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Contact lichenoid reaction in the oral cavity: A comprehensive focus on amalgam restoration

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Abstract

For many years, amalgam was the preferred repair material; however, because of worries about aesthetics, mercury toxicity, and the development of lichenoid diseases, its use has decreased. The oral mucosa has a reaction known as the oral lichenoid lesion (OLL). Dental materials, particularly amalgam, medications, and graft-versus-host disease (GVHD), are among the backgrounds of OLL. When restorative materials, most frequently amalgam, come into close touch with the mucosa in hypersensitive people, OLL to dental materials might result. The aim of this review paper is to introduce different aspects of OLL, especially amalgam restorations. The oral mucosa may experience type IV hypersensitivity responses to amalgam and, or its constituents. The clinical appearance, absence of migrations, and direct connection with the afflicted mucosa with the amalgam restorations are often used to confirm the diagnosis. In this regard, dental professionals should considered the OLL incidence around amalgam restorations. In most cases, OLL may be resolved by replacing amalgam restorations with non-metallic restorations. Therefore, a helpful prognostic marker is a topographic link between OLL and amalgam restoration.

Keywords: Oral lichenoid lesion; Amalgam restorations; Mucosa; Prognostic marker

1. Introduction

The oldest history of amalgam usage as a restorative dental material dates back to 659 AD (1), and it has been a popular option for decades (2) due to its longevity, which is supported by several research (3, 4). Due to environmental (5, 6) and mercury toxicity worries, as well as the rising patient desire for esthetic restorations (7, 8), the amalgam usage has significantly reduced in recent years. The allergic sensitivity of the oral mucosa to one or more of amalgam's components, most frequently mercury, is another factor in its decreased usage. Numerous research has shown this specific hypersensitive reaction, and they were referred to as oral lichenoid responses (OLRs) by Finne et al (9). Their symptoms are often categorized as delayed hypersensitivity reactions (type IV). (8, 10, 11).

Oral lichenoid lesion (OLL), also known as delayed hypersensitivity type of reaction, is another health issue linked to dental materials, including amalgam, and dental materials specifically (12-14). The tongue, gingiva, and buccal mucosa in direct connection with amalgam restorations commonly exhibit OLL (15, 16). These OLL are divided into four categories: lesions related to direct contact (OLLC), which are most frequently connected to amalgam restorations; lesions related to drugs (OLLD); lichenoid lesions in chronic graft versus host disease (cGVHD); and lesions linked to systemic diseases, like lupus erythematosus (10, 17). The clinical signs of OLL can be very diverse, ranging from homogenous white plaques to ulcerations to white linear plaques that are either linked or not with erythema (10). Additionally, several forms may exist simultaneously (18). In terms of their symptomatology, these lesions can cause everything from mild discomfort to intense pain. To differentiate OLL from the actual lichen planus, OLL does not

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migrate and exclusively affects the oral mucosa in contact with dental amalgam restorations (19). Numerous dermatoses, such as hand dermatitis, palmoplantar pustulosis, and nummular dermatitis, can be brought on by direct contact with metals (10, 20).

Regarding OLL and its connection to amalgam restorations, several investigations and a systematic review have been published (21). Therefore, in the present study, we provide a comprehensive review of previous studies and a case report to clarify the OLL prevalence in cases with amalgam restorations.

1.1. OLL prevalence

With a frequency of 2.4% in the general population, OLL is a common disorder (22). These lesions often affect the oral mucosa of adolescents (23), primarily affecting female with a medium age of 53 (24). When linked with composite restorations, the lesions are mainly found in the buccal mucosa, lateral border of the tongue, and oral mucosa of the lips. OLRs and oral lichen planus share a similar clinical incidence. OLRs can be reticular, in the shape of plaques, atrophic and erosive, or a mix of those as mentioned above. They are frequently observed in close topographic proximity to the offending chemical. Indeed, OLLs are unilateral and small in size (13, 25, 26).

1.2. OLL diagnosis

The clinical manifestation of the lesions, the absence of migration, and the relationship with nearby amalgam restorations are crucial factors in the diagnosis of OLL. Skin-patch testing can help identify the allergen causing the hypersensitivity, though it must be carried out by a dermatological or immunology expert (10). However, once the long-term prognosis is particularly challenging, it may be essential to conduct a clinical examination by a multidisciplinary team. This team should include a dermatologist or immunologist who will perform an epicutaneous test to confirm type IV hypersensitivity (27). However, it is unusual for patients to request an appointment with a dermatologist to diagnose and treat OLL. The diagnosis is frequently made in the dentist´s clinic, especially in patients with OLL resulted from direct exposure (10).

1.3. OLL clinical features

Most of OLLs are recognized as non-symptomatic; however, some cases a discomfort from spicy and hot food could be observed in relation to the conversion of lesion to erythematous or ulcerative forms. The time of contact with dental material showed a crucial function with the development of LCRs on the oral mucosa. LCRs resulted from dental composites have been recognized on the mucosal side of both upper and lower lips. The clinical features of OLLs are indiscoverable from those of OLPs (21)– to a great degree of erythematous erosive lesions and an significant ulcerative part. All these lesions are recognized via the existence of whitish streaks defined as Wickham striae, alike with those observed in OLPs (28). Some symptoms of OLLs resulted from drugs include small red or purple bumps on the skin (often shiny), white scales or flakes, wavy white lines, defined as Wickham striae, blisters, itching, brittle, and ridged nails. Nevertheless, a very important distinguishing factor with regard to OLP is their atypical locus, and especially the lack of bilateral demonstrations (28-31).

1.4. OLL etiologic factors

1.4.1. Drugs

Drugs are recognized as oral lichenoid lesion (OLL-d) inducers, primarily linked to prolonged drug use (32). The alteration of them should be taken into consideration when a medicine is suspected of causing OLL-d (33). The OLL-d is not frequent, unlike the cutaneous lichenoid lesions caused by medication (32). The OLL-d inducers are listed in Table 1. Readministering the medicine in determining whether the oral lesions are drug-induced, albeit doing so could be risky for the patient (32, 34). The definitive diagnosis of OLL-d is challenging. Usually, the lesion goes away once the treatment is suspended (32, 34). The lesion's complete recovery, however, may take a long time. In extreme circumstances, the drug may be essential for the patients to survive, making its suspension or replacement impossible (32, 34). The lesions must be treated as oral lichen planus (OLP) in these situations. A reduction in unstimulated whole saliva production has been documented in individuals with OLL-d. They are taking medications for cardiovascular disease (35), which suggests that hyposativation may be a trigger for OLL-d in these patients (29). OLL-d and OLP have been associated with other drugs (16). IFN´s ability to cause or exacerbate immunological disorders has been well shown. Since the development of pegylated IFN, a causal relationship has been proposed between the use of pegylated IFN in conjunction with ribavirin to treat chronic hepatitis C and a number of autoimmune reactions. Following the advent of IFN for treating hepatitis C, the formation or worsening of OLP has also been documented (34, 36-41). This can also lead to the improvement of novel lesions such as OLL. IFN-'s involvement with the cytokine cascade makes it highly possible that it might cause new lesions or exacerbate existing ones (42). When treating chronic hepatitis C with

pegylated IFN and ribavirin, Grossmann et al. (16) documented three cases of OLP aggravation. Nevertheless, it is challenging to determine whether the lesions were aggravation of prior OLP lesions or brand-new OLL-d lesions. In order to distinguish between idiopathic OLP and OLL-d, McCartan and Lamey (39) looked into using a lichen planus-specific antigen as a marker. They found that this marker is ineffective.

Table 1 A list of drugs induced OLL**.**

Drug categories	**Drug examples**
Antihypertensive	Methyldopa, Oxprenolol, Practolol
Antimalarials	Chloroquine, Pyrimethamine, Quinacrine, Ketoconazole
Antimicrobials	Tetracycline, Sulfamethoxazole, Fenclofenac
NSAIDs	Phenylbutazone, Naproxen, Rofecoxib, Tolbutamide
Hypoglycemic drugs	Chlorpropamide
Penicillamine	Penicillamine
ACEIs	Captopril,
Thyrokinase-selective immuneosuppressors	Imatinib,
Miscellaneous	Allopurinol, Amiphenazole, Amiphenazole, Carbamazepine, Cyanamide, Levamisole, Lithium

1.5. Chronic Graft Versus Host Disease (cGVHD)

In allogeneic bone marrow transplants (BMT), GVHD is prevalent complication that can cause morbidity and death. Dermatological, gastrointestinal, and hepatic lesions are its defining features (42-44). While the donor immune system perceives the host tissue as alien and begins to assault its biological components, GVHD happens. T cells from the donor respond to antigens from the recipient (32, 41-45). Patients with GVHD may exhibit one of three characteristics: the graft should include immunologically competent cells; the recipient should express tissue antigens that are sufficiently distinct from the donor; or the recipient must be unable to reject the graft due to tolerance, limited understanding, or immunosuppression. Acute GVHD (aGVHD) happens within the first 100 days of transplant, whereas chronic GVHD (cGVHD) develops more than 100 days following BMT (32, 42-44), and involves both systemic organs and the oral mucosa. Troublesome desquamative and ulcerative lesions in the oral cavity are how the aGVHD manifests. Clinical signs of cGVHD include white papular eruptions or reticular lesions with regions of erythema, erosion, or ulceration, which are remarkably alike with the autoimmune connective tissue disorders. The tongue, buccal, and labial mucosa are usually involved, and the distribution is typically symmetrical (41, 42, 44, 45). It frequently occurs when an infectious insult or while immunosuppression is decreased (32, 42), and these events might affect patients' quality of life[36]. Patients with cGVHD frequently exhibit erythema, mucosal atrophy, and lichenoid alterations, with lichenoid responses indicating the highest positive predictive value (42). OLL was the unique clinical symptom showed a statistically significant correlation with the cGVHD diagnosis (46), according to research by Nakamura et al. Clinically, the OLL on cGVHD resembles the Wickham striae in the OLP and takes the form of lacy white striations (42). Histologically, these responses are characterized by lymphocyte infiltration in the submucosa and basal cell layer degradation. Epithelial cell intracellular edema can occasionally be seen (44). When the systemic GVHD is treated with immunosuppressive medication, the OLL can be managed. Potent topical corticosteroids should generally be used for treatment if the oral lesions are persistent or are an independent GVHD phenotype (41). Diphenhydramine with kaolin and pectin or clobetasol gargles, topical fluocinonide, oral prednisone (20 to 50 mg/d), or thalidomide (50 to 200 mg/d) are a few drugs used to treat OLL associated with GVHD (43).

1.6. Topical agents

1.6.1. Cast metal prosthesis

A major quantity of the population in the world utilize prostheses and instruments containing different dental alloys. These restorations may be related to different impacts on oral safety like burning mouth syndrome, oral pigmentation, hypersensitivity, lichenoid reactions, and genotoxic and cytotoxic impacts(47). OLRs are histologically and clinically

similar from OLPs. Nevertheless, a known agent can be determined with regard to the previous lesions such that when recognized and removed results in its recurrence. In some cases, OLRs occur as a consequence of chronic irritation or a postponed hypersensitivity mechanism(48). Although dental amalgam is the most commonly implicated dental material for causing lichenoid reactions(49), other materials may also be involved such as cobalt, chromium, nickel, palladium, and mercury(50). The reactions to these metals are almost scarce, therefore making this case a special one. An allergy to Nickel allergy is more prevalent in female (10%) than male (1%), while chromium allergy (10% in men and 3% in women) is the opposite. In a previous investigation, it was shown that from 500 children evaluated for allergic reactions to metals, 133 of them showed a positive reaction, from which nickel sulfate were the most prevalent positive test with 44 reactions (33%), while it was determined to be related in only 3 cases(51, 52). Restorations of dental cast metal have frequently been related to plaque induced gingivitis, gingival recession and sometimes with improved periodontitis. It has been reported that a lot of causes are under these occasions. Dealing with the biological width of the gingiva, raised or incomplete edges, inappropriate contours, traumatic occlusion, open or excessively tight contacts, each may contribute to this phenomenon and are undoubtedly the main factors of periodontal diseases associated with local restoration. Nevertheless, hypersensitivity reactions to cast metal alloys could also have a significant function and could present the most likely possible factor when locally destructive periodontitis is obvious on restored teeth. Patch testing is a reliable and valuable diagnostic way in diagnosing numerous cases having hypersensitivity to dental agents, although recognition of metal sensitivity does not presently mean that a patient will try symptoms related to an oral allergy(53).

1.6.2. Amalgam

The oral mucosa could become hypersensitive to resin-associated composite, gold, and amalgam and its elements (21, 24, 29, 32, 54, 55). Amalgam fillings accounted for 84% of instances of OLL, according to Lygre et al. (56), and were linked to an unfavourable response to dental materials. About 2% of the population can be found to have the OLL connected to amalgam restorations (33, 56-58). Although OLL is rare, it can also be linked to composite resin (59, 60). OLL is most likely introduced to dental materials over a lengthy time. When dental material touches the oral mucosa, a hypersensitive response develops over a few days, and the clinical symptoms may not show up for years (57). When it comes to amalgam, a response that results in the distribution of corrosion products from the restoration surface could also cause lymphocyte activation and the production of an autoimmune reaction that is targeted at basal keratinocytes (54). Basal keratinocytes may be immune-mediated damage due to the cell-mediated type IV hypersensitivity response of amalgam restoration (32, 33, 57). Nevertheless, other amalgam-filling elements such as copper, tin, or zinc might also be linked to the reaction (21, 24, 33). In the majority of instances of OLL, mercury is the source of hypersensitivity. OLR does not always manifest in people who have amalgam alloys in touch with their oral mucosa, according to researches (33, 54), who hypothesized that this reaction develops in vulnerable individuals after prolonged exposure. However, individuals who had amalgam fillings replaced had significantly lower IL-6 and IL-8 levels in their saliva (61). A previous study (54) demonstrated that the combination of a positive patch test and the existence of oral lesions together with amalgam restoration were an essential predictor of lesion enhancement, even though the use of patch tests for OLL to dental agents is debatable and shows limited value (21, 46, 62). These authors reported the intriguing fact that none of the patch test-positive individuals or cases with a significant clinical correlation among the lesions and their fillings had the clinical manifestation of desquamative gingivitis. Furthermore, none of these individuals had a history of skin lesions. The same components to apply in the test, how to discern between sensitivity and irritating reactions, how long the material must be in connection with the skin, and the usefulness of skin patch testing in diagnosing actual oral lichenoid lesions are all contentious issues. The validity of extrapolating skin reactions to mucosal responses is also up for discussion (32). However, the patch test may be effective in determining which material should be used in place of amalgam (32, 46). Clinical and histological features connected to the resolution of the lesions following replacement of the restoration are evidence of the terminal recognition of OLL to dental material (21, 24). After the restoration was modified, the majority of OLR related to amalgam disappeared in 3 to 15 months (24).

Thornhill et al (54) has shown that only one-third of patients could be distinguished between the two diseases by five oral pathologists, confirming the difficulties of histological differentiation among OLL and OLP. The following characteristics may be present in OLL but not in OLP, according to the authors: a localized perivascular infiltration; deep to superficial inflammatory infiltrate in some or all locations; plasma cells and neutrophils in the connective tissue. According to Juneja et al. (37), the greater epithelial width was seen in OLL compared to OLP. This finding is most likely the result of the release of inflammatory mediators from the cellular inf(63)iltration, which encouraged basal keratinocyte growth. Aside from a continuous thin, linear strip of basement membrane and multiple strands extending into the irregular connective tissue, the number of mast cells, neutrophils, and macrophages are noticeably significant in OLP than in OLL. As a result, these factors might be helpful for differentiating between OLP and OLL(37). However, it is crucial to stress the significance of ruling out the existence of Candida infection, frequently associated with OLLs (64),

particularly in regions of ulceration because both can lead to neutrophil and plasma cell accumulations (54). Figure 1 shows a sample of OLL in buccal mucosa, and alveolar ridge owing to amalgam restoration.

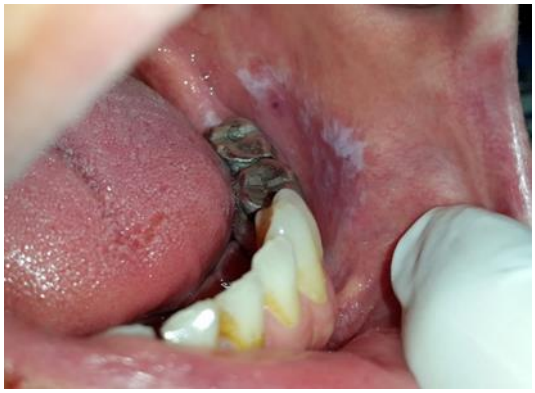

Figure 1 A sample of OLL in buccal mucosa, and alveolar ridge owing to amalgam restoration of 1st and 2nd mandibular molar(65).

1.7. Recent perspectives

The mercury in amalgam causes neurotoxicity, kidney dysfunction, reduced immune efficiency, intestinal and oral bacterial changes, congenital disabilities, and harmful effects on public health. Despite this, it seems that there is no connection between physical disorders and the use of amalgam. Examination of patients who had amalgam showed that the main complaints of most of them are oral, dental and medical problems not related to these restorations. A small percentage of those sensitive to mercury, 1-2 %, may react to mercury released from dental amalgam. The occurrence of adverse effects is estimated to be 1 person in every 1 million cases. Acute hypersensitivity reactions occur 2-24 hours after amalgam removal and replacement, and symptoms disappear after 10-14 days. Rarely, chronic reactions due to toxic reactions or increased sensitivity also occur. When the response is in the form of increased sensitivity, the most common antigens are mercury or bonded mercury(66). In rare cases, they are copper, palladium, silver and zinc. Boghazi researchers call this type of reaction "galvanic waste" and believe that the electric current produced between the restorative materials of the tooth is responsible for it. Neither clinical nor laboratory evidence supports this hypothesis. Histopathologically and clinically, the lesions are similar to true lichen planus, there is no evidence of a specific hypersensitivity reaction to tooth filling materials, and no improvement in symptoms was observed after amalgam removal.

There is a subgroup whose lesions are not displaced and usually involve only the mucosa in direct contact with the amalgam. These lesions heal rapidly after removal of the adjacent amalgam and should be considered a contact lichenoid reaction rather than a true lichen planus. By performing a mercury skin test, almost 50% of patients with contact lichenoid reaction are positive, but in patients with idiopathic lichen planus, the test is positive in about 5%. Although the number of patients a positive skin reaction is more than the amount in the control group, the number of patients who do not respond at first is impressive. This difference can be the result of contact reactions caused by direct toxicity with the toxic substance or an allergic reaction to another substance of amalgam except for mercury.

1.8. Clinical perspective

The most common site of reaction to amalgam is the posterior part of the buccal mucosa, and the ventral surface of the outer edge of the tongue. The gingival ring that is in direct contact with the subgingival amalgam may also be involved. The lesions are often around the contact area, and are usually white or erythematous, and may be associated with or without peripheral striae. Most patients do not have any symptoms, but frequent erosions may be seen.

1.9. Diagnosis

The diagnosis is based on the clinical manifestations of the lesions, lack of migration, and connection with the adjacent amalgam. However, its histopathological appearance is indistinguishable from lichen planus. Sometimes, a biopsy is helpful to confirm the clinical guess and rule out other diseases (such as epithelial dysplasia). In the past, the mercury skin test was an essential diagnostic method, but many researchers showed that this test was falsely negative in many patients. Therefore, the best way to diagnose is to have clinical symptoms and histopathological appearance regardless of skin test results.

1.10. Treatment and prognosis

Local measures such as improving oral and dental hygiene, smoothing, polishing and creating a new contour should be used before more invasive methods because many similar lesions have also been reported as a result of surface plaque accumulation. If this treatment is not successful, if possible, the amalgam material should be replaced with another non-metallic material. Other materials chosen as alternatives include: yellow gold, white gold, and PFM (persan attached to metal). In a study on 142 patients, with contact liquid reaction, amalgam was replaced with yellow gold and PFM. In this group, all mucosal lesions were removed or improved after replacement with yellow gold. While replacement with PFM, 95% of lesions improved.

Even if there is no liquefied contact reaction, amalgam replacement is useful in many patients, because many of these teeth have a significant extension in the buccal mucosa and sound effects are obtained by replacement. The prevalence varies between 87 and 100%. Although the numbers of lesions that do not respond to replacement is tiny, many of the same number are caused by the improper choice of replacement material. Some researchers reported the recurrence of lesions after replacement with composite resin(67, 68). However, some believe it is caused by plaque accumulation in the lesions and is not a true recurrence(69-71). If the clinical diagnosis is in doubt or the mucosal changes do not respond to the proposed treatment, a biopsy should be performed.

2. Discussion

In spite of the widespread application of amalgam as a posterior restorative agent, a small number of cases of amalgam hypersensitivity have been documented; the most typical kind is a delayed oral lichenoid response (72, 73). The literature describes OLRs brought on by amalgam restorations and includes symptoms including eczema, urticaria, wheals on the face and limbs, rashes, and sometimes pink or Kawasaki illness (13, 14, 74). Systemic responses have been reported in a number of cases (63). Due to amalgam's insolubility and the washing action of saliva, OLRs are seldom observed (75, 76).

Type 1V hypersensitivity has a complicated etiology. The response begins when haptens come into touch with the mouth mucosa. A hapten is an unfinished antigen interaction with proteins or their equivalents to form a finished antigen (77). Sensitization often happens when haptens come into touch with the mouth mucosa. Occasionally, skin contact with haptens can also cause sensitization. The activation of memory T cells occurs shortly after the initial encounter. A type IV hypersensitivity reaction takes place after being exposed to the same allergen once again (63, 74). Depending on how severe the response is, this reaction may not occur for a minimum of 48 hours, and the clinical presentation could change. Acute or chronic responses are also possible (63).

Depending on the kind of allergic reaction, the allergen location and the length of exposure, several clinical manifestations may occur. The lesion was entirely gone once the problematic amalgam restoration was removed, and filled with composite restorations. Burning or redness may be evident in patients with acute lesions (63). Vesicles are infrequently observed and, when they do, they usually burst soon after they develop. Areas of erythema, oedema, desquamation, and possibly ulceration characterize chronic lesions in most cases. A red halo is evident, and erosions with a rough surface and uneven boundaries can also be a symptom of allergic contact stomatitis (58, 63, 75). Mercury, tin, copper, and zinc, which are corrosion products of amalgam in this instance, may have functioned, as haptens and sparked the inflammatory process, causing a delayed oral lichenoid response. OLP and OLR lesions are comparable. OLP lesions can be distinguished from OLRs, though. OLR lesions are frequently asymmetrically located and frequently adjacent to amalgam restorations (78). OLP lesions, on the other hand, are more common, bilateral, and draw attention due to their symmetrical prevalence. When diagnosing an OLR, a thorough medical history, and clinical and histological tests, are crucial. Histopathological analysis can be used to differentiate OLRs from other oral disorders like bullous diseases, leukoplakia, lupus erythematosus, etc. A thorough history of the current symptom and the clinical course is the first step in the identification of allergy-induced disorders. Several papers demonstrate using MELISA (memory lymphocyte immunostimulation assay) and patch tests to assess mercury sensitivity. Patch testing is used to show that cell-mediated hypersensitivity responses, such as contact dermatitis, exist (79). The approach entails the epicutaneous injection of a particular allergen at a set concentration and in a defined medium that, in a sensitized individual, will result in a cutaneous inflammatory reaction but not in a non-sensitized person. In order to do the epicutaneous test, Fregrert (58)and several others (80-82) developed a classic sequence of dental materials applied to the skin. In order to clarify any potential contact allergies to amalgam, Hensten-Apaettersen and Holland created a standard collection of allergens to be used in epicutaneous testing (58). Another popular method is the dental series epicutaneous test batteries of the patch test (Trolab® allergens, Trolab Biodiagnostics Ltd, Worcestershire, UK) (33). A modified lymphocyte stimulation test based on assessing the proliferation of peripheral blood memory cells is called MELISA (memory lymphocyte immuno stimulation assay test). It is utilized to detect such people and quantify immunological

sensitization brought on by metals (83, 84). Using MELISA®, Podzimek et al. (85) discovered that following mercury stimulation of their lymphocytes, people with mercury allergies generate less gamma interferon and more anti-sperm antibodies in supernatants. If the lesions are near amalgam fillings, it is advised that patch tests be carried out on individuals with OLR. Whether there is a positive patch test reaction to mercury or amalgam components and no indications of concurrent global lichen planus, replacement of such restorations are advised.

3. Conclusion

Dental amalgam has been effectively employed as a therapeutic material, due to its longevity and insensitivity. As amalgam offers a long-lasting, robust, and reasonably priced restorative alternative, the clinician should not be discouraged from using it in situations where it is suggested by the presence of an allergy to it or any of its components.

Cases with only obvious OLL symptoms and a detailed medical history should be assessed for amalgam replacement to evaluate for repair. If the lesions are near amalgam fillings, it is advised that patch tests be carried out on cases with OLL. Whether there is a positive patch test reaction to mercury or amalgam components and no indications of concurrent global lichen planus, replacement of such restorations are advised.

Compliance with ethical standards

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Disclosure of Conflicts of Interest

The authors declare no potential conflict of interest.

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