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The Challenge of Accurate Diagnosis of Oral Lichenoid Lesions in Diabetic Patient: A Case Report

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Abstract

Background: Mercury in amalgam restoration is one of allergen-induced oral lichenoid lesions which resemble oral lichen planus clinically and histopathologically. Thus, an accurate clinical diagnosis is frequently challenging for clinicians, and it is further complicated because similar oral lesions in oral lichenoid lesions can occur as a manifestation of oral lichenoid drug reactions. This case report illustrates the difficulty of an accurate diagnosis of oral lichenoid lesions due to amalgam restorations in type II diabetes mellitus patient. **Case presentation:** A 59-year-old male patient presented with a 12-month history of oral ulceration and white striations on left lateral tongue, bilateral distribution of white non scrapable plaque-like lesion mixed together with erosion on buccal mucosa adjacent to amalgam restorations on 37 and 47. The patient's history for any associated skin lesions was negative. The patient had type II diabetes mellitus with inconsistent intake of oral hypoglycemic drugs, and atopy history of house dust mite and shrimp. We initially diagnosed the case as oral lichen planus. Systemic and topical corticosteroids were instituted, but after a month follow-up, all lesions still showed slight improvement. The final diagnosis of oral lichenoid lesions due to amalgam restorations was made following a positive patch test for amalgam. All lesions were gradually resolved in 3-month follow-up after the causative teeth being extracted. **Conclusions:** Patch test is useful to differentiate between oral lichenoid lesions and oral lichen planus. The treatment of oral lichenoid lesions due to amalgam restorations is simply removal or replacing the offending materials.

Key words: Oral lichenoid lesions, patch test, amalgam restoration

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Tantangan Keakuratan Diagnosis Lesi Likenoid Oral pada Pasien Diabetes: Laporan Kasus

Abstrak

Latar belakang: Merkuri dalam restorasi amalgam merupakan alergen pemicu lesi likenoid oral yang secara klinis dan histopatologis serupa dengan liken planus oral. Oleh karena itu, diagnosis akurat merupakan tantangan bagi klinisi dan penegakkan diagnosis klinis menjadi sulit karena terdapat lesi likenoid oral lain yang mempunyai kemiripan klinis yaitu reaksi likenoid oral akibat obat. Laporan kasus ini mengilustrasikan kesulitan menegakkan diagnosis akurat lesi likenoid oral akibat restorasi amalgam pada pasien diabetes mellitus tipe II. **Laporan Kasus:** Seorang laki-laki 59 tahun dengan riwayat 12 bulan menderita ulserasi oral dan lesi putih *striae* pada lidah lateral kiri, lesi putih seperti plak yang tidak dapat dikerok dan erosi pada mukosa bukal bilateral yang berdekatan dengan restorasi amalgam 37 dan 47. Tidak terdapat riwayat lesi pada kulit. Pasien mempunyai riwayat diabetes melitus tipe II dengan pengkonsumsian obat hipoglikemik oral yang tidak teratur serta riwayat alergi debu dan udang. Pada awalnya kami mendiagnosis kasus ini sebagai liken planus oral. Diberikan terapi kortikosteroid sistemik dan topikal, tetapi setelah 1 bulan perawatan tidak terdapat penyembuhan yang siginifikan. Diagnosis akhir lesi likenoid oral akibat alergi amalgam ditegakkan setelah uji tempel amalgam menunjukkan hasil positif. Seluruh lesi intraoral perlahan mengalami penyembuhan selama 3 bulan setelah gigi 37 dan 47 dengan restorasi amalgam sebagai penyebab alergi diekstraksi. **Kesimpulan:** Uji tempel berguna dalam membedakan lesi likenoid oral dengan liken planus oral. Penatalaksanaan lesi likenoid oral akibat alergi restorasi amalgam dilakukan dengan menghilangkan atau mengganti bahan restorasi tersebut.

Kata kunci: Lesi likenoid oral, uji tempel, restorasi amalgam

Introduction

Oral mucosa is often subjected to a wide spectrum of antigenic agents, including foodstuffs, cosmetics, drugs, microorganisms, immune-mediated disorders, and dental materials. Mercury in dental amalgam restoration represent causes of metal-induced oral contact allergy (OCA) via delayed type IV hypersensitivity reaction which may clinically manifest as lichenoid changes or reaction.[1-4] The term "lichenoid" refers to papular lesions of which lichen planus is a prototype. The term "lichen planus" was derived from Greek word "leichen" meaning tree moss and the latin word "planus" meaning flat.[5]

The concept of Lichenoid Tissue Reaction/Interface Dermatitis (LTR/IFD) was introduced in dermatology to define a

number of diverse inflammatory skin diseases linked together by the presence of common histopathological features. Similarly to the skin, the oral mucosa is affected by a variety of oral LTR/IFD, including Oral lichen planus (OLP) and Oral lichenoid lesions (OLL).[5] OLL can be considered as a separate disease or as a variant of OLP or OLP like lesions which is an exacerbation of already existing OLP.[5]

Typically, the clinical appearance and histopathological features in both conditions can be similar and or overlapping. The clinical diagnosis is further complicated because similar oral lesions in OLL can occur as a manifestation in immunocompromised patients, for example, Graft-versus-host Disease (GVHD), Systemic lupus erythematous (SLE) or as a result of oral lichenoid drug reactions (OLDR) and oral lichenoid contact lesions (OLCL) triggered by local hypersensitivity reaction to mostly dental materials.[5,6] The clinicians encounter with accurate diagnosis in differentiating between OLP and OLL which remains inconclusive till today. There is no universal diagnostic on these two clinical categories which share similarity or commonly overlapping in clinical and histopathological features. There are neither clear nor distinct clinical or histopathological features available in order to distinguish between clinical entities in OLL which make accurate diagnosis is frequently challenging.[2,4-6] This case report illustrates the difficulty of accurate diagnosis between OLCL due to mercury in amalgam restorations and OLP in type II diabetes mellitus (T2DM) patient.

Case Presentation

Patient history

A 59-year-old male was referred to the outpatient clinic of Oral Medicine department of dr Hasan Sadikin hospital by his general dentist. The patient complained of soreness and burning sensation on his left lateral tongue and both buccal mucosa which were worsened by consuming spicy foods and acidic drinks. He first noticed symptoms 1 year before being referred to us which became progressively worsened with time, especially on the ulceration of his left lateral tongue. A month before being referred, he was given various treatments, including grinding the rough edges of lingual cusp of 47, mouthwash, and triamcinolone acetonide 0,1% in orabase by two dentists and an internist, respectively. The tongue symptoms were showing slight improvement but still not healed with time.

The medical history showed that the patient has been diagnosed with T2DM since 6 years ago. Although the internist had prescribed him oral hypoglicemic drugs (glibenclamide and metformin) and also statin/HMG CoA reductase inhibitor (simvastatin), but he did not consume it consistently. His history for any associated skin lesions was negative. The 8 parameters hematological laboratory investigation revealed good results. He also had an atopy history of house dust mite and shrimp. His dental history showed that 4 years before he had received amalgam restorations on 37 and 47 which had already been worn out

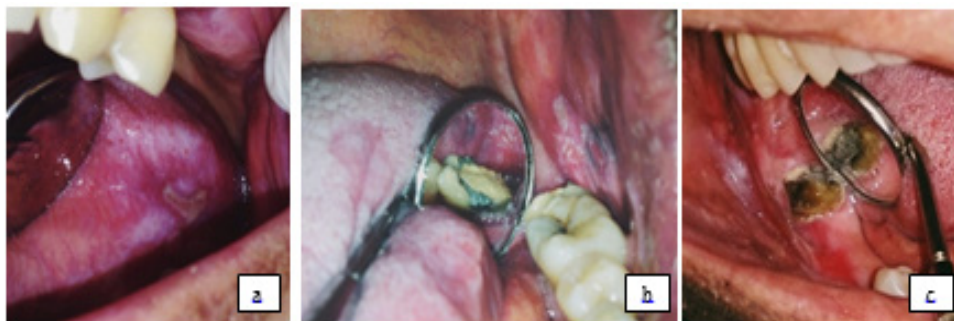

Fig. 1.(a-c) Clinical manifestations of OLCL due to mercury in amalgam restorations on 37 and 47.

and proximity close contact to both buccal mucosal surfaces, left lateral tongue, and alveolar ridge of 45-46.

Clinical assessment

Intraoral examination revealed ulceration surrounded by white reticular lesion affecting the left lateral tongue (Figures 1a); white non scrapable plaque-like lesion mixed together with erosion and also multiple and diffuse oral black-brownish pigmentation affecting left buccal mucosa adjacent to 35-37 (Figures 1b); diffuse erythematous lesion affecting buccal edge of alveolar ridge of 45-46 and white non scrapable plaque-like lesion mixed together with erosion on right buccal mucosa (Figures 1c).

Diagnosis

Based on anamnesis and clinical examination, we initially did not suspect it as OLCL, rather diagnosed the case as OLP. Systemic and topical corticosteroids were instituted, but after a month follow-up all intraoral lesions still showed slight improvement. Thus, we consulted the patient to dermatology department for a patch test against mercury in amalgam restorations which showed positive result (+1; non-vesicular; weak reaction) (fig. 2b). The final diagnosis of OLCL due to mercury in amalgam restoration on 37 and 47 was made.

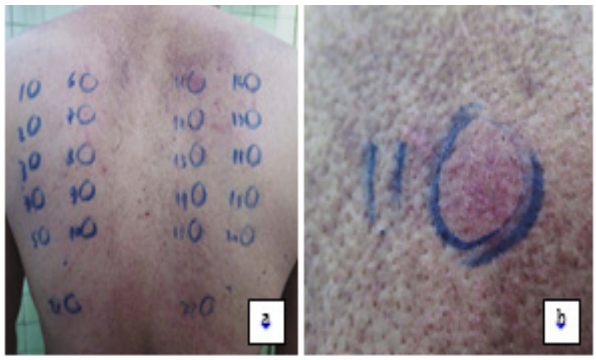

Fig.2.(a) Patch test (b) Postive patch test for contact allergy to mercury in amalgam restorations

Management, follow-up and outcomes

We treated the patient from initial treatment until the third visit by following management: a. Topical corticosteroids (Mouthwash compounding of dexamethasone injection 5 mg/ml in 500 ml aqudest three times daily for seven days); b. Vitamin B_{12} 50mcg three times daily and folic acid/vitamin B_9 1mg once daily. Both of them were taken before meal for seven days; c. We instructed him not to consume acidic drinks, spicy and rough texture foods, besides tongue scraping as oral hygiene instruction.

At the fourth visit or 1-month follow-up, all the intraoral lesions showed slight response or improvement, so we advised him to do the patch test after and change the medication into prednisone 5mg tablet 30 mg/day tapered off by 5mg/week in 2 months. We still gave the patient with vitamin B_{12} 50mcg three times daily and folic acid/ vitamin B_9 1mg once daily. Both of them were taken before meal for seven days. The patch test showed positive result. The causative teeth of 37 and 47 were being extracted, and the lesions were gradually resolved after 3-month follow-up. {Fig.3.(a-c)}

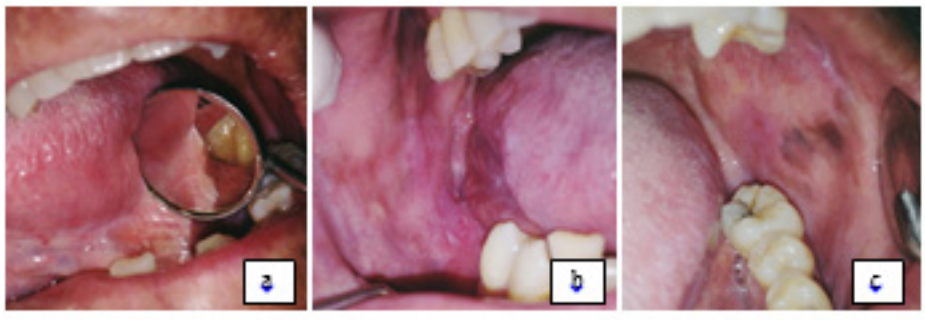

Fig.3.(a-c) 3-months follow-up: Resolve of all lesions after removal of amalgam restorations.

Discussion

The clinical manifestations of oral allergy or hypersensitivity are vary in response to diverse antigens. The oral allergy syndrome (OAS) represents food-pollen allergic reaction and OCA represents others oral mucosal immune-mediated diseases in response to antigens, such as drugs, cosmetics, and dental materials with various clinical morphologies, including stomatitis (recurrent aphthous stomatitis, stomatitis venenata, medicamentous allergic stomatitis) , cheilitis (cheilitis venenata), plasma cell gingivitis, perioral dermatitis, orofacial granulomatosis (OFG), angioedema, erythema multiforme (EM), fixed drug reaction/eruption, burning mouth syndrome, and lichenoid reactions.[1-4]

Terminology

OLP is a chronic inflammatory, predominantly T-cell mediated autoimmune oral mucosal disease affecting stratified squamous epithelia with unclear antigen and multifactorial pathogenesis. OLP typically presented in several clinical morphologies which may appear alone or in combination: white striations/reticular (Wickham's striae: erythematous-violaceous, polygonal, shiny, non-confluent, symmetrical papules on the surface which are whitish streaks), white papular, white plaque-like, erosive/ erythematous/atrophic, ulcerative, bullous.[5-7] There have been many different terminologies to describe lichenoid reaction in oral mucosa, include oral lichenoid lesion, oral lichenoid reaction, contact allergy, contact lesion, oral lichenoid contact lesion, oral lichenoid contact reaction, drug-induced oral lichenoid reaction/ oral lichenoid drug reaction, oral lichenoid disease, oral lichenoid tissue reaction, lichenoid contact stomatitis, lichenoid mucositis, chronic mucositis with lichenoid features, and LP like lesions which are used interchangeably and confusing.[4-11] Some authors do not differentiate between OLP and OLL, but others believe that the two conditions are distinct.[2] In this case report, we agree with the later opinion and will use the term OLL to describe oral lesions, which are clinically and histopathologically similar or overlap to OLP but with identifiable etiology, antigen or allergen, and when its identified etiology eliminated often causes a regression of the lesions. (Table 1)

Etiology

The etiology of OLL, including OCA to dental materials or OLCL, adverse event of systemic drugs or OLDR, or as manifestation of SLE,GVHD.[2] OLCL is a term used to describe oral lesions, which may resemble OLP both clinically and histoptahologically, caused by contact allergy with dental materials, mainly amalgam restoration.[5] Amalgam restoration is an alloy composed of a mixture of approximately equal parts of 50% liquid mercury, and a powder consisting of Ag/silver (67-74%), Sn/tin (16-28%), Cu/ copper (6%), Zn/zinc (1%). All the metals in the amalgam alloy are potentially toxic.[13-15] In almost all cases, mercury in amalgam restoration is one of metal allergen-induced OLCL due to direct contact with the oral mucosa of sensitized patients.[2,7,9,10]

There are many factors play a role in each person's unique response to mercury, including genetic, gender, the number of amalgam restorations, dental plaque, selenium levels, exposure to lead, consumption of milk or alcohol, and other circumstances.[14] Although the association between atopy and contact allergy remains a point of contention,[16] patients with atopic dermatitis (AD) are significantly more likely to have at least 1 positive patch test reaction and to develop contact allergy to metal allergens,[17] as in our patient who had atopy history and positive prick test to house dust mite and shrimp while also having positive patch test to amalgam restorations.

The medical history also showed that the patient had type II diabetes mellitus with inconsistent intake of oral hypoglycemic drugs (glibenclamide and metformin) and statin/HMG CoA reductase inhibitor (simvastatin). Insulin resistance, decrease insulin secretion, and increased hepatic glucose output are the hallmarks of T2DM. Oral hypoglicemic drugs, for instance,

Table 1. Oral Lichenoid Tissue Reactions[1-12]

Disease	OLP	OLL		
Features/Parameters		OLCL	OLDR	GVHD
Etiology/antigen	Idiopathic	Dental materials (Most common: amalgam, nickel, gold)	Drugs (Most common: NSAID, antihypertensives, oral hypoglicemics)	Marrow graft
Clinical assessments:	Clearly differentiated by etiological factors		Clearly differentiated by medical history	
Morphology	Six clinical morphology, manifest alone or in combination: reticular/ wickham's striae, white papular, white plaque-like, erosive/erythematous/atrophic, ulcerative, bullous		Mostly similar if not identical to OLP	
Pattern	Usually bilateral & symmetrical	Either unilateral or bilateral. Topographic relationship with amalgam restoration	Tend to be unilateral Temporal relationship with (new) drug intake, may occur at any time	Previous transplantation history, frequently chronic GVHD
Predilection and onset (age,sex,anatomical sites)	More (twice as) commonly in female with onset 30-60 y.o. Frequently buccal mucosa along the occlusal line, tongue, gingiva (desquamative gingivitis)	3x times higher in female, highest range in 50 y.o. Frequently buccal mucosa, lateral edge of tongue Contact duration is an important factor	15-83 y.o., more common in > 30 y.o. Frequently buccal mucosa, tongue, palate, lips Onset after 1 year drug intake, although there may be a lag phase between intake and onset	
Other symptoms		Pain, metallic taste, xerostomia	Pain	
Histopathology	Hyperkeratosis Vacuolar degeneration of basal keratinocytes Band-like infiltration of lymphocytes at membrane basal zone Focal or widespread destruction of membrane basal zone by inflammatory infiltrate Absence of dysplasia	Same with OLP but sometimes mixed inflammatory infiltrate with plasma cells and neutrophils	Same with OLP but sometimes mixed inflammatory infiltrate with plasma cells and neutrophils Sometime more diffuse and extends deeper into lamina propria	Similar if not identical to OLP Sometimes more sparse lymphocytic infiltration
DIF	Commonly negative shaggy fibrinogen deposition at membrane basal zone Civatte bodies		Mostly similar if not identical to OLP	
IIF	Usually negative	Usually negative	Sometimes BCC antibody	n/a
Other	Insufficient evidence to support routine removal of all amalgam restorations. Some patients may be benefit with amalgam removal procedures.	Patch testing is good diagnostic value in replacing restorative dental materials Lymphocyte Transformation test not usually helpful	Resolution of lesions with suspected drug discontinuation, and determine if reaction recurs after retake the same suspected drug (Impractical method because reaction may take months to resolve and potentially dangerous to patients)	n/a
Comorbidity	HCV Oral potentially malignant disorder Sometimes with extraoral or other mucocutaneous lesions	Unclear malignant potential Unlikely to cause extraoral lesions	Unclear malignant potential Sometimes causes extraoral lesions	Potentially malignant jogren's like sialdenitis Lung, GIT, skin, genitals involvement
Management	No strong evidence suggesting superiority of any specific intervention in reducing pain and clinical signs of OLP. Pharmacological: topical corticosteroids and calcineurin inhibitors	Identify the offending agent/antigen; Manage the palliative symptoms; Removal/replacement of the offending agent/ antigen	No adequate evidence which treatments are most effective: Cessation of drug and substitution with an alternate drug Topical and/or systemic corticosteroid Lesions typically may resolve within week to months or delayed responses following drug cessation	Topical corticosteroids

sulphonylureas (glibenclamide), biguanides (metformin) target one or more of these defects,[18] but may cause an adverse drug events in oral mucosa called OLDR.[8,10,11]

Immunopathogenesis

There are 3 distinct reactions of oral mucosa to mercury in amalgam restorations in susceptible patients: toxic reactions, acute or generalized hypersensitivity, and delayed type IV hypersensitivity.[2,11] (Table 2) OLL may represent the oral mucosal manifestation of a chronic irritation lead to local inflammation induced by primary contact with chemicals or allergens in some patients or be the hypersensitivity reaction mediated by lymphocytes in others.[2,11]

OLCL due to mercury in amalgam restoration represent OCA.[19] Contact allergy is the consequence of an immune reaction mediated by T cells against low molecular weight chemicals known as haptens. Haptens are incomplete antigen or small reactive molecules with molecular weight below 500 Da, which are not immunogenic by themselves, but when bind to peptides and proteins thus becoming recognized by the immune system. Contact allergy occurs into two phases: induction, also called afferent, and elicitation or efferent. The afferent phase involves all of the steps, from the initial contact with the hapten as allergen to the development of sensitization in oral mucosa. The efferent phase begins after reexposure with the same hapten in a previously sensitized individual and results in contact allergy.[20]

In order for a OCA reaction to be established, mercury salts or $HgCl_{2,}$ which act as haptens in this afferent phase will penetrate the epithelial lining and bind with host keratinocyte surface proteins. Macrophages as the antigen presenting cell will recognize this mercury salts then induced activation of oral keratinocytes resulted in the expression of ICAM-1, increased binding of T cells and release of TNF-α and IL-8. In susceptible patients, the efferent phase resulted in a cell mediated response directed at basal epithelial keratinocytes through accumulation of T cells in the lamina propria and epithelium, resulting a delayed type IV hypersensitivity. [2,5,19-21] The mercury salts, which accumulate in healthy and damaged oral mucosa initiate or promote the development of lesions in OLCL that clinically manifest as reticular white patches, papules, plaques, erosions, or ulceration, similar to that found in OLP-hence the terminology lichenoid.[2]

Clinical Manifestations

The clinical presentations of OLL can be vary based on nature of reaction which can be either acute or chronic, on type of allergen, sites of presentation, and duration of contact. The clinical presentation of lesions in OLL resemble those of OLP, which can be reticular white patches, papules, or plaques with or without erosions or ulcerated areas.[2,9,19] In general, the clinical appearance of OLCL is difficult to be distinguished from chronic trauma. Erythema, edema, desquamation, and ulceration are the hallmarks of OLCL.[18] Those clinical findings in line with our patient which shares common features, including ulceration surrounded by white reticular lesion, white non scrapable plaque-like lesion mixed together with erosion, and also diffuse erythematous lesion.

The symptoms of OLL that can be observed, including metallic taste, xerostomia, burning sensation, or pain, which is the most prevalent symptom and is generally related to atrophic or erosive forms,[9] especially when taking hot or spicy food.[2,3] Those symptoms found in parallel with our patient, including soreness and burning sensation which were being worsened by consuming spicy foods and acidic drinks.

The contact duration between oral mucosa and amalgam restoration is an important factor for the development of OLCL.[9,19] Prolonged intimate contact of oral mucosa with amalgam restorations over a long period, often many years, appears to be necessary,[2,10] and in our patient, the contact duration had already been 4 years and he first noticed symptoms 1 year before being referred to us. The buccal mucosa and

Table 2. Characteristics of Oral Mucosa Reactions Associated with Amalgam Restorations[2,11,15,22]

Features	Toxic Reaction	Acute Hypersensitivity Reaction	Delayed Hypersensitivity Reaction (OLCL)
Onset	1-3 days	Appear within hours	Gradual – may be several years
Location	Localized area of oral mucosa in direct contact with amalgam restoration	Ipsilateral side of the body as the dental intervention: skin of face, neck and limbs, usually on flexural aspect. Rarely affected oral mucosa	Buccal or lingual mucosa in direct contact with amalgam restoration
Mechanism	Nonspecific (non lymphocyte-mediated) chronic irritant reaction à invasion of inflammatory cells à tissue dammage	Type I hypersensitivity	Delayed type IV hypersensitivity
Clinical Appearance	Resemble OLL	Extraoral: erythematous,pruritic,urticarial skin rash. Rarely, facial oedema or difficulty breathing Intraoral: erythematous,vesicubullous,erosion	Resemble OLP but usually unilateral and asymmetrical
Duration	Three phases: initial (flulike symptoms) – intermediate (severe pulmonary toxicity) – final (gingivostomatitis, tremor,erethism)	Self-limiting/resolves spontaneously within a few days	Prolonged – lasts as long as the oral mucosa remains in contact with the restoration
Patch Test Response to Amalgam	Negative	Positive within 24 hours and often within 2-4 hours. Reaction may spread to surrounding tissues or become generalized	Usually positive by 48 and 72-96 hours
Response to Amalgam Removal	A complete resolution or regression	May provoke a reaction. Should be performed with rubber dam and high volume suction to reduce exposure to released mercury	Resolutions within several days to 5 weeks or longer

lateral tongue are most commonly affected areas in OLCL,[7,9,19] while palate, lip and labial involvement is seen in OLDR.[7,23] Those predilection sites in OLCL are similar with affecting our patient, including left lateral tongue, both buccal mucosa, and buccal edge of alveolar ridge without other oral mucosal involvement.

There are two clinical features that can be used as a guide to distinguish between OLP and OLL: lesions in OLP usually bilateral and symmetrical distribution, while lesions in OLL usually unilateral and asymmetrical distribution. The second clue is a close topographical relationship between amalgam restorations and the lesions. However, it still can be difficult for the clinician to make a clear distinction, if amalgam restorations are widespread in the mouth or located on both sides of the mouth.[2,23] Those difficulties are what we encountered in our patient which had lesions on both bucal mucosa and amalgam restoration on both sides of the mouth (37 and 47 teeth). That is why we initially didn't suspect it as OLCL but rather as OLP.

Diagnosis

Diagnosis of OLCL is facilitated by detailed history, clinical, and histopathological findings.[2,7] Signs and symptoms of OLCL may mimic other common oral disorders, making diagnosis difficult. Patients frequently seek multiple consultations and do not receive the correct diagnosis or effective management,[19] which exactly the same thing happened to our patient who has already seeing 3 healthcare providers before being treated by our department.

Although amalgam restorations and oral hypoglicemic drugs as identifiable etiology and patient's history may help to distinguish between OLP and OLL,[2,24] but making the accurate diagnosis is still challenging because there are neither clear

nor distinct clinical or histopathological features available in order to distinguish between OLDR and OLCL[2,4-6,24] in our patient. We did not perform histopathological examination because there are no signs and symptoms of malignancy in our patient. The histopathological examination is not always necessary,[9,24] except when the lesions exhibit atypical clinical features and to exclude malignancy.[7,9]

OLL often resolves when the offending agent is eliminated.[10] Adverse drug events may occur at any time, even years after intake of the drug. Clinically, to consider the drug history of at least one year previous to the first onset of lesions for suspecting OLDR,[8] and our patient had already intake oral hypoglycemic drugs for 6 years. The most reliable way to diagnose OLDR is to note the resolution of reaction after the suspected drug is withdrawn, and to determine whether the reaction recurs when the patient is rechallenged with the same suspected drug. This is both impractical since such reaction may take months to resolve and cessation of drugs potentially danger to the patient.[8]

To clarify whether lichenoid reaction in our patient indicate OLCL due to mercury allergic in amalgam restorations, we consulted the patient to dermatology department to perform the patch test. The patch test is the gold standard to diagnose contact allergy due to delayed type IV hypersensitivity. Mercury in amalgam restorations is one of the substance that potentially should be considered for diagnostic patch testing.[25] Systematic review and meta-analysis by Ataei et al (2015) showed that patch test has good diagnostic value in replacing dental materials in patients with OLCL.[26] The combination of a positive patch test and a strong clinical association between lesions and restorations was an excellent predictor of lesion recovery after amalgam replacement, and was a better predictor than either the patch test or clinical association alone.[7,9]

The evaluation of patch test based on clinical morphology and grading scale that usually read and interpret twice, at 48 hours and 72-96 hours, or rarely sometimes at 10-14 days as late readings.[1-3,9,24] One of the scoring systems by The International Contact Dermatitis Research Group is widely used:[24] a. (-) Negative reaction; b. (?+) Doubtful reaction with faint erythema only; c. (1+) Weak positive reaction with nonvesicular erythema, infiltration, possibly papules; d. (2+) Strong positive reaction with vesicular erythema, infiltration, and papules; e. (3+) Extreme positive reaction with intense erythema and infiltration, coalescing vesicles, bullous reaction; f. (IR) Irritant reaction; g. (NT) Not tested

The patch test result of our patient showed (1+) weak positive reaction with nonvesicular erythema which read at 48 hours and 72 hours. Many variables contribute to the strength of patch test reaction, including the concentration and potency of allergen, the degree of subject sensitization, the length of application time, and the timing of readings.[24] It is important to note that the patient should not be taking anti-allergic drugs during examination.[1]

Management

The management of OLL first requires identification of the etiological or trigerring factors and then eliminate it. Therapeutic objectives depend on the location and severity of lesions, also comfort of patient.[1,7,19] Clinical evalution of the extent and severity of OLL can be graded as:[27] a. Healed (No lesions remaining); b. Marked improvement (>80% improvement); c. Improved (50% improvement); d. No improvement or worsening of the symptoms (Increasing OLL) A conservative treatment approach of OLCL that may be valuable to avoid unnecessary replacement of dental restorations and increase lesions regression after replacement include improve oral hygiene, remove sharp edges, and rough surfaces, try to reduce mechanical wear of oral tissue that might affect the lesions.[2] As we observed in our patient, before being referred to us, his dentist had already been grinding the rough edges of 47 lingual cusp, but the tongue ulceration were still not healed with time. If the causative agent cannot be discontinued

or if residual lesions persist after elimination, topical or systemic corticosteroids often can be conducted.[1,7,19] At the fourth visit or 1-month follow-up, there is still slight improvement (<50% improvement) by topical corticosteroids and oral hygiene instruction. Thus, we changed the medication into systemic corticosteroids and suspected amalgam restorations and oral hypoglicemic drugs as etiological factors. After the patch test showed positive result, we advised the patient to extract the causative teeth.

Amalgam replacement is not beneficial in treatment of idiopathic OLP. There is insufficient evidence to support routine removal of all amalgam restorations in patients with OLP or OLL. It is not necessary to replace amalgam restorations that are not in direct contact with mucosal surfaces. The potential benefits and risks of amalgam removal should always be discussed with patients. However, it cannot be excluded that a very small percentage of highly selected patients may benefit in part or in full from amalgam removal.[28] Amalgam removal had strongest effect on tongue lesions.[2] OLCL may improve or resolve as early as 2-3 days after amalgam removal but this could take up to 5 weeks or longer (3-15 months).[2,11] Similarly, all intraoral lesions in our patient were gradually resolved after 3-month follow-up after the causative teeth of 37 and 47 were being extracted.

The 8 parameters hematological laboratory investigation (Hb, ht, leukocyte, erythrocyte, thrombocyte, MCV, MCH, MCHC) in our patient revealed good results. We did not find any clinical manifestation related to vitamin B_{12} and folic acid deficiency such as anaemia, so we did not screen the patient for serum vitamin B_{12} and folic acid level. In spite of that, a systematic review and meta-analysis by Chapman et al. (2016) stated that there is association between metformin usage up to 4 months and lower levels of vitamin B_{12} by 57 pmol/L, which leads to frank deficiency or borderline status in some patients with DM.[29] There are no evidence-based guidelines to address how often patients with DM should be supplemented with vitamin B_{12}. The optimal supplementation dose of vitamin B_{12} is also unknown for patients being prescribed metformin.[30]

A systematic review by Gonzalez-Serrano et al. (2016) concluded that there was a higher prevalence of oral mucosal disorders found in patients with DM, but there was still no conclusive result or they did not specify if oral hypoglicemic drugs may influence the occurrence of oral lesions in OLP and or OLDR.[31] Some clinical research, although still showed conflicting result, stated that there might be significant association between vitamin B_{12} and folic acid deficiency with OLP and or OLDR.[32-34] In this case report, the reason we gave oral supplementation of vitamin B_{12} and folic acid from initial treatment until 3-month-follow-up in our patient who had already intake oral hypoglycemic drugs for 6 years was supplementation of hematinics may be beneficial for the specific group of OLP patients.[32]

Conclusion

The accurate diagnosis of OLL case is challenging, either by clinicians or pathologists. Patch test is useful to differentiate between OLP and OLL. The treatment of OLCL due to amalgam restorations is simply removal or replacing the offending materials.

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