ORIGINAL ARTICLE

Oral Lichenoid Reactions and Contact Sensitization: A 5-year Review in the Department of Dermatology, Hospital Kuala Lumpur, Malaysia

Sharifah Rosniza Syed Nong Chek, *AdvMDerm,* Min Moon Tang, *AdvMDerm,*

Department of Dermatology, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

Abstract

Background

Oral lichen planus is an idiopathic autoimmune inflammatory condition and oral lichenoid reactions are lesions that resemble oral lichen planus clinically and histopathologically, but develop secondary to various underlying causes. Oral lichenoid reactions have been reported to be caused by contact allergy to dental materials. This study aims to describe the characteristics of patients with a clinical and/or histopathological diagnosis of oral lichen planus who underwent patch testing in Hospital Kuala Lumpur, Malaysia.

Methods

This is a 5-year retrospective study of patients who had oral lichen planus and had undergone patch testing at the Department of Dermatology, Hospital Kuala Lumpur, Malaysia between January 2015 and Cecember 2019. Patch tests were performed with European Baseline Series and relevant extended series, which include dental and metal series as well as patients' own products. Patch test results were recorded according to the International Contact Dermatitis Research Group recommendation.

Results

There were 41 patients with oral lichen planus who underwent patch test. The median age was 56 (range 21 to 73) with 70.7% of patients being female. There were 29 (70.7%) patients who developed at least one positive reaction. The most frequent sensitizing allergens were nickel sulfate (34.1%), gold(I)sodium thiosulphate dihydrate (22.0%), fragrance mix I (19.5%), cobalt chloride (14.6%), Peru balsam (12.2%) and sodium tetrachloropalladate (II) hydrate (12.2%). Current relevance was recorded in 16 patients (39.0%) and of these patients, 12 of them had positive patch test reactions to allergens found in dental materials such as dental fillings, dental implants, orthodontic braces, dentures and dental crowns.

Conclusion

Contact sensitization was detected in about 70% of our patients with oral lichen planus. The most common sensitizing allergen was nickel sulfate. Current relevance was found mainly towards dental materials.

Key words*: Allergic contact dermatitis, Patch test, Oral lichen planus, Oral lichenoid reactions***,** *Oral lichenoid lesions, Oral lichenoid diseases, Lichen planus-like lesions, Oral lichenoid tissue reactions*

Corresponding Author
Dr Sharifah Rosniza Syed Nong Chek
Department of Dermatology,
Hospital Kuala Lumpur,
Jalan Pahang,
50586 Kuala Lumpur, Malaysia
Email: srsyed@doctors.org.uk

Introduction

Lichen planus is an inflammatory disease of unknown aetiology that primarily affects the skin and oral mucosa. Apart from oral mucosa, other mucous membranes that can be involved include the genitalia, esophagus

and conjunctiva. [1] Cutaneous lichen planus is characterized by erythematous-violaceous, polygonal, shiny and symmetrical papules with the presence of whitish streaks on the surface known as Wickham striae. Oral lichen planus usually presents in two ways, either as painful and erythematous erosions and ulcerations or as painless radiating white papules or patches on the buccal mucosa. These lesions may also involve the lips, tongue and palate.[2]

Oral lichenoid reactions are lesions that resemble oral lichen planus clinically and histopathologically but develop secondary to various underlying causes. There are several synonyms that have been used to describe oral lichenoid reactions and these include oral lichenoid lesions, oral lichenoid diseases, lichen planus-like lesions and oral lichenoid tissue reactions. [3] These lesions can be caused by exogenous factors such dental restoration materials and systemic medications, whereas others may be due to systemic diseases such as graft-vs-host disease (GVHD), systemic lupus erythematosus or malignant tumours.[3] Patch test plays an important role in diagnosing oral lichenoid reactions related to contact allergy, especially from dental materials.

This study aims to describe the characteristics of patients with a clinical and/or histopathological diagnosis of oral lichen planus who underwent patch testing in Hospital Kuala Lumpur, Malaysia.

Materials and Methods

This is a 5-year retrospective study of patients who had oral lichen planus and had undergone patch testing at the Department of Dermatology, Hospital Kuala Lumpur, Malaysia between January 2015 and December 2019. Patch tests were performed with European Baseline Series and relevant extended series from Chemotechnique Diagnostics using IQ chambers™. Extended series used include dental screening series, metal series, cosmetic series, and plastic and glue series. Patients were also tested with their own products, which include toothpaste and mouthwash. Toothpaste was tested "as is". Mouthwash was diluted with water to 10% (w/w).

Patches were applied to the patients and removed after 48 hours. Initial reading was done at 48 hours and final reading was recorded at 96 hours after patch application. The parameters studied include positive patch test reactions and the source of allergens. Readings were recorded according to the International Contact Dermatitis Research Group recommendation. [4]

Results

There were 41 patients with oral lichen planus who underwent patch test. The demographic data is shown in Table 1. The median age was 56 (range 21 to 73) and the majority of patients (70.7%) were female. In addition to the oral lichen planus, cutaneous involvements were found in 5 patients. These patients had involvement of the trunk (3 patients), upper and lower limbs (1 patient) and lower limbs only (1 patient). Twenty-four (58.5%) patients had dental procedures done which include dental fillings, crown, bridges, implant, dentures and orthodontic braces. The diagnosis of oral lichen planus was confirmed histopathologically in 31 patients (75.6%), whereas the rest of the patients had no biopsy, inconclusive biopsy results or the biopsy results were not available. All patients were referred to our centre from dental departments in hospitals based in Klang Valley areas.

More than half of the patients (53.7%) had symptoms of six months or less, 8 patients (19.5%) had symptoms between 6 months to 1 year and the rest (26.8%) had symptoms lasting more than 1 year. All patients described symptoms of pain and discomfort, especially when eating spicy foods.

There were 29 (70.7%) patients who developed at least one positive reaction. As shown in Table 2, the most frequent sensitizing allergens were nickel sulfate (34.1%), gold (I) sodium thiosulphate dihydrate (22.0%), fragrance mix I (19.5%), cobalt chloride (14.6%), Peru balsam (12.2%) and sodium tetrachloropalladate (II) hydrate (12.2%). Current relevance was recorded

in 16 patients (39.0%) and of these patients, 12 (75%) of them had positive patch test reactions to allergens found in dental materials such as dental amalgam, dental implants, orthodontic braces and dental crowns. Four (25%) of these patients had current relevance attributed to their own toothpastes.

Table 1. Characteristics of 41 patients who underwent patch test for oral lichen planus

Characteristics		**n=41**
Median age in years (range)		56 (21-73)
Male:Female ratio		1:2.4
Ethnicity, n (%)	Chinese	19 (46.3)
	Indian	15 (36.6)
	Malay	6 (14.6)
	Others	1 (2.4)
Presence of cutaneous involvement, n (%)		5 (12.2)
Oral lichen planus confirmed by histopathological examination, n (%)		31 (75.6)
Series used, n (%)	European Baseline	41 (100.0)
	Dental	41 (100.0)
	Metal	15 (36.6)
	Cosmetics	3 (7.3)
	Plastic and glue	1 (2.4)
	Own products	15 (36.6)

Table 2. Sensitization pattern of current cohort

Positive Patch Test	**n (%)**
Nickel sulfate	14 (34.1)
Gold(I)sodium thiosulphate dihydrate	9 (22.0)
Fragrance mix I	8 (19.5)
Cobalt chloride	6 (14.6)
Peru balsam	5 (12.2)
Sodium tetrachloropalladate (II) hydrate	5 (12.2)
Palladium chloride, formaldehyde, mercury	4 each (9.8)
Colophony, MCI/MI	3 each (7.3)
Thiuram mix, potassium dichromate, textile dye mix, butylphenol formaldehyde resin	2 each (4.9)
Epoxy resin, neomycin, Quaternium-15, methylisothiazolinone, fragrance mix II, carvone, mercury ammonium chloride, triethylene glycol dimethacrylate, amalgam, BIS-GMA, MDBGN, thimerosal, 2-Hydroxyethyl methacrylate	1 each (2.4)

MCI/MI - methylcholoroisothiazolinone/methylisothiazolinone; BIS-GMA - Bisphenol A glycerolate dimethacrylate; MDBGN-methyldibromoglutaronitrile

Discussion

Contact sensitization was detected in about 70% of our patients with oral lichen planus. The 3 most common sensitizing allergens were nickel sulfate, gold sodium thiosulphate and fragrance mix. These findings were similar to studies conducted in other countries (Table 3). Other metals that were also found as common sensitizers in our study include cobalt chloride and palladium.

The high number of positive reactions to metal allergens in our study can be explained by the presence of metal in dental restoration materials. Most metals found in dentistry are in the form of alloys. Alloys are mixtures of metals and non-metals. They are preferred as pure metals do not have the appropriate physical properties to function as dental restoration materials. [5] Metal-ceramic alloy has been used in dental restoration materials since the 1950s. The durability of these alloys was proven by studies. Nearly 90% of metal-ceramic crowns and 80.2% of metal-ceramic fixed partial dentures were still in function after 10 years. [6] Nickel, gold, cobalt and palladium are present in dental restoration materials in variable combinations with ceramic and other metals to optimize their clinical performance, aesthetics and physical properties. This possibly explains why these metals were found as top sensitizing allergens in our study.

Metal alloys used in dentistry can be divided into noble and base metal alloys. Noble metals are gold, palladium, iridium, ruthenium, and platinum. [7] Base metals in dentistry are further divided into two main systems, which are nickel based and cobalt based. Alloys in both systems contain chromium as their second largest constituent. Other base metal used in dentistry include titanium. [8] Adverse effects due to these metals are chiefly caused by corrosion, which results in release of metal ions and subsequent metal-protein or metal-cell interactions.[9]

The most common sensitizing allergen found in our study was nickel sulfate. Nickel is widely used in dental restoration materials as it is cheaper compared to metals such as gold and possesses better mechanical properties to gold when combined with other metals.[8] Nickel

is found in alloys such nickel-chromium-beryllium, nickel-chromium and nickel-high chromium alloys. [5] Beryllium was used in the past with nickel as it facilitates casting and enhanced porcelain bonding but due to the increased corrosion especially at low pH, this alloy is no longer recommended. [8,9] As nickel is a highly sensitizing metal, there is a need for other affordable metal alloys that are free of nickel yet confer similar properties as nickel containing alloys. An alternative to nickel containing alloys is chromium-cobalt alloys, which have a high biocompatibility and since they are nickel-free, they can be used in patients who are known to be allergic to nickel. [5]

The relevance of contact sensitization to nickel and oral eruptions is however controversial as it is abundant in our environment and sources of exposure can be unrelated to the dental restoration materials. Nickel allergy presenting as oral eruption alone is thought to be rare. Exposure to nickel during treatment of with orthodontics braces is thought to confer tolerance in nickel insensitive patients. [10] In nickel sensitive patients however, exposure to nickel via orthodontic implants have shown conflicting findings. Studies have shown exacerbation of dermatitis together with lip swelling and burning after fixation of orthodontic implants in previously nickel sensitized individuals. [11] On the other hand, there were also patients who were nickel-sensitive but developed lower incident of oral contact reactions following orthodontic implants, which is thought to be due to the development of tolerance.[12] With this in mind, determining the relevance of nickel in causing oral lichenoid reactions requires careful consideration and interpretation. Often times, current relevance can only be made retrospectively when there is improvement of lesions upon removal of the suspected dental materials that contain nickel as a constituent.

The second most common allergen in our study is gold sodium thiosulphate. Gold is used in dental restorations because it is easily malleable and is highly resistant to corrosion.[13] It is also inert and is fairly nonreactive with other metals. Gold alloys as dental restoration materials comprised of over 70% of gold predominated until the price of gold skyrocketed in the mid-1970s. Subsequently, the demand for lower cost of metal alloys paved the way for the use of cheaper metal alloys such as nickel.[5] The gold-platinum-palladium alloys were the first to be used successfully for metal-ceramic restorations; however their used decreased after more economical alloys were developed with significantly better mechanical properties.[8] Gold dental alloy that is still used nowadays has a reduced gold content, typically in the range of 35 to 50%, which is less costly.[5]

The clinical features of intra-oral contact allergy related to gold exposure are not specific, although lichenoid reactions appear to be the most common manifestation of gold contact allergy in the oral mucosa.[14] Patients with oral lichenoid reactions have been found to have an increased frequency to patch test positivity to gold compared to patients undergoing evaluation of other dermatitis not affecting the oral lesions.[15] Other manifestations of gold allergy in the oral cavity include non-specific stomatitis and burning mouth syndrome. [16] Additionally, studies have also shown that there is a statistically significant and dose-dependent relationship between contact allergy and the number of dental gold restorations.[17] Metallic gold (foil) and trivalent auric chloride were previously used for patch testing but they are no longer recommended today. At present, monovalent gold salts in the form of gold sodium thiosulfate in petrolatum is used as the gold allergen in patch test. [18] It is also recommended that patch test reading for gold allergy is extended to day 7 as the development of a positive reaction may be delayed.[18] In dentistry, gold is mostly alloyed with other metals such as palladium, platinum and silver and therefore it is important to patch test these metals as well.

Fragrances are also common allergens in our study as evidenced by the high sensitization to fragrance mix I and Peru Balsam. Fragrance mix I contains eight fragrances, consisting

of seven defined chemicals (amyl cinnamal, cinnamal, cinnamyl alcohol, eugenol, geraniol, hydroxycitronellal and isoeugenol) and oakmoss absolute (*Evernia prunastri extract*).[19] Peru Balsam is the balsam obtained from the bark of *Myroxylon balsamum* (L.) Harms var. *pereirae* (Royle) Harms tree and contain allergenic ingredients such as isoeugenol, eugenol and cinnamyl alcohol, but there are also other unknown chemicals in Peru Balsam that can cause contact allergy.[20] Fragrances are used as flavouring agents in food products and oral hygiene products such as toothpaste and mouthwash.[21] Flavourings are added to toothpaste as they make the toothpaste more pleasant to use and at the same time freshen the breath. Eugenol is also used in dentistry in the form of zinc oxide eugenol cement due to its anti-inflammatory and antibacterial properties and this has been shown to cause oral lichenoid reaction.[22]

Apart from containing fragrance allergens listed above, toothpaste can also contain carvone. Carvone is used as a flavoring agent in toothpaste and chewing gum and it is one of the main constituents of spearmint oil. Carvone gives out a mint flavor and hence is an ingredient of most toothpastes.[23] Carvone is available as an allergen in the dental screening series used at our centre. In our study, we only had one patient who was found to have positive patch test reaction to carvone. Interestingly, a study in Sweden has found that 57% of patients with carvone allergy had oral lichenoid reactions and this over-representation of oral lichenoid reactions is not connected with concomitant contact allergy to gold or mercury.[24] These findings were also found in few other similar studies.[25-27]

As fragrances and carvone present in toothpaste may be the causative allergens causing oral lichenoid reactions, patch testing to patient's own toothpaste should strongly be considered. However, there is currently no consensus on patch testing to toothpaste. Irritant reaction is deemed to be common when patch testing using undiluted toothpaste due to the presence of abrasives and detergents. Diluting the toothpaste on the other hand will reduce its irritant potential but may cause false negative reaction. As a starting point, a semi-open test or closed patch test with the undiluted toothpaste can be performed. If a positive patch test reaction to an undiluted toothpaste developed, it should be followed with retesting and/or testing a dilution series (e.g. undiluted, 40% pet or water and 20% pet or water) and/or control testing.[28]

All of our patients complained of pain or discomfort especially after eating spicy foods. Around 70% of them sought medical attention within 1 year of onset of symptoms. This suggests that oral lichen planus negatively impacts their quality of life, prompting them to seek treatment early. This is especially true in Malaysia whereby spicy foods, which form part of our normal diet, may exacerbate or perpetuate this condition. Therefore, it is imperative that the cause of oral lichenoid reactions is assessed carefully. In order to distinguish contact allergy from other causes of oral lichenoid reactions, we recommend that patch test is performed in all patients who presented with oral lichen planus.

As with other cases of contact allergy, avoidance of the causative allergen remains the pivotal part of management. Treatment of oral lichenoid reactions related to contact allergy to dental restoration materials includes removal, replacement or recovering of fillings in direct contact with the lesions. [29] Upon removal, improvement can be expected within 1 to 6 months.[30] The criteria for replacement of restorations vary considerably in different practices. In some studies, the replacement of restorations was undertaken only in cases of a positive patch test, while others replaced all restoration in contact with the lesion, irrespective of the patch test result.[30] Despite a negative patch test, improvement can still be observed after removal of the dental restoration materials in close proximity to the oral lichenoid lesions. This is because these lesions may be due to the irritant effect of the dental restoration materials

as well.[31] However, results from a positive patch test is still useful in providing guidance on the types of replacement restoration materials.

For contact allergy related to fragrances, patient should be advised to avoid foods and oral hygiene products that contains fragrances and flavourings. Although difficult to achieve, studies have shown that avoidance of fragrance allergens in these patients gave better control of their lesions than what they had achieved previously.[32] Due to the widespread presence of these allergens in our foods, complete avoidance may not be possible and occasional adjunctive therapy (such as topical steroids) may be required. Apart from cinnamon derivatives, the most common flavourings used in toothpaste are derivatives extracted from the main varieties of mint, such as spearmint, peppermint, menthol and carvone, as they produce sensation of freshness.[33] One study showed a dramatic improvement in a patient with oral lichen planus when spearmint oil was avoided.[34] Therefore, in patients with oral lichenoid reactions showing positive patch test reaction to fragrance, we may empirically recommend alternative-flavoured toothpaste that uses flavourings derived from fruit extracts instead such as orange, banana, strawberry and pineapple.[35]

There are several limitations to this study. This is a single centre study and our findings may not be representative of the Malaysian population as a whole. We did not follow up these patients after the patch test is completed. We are not aware of the progress of the patients after the patch test results were revealed and the measures taken for these patients. We did not perform delayed reading after 5 days and patients with late positive patch reactions might have been missed. We also did not repeat the patch test with 40% or 20% dilution in patients who had positive patch test reaction to undiluted toothpaste and this could pose a risk of a false positive patch test reaction. In the future, we will extend our readings to day 7 for patients tested with dental screening series and offer a repeat patch test with serial dilutions of toothpaste at 20% and 40% for patients who develop a positive patch test to their toothpaste. Future studies should also include follow-up these patients after completion of their patch tests, in order to evaluate whether avoidance of causative allergens has resulted in improvement of their symptoms.

Table 3. Oral lichen planus and oral lichenoid reactions: a review of the literature

Author	Study period	No of patients	Positive reaction	Top 3 allergens
Our study, Malaysia	**2015 - 2019**	**41**	**70.7%**	**Nickel sulfate, gold sodium thiosulphate, fragrance mix**
Torgerson et al[36] USA	2000 - 2004	59	55.9%	Potassium dicyanoaurate, fragrance mix, gold sodium thiosulphate
Khamaysi et al[37] Israel	2000 - 2004	17	35.3%	Gold sodium thiosulphate, nickel sulfate, mercury
Kim et al[38] South Korea	2004 - 2011	24	75.0%	Nickel sulfate, gold sodium thiosulphate, potassium dichromate
Lomaga et al[39], Canada	2006 - 2007	24	66.7%	Nickel sulfate, fragrance mix, cobalt chloride

Conclusion

Contact sensitizations were detected in about 70% of our patients with oral lichen planus and the most common sensitizing allergen was nickel sulfate. Current relevance was found mainly towards metals in dental restoration materials. Apart from metals, other source of exposure to contact allergens included fragrances as part of the ingredients in oral hygiene products. Patch test should be considered in all cases of oral lichen planus. Studies evaluating the trends of contact allergens in oral lichen planus would help in determining the appropriate dental restoration materials in our population.

Conflict of Interest Declaration

All authors have no financial/conflict of interest to disclosed.

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