series until February 2020

Benzocaine	Methylisothiazolinone	Lanolin alcohol
Cobalt(II) chloride hexahydrate	Neomycin sulfate	Methylisothiazolinone + methylchlorisothiazolinone
Sesquiterpene lactone mix	Nickel(II) sulfate hexahydrate	Lyril
Colophonium	<i>P</i> -phenylenediamine (PPD)	Quaternium-15
Epoxy resin	Potassium dichromate	Budesonide
Fragrance mix I	Peru balsam	Tixocortol-21-pivalate
Formaldehyde	4- <i>tert</i> -butylphenolformaldehyde resin (PTBP)	Methyldibromo glutaronitrile
N-Isopropyl-N-phenyl-4-phenylenediamine (IPPD)	Paraben mix	Fragrance mix II
2-Mercaptobenzothiazole (MBT)	Thiuram mix	Sodium tetrachloropalladate(II) hydrate
Mercapto mix	2-Methoxy-6- <i>n</i> -pentyl-4-benzoquinone	Propolis

Table 2. Test substances used in the Polish Baseline Series since February 2020

Caine Mix III	Methylisothiazolinone	Lanolin alcohol
Cobalt(II) chloride hexahydrate	Neomycin sulfate	Methylisothiazolinone + methylchloroisothiazolinone
2-Hydroxyethyl methacrylate	Nickel(II) sulfate hexahydrate	Hydroperoxides of limonene
Colophonium	<i>P</i> -phenylenediamine (PPD)	Quaternium-15
Epoxy resin,	Potassium dichromate	Budesonide
Fragrance mix I	Peru balsam	Tixocortol-21-pivalate
Formaldehyde	Hydroperoxides of Linalool	Methyldibromo glutaronitrile
Gentamicin sulfate	Paraben mix	Fragrance mix II
2-Mercaptobenzothiazole (MBT)	Thiuram mix	Sodium tetrachloropalladate(II) hydrate
Hydroxyisohexyl 3-cyclohexene carboxaldehyde	Textile dye mix	Propolis

Table 3. Test substances used in the Dental Screening Series

Methyl methacrylate	Potassium dichromate	Formaldehyde	Drometrizole	Ammonium hexachloroplatinate(IV)
Triethylene glycol dimethacrylate	Mercury	4-Tolyldiethanolamine	Tetrahydrofurfuryl methacrylate	Benzoylperoxide
Urethane dimethacrylate	Cobalt(II) chloride hexahydrate	Copper(II) sulfate pentahydrate	Tin	Menthol
Ethylene glycol dimethacrylate	2-Hydroxyethyl methacrylate	Methylhydroquinone	Titanium	Epoxy resin
Bisphenol A glycerolate dimethacrylate (BIS-GMA)	Gold(I) sodium thiosulfate dihydrate	Palladium(II) chloride	Vanadium	Peru balsam
N,N-Dimethyl-4-toluidine	Nickel(II) sulfate hexahydrate	Aluminium(III) chloride hexahydrate	Molybdenum	Carvone
Benzophenone-3	Eugenol	Camphoroquinone	Tungsten	2,2-bis(4-(2-Methacryl-oxoethoxy) phenyl)propane (BIS-EMA)
1,4-Butanediol dimethacrylate	Colophonium	Dimethylaminoethyl methacrylate	Ferric chloride	Glutaral
Bisphenol A dimethacrylate (BIS-MA)	<i>N</i> -Ethyl- <i>p</i> -toluenesulfonamide	1,6-Hexanediol diacrylate	Silver nitrate	Sodium tetrachloropalladate(II) hydrate

Table 4. The distribution of positive PT reactions according to the clinical type of OLP

Variable	N (%)	Patch test positive reactions n (%)
Total	20 (100)	10 (50)
Reticular	8 (40)	5 (62.5)
Atrophic/erosive	8 (40)	3 (37.5)
Atrophic/erosive + desquamative gingivitis	3 (15)	2 (66.7)
Plaque-like	1 (5)	0

There were only 4 positive patch test reactions after 48 h. During the skin assessment, 72 h after the test application, an additional 14 positive responses were found. The results of positive reactions after 48 and 72 h are presented in Table 5.

Some participants displayed more than one positive patch test reaction. The most frequently identified contact allergens in patients with positive patch test reactions were nickel (5) fragrance mix I (2) and gold (2).

Five patients had a positive reaction to only one test substance, four to 2–3 allergens, and only one to more than three allergens (Figure 2).

Discussion

The clinical manifestations of contact allergy in oral and perioral diseases may present a broad spectrum of symptoms including cheilitis, stomatitis, perioral dermatitis, lichenoid lesions and even burning mouth syndrome [9, 14]. In this study, 50% of the examined patients had at least one positive reaction in PT, which is in agreement with studies performed by Yiannias *et al.* and Issa *et al.* [15, 16]. An even higher rate of positive responses to contact allergens in patients with OLP, namely 75% was presented by Kim *et al.* [17].

Many previous studies documented a strong association of OLL with amalgam restorations. The incidence of positive patch test reactions to amalgam compounds in several studies varied from 9.9% up to 65% and depended on the direct contact of the affected oral mucosa with the restorations [12, 14, 16, 18–20]. In patients with OLL, the replacement of amalgam fillings led to the resolution of the mucosal lesions. The improvement also depended on the topographical relationship between lesions and restorations. Lesions in complete contact with amalgam healed in 63% to 97% of cases, whereas in the case of partial contact, only about 27% of patients benefited [12, 16, 18]. However, it was ineffective in patients with OLP due to the disease’s autoimmune background [15, 16, 18–20]. Moreover, Laeijendecker *et al.* found no positive patch test reactions to mercury in patients with concomitant cutaneous LP and Dunsche *et al.* reported a weak effect of amalgam replacement in a group with concomitant cutaneous LP [12, 18]. In our study, only 1 patient retained a positive reaction to mercury, despite the removal of amalgam many years before. On the other hand, she showed no positive response to any other applied allergens, including other amalgam metals such as copper or tin. The low rate of positive amalgam patch

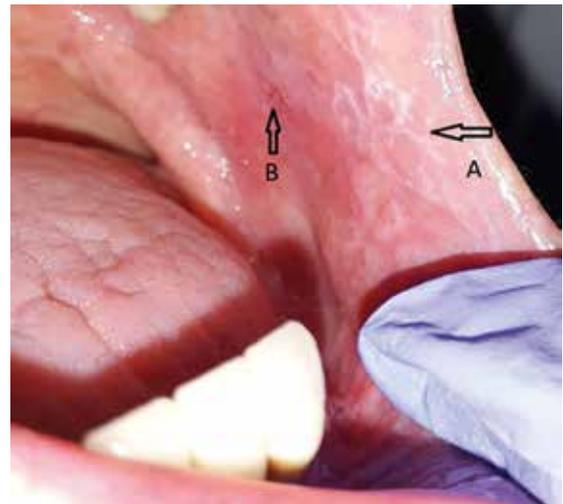


Figure 1. The white striae (A) and an erosion (B) on the buccal mucosa in a 72-year-old female patient allergic to the mercury

response may result from the inclusion of only OLP patients in our study. Likewise, Kim *et al.* and Raap *et al.* reported a low incidence of delayed mercury hypersensitivity in the OLP population [17, 21].

Nickel in stainless steel is one of the most common contact allergens worldwide. It is widely utilized in the household environment, e.g. in jewellery, watches, keys, clothing and kitchen accessories. Delayed type of hypersensitivity to nickel is found in 13% of the general adult population, and 8.6% of patients with contact dermatitis react positively to this allergen [22–24]. A retrospective analysis conducted in the Dermatology Department of the Poznan University of Medical Sciences showed a 56% nickel hypersensitivity reaction among patients with positive patch test results, corresponding to 18% of the studied population [25]. Similar outcomes were described in the studies of Polish population groups in Lodz (24%) and Bialystok (21%) [26, 27]. A recent multicentre study conducted in six European clinics revealed nickel sensitization in 25% of the studied population ($n = 906$) and excluded the association of OLL with nickel and palladium

Table 5. Positive PT reactions after 48 and 72 h

Parameter	48 h		72 h	
	n	%	n	%
Nickel sulfate	1	5	5	25
Fragrance mix I	0	0	2	10
Fragrance mix II	0	0	1	5
Neomycin sulfate	0	0	1	5
Methylisothiazolinone	0	0	1	5
Lyral	0	0	1	5
Methyldibromo glutaronitrile	0	0	1	5
Balsam Peru	0	0	1	5
Gold sodium thiosulfate	1	5	2	10
Mercury	1	5	1	5
Carvone	1	5	1	5
2 hydroxyethyl methacrylate	0	0	1	5

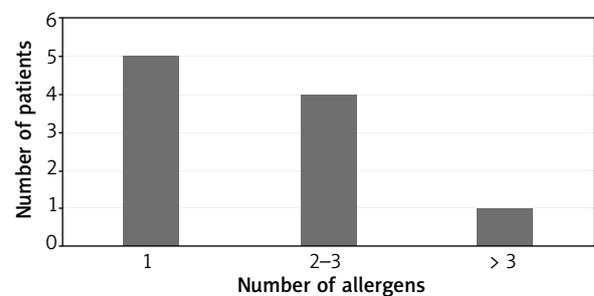


Figure 2. Positive PT reaction in patients with OLP

sensitization [28]. Our results which showed a positive patch response in 50% of the test group and 25% of the studied population confirmed those observations. In dentistry, nickel alloys (Ni-Cr) are widely used in fixed prosthodontic appliances, metal and porcelain-fused-to-metal crowns and bridges, especially in developing countries [29]. Ahlgren *et al.* reported a similar rate of nickel hypersensitivity in their study, although this metal is not used in Sweden, except for orthodontics [19]. Likewise, Kim *et al.* and Rai *et al.* described a similar positive reaction to nickel sulfate and also to potassium dichromate [14, 17]. On the other hand, we failed to confirm any allergic reaction to chromium both as the metal and as metal ions.

Gold is another frequently identified metal allergen affecting dental patients with positive patch test reactions. Marell *et al.* reported the hypersensitivity to gold sodium thiosulphate in 50% of OLL patients with contact hypersensitivity (19.3% of the whole OLL subgroup) and 17% of OLP patients with contact hypersensitivity (8% of the entire OLP subgroup), which is in agreement with Khamayasi' and our results [20, 30]. A slightly more frequent reaction among OLP patients was described by Kim *et al.* (33% of the whole OLP population and 44% of those with contact allergy) and Raap *et al.* (22% of OLP population) [17, 21]. In other studies conducted on subjects with OLL, the positive patch test response to gold ranged from 3.3% up to 29% of the subjects [30–35].

Fragrances, as ingredients of cosmetics, are considered one of the most common contact allergens worldwide [36]. They are also found in medication, food flavourings, household and washing detergents. Studies conducted in various Polish centres revealed contact hypersensitivity to fragrance mixtures in 8.3–20.4% of subjects, which is consistent with our results [25, 27, 37]. Larsen *et al.* reported positive PT reactions among 14.3% of patients with OLP and OLL in line with Torgerson *et al.*, who described fragrance contact allergy in 17.1% of patients with lichenoid lesions and subjects with cheilitis and burning mouth syndrome [34, 38]. On the other hand, this was not supported by Budimir *et al.*, who observed fragrance hypersensitivity only in patients with perioral dermatitis [31]. Similarly, Polańska *et al.* presented a case report of a 66-year-old female with papular and erythematous lesions in the upper and lower lip regions, who had both allergic and toxic reactions to fragrances (fragrance mix I and II and Lyril) [39].

Acrylates and methacrylates polymerize in ultraviolet light (or spontaneously) and are widely used in the production of plastics, textiles, glass fibres and artificial nails. Before the popularization of artificial nails, contact allergy to acrylates was considered an occupational disease mainly affecting dental personnel and orthopaedic surgeons. In dentistry, acrylates are present in dentures, composite resins, bonding materials and glass-ionomers [40–45]. Ramos *et al.* reported 30.3% of positive patch test reactions attributable to methacrylate, and 10.8%

of the positive responses were related to the use of the acrylic dentures [40]. Muttardi *et al.* found 2-hydroxyethyl methacrylate to be the most common allergen among methacrylates and cyanoacrylates in their study, similar to Ramos *et al.* and Aalto-Korte *et al.* [40–42]. In our study, only 1 patient had a positive reaction to 2-hydroxyethyl methacrylate among all methacrylates tested, which supports their findings.

Although the skin assessment is commonly conducted 48 and 72–96 h after PT application, some authors suggest the use of additional tests due to delayed reactions [13, 46, 47]. Allergens generally associated with late positive responses are nickel, gold, mercury, cobalt, chromium, and neomycin [48]. Laeijendecker *et al.* showed that 35% of positive patch test responses occurred after 5 to 18 days [12]. Ahlgren *et al.* reported 26 additional positive allergic reactions seen only on day 7, which was a 25.2% increase and was statistically significant [48]. This observation may explain the difference between positive allergic response after 48 and 72 h in our study, however it has to be emphasized that each patient is informed about the necessity of an additional consultation in case of the appearance of a new skin reaction within the testing area.

The main limitation of this study is a relatively small sample size due to time-consuming test assessments, and the multiple visits, which were very challenging for the patients during COVID-19 pandemic.

Conclusions

This study has presented a high rate of contact allergic reactions in patients with OLP. It appears to be the first study to report the association between OLP and contact allergy in the Polish population. Further investigations on a larger group with the introduction of additional tests on day seven are required to confirm the influence of delayed hypersensitivity reactions on patients with OLP exacerbation.

Conflict of interest

The authors declare no conflict of interest.

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