

A Burning Issue on Oral Mucosal Diseases: Case Series with Review

14 ABSTRACT

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Oral Lichenoid Reaction (OLR) is a chronic inflammatory lesion of the oral mucosa that occurs as an allergic response to certain dental materials, medications and systemic diseases. The frequency of OLR in the general population has been documented to be very less. The clinical and histological features of OLR closely resemble those of Oral Lichen Planus (OLP), making it challenging to distinguish between the two clinically. OLRs might have a higher malignant potential than OLP. The diagnosis and treatment of OLR is very crucial as misdiagnosis may result in detrimental effects on the biophysical health of the patient. Here, we present case series of two patients who presented with amalgam restorations and burning sensation on the buccal mucosa while consumption of hot and spicy food. An immunohistopathological evaluation confirmed the diagnosis as Oral Lichenoid Reaction. Elimination of causative factors remain the mainstay of treatment which markedly reduces the sufferings of the patient with a commendable result.

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17 *Keywords: Lichenoid Reaction, DIF, Burning, Mucous membrane, Amalgam*

18 1. INTRODUCTION

19 The oral mucosa provides effective barrier which is often in constant contact with various deleterious substances, acidic or
20 alkaline compounds, spicy or non-spicy food, allergens like chemical products used in toothpastes, mouthwashes or oral
21 flavouring agents, preservatives and dental materials [1]. Oral lichenoid reaction (olr) is characterized as a persistent
22 inflammatory condition affecting the oral mucosa, triggered by allergic reactions to dental products, specific medications,
23 individuals with graft-vs-host disease (gvhd) and systemic conditions [2]. Histologically, olrs mimic oral lichen planus (olp),
24 thus, clinical interpretation is mandatory [3]. The occurrence of olr is a common phenomenon, manifesting with a
25 prevalence of 2.4% among the general populace [2]. These lesions most commonly occur in middle-aged adults with a
26 slight female predilection [4]. Areas commonly involved are the buccal mucosa, lateral border of the tongue and labial
27 mucosa that are in direct contact with metal restorations or other allergens. It is generally limited in size and unilateral in
28 distribution. On the contrary, olp lesions are frequently found bilaterally in the oral mucosa which serve as the
29 distinguishing feature. Clinically, the lesion shows a wide range of variations, from white interlacing striations to
30 ulcerations even blister formation, and are asymptomatic in nature. Patients may complain of burning sensation along with
31 intolerance to spicy meals [2]. Based on an admixture of clinical diagnosis, histopathological evaluation and
32 immunofluorescence test, a final diagnosis was made and patients were successfully treated.

2. CASE PRESENTATION

CASE 1:

A 61-year-old female patient from a semiurban area reported to the Department of Oral and Maxillofacial Pathology, Guru Nanak Institute of Dental Sciences and Research, Kolkata with the chief complaint of mild burning sensation over left buccal mucosa, lower labial mucosa and tongue since last 1-2 years, which was small initially but progressively increased over time to the present size (measuring about 1.5x1.2 cm) being associated with burning sensation on taking hot and spicy food. At the time of presentation, the patient had a class i amalgam restoration on 38 that was performed approximately 6 years ago which is now considered as poor or defective. However, the affected site is free from traumatic occlusion or from sharp cuspal edges of tooth or dentures. The medical history revealed that she was hypertensive and under medication.

Intraorally, the presence of inflamed and erythematous attached gingiva and interdental papilla with respect to 31,32,33 and 41,42,43 tooth region was observed. Gingival recession was noted wrt 31,32 and poor oral hygiene is present. There was also presence of small erythematous ulcerated lesion over gingivobuccal sulcus and buccal mucosa with respect to 36. The patient also had a fissured depapillated tongue [figure 1 (A, B, C)]. These led to a provisional diagnosis of oral mucositis.



Figure 1: Intraoral photograph of the patient showing (A) presence of inflamed and erythematous attached gingiva and interdental papilla with respect to 31,32,33 and 41,42,43 tooth region; (B) Fissured depapillated tongue; (C) Small erythematous area over gingivobuccal sulcus and buccal mucosa wrt edentulous space of 37.

Thereafter, the patient was advised for oral prophylaxis along with empirical antibiotic therapy and antibacterial mouthwash. Most of the lesions started to regress after 1 month of therapy but the lesion adjacent to 36 was still persistent and the incisional biopsy was planned from that representative area.

The patient was then advised to undergo routine hematological and biochemical investigations which were within normal limits.

Incisional biopsy was performed under local anesthesia and submitted in buffered formalin for routine histopathological examination. Sections stained with h & e revealed the presence of hyperplasia of surface epithelium with basal cell degeneration. Spongiosis can be encountered due to presence of intercellular edema. Subepithelial stroma showed numerous diffuse chronic inflammatory cells infiltrate extending from juxta epithelial area to deep into the connective tissue accompanied by plasma cells and histiocytes. No cellular atypia was evident [figure 2A to E]. The light microscopic features were suggestive of lichenoid reaction.

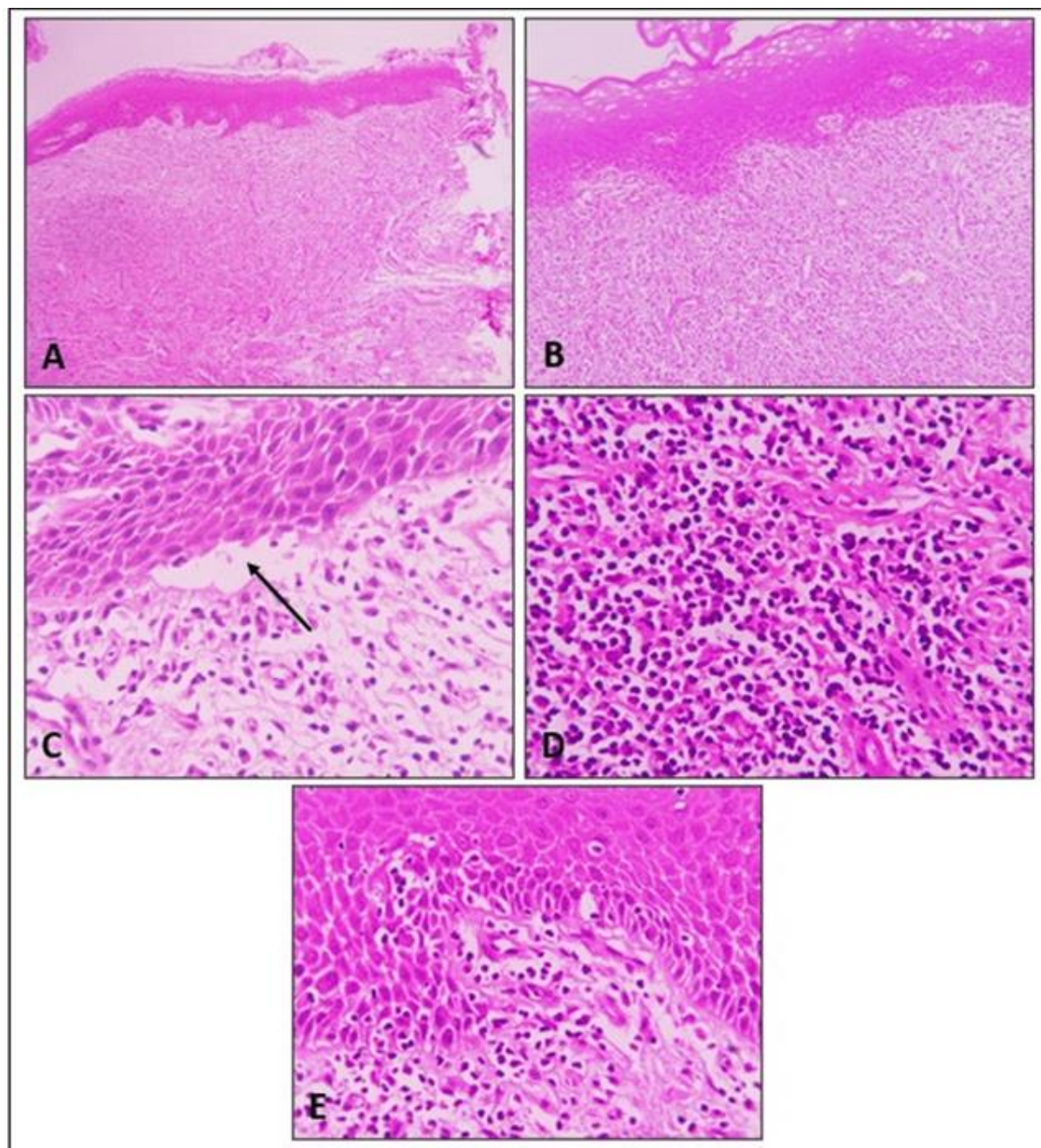


Figure 2: (A) Photomicrograph showing hyperplastic stratified squamous surface epithelium with underlying connective tissue stroma (H and E; 4X); (B) Spongiosis and diffuse chronic inflammatory cells infiltrate deeper into the lamina propria (10X); (C, D, E) Max Joseph spaces (arrow) and basal cell degeneration; numerous chronic inflammatory cells infiltrate chiefly characterized by lymphocytes, histiocytes along with plasma cells (40X)

To confirm the diagnosis, direct immunofluorescence (DIF) was advised. A perilesional tissue was taken and sent for the DIF testing directly in Michel's medium, which revealed no appreciable staining deposits for IgG, IgA, IgM and C3 [FIGURE 3A to 127 D].

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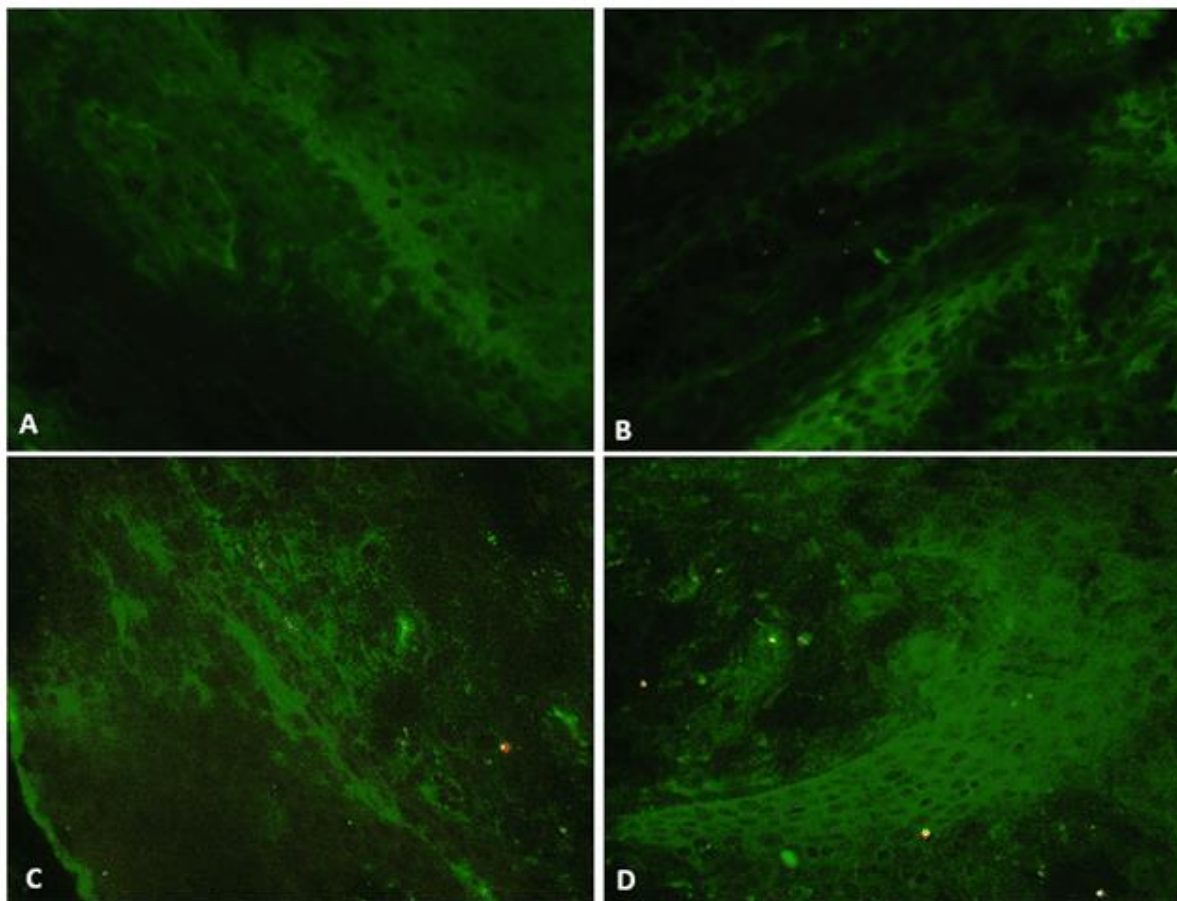


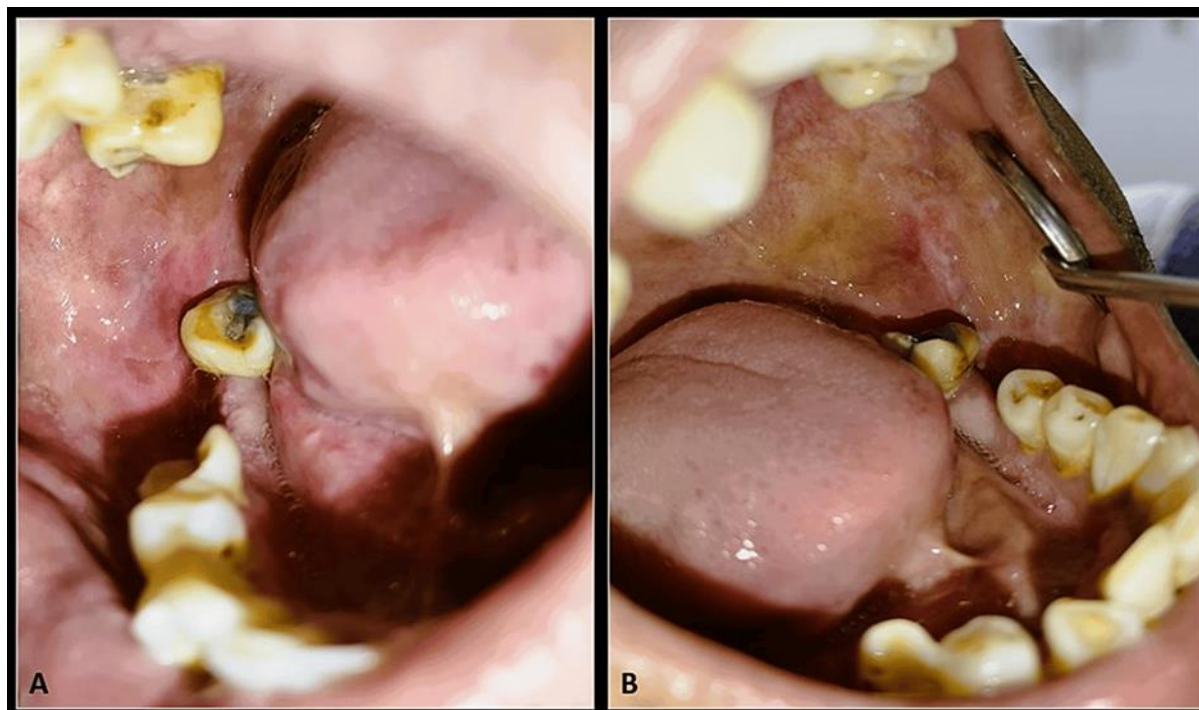
Figure 3: DIF showing a negative staining deposits for (A) IgG (B) IgA (C) IgM and (D) C3

159 The overall clinical, histopathological features and immunofluorescence study were consistent with lichenoid inflammation.

160 The treatment includes elimination of the amalgam filling in the lower back tooth region by composite resin restoration and
161 application of topical clobetasol (0.05% w/w) and miconazole (2% w/w) on the affected areas along with benzydamine (0.15%
162 w/v) mouthwash and followed for 2 months. The patient responded well to the above-mentioned treatment and no further
163 exacerbations were noticed.

164 **CASE 2**

165 A 57-year-old male patient reported to the department of oral and maxillofacial pathology with a chief complaint of burning
166 sensation in his cheeks while consumption of hot and spicy food for the last 1 year. The patient visited to dental surgeon for
167 similar sufferings 6 months ago and applied steroid ointment as per prescription. Remission of the lesion was observed after
168 4 months of treatment but recurrence was noted over a period of 2 months after termination of medication. Medical history
169 revealed that the patient was hypertensive under medication. On intraoral examination, we noted the presence of white
170 striations with central erythema on bilateral buccal mucosa. Amalgam restoration in the left mandibular second molar and
171 right mandibular third molar was done approximately 3-4 years ago. The rest of the oral mucosa appears normal.
172 [FIGURE 4(A,B)]

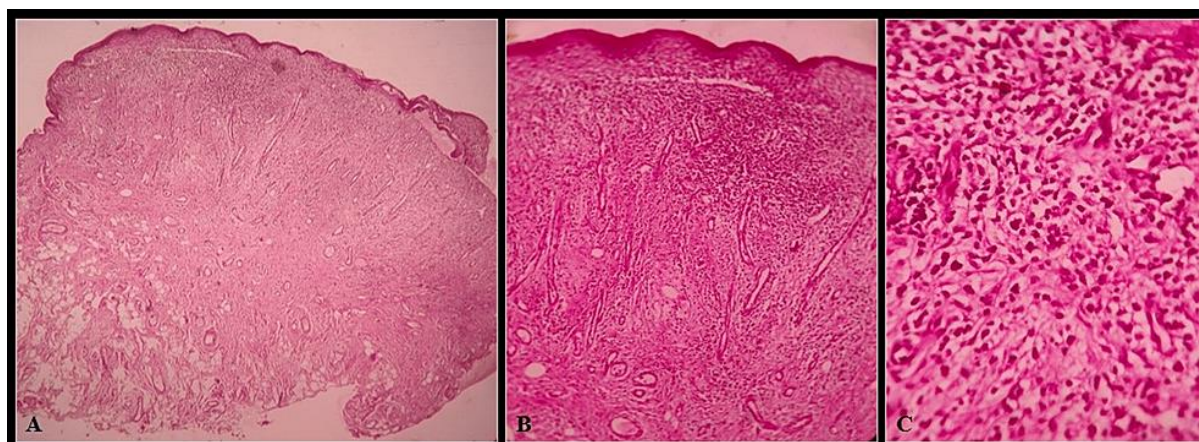


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174 Figure 4: (A,B) Intraoral examination showing presence of white striations with central erythema on bilateral buccal mucosa adjacent to teeth wrt 37 (left
175 mandibular second molar) and 48 (right mandibular third molar) filled with amalgam

176 A provisional diagnosis of oral lichen planus was made based on the clinical findings. The patient's hemogram was within
177 normal limits. Incisional biopsy was performed under local anesthesia from the representative site and finally sent for routine
178 light microscopic histopathological evaluation to confirm a diagnosis.

179 Sections stained with H&E revealed the presence of stratified squamous surface epithelium with irregular rete ridges, focal
180 acantholysis and occasional basal cell degeneration. Underlying stroma revealed diffuse chronic inflammatory cell infiltrate
181 extending deeper into the connective tissue layer with engorged blood vessels and large number of eosinophils. No signs of
182 malignancy could be detected [FIGURE 5].



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184 Figure 5: (A TO C) Photomicrograph showing hematoxylin and eosin-stained sections revealing stratified squamous epithelium with irregular rete ridges
185 (4X); Focal acanthosis, occasional basal cell degeneration and chronic inflammatory infiltrate deeper into connective tissue layer (10X); Inflammatory
186 infiltrate along with engorged blood vessels and large no of eosinophils (40X)

187 Thus, the diagnosis of oral lichenoid reaction was made based on histopathological evaluation.

188 The patient was then advised to replace the amalgam restorations with a tooth-colored restorative material and composite
189 resin restoration was done. His symptoms regressed and complete healing was noted after 2.5 months. There has been no
190 evidence of recurrence or discomfort over a period of 1 year.

191 **DISCUSSION**

192 Pinkus first introduced the term "Oral Lichenoid Tissue Reaction" in 1973 to describe the histological pattern indicating
193 damage to keratinocytes along with the infiltration of inflammatory cells in the connective tissue that may also extend into the
194 epithelium [1]. Oral Lichenoid Tissue Reaction has also been termed as Oral Lichenoid Lesions (OLL), Oral Lichenoid
195 Reaction (OLR), lichenoid contact stomatitis, or lichen-planus-like lesions due to the clinical and histological similarities
196 between OLR and Oral Lichen Planus [2]. OLRs can manifest either as a distinct pathological condition or as an exacerbation
197 of pre-existing oral lichen planus. According to Van der Waal (2009) OLRs can be categorized into four types: Amalgam
198 restoration topographically associated lesions, Drug-associated lichenoid lesions, Lichenoid lesions in individuals having
199 chronic graft versus host disease and lesions that have a lichen planus like aspect but that lack one or more characteristic
200 clinical aspects [1].

201 Lichenoid reactions have been attributed to several drugs such as Beta Blockers, Nonsteroidal Anti-Inflammatory Drugs
202 (NSAIDs), Dapsone, Oral Hypoglycemics, Penicillamine, Sulfonyleureas, and Anti-Psychotic like Phenothiazines, Vasodilators.
203 They have also been associated with dental materials including amalgam, dental acrylics etc. [4,5]. Association of systemic
204 diseases such as Chronic Hepatitis C and patients vaccinated against Hepatitis B have been observed in numerous
205 cases [6]. In our case, one of the patients had the amalgam restoration on 38 (class I) while the other had on 38 and 48
206 respectively.

207 The pathogenesis of OLRs is still largely unknown. It is postulated that various pathways of antigen presentation could serve
208 as a fundamental determinant. At the time of restoration, OLRs are barely encountered due to insolubility of amalgam into the
209 saliva and its washing mechanism [7]. The response initiates when haptens (incomplete antigens, combine with
210 proteins/counterparts to create full antigens) interact with the oral mucosa. Following the first encounter, an initial local
211 immune and inflammatory response takes place and the antigen internalized by macrophages and monocytes is
212 subsequently displayed to T cells leading to their sensitization and activation of CD4+ T cells. Upon subsequent exposure to
213 the identical allergen, these cells secrete cytokines and chemokines that have the potential to incite an immune reaction
214 against epithelial antigens, thereby instigating the formation of OLR and this seems to manifest as a T-cell mediated delayed
215 hypersensitivity reaction (Type IV) upon contact with either the mercury or another constituent of amalgam. This response
216 could be delayed for a minimum 48 hours and the manifestation of symptoms may vary based on the severity of the reactions
217 which can manifest as either be acute or chronic [8,9,10,11]. Previous studies demonstrated that the expression of nuclear
218 factor κ B -dependent cytokines in serum, oral keratinocytes and tissue-infiltrated mononuclear cells including TNF- α , IL-1 and
219 IL-6 was increased in individuals with OLR [5].

220 The prevalence of LR has been reported to be approximately 2.4% in the general population and middle-aged individuals are
221 commonly affected [2]. In our case series, our patients also belonged to the mentioned age group.

222 Clinical presentations may vary depending on the type of reaction, allergen location and duration of contact. The asymmetry
223 of the lesion is notable; however, it can be present bilaterally if there are amalgam restorations on both sides. The buccal
224 mucosa is the most frequently affected site followed by border of tongue [5]. Acute lesions may present with symptoms such
225 as burning sensation and redness. Vesicles are not commonly observed, but if present, they tend to rupture shortly after
226 forming, leading to the presence of erythematous areas. Chronic lesions typically manifest as regions of erythema, oedema,
227 desquamation and occasionally ulceration [11]. Both the patients had a lesion over the buccal mucosa which was consistent
228 with the clinical presentation documented in the existing literature. In the 2nd case, the patient had white striations with
229 erythema in certain areas of buccal mucosa which was clinically corroborative with the features of OLP.

230 Histopathologically, there is the presence of hyperkeratosis of surface epithelium along with spongiosis, liquefactive
231 degeneration of the basal cell layer and diffuse inflammatory infiltrate extending deeper into the lamina propria unlike OLP
232 where chronic inflammatory cells are restricted to the juxta-epithelial connective tissue in a band like fashion. This infiltrate
233 comprises of plasma cells and eosinophils in addition to lymphocytes and increased numbers of colloid or Civatte bodies in

234 case of OLR. Perivascular chronic inflammatory cell infiltrate may be seen in drug related lichenoid lesions [12]. Our cases
235 showed similar histologic presentations. Since, in both the cases, there is presence of chronic inflammatory cell infiltrate
236 extending deeper into the connective tissue layer and large number of eosinophils, the possibility of OLP is excluded.

237 Clinically and immunohistopathologically, differential diagnosis of OLRs include: Vesiculo-Bullous Diseases such as
238 Pemphigus Vulgaris, Leukoplakia, Lupus erythematosus (LE) etc. [11]. Histopathological evaluation of bullous diseases
239 reveals intraepithelial, subepithelial and suprabasilar split. We can also exclude Leukoplakia from OLR as Leukoplakia
240 clinically appears as greyish-white with cracked mud appearance and shows dysplastic epithelium [12]. All these features
241 were missing in our cases.

242 Direct Immunofluorescence (DIF) was used to examine the fluorescence patterns in oral lichenoid reactions and to compare
243 the degree of intensity of their fluorescence [13]. It was observed that the immunofluorescence pattern of OLP is more
244 ragged and fibrillary whereas it is more uniform and less intense in OLR. However, fibrinogen deposition at the basement
245 membrane zone was absent in 29.2% of OLR [3]. No appreciable staining was also noted in our case.

246 In case of Lupus, DIF of lesional tissue typically reveals the presence of one or more immunoreactants (usually IgM, IgG, or
247 C3) forming a shaggy or granular band at the basement membrane zone [14] which was negative in our cases.

248 The confirmation of pemphigus vulgaris diagnosis necessitates the direct immunofluorescence evaluation of the perilesional
249 tissue, demonstrating the presence of antibodies (usually IgG or IgM) and complement components (usually C3) in the
250 intercellular spaces between the epithelial cells, characterized by a pattern resembling a fish net or chicken wire which is not
251 present in our case series. [15].

252 In the present case series, we pinned our confirmatory diagnosis as Oral lichenoid reaction based on clinical findings,
253 histopathological features and diagnosis of exclusion.

254 Remission of OLR involves the substitution of causative restorations with non-allergic material. Replacing amalgam
255 restorations has resulted in significant enhancements in 93% of hypersensitivity lesions associated with amalgam
256 contact [16]. In both the cases, the amalgam restoration was replaced by a tooth-coloured restorative material like composite
257 resin. The patient started experiencing relief around 2.5-3 months and complete healing was seen in subsequent follow-up.
258 There has been some controversy about the malignant potential of lichenoid reactions (2.43%) which is usually thought to be
259 extremely rare [1,17]. Iocca et al. (2020) stated that the true potential of the malignant transformation of OLRs is high
260 (3.8%) [18]. However, the patients should be regularly monitored until the complete remission of the lesion is noted [1].

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TABLE 1: Comparative analysis of both cases with following criteria

FEATURES	CASE 1	CASE 2
Age & sex	61-year-old female patient	57-year-old male patient
Type of reaction	Delayed	Delayed
Allergen location	Amalgam restoration on 38	Amalgam restoration on 38 and 48 respectively.
Duration of contact	6 years	3-4 years
Burning sensation	Present	Present
Erythema	Present	Present
White striations	Absent	Present
Site	Buccal mucosa vicinity to amalgam restoration	Buccal mucosa on both sides vicinity to amalgam restoration
Histological features	Diffuse inflammatory infiltrate extending deeper into the lamina propria; basal cell degeneration; numerous chronic inflammatory cells infiltrate chiefly characterized by lymphocytes, histiocytes along with plasma cells	Diffuse inflammatory infiltrate extending deeper into the lamina propria. Occasional basal cell degeneration and chronic inflammatory infiltrate along with engorged blood vessels and large no of eosinophils
DIF	No appreciable staining deposits for IgG, IgA, IgM and C3	Not performed
Treatment	Amalgam restoration was replaced by a tooth-coloured restorative material like composite resin.	Amalgam restoration was replaced by a tooth-coloured restorative material like composite resin.
Follow-up	Started experiencing relief after 3 months of therapy	Started experiencing relief around 2.5 months and complete healing was noticed in subsequent follow-up

4. CONCLUSION

Dental amalgam continues to be the most preferred and affordable restorative material in the field of restorative dentistry before a decade despite the availability of new synthetic non-metallic alternatives, predominantly due to its superior strength as well as minimal technique sensitivity. But it might result in oral lichenoid reaction in susceptible patients. When the lesion appears in the close proximity to amalgam restoration, replacement of such restoration can be eliminated by substitution with alternative tooth colored restorative material like Glass ionomer or composite resins are recommended. Although the clinicopathological characteristics of OLP are similar, OLR and OLP must be distinguished from one another

283 due to differences in etiology, diagnosis and prognosis, failure to do so may result in detrimental effects to the patient.
284 OLRs exhibit a high susceptibility to undergo malignant transformation. So, early diagnosis and periodic follow-up
285 represent crucial measures in impeding the progression of the condition.
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CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

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