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Original Article

# Oral lichenoid contact lesions related to dental metal allergy may resolve after allergen removal



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## KEYWORDS

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Skin patch test

**Abstract** *Background/ purpose:* Distinguishing oral lichenoid contact lesions (OLCLs) from oral lichen planus (OLP) is challenging. This study aimed to identify clinicopathological findings to distinguish OLCLs from OLP, and to evaluate the effectiveness of removing metal allergens in the treatment of OLCLs.

*Materials and methods:* This study retrospectively evaluated 30 patients diagnosed with OLCLs, and 30 age- and sex-matched OLP patients. We also evaluated the effectiveness of removing dental metal containing positive metal allergen, confirmed by skin patch test and metal component analysis in patients with OLCLs.

*Results:* Palladium and gold were the most common patch test-positive metals observed in the oral cavity of patients with OLCLs. The patients with OLCLs were more likely to present with white type lesions in the buccal mucosa and gingiva than were the patients with OLP ( $p = 0.030, 0.009$ , respectively). Overall, 50.0% of patients with OLCLs failed to meet the histopathological diagnostic criteria of OLP. Twenty-three of 24 (95.8%) patients with OLCLs showed a complete or partial improvement after the removal of dental metal.

*Conclusion:* The present findings suggest the importance of a skin patch test and metal component analysis to confirm suspected OLCLs related to dental metal allergy, as these lesions may improve with the removal of the allergy-inducing metal.

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## Introduction

Oral lichenoid contact lesions (OLCLs) were classified as a sub-category of oral lichenoid lesions (OLLs) at the 2006 World Workshop of Oral Medicine IV.<sup>1</sup> OLCLs may be caused by contact hypersensitivity related to dental materials.<sup>1</sup> Allergic contact stomatitis (ACS) is an immunoinflammatory disorder caused by an antigen specific T-cell-mediated delayed hypersensitivity immune response to allergens that are in direct contact with the oral mucosa.<sup>2</sup> Dental amalgam has been reported to cause ACS-related OLCLs.<sup>3,4</sup> The clinical presentation of OLCLs is usually unilateral and asymmetrical, in contrast to that of Oral lichen planus (OLP), as these lesions tend to have a clear anatomical relationship to the site of metallic restoration and/or prosthesis.<sup>5</sup> Histopathologically, distinguishing between OLCLs and OLP remains challenging, as there are no validated histopathological diagnostic criteria. However, the following features may help to distinguish OLCLs from OLP: absence of basal cell liquefaction, presence of an inflammatory infiltrate located deep to superficial infiltrate in some or all areas (as opposed to a band-like distribution), a focal perivascular infiltrate, high plasma cell count, and neutrophil infiltration into the connective tissue.<sup>3,6</sup>

Skin patch testing may help identify patients with suspected hypersensitivity reactions to dental metal<sup>7,8</sup> and is recommended for diagnosis. Given a positive skin patch test, dental metal should be removed, provided it contains elements associated with the observed ACS.<sup>7</sup> However, there are cases where it has not been confirmed whether the patch test positive metal is actually contained in the dental metal, or the dental metal removed does not contain the positive metal. This study aimed to identify the clinical and pathological features of OLCLs associated with ACS to metal allergens present in the dental metal, and to compare these features with those of OLPs. The secondary aim of this study was to evaluate the effectiveness of replacing the allergy-inducing metal with an alternative material in the treatment of OLCLs.

## Materials and methods

### Ethical approval and informed consents

All procedures performed in studies were in accordance with the ethical standards of the ethics committee board of the faculty of dentistry of Tokyo Medical and Dental University (D2015-575) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, the need for formal consent was waived by the ethics committee board.

### Patients

This comparative study retrospectively evaluated 30 patients (two men and 28 women, age range: 34–80 years, median: 60.5 years), diagnosed with OLCLs related to dental metal allergy at our Department between 2001 and

2017. They were referred for a skin patch test, because the lesions were anatomically related to metallic restorations and prostheses or were resistant to topical steroid treatment for OLP. Furthermore, OLCLs related to dental metal allergy were diagnosed, based on fluorescence X-ray analyzer findings that confirmed the presence of metal allergen in the oral cavity.

Thirty age- (within 5 years) and sex-matched patients diagnosed with OLP at our department between 2001 and 2017 were randomly selected as a comparison group. These patients had negative skin patch test findings to any metal reagents. The patients' medical history, clinical type and distribution of lesions, and histopathological findings were compared between the groups.

### Diagnostic criteria for oral lichen planus

The diagnosis of OLP was based on the American Academy of Oral and Maxillofacial Pathology proposed criteria (Table 1).<sup>9</sup>

### Skin patch tests

The skin patch test was performed at the dermatology or dental allergy outpatient clinic of our hospital, based on the International Contact Dermatitis Research Group criteria. The metal reagents, including 1% palladium (Pd) chloride, 0.5% potassium dichromate (Cr), 5% nickel (Ni) sulfate, 2% cobalt (Co) chloride, 1% stannic (Sn) chloride, 0.2% tetrachloroauric acid (Au), 0.5% chloroplatinic (Pt)

**Table 1** The American Academy of Oral and Maxillofacial Pathology proposed diagnostic criteria for OLP<sup>9</sup>.

#### Clinical criteria

Multifocal symmetric distribution

White and red lesions exhibiting one or more of the following forms:

- Reticular/papular
- Atrophic (erythematous)
- Erosive (ulcerative)
- Plaque
- Bullous

Lesions are not localized exclusively to the sites of smokeless tobacco

Lesions are not localized exclusively adjacent to and in contact with dental restorations

Lesion onset does not correlate with the start of a medication

Lesion onset does not correlate with the use of cinnamon-containing products

#### Histopathologic criteria

Band-like or patchy, predominately lymphocytic infiltrate in the lamina propria confined to the epithelium-lamina propria interface

Basal cell liquefactive (hydropic) degeneration

Absence of epithelial dysplasia

Absence of verrucous epithelial architectural change.

Lymphocytic exocytosis

OLP: Oral lichen planus.

acid, 2% ferric (Fe) chloride, 1% indium (In) trichloride, 1% iridium (Ir) tetrachloride, 2% silver (Ag) bromide, 2% zinc (Zn) chloride, 2% manganese (Mn) chloride, and 2% aluminum chloride were supplied by Torii Pharmaceutical Co., Ltd. Tokyo, Japan. The other metal reagents, including 2% copper (Cu) sulfate, 2% Ni sulfate, 0.2% mercuric (Hg) chloride, 1% molybdenum (Mo) chloride, 30% titanium (Ti) oxide, 0.1 and 0.05% Ti chloride, 0.5% niobium (Nb) chloride, 0.2 and 0.1% rhodium (Rh) chloride, 0.5 and 0.1% vanadium (V) chloride were prepared at our pharmaceutical department.

The metal allergens were applied to a patch tester (Torii Pharmaceutical Co., Ltd), placed on the back of each patient, and removed after 48 h. Assessment was performed on day 2, 3, and 7. "Positive" results were graded as a positive reaction (palpable erythema), strong positive reaction (palpable erythema, vesicular), and an extreme positive reaction (bullous) on day 7. No response, false-positive reactions, and irritant reactions were considered "negative" results.

### Metal component analysis and replacement of restorations

The composition of each metallic restoration and prosthesis in the oral cavity of the patients was examined, using X-ray fluorescence spectroscope: EDX-7000 (Shimadzu Corporation, Kyoto, Japan) at our dental allergy outpatient clinic.

OLCLs were mostly treated with topical steroids, including 0.1% triamcinolone acetonide, to control inflammation and reduce painful symptoms prior to metal replacement. After metal component analysis, replacement of metallic restoration and prosthesis containing positive metal allergen was suggested to patients with OLCLs. Replacement was performed by the patient's regular dental practitioner. Non-metallic dental materials such as composite resins and ceramics were selected as post-removal replacements. During the follow-up, clinical changes in the appearance of OLCLs were evaluated and categorized as "complete healing", "partial improvement", and "no improvement".

### Statistical analysis

The chi-square and Fisher exact tests were used to compare the patients' characteristics, clinical type and distribution of lesions, and histopathological finding between the groups. P-values of <0.05 were considered indicative of a statistically significant finding.

## Results

### Patients

Although 21 (70%) patients with OLCLs and 20 (66.7%) patients with OLP had one or more comorbidities ( $p = 0.781$ ), there was no significant difference in clinical characteristics between the groups (Table 2). A history of allergy to medication, food, pollen, or latex was recorded in eight

**Table 2** Medical history of patients with OLCLs and OLP.

Medical history	OLCLs (n = 30) (%)	OLP (n = 30) (%)	p values
One or more diseases	21 (70.0)	20 (66.7)	0.781
Hypertension	5 (16.7)	9 (30.0)	0.222
Diabetes mellitus	4 (13.3)	2 (6.7)	0.335 <sup>a</sup>
Cardiovascular diseases	3 (10.0)	1 (3.3)	0.306 <sup>a</sup>
Thyroid diseases	1 (3.3)	4 (13.3)	0.176 <sup>a</sup>
Gastrointestinal disorder	4 (13.3)	6 (20.0)	0.365
Skin diseases	1 (3.3)	2 (6.7)	0.500 <sup>a</sup>
Respiratory diseases	4 (13.3)	2 (6.7)	0.335 <sup>a</sup>
Dyslipidemia	6 (20.0)	4 (13.3)	0.365
Depression	0	1 (3.3)	0.500 <sup>a</sup>
Hepatitis C virus	0	1 (3.3)	0.500 <sup>a</sup>
Other liver diseases	0	1 (3.3)	0.500 <sup>a</sup>
Any allergy	8 (26.7)	3 (10.0)	0.090

n: number; OLCLs: Oral lichenoid contact lesions; OLP: Oral lichen planus.

<sup>a</sup> Fischer exact test were used.

(26.7%) patients with OLCLs and three (10.0%) patients with OLP ( $p = 0.090$ ).

### Patch test and metal component analysis

The results of patch tests in the patients with OLCLs are shown in Table 3. The most common allergen was Pd (56.7%) (Table 2). Metal component analysis was performed on 10 (33.3%) patients, 61 teeth, and four clasps. The remaining 20 patients did not require metal component analysis because the composition of the dental metal was clear. The most common metal component observed in the oral cavity of the patients with OLCLs was Pd (56.7%) (Table 3).

**Table 3** Metal component with positive patch test reactions in patients with OLCLs.

Metal elements	Patch test positive n (%)	Dental metal component n (%)
Palladium	17 (56.7)	17 (56.7)
Nickel	12 (40.0)	2 (6.7)
Gold	10 (33.3)	9 (30.0)
Cobalt	9 (30.0)	2 (6.7)
Platinum	5 (16.7)	
Mercury	5 (16.7)	2 (6.7)
Chromium	5 (16.7)	2 (6.7)
Zinc	3 (10.0)	3 (10.0)
Iridium	3 (10.0)	2 (6.7)
Indium	3 (10.0)	3 (10.0)
Tin	2 (6.7)	1 (3.3)
Copper	2 (6.7)	1 (3.3)
Vanadium	2 (6.7)	
Titanium	1 (3.3)	1 (3.3)

n: number; OLCLs: Oral lichenoid contact lesions.

The distribution and clinical type of lesions with oral lichenoid contact lesions and oral lichen planus.

The clinical characteristics of the lesions are presented in Table 4. There was no significant difference in the bilateral localization of lesions in the buccal mucosa, gingiva, and ventral tongue between the groups ( $p = 0.668$ ,  $0.822$ ,  $0.090$ , respectively). However, white type lesions were found in the buccal mucosa and gingiva more frequently in patients with OLCLs than in those with OLP ( $p = 0.030$ ,  $0.009$  respectively).

### Histopathological finding in patients with oral lichenoid contact lesions and oral lichen planus

The distribution of histopathologic features in patients with OLCLs and OLP is shown in Table 5. Fifteen of 30 (50.0%) OLCLs did not meet the histopathologic criteria of OLP (Fig. 1c and d). OLCLs were less likely to present with basal

**Table 4** Distribution and Clinical types of lesions in patients with OLCLs and OLP.

Distribution and Clinical type		OLCLs (n = 30) (%)	OLP (n = 30) (%)	p values
Buccal Mucosa	Bilateral	21 (70.0)	23 (76.7)	0.668
	Unilateral	5 (16.7)	4 (13.3)	
	White type	20 (66.7)	13 (43.3)	0.030*
	Red type	6 (20.0)	14 (46.7)	
Gingiva	Bilateral	15 (50.0)	19 (63.3)	0.822 <sup>a</sup>
	Unilateral	2 (6.7)	2 (6.7)	
	White type	12 (40.0)	6 (20.0)	0.009*
	Red type	5 (16.7)	15 (50.0)	
Ventral tongue	Bilateral	5 (16.7)	4 (13.3)	0.090 <sup>a</sup>
	Unilateral	0	3 (10.0)	
	White type	4 (13.3)	6 (20.0)	0.681 <sup>a</sup>
	Red type	1 (3.3)	1 (3.3)	
Dorsum tongue	Bilateral	2 (6.7)	0	1.00 <sup>a</sup>
	Unilateral	0	0	
	White type	2 (6.7)	0	1.00 <sup>a</sup>
	Red type	0	0	
Palate	Bilateral	2 (6.7)	1 (3.3)	1.00 <sup>a</sup>
	Unilateral	0	0	
	White type	0	0	1.00 <sup>a</sup>
	Red type	2 (6.7)	1 (3.3)	
Lips	Bilateral	2 (6.7)	0	0.720 <sup>a</sup>
	Unilateral	1 (3.3)	1 (3.3)	
	White type	1 (3.3)	0	0.720 <sup>a</sup>
	Red type	2 (6.7)	1 (3.3)	
Floor of mouth	Bilateral	1 (3.3)	0	1.00 <sup>a</sup>
	Unilateral	0	0	
	White type	1 (3.3)	0	1.00 <sup>a</sup>
	Red type	0	0	

\* $p < 0.05$  considered statistically significant.

n: number; OLCLs: Oral lichenoid contact lesions.

<sup>a</sup> Fisher's exact test were used.

**Table 5** Histopathological finding in patients with OLCLs and OLP.

Histopathological finding	OLCLs (n = 30) (%)	OLP (n = 30) (%)	p values
OLP Epithelium	15 (50.0)	30 (100.0)	0.000*
Liquefaction degeneration of basal layer	22 (73.3)	30 (100.0)	0.002*
Epithelial dysplasia	5 (16.7)	0	0.026** <sup>a</sup>
Connective tissue Band-like infiltrate predominately lymphocytic infiltrate in the lamia propria	25 (83.3)	30 (100.0)	0.020*
Inflammatory infiltrate located deep to superficial infiltrate in some or all area	13 (43.3)	17 (56.7)	0.301
Focal perivascular infiltrate	3 (10.0)	6 (20.0)	0.236 <sup>a</sup>
Plasma cells in the connective tissue	6 (20.0)	7 (23.3)	0.500
Neutrophils cells in the connective tissue	3 (10.0)	1 (3.3)	0.303 <sup>a</sup>

\* $p < 0.05$  considered statistically significant.

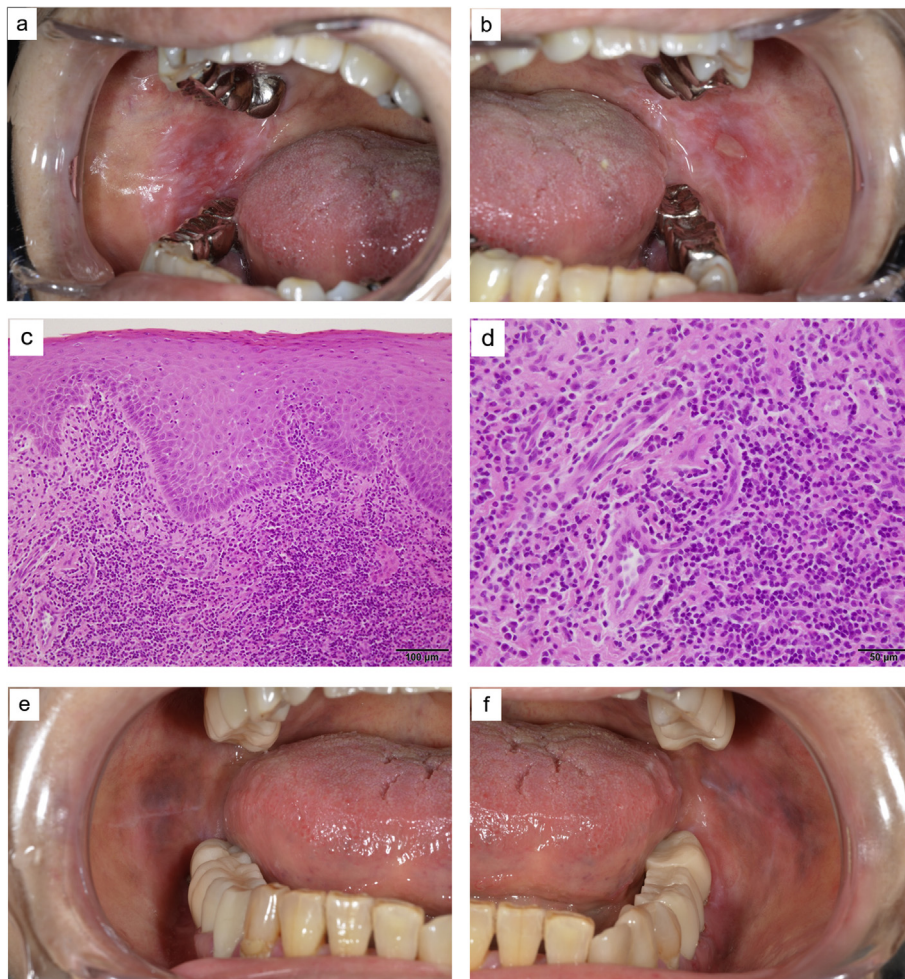
n: number; OLCLs: Oral lichenoid contact lesions; OLP: Oral lichen planus.

<sup>a</sup> Fisher's exact test were used.

cell liquefactive regeneration and band-like predominately lymphocytic infiltrate in the lamina propria, and significantly more likely to present with epithelial dysplasia ( $p = 0.002$ ,  $0.020$ ,  $0.026$  respectively) than were OLP.

### Healing of oral lichenoid contact lesions

Twenty-four of 30 (80%) patients with OLCLs agreed to partial or complete removal of their metal prosthetic appliances (Table 6). A total of 123 metallic restorations and prostheses were replaced with alternatives made of composite resin or ceramics. In addition, four crowns were replaced with new crowns; among them, three were gold, one was zirconia; eight teeth were extracted. Acrylic partial dentures were provided to avoid the use of metal clasps. In 14 of 24 (58.3%) patients, all dental metal containing positive metal allergen was removed. Only restoration and prostheses, containing positive metal allergen, in direct contact with the lesions were removed in 10 patients (41.7%). Complete and partial healing was achieved in five (20.8%) and 18 (75.0%) patients, respectively; no improvement was observed in one (4.2%) patient. Fig. 1 illustrates a case with marked improvement to the OLCLs, following Au–Ag–Pd alloy prosthesis replacement with a ceramic one. Only one of six patients



**Figure 1** Oral lichenoid contact lesions (OLCLs) related to Au–Ag–Pd alloy in the right buccal mucosa with atrophic lesions (a) and atrophic lesions with erosion on the left buccal mucosa (b), patch test positive to Au and Pd. Biopsy of (a) showed absence of a basal cell liquefaction, an inflammatory infiltrate located deep to superficial infiltrate (c), and a substantial number of plasma cells, neutrophils infiltrate in connective tissue (d) (HE stain). The all Au–Ag–Pd alloy was replaced by a ceramic prosthesis, and there was marked improvement of the OLCLs on the right buccal mucosa (e) and the left buccal mucosa (f).

that did not comply with the recommendation to replace their restorations showed partial improvement. The patients with OLCLs showed significant improvement in their lesions by replacing dental metal containing positive metal allergen ( $p = 0.0002$ ).

## Discussion

Differentiating OLCLs from OLP is paramount to treatment and prognostication. Although OLP may be associated with some systemic diseases, including hypertension, diabetes mellitus, thyroid diseases, hepatitis C virus infection, hyperlipidemia, and anxiety and depression,<sup>10</sup> in this study, no significant difference in the prevalence of systemic diseases was observed between the patients with OLCLs and those with OLP. Consequently, medical history may not be sufficient to effectively distinguish these diseases.

In this study, Pd and Au were the most common patch test-positive metals observed in the oral cavity of patients with OLCLs, likely because dental Au–Ag–Pd alloy is covered by the Japanese health insurance and is the most used. Pd is unstable in the oral cavity, releasing metal content into the saliva, increasing the risk of a serious allergic reaction.<sup>11</sup> Au salts are highly sensitizing; OLCLs are the most frequent manifestation of Au allergy.<sup>12</sup> Therefore

**Table 6** Healing of OLCLs patients after replacing removing restorations.

	Removing n/N (%)	No Removing n/N (%)	p values
Compete healing	5/ 24 (20.8)	1/ 6 (16.7)	0.0002*, <sup>a</sup>
Partial Improvement	18/ 24 (75.0)		
No Improvement	1/ 24 (4.2)	5/ 6 (83.3)	

<sup>a</sup> Fisher's exact test were used.

\* $p < 0.05$  considered statistically significant;  
n: number; N: number; OLCLs: Oral lichenoid contact lesions.

it was considered that Pd and Au are the major metals that cause OLCLs.

Clinically, OLCLs are usually unilateral and asymmetrical; they are most commonly seen on the buccal mucosa and ventral tongue.<sup>4,13</sup> In this study, the distribution of lesions was similar in both groups, which may be accounted for by the fact that most patients with OLCLs were treated with dental metal on both sides.

However, white type lesions were observed in the buccal mucosa and gingiva more frequently in patients with OLCLs than in those with OLPs. The classic bilateral keratotic reticular or papular form of OLP is not usually biopsied<sup>5</sup> and may have been excluded from this study. These findings highlight the difficulties in distinguishing OLCLs from OLP, based on clinical findings only. Holmstrup<sup>14</sup> reported that patients with the following characteristics needed a patch test: oral mucosal lesions presenting as lichen planus or mucositis resistant to treatment, clear anatomical relationship between oral mucosal lesions and the suspected restorative material, and lack of symmetry of affected sites. Since skin patch testing may help in the diagnosis of OLCLs, we performed these tests on patients with lesions associated with metallic restorations and prostheses, and resistant to topical steroid treatment.

The histopathology of OLCLs is not specific and overlaps with that of OLP.<sup>9</sup> In this study, 50% of patients with OLCLs were diagnosed with OLP. This finding was similar to that of previous reports.<sup>6,15</sup> Thornhill et al.<sup>3</sup> reported that four histopathological features did appear to be useful in discriminating between OLCLs and OLP: An inflammatory infiltrate located deep to superficial infiltrate in some or all areas, focal perivascular infiltrate, plasma cells present in the connective tissue, and neutrophils present in the connective tissue. However, in this study, there were no significant differences in these four features between the groups. Instead, OLCLs had significantly less basal cell liquefactive regeneration and band-like predominately lymphocytic infiltrate in the lamina propria, both of which have been previously reported primarily in OLCLs.<sup>16</sup> These findings indicate that both clinical and histopathological evaluation are necessary for the diagnosis of OLCLs.

OLLs have malignant potential similar to that of OLP; OLL was recognized as a potentially malignant oral disorder in 2020.<sup>17</sup> In this study, five patients with OLCLs were histopathologically diagnosed with oral epithelial dysplasia (OED), which has both histopathological features of OLP and dysplasia and is associated with the risk of malignant transformation higher than that associated with OLP and OLLs.<sup>18</sup> OLCLs should be histopathologically differentiated from OED and OLP.

Identification and subsequent removal of causative allergen is essential for definitive diagnosis and management of OLCLs. In this study, 23 of 24 (95.8%) patients that underwent material replacement experienced improvement in their OLCLs; however, only 5 (20.8%) patients showed complete improvement. Total removal of causative metallic restorations was not performed in all patients due to the burden of cost, time, and inconvenience. Some reports have suggested that the removal of only amalgam fillings that are in contact with OLCLs may suffice to achieve recovery.<sup>13</sup> The metal component analysis detects even trace metals and may help identify the causative

metal. Removal and replacement of causative dental metal is recommended in cases where a clear relationship between the metal allergen, dental metal, and OLCLs has been established.

Our retrospective study had some limitations. We did not perform the removal of dental metals that did not contain positive metal allergen. OLCLs may include irritant contact stomatitis (ICS) in addition to ACS.<sup>12</sup> The patients with ICS were considered negative for the skin patch-test and were not included in this study. Therefore, the association between OLCLs related to ICS was not evaluated. The removal those metals might improve OLCLs. In a further report, we will increase the number of cases and investigate cases of suspected OLCLs in comprehensive manners.

The present findings suggest that skin patch tests and metal component analysis were recommended to confirm suspected OLCLs related to dental metal allergy. OLCLs may improve with the replacement of dental metal containing positive metal allergen.

## Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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