Oral Lichenoid Reaction: A Review
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Abstract
Oral lichenoid reactions are disease conditions with definite identifiable aetiology. It can occur either due to intake of drug i.e. lichenoid drug eruptions or due to contact with some potential irritants which majority of times are dental materials. Some other allergens including certain food items are also reported. Some systemic conditions such as chronic liver disease, hepatitis C virus infection and Graft versus Host disease are also reported to be associated with oral lichenoid reactions. Intraoral contact allergy reactions are clinically not very well differentiated and understood, and are not very commonly described in the literature. Although such reactions appear to be barely relevant, reports suggest that they may be more frequent than believed. Oral lichenoid reaction is known to be a difficult diagnosis because of its close resemblance to oral lichen planus; however there are some discriminatory features between the two conditions. Epicutaneous patch testing, together with the clinical manifestations, and the most widely used diagnostic approach for this condition. The potential risk of malignant transformation in oral lichenoid reaction makes this entity of more clinical significance and thereby increases the need of proper understanding of its diagnosis and management.

Key words: Oral lichenoid reaction; Oral lichenoid lesion; Oral lichenoid drug reaction; etiopathogenesis; Lichen planus

Introduction
Oral lichenoid reaction (OLR) is considered as a variant of oral lichen planus (OLP) as long ago as 1929.1 It can be considered as a separate disease or as an exacerbation of already existing OLP, by intake of medication or presence of dental material.2,3 In recent consensus, oral as well as cutaneous involvements has been reported. Reports say that lichenoid reactions are lesions with an identifiable aetiology but are clinically and histologically similar to lichen planus and in many cases, differentiation is difficult or impossible. Various drugs which are known to cause OLRs include beta blockers, dapsone, oral hypoglycemics, non-steroidal anti-inflammatory drugs (NSAIDs), penicillamine, phenothiazines, sulfonyleurases and gold salts.4 Other than drugs, OLPs have also been associated with dental materials. OLR as an allergic reaction to dental materials has been widely reported.4,5 In most cases, OLR is indistinguishable from idiopathic OLP, clinically or histologically. However, these lesions are known to be distinguishable by indirect immunofluorescence study and patch test. The present paper serves a comprehensive discussion on the various aspects of OLRs, and makes an attempt to illustrate a better understanding of the entity.

Pathogenesis
Cell-mediated immune dysregulation has been associated with pathogenesis of OLR.6 There has been recent data published suggesting that OLP is a T-cell mediated autoimmune disease in which auto-cytotoxic CD8+ T cells stimulate the apoptosis of oral epithelial cells.7 However in OLR, considering it as a progression of OLP, the evidence seems to support a varied mechanism.8 Keratinocyte antigen expression is probably induced by systemic drugs (lichenoid drug eruptions), contact allergens in dental restorative materials (contact hypersensitivity reaction), mechanical trauma (Koebner phenomenon), bacterial or viral infection or unidentified agent. The CD8+ cytotoxic T cells may trigger keratinocyte apoptosis through activation of the cells by an antigen associated with major histocompatibility complex (MHC) class I on basal keratinocytes.9 As also, the activity of any drug may be at both the tissue as well as at the nodal sites. The presence of autoantibodies and plasma cells in the infiltrate has been mentioned. If there is a direct effect on the B lymphocytes, this also

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happens in the peripheral blood and regional lymph nodes.\textsuperscript{10}

Many drugs, however, are able to act locally in the tissues and for cause mast cell degranulation or perhaps local release of neuropeptides which act directly on mast cells. The subsequent release of TNF-\(\alpha\) and other cytokines must cause lesion progression and persistence.\textsuperscript{10} This process provides explanation for exacerbation of lichenoid reactions from OLP. Furthermore, it provides a nexus between OLP and lichenoid drug eruption (LDE). at least in those instances where a drug is responsible for a flare in lesion activity.\textsuperscript{11} Moreover, dental materials also induce hypersensitivity reaction. Thornhill et al.\textsuperscript{15} found that of about 70\% of amalgam hypersensitivity lesions which were presented as lichenoid reactions showed patch test positive results for amalgam or mercury compared with only 3.9\% of OLP cases, and thereby 93\% of cases resulted in improvement after replacement of amalgam restoration.\textsuperscript{12} As also the literature suggests that OLR may be at higher risk of malignant transformation as OLP.\textsuperscript{15}

The pathogenesis of LDE appears to have different routes of antigen presentation.\textsuperscript{13} However, exact mechanism is still unknown. Patch test in subjects with lichenoid eruptions indicates that most of them are in fact allergic to the substance. Penicillamine is known to change surface antigen and the sulphhydryl groups of captopril change enzyme systems.\textsuperscript{14} These aberrations may precipitate an immune response to epidermal antigens leading to LDE.

Contact allergy to dental materials (presented as lichenoid reactions) mostly involves Type IV delayed hypersensitivity reaction.\textsuperscript{15} Type IV hypersensitivity involves cell mediated immunity primarily macrophages and T lymphocytes which are sensitized to antigens (haptons).\textsuperscript{4} In most cases, haptons are the substances responsible for the induction of contact sensitivity. A hapten is an incomplete antigen of low molecular weight (usually under 500 Daltons) that binds to proteins to produce the complete antigen. In this sense it is essential for the hapten to penetrate the skin or mucosa, with uptake by the Langerhans cells (LCs) and binding to the type II major histocompatibility complex for presentation of the antigen to the lymphocytes. Within the lymph nodes, the LCs with the antigenic peptide come into contact with the HLA-DR molecules of virgin lymphocytes, resulting in the induction of a series of metabolic and morphological changes in these latter cells, with the production of different cytokines capable of modulating and amplifying the corresponding immune response. Type I (i.e., IgE-mediated immediate hypersensitivity) reactions are comparatively much less frequent.\textsuperscript{16} Type I reaction is not mediated by immunocompetent cells but by antibodies. The manifestations may occur at any point of the skin (though with a predilection for the face and limbs), and particularly the mucosal membranes.\textsuperscript{15}

**Etiological Agents:**

Although the precise aetiology of OLP is unknown, the OLR are disease conditions with definite identifiable aetiology\textsuperscript{13}

**Systemic Medications:** Multiple cases of LDE were diagnosed in allied military personnel in the Pacific, the southern European and the Indo-Burman theatres in World War II, who were taking prophylactic antimalarial drugs, but reports were suppressed until after the cessation of hostilities.\textsuperscript{3,17-20} In LDE, there is a latent period right from ingestion of the drug to the appearance of the symptom. This latent period depends on the type of drug.\textsuperscript{3,15,11} Many drugs have been reported to show LDE. Table 1 shows the common medications which are known to produce LDE.

NSAIDs especially fenofenac, fenybutazon and Salsalate are known to cause LDE, specially the erosive type. Anti-hypertensives causing the lesion are propranolol, methyldopa, practolol, oxprenolol etc (Fig 1a & b). LDEs are also reported to occur after use of antimicrobials penicillin, tetracycline, cyclosporine, indomethacin, prednisolone.\textsuperscript{23}

Recent reports regarding Imatinib mesylate STI571 causing the lesions is being published. It is an oral cancer drug that selectively inhibits several protein tyrosine kinases associated with human malignancy. The drug is used for the treatment of chronic myeloid leukaemia (CML), malignant gastrointestinal stromal tumors, and some other conditions. Because of the excellent clinical response in CML the drug has recently been approved as a first line treatment for CML patients. Because the
drug is orally available and has a high haematological and cytogenetic response, it has become the gold standard for treatment of CML. Moreover, Carbamazepine which is a drug with GABAnergic properties and blocker of N-methyl D-aspartate (NMDA) receptor and with potential to induce the appearance of LDE type lesions, reports show that the appearance of LDE generally occurs a long time after the patient has started the use of the medication.

Dental Materials
- Dental amalgam
- Composite and resin-based materials
- Porcelain
- Glass ionomer cement

Metals
- Gold
- Nickel
- Copper
- Palladium
- Cobalt
- Indium

Drugs
- Anti malarials
- NSAID’s
- Angiotensin- converting enzyme inhibitors
- Diuretics
- β- Blockers
- Oral hypoglycemics
- Gold salts
- Penicillamine
- Anti- retrovirals
- Imatinib mesylate STI571
- Carbamazepine
- Fludarabine

Systemic Condition
- Chronic liver disease and Hepatitis C virus
- Graft versus Host disease

Other Allergens
- Flavouring agents in dentrifices
- Tobacco chewing
- Spices (Cinnamon)
- Menthol
- Chewing gums

Table 1: List of causative / exacerbation factors for OLR

Fludarabine a purine antimetabolite is an immunosuppressive drug given in hematologic malignancies is thought to develop graft versus host disease. Sometimes even synergistic action of drugs in multiple drug therapy gives rise to these lesions. For example, it is stated that in Grinspan’s syndrome, OLP like reactions may be LDE that are induced my multiple drug regimen in the same. Drug reactions may occur anytime, even years after the introduction of the drug.

There are no clear or distinct clinical or histological features that reliably distinguish LDE from OLP or other lichenoid lesions. However, oral LDEs can appear at sites atypical for OLP and unlike OLP, lesions tend to be unilateral. LDEs involve labial mucosa more commonly than OLP. As also, HIV infections are associated with increased labial involvement.

Dental Materials: Contact of the oral mucosa to selected dental restorative materials, particularly mercury-containing amalgam, appears to induce a sensitivity response resulting in immune-mediated damage of the basal epithelial keratinocytes. Common dental materials causing OLRs are enlisted in Table 1. Amalgam fillings inducing OLRs have been reported in many studies. Some studies claim that OLR due to amalgam may possibly have a risk of malignant transformation. Dental cast alloys contain nickel, gold, palladium, cobalt or copper which could lead to reactions such as OLRs and gingival inflammation. Amongst them, the most common metal known to cause OLRs is nickel, which holds special importance in dentistry as it is the most used metal in orthodontic appliances and crown/bridge restorations. Interestingly, gold which is known to be an inert metal is the dental material which most often shows positive epicutaneous testing, even more so than mercury. Although a common physiopathological basis is involved, dermatitis caused by gold in jewellery seems to be independent to a point of the reactions seen at oral mucosal level. Gold in the mouth appears to be more prone to induce sensitization than gold at skin level due to factors such as temperature, chemical products in foods and drinks, continuous friction, and the presence of saliva.

The contents of composite resins which include HEMA, Bis-GMA and methacrylate resins have also been described to cause...
reactions, although light curing of the material inhibits the free molecules of the material.\textsuperscript{32} The study done by Ali et al.\textsuperscript{23} Which investigated the relationship between OLR present in inflammatory fibrous hyperplasia and the hypersensitivity to the methacrylate, has shown that 23% of patients with positive cutaneous tests after removal of the prosthesis showed resolution of the complaint of burning mouth. Composites has got less frequency to cause hypersensitivity reactions since free-monomer rates are lower than 1% of the whole product, which are still lower in materials of dual polymerization and higher in self-curing ones.\textsuperscript{32} Allergic reactions have also been described to provisional acrylic crowns - the cause being attributed to the non-polymerized resin.\textsuperscript{16} (Fig 1c)

**Chronic Liver Disease and Hepatitis C:** Association between OLP and chronic liver disease and hepatitis C viral infection (HCV) has been demonstrated in some studies.\textsuperscript{33,34,35} There are many theories which described association between OLP and HCV infection. First, alteration in the epidermal antigenicity induced by HCV infection leading to proliferation of keratinocytes and secondly, cytopathic replication of HCV eliciting an autoimmune response.\textsuperscript{33,36,34} The treatment rendered for HCV infection, namely, interferon and ribavirin therapy are known to cause exacerbation of OLP to OLR.\textsuperscript{35}

At present, the mechanism of interferon causing exacerbation of these lesions after starting the therapy is not known but it is probably related to HCV associated cell-mediated immune response that is stimulated by the interferon or it can be drug related hypersensitivity reaction.\textsuperscript{36} Nagao et al.\textsuperscript{35} reported an aggravation of OLP after treating a patient with interferon alpha-2b and ribavirin for 18 weeks which needed to be discontinued, with partial improvement of oral lesions after eight months of discontinuation of interferon therapy. LP has an unpredictable course in the setting of HCV and interferon treatment. Informed consent, when using interferons in the setting of lichen planus, therefore should include possible worsening of condition.\textsuperscript{36}

**Tobacco Chewing:** OLP like lesion at the site of placement of the betel quid placement is termed as ‘betel quid lichenoid lesion’ by Zain et al.\textsuperscript{37} The lesion consists of white, linear, wavy, parallel, non-elevated streaks which could not be scraped off. In some instances the lesions radiated from a central erythematous area can be observed. (Fig 1d)

**Graft-Versus-Host Disease (GVHD):** It is a major complication that arises in recipients of allogeneic hematopoietic stem cell or bone marrow transplantation. Although the etiopathogenesis of GVHD is not fully understood, it appears to be due to donor T-lymphocytes’ reaction to minor histocompatibility tissue antigen expression by recipient cells, epithelial basement membrane disruption and basal keratinocyte apoptosis.\textsuperscript{2,3} GVHD is divided into acute, that is occurring within 100 days after transplantation, or chronic, appearing more than 100 days after transplantation. Acute GVHD affects predominantly 3 specific organ systems: the skin, the liver, and the gastrointestinal tract, including the oral cavity. In chronic GVHD, a greater number of organs tend to be involved, and oral involvement, including salivary glands, is more prevalent.\textsuperscript{38,39} Previous studies suggest that GVHD and concomitant immunosuppressive therapy may increase the risk for solid cancers, particularly squamous-cell carcinomas of the oral cavity and skin.\textsuperscript{40,41} This would indicate that oral lichenoid lesion associated GVHD i.e. (OLL-GVHD) like OLP, is a condition associated with risk of malignant transformation.

**Clinical Features**

Pain is the most prevalent symptom of OLRs. The patient symptoms vary from slight to severe. But most of the cases manifest moderate symptoms. Certain oral complications such as metallic taste or dry mouth can be observed. The prevalence rate of OLRs is approximately three times higher in women than men, the peak range being found from the age of 50 years onwards.\textsuperscript{32}

OLRs usually have the same clinical features as those of idiopathic OLP. However, few clinical features suggestive of OLR include:

1) Atypical sites for OLP such as palate, unilaterality and erosions.\textsuperscript{42,43}
2) OLR has direct topographic relationship to the suspected causative agent. (i.e., direct contact) with filling/dental restoration(s) or another offending contact agent (e.g., cinnamon)\textsuperscript{12,43}
3) Typical sites include the lateral borders of the tongue and the buccal mucosa,
sites that have a direct anatomical relationship.\textsuperscript{12,44,45}

4) These reactions can represent in reticular, plaque, atrophic, or erythematous form.\textsuperscript{11}

**Histological Features**

Histological features of LDE and idiopathic OLP are very similar (Fig 1e). However, certain studies have shown some distinguishing features of lichenoid reactions. These are:

- Inflammatory infiltrate in deeper focal areas
- Focal perivascular infiltrate.
- Plasma cells and neutrophils in the connective tissue.\textsuperscript{10,46}
- Eosinophils are present in the sub-epithelial infiltrate.\textsuperscript{47} Parakeratosis and presence of colloid bodies in the epithelium are some of the other histological features of lichenoid reactions.\textsuperscript{47-49} Some researchers have commented that the histological appearances of LDE lesions can resemble those of discoid lupus erythematosus as both the lesions show common features like (hyperkeratosis, deep patchy distribution of lymphoid infiltrate, plasma cells, eosinophils, intra-epithelial colloid bodies).\textsuperscript{48,50} Hence, histopathology alone cannot give an accurate diagnosis of lichenoid reactions.

Figure 1: The various clinical appearances like erosive lesion in diabetic patient on the buccal mucosa (a) which disappeared after discontinuation of drug (b), oral lichenoid reaction associated with metal ceramic restoration (c) and tobacco associated lichenoid reaction (d). The photomicrograph shows Juxta-epithelial chronic inflammatory cell infiltration (e). (H and E stain 10x)
Immunofluorescence
Direct immunofluorescence proves to be useful for early diagnosis of these lesions. It is used to detect autoantibodies that are bound to the patient’s tissue. It show a linear pattern and intense positive fluorescence with anti-fibrinogen that outlines the basement membrane zone in frozen sections.\(^{51,52}\) Immunoglobulin’s and complement factors may be formed as well, but they are less common than fibrinogen deposit. There are some studies which have suggested that immunofluorescent changes in the lesion are secondary events, following damage to the lower epithelial and basement membrane zone.\(^{53}\) These findings are similar in idiopathic OLP and LDE.\(^{54}\)

Detection of the presence of circulating antibodies in the blood is done by indirect immunofluorescence. ‘String of pearls’ reaction or basal cell cytoplasmic autoantibody (BCCA) reaction is seen by indirect immunofluorescent in OLRs. This aids in diagnosis of these lesions.\(^{55,57}\) The technique however is not suitably reliable to be used as a substitute for clinical diagnosis of the lesion.

**Diagnostic Criteria:** The diagnostic criteria for oral lichenoid contact lesions are as follows.\(^{11,32}\)

<table>
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<tr>
<th>Diagnostic Criteria</th>
<th>Commentary</th>
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<tr>
<td><strong>Clinical presentation</strong></td>
<td>A direct topographic relationship between the suspected causative restorative material and the lesion.</td>
</tr>
<tr>
<td><strong>Histopathology</strong></td>
<td>Not always required, except for exclusion of malignancy.</td>
</tr>
<tr>
<td><strong>Patch test</strong></td>
<td>Patch testing can assist in determining what alternate materials to use.</td>
</tr>
<tr>
<td><strong>Covering replacement</strong></td>
<td>Coverage / removal of the suspected causative restorative material(s) should result in resolution of the lesion thereby establishing the diagnosis.</td>
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Table 2: Parameters for diagnosis of OLRs

**Patch Test:** Skin provocation testing appears promising and may help to define those people who show a ‘true’ LDE and those with an exacerbation of pre-existing LP. It is known that patients with OLR are allergic to dental materials. The diagnosis is usually made based on a negative patch test. The most recognized & accepted method of identifying allergens responsible for type I and type IV allergic reactions is cutaneous patch testing, commonly being used one is dental series epicutaneous test battery (Trolab) of patch test allergens. The test substances are applied to normal skin on the back and read after 72 hours of exposure. The patients are considered as patch test positive to an allergen if they develop erythematous, oedematous (vesicular) or bullous (ulcerative) reaction at the site of contact.\(^{53}\) However, there is as yet no specific test for LDE. Although resolution and recurrence of LDE on withdrawal and exposure of drug is probably diagnostic.\(^{58}\)

Basal cell cytoplasmic autoantibodies are a known phenomenon in drug eruptions and this has been shown to be a useful corroborative test of LDE but its full implications are yet to be understood. However, presence of circulating BCCA along with other factors enumerated in above table can make diagnosis of LDE probable.\(^{56,57}\)

**Malignant Transformation**
The malignant transformation rate of this controversial pathology varies widely in the literature from 0.4 to 6.5%, in most studies it does not exceed 1%\(^{54,55}\). In comparison malignant transformation rate of OLP ranges from 0% to 5.3% with the highest rate noted in erythematous and erosive lesions.\(^{60,61}\) In recent years, the process of malignant transformation of the OLR has been related to a possible “field cancerization” phenomena, by which all associated events would predispose these patients to a greater risk of multiple and/or multifocal neoplastic malignancies in the oral cavity.\(^{62}\) Classically a greater risk has been described for malignant transformation of the “atypical” clinical presentation, specially the atrophic and erosive-ulcerative types.\(^{59}\) The first evidence of the association of inflammation with cancer was made in the 19th century, based on the observations that the sites of chronic inflammation gave rise to tumours and that inflammatory cells were present in tumour tissues. This could be related to the presence of severe chronic inflammatory response in OLR, behaving similarly to other inflammatory diseases associated with
malignant growth, for instance, inflammatory intestinal disease, chronic esophagitis or chronic colicystitis. The increase of cytokines and growth factors, promote and/or facilitate oral carcinogenesis.63

Chronic inflammation produces oxidative damage of the DNA by products derived from inflammatory induced enzymes, such as nitric oxide synthase (iNOS). Another inducible inflammation enzyme is cyclooxygenase-2 (COX-2) that acts inhibiting apoptosis of the keratinocytes and in so doing, facilitates carcinogenesis.59 Moreover, patients with GVHD & its therapy elicitting OLR are at increased risk of developing oral squamous cell carcinoma, thus long term surveillance is indicated for early detection & treatment of associated malignancy.58,60,61 Thus, according to recent definition of precancer OLR can be considered as oral potentially malignant disorder.64 The recent classification by Sarode et al.65 includes this entity as potentially malignant disorders under group IIb (chronic inflammation mediated carcinogenesis caused by external factors).

Management

Accurate management of this lesion follows accurate diagnosis of this ambiguous pathology, as it bears clinical & histological resemblance with OLP.2,3,29,42,43 Since the management and also the risk of malignant transformation of both these lesions differ, expert opinion from an experienced oral pathologist is a must to avoid major discrepancy in it being diagnosed as OLP.66 OLR are seen in direct topographic relationship to an offending agent. With the removal and replacement of the putative causative material, the majority of such OLCLs resolve within several months. The use of alternate dental material in case of allergic response to the material, and use of alternate drug in cases of LDE proves to be fruitful.22 Local therapies for oral chronic GVHD rely on topical agents, predominantly corticosteroids. Other agents include topical budesonide, dexamethasone mouth rinse, cyclosporine, azathioprine, topical tacrolimus is also promising.11

Given that GVHD often will involve multiple systems or organs, treatment for OLL-GVHD is usually an integral part of the systemic management. Treatment specific and solely for OLL-GVHD, is indicated as a supplement to systemic therapy, only if intensifying the systemic immunosuppressive therapy can be avoided. Unfortunately, to date there are few well controlled trials of systemic therapy for GVHD that have explicitly assessed the effect or benefits on OLL-GVHD, and even more infrequent has been the assessment of therapies, local (topical) or systemic, specifically for OLL-GVHD.40,41

Conclusion

OLR is a disease condition with definite identifiable aetiology. Cell-mediated immune dysregulation has been associated with pathogenesis. The diagnosis is problematic because of its close resemblance to OLP both clinically and histopathologically. However, there are some discriminatory features between the two conditions. Epicutaneous patch testing, together with the clinical manifestations, being the most widely used diagnostic approach in such situations. The potential risk of malignant transformation in OLR makes this entity of more clinical significance and thereby increases the need of proper understanding of its diagnosis and management.

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