Aetiology, diagnosis and treatment of oral lichen planus

Oral lichen planus is a common condition which can have negative effects on a patient's quality of life. This article reviews the aetiopathogenesis, management and malignant potential of oral lichen planus.

Oral lichen planus is a chronic immune-mediated inflammatory disease. A meta-analysis calculated an incidence of 1.27% in the general population (Carrozzo, 2008).

Oral lichen planus can appear at any age, in either gender, but it is more common in females with an onset between 30–60 years of age. Lichen planus can also affect the skin and genital mucosa – genital and cutaneous lichen planus are respectively associated with about 20% and 15% of cases of oral lichen planus (Farhi and Dupin, 2010). Less commonly, other sites such as the pharynx, oesophagus, nails and nasal mucosa are involved.

The basis of oral lichen planus is likely a T-cell mediated response to an unknown trigger (Payeras et al, 2013). Factors implicated in oral lichen planus include systemic medications, dental materials, viruses and genetic susceptibility (Farhi and Dupin, 2010).

Oral lichen planus is considered a potentially malignant disorder, and regular reviews and self monitoring are advocated long term (Gonzalez-Moles et al, 2008). Treatment is predominantly directed at symptomatic relief and most commonly includes topical analgesics and topical immunosuppressants (Al-Hashimi at al, 2007). Recalcitrant disease may require systemic immunosuppression.

Clinical appearance

Clinically oral lichen planus has a wide spectrum of presentations varying from asymptomatic lesions to painful ulcerated lesions, resulting in a negative effect on patients' quality of life and affecting eating, drinking and speaking. Often, acidic, hard or spicy food exacerbates symptoms.

Oral lichen planus typically presents as white lace-like or plaque lesions which may have associated ulcerated lesions. Usually it presents with a bilateral distribution, affecting the buccal mucosae, tongue and gingivae most commonly (*Figures 1* and *2*). Areas of erythema may also be interspersed throughout and where the gingivae are involved the term 'desquamative gingivitis' (*Figure 3*) aptly describes the gingival presentation.

Dr Kevin Ryan *is Specialist Registrar in Oral Medicine and* **Dr Anne M Hegarty** *is Consultant in Oral Medicine in the Department of Oral Medicine, Charles Clifford Dental Hospital, Sheffield S10 2SZ and* **Dr Tim Hodgson** *is Consultant in Oral Medicine, Eastman Dental Hospital UCLH Foundation Trust and Eastman Dental Institute UCL, London*

Correspondence to: Dr K Ryan (Kevin.Ryan@sth.nhs.uk)

Figure 1. Oral lichen planus lesions in the right buccal mucosa.

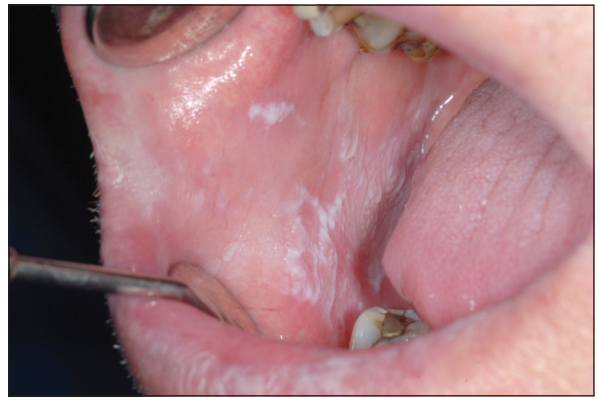


Figure 2. Ulcerative oral lichen planus in the left buccal mucosa.

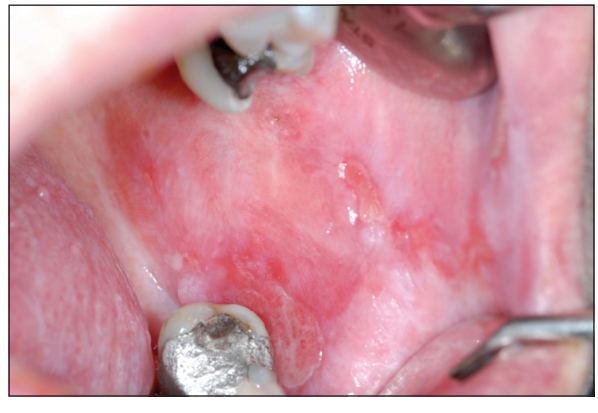
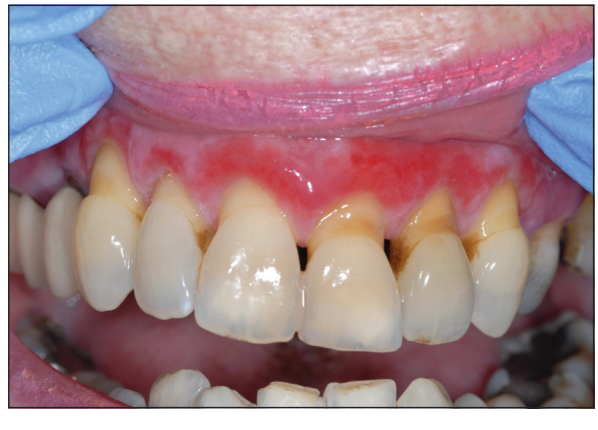


Figure 3. Desquamative gingivitis.



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Six types of lesions have been described (Andreasen, 1968):

1. Reticular
2. Papular
3. Plaque-like
4. Atrophic or erythematous
5. Erosive or ulcerative
6. Bullous.

The most common of these is the white reticular type (*Figure 4*), although in many individuals more than one type of lesion is present at a time.

Oral lichen planus tends to follow a chronic course and, where symptoms are involved, periods of exacerbation and remission are common. In comparison to cutaneous lichen planus (*Figure 5*) where lesions frequently resolve with treatment, oral lichen planus tends to persist despite symptomatically beneficial treatment.

Pathogenesis

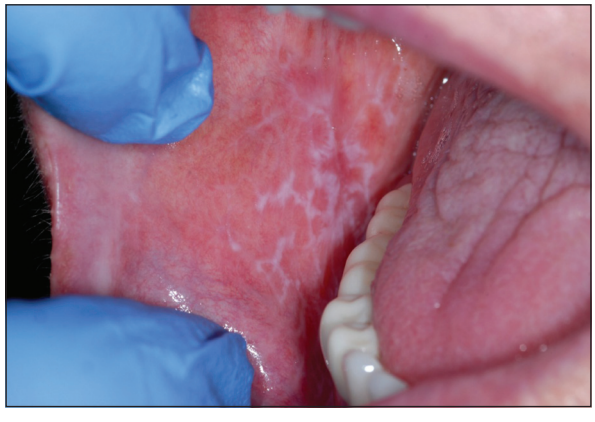
There remains no clear pathogenesis for oral lichen planus. Current evidence supports an inflammatory immune response mediated chiefly by CD8+ T lymphocytes causing epithelial cell apoptosis (Payeras et al, 2013).

Data suggest that these CD8+ T lymphocytes may be activated by an as-yet unknown antigen associated with MHC class I on basal epithelial cells (Lodi et al, 2005). Presentation of antigen by Langherhans cells or epithelial cells to CD4+ T lymphocytes is also thought to occur with MHC class II expressed on these cells. There is a high number of Langerhans cells present in oral lichen planus lesions along the basal layer of epithelium (Villarroel Dorrego et al, 2002).

These activated CD4+ T lymphocytes release cytokines IFN gamma, IL2 and TNF alpha which can also stimulate the CD8+ T cell apoptosis of epithelial cells.

Non-specific immune processes are also involved in the pathogenesis of oral lichen planus. An increase in mast cell density and degranulation has been seen in oral lichen planus lesions (Zhao et al, 2001) and the cyclical interaction between mast cells and T lymphocytes may be a factor in the chronic nature of oral lichen planus.

Figure 4. Reticular oral lichen planus right buccal mucosa.



Aetiology

The nature of the triggering antigen remains unknown. Both intrinsic and extrinsic antigens have been implicated.

When discussing the aetiology of oral lichen planus the term oral lichenoid reaction can cause some confusion. This is a term used to distinguish lesions which are both clinically and histologically similar to oral lichen planus but which have distinct causes in the form of either medications, dental materials or sometimes as a result of graft *vs* host disease (Scully and Carrozzo, 2008).

Drugs implicated include beta blockers, angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory drugs, thiazide diuretics, oral hypoglycaemics, antimalarials, gold and penicillamine.

Dental materials, most commonly amalgam, which are in direct contact with the oral mucosa can also cause distinct isolated lichenoid reactions. These lesions represent a type IV hypersensitivity reaction. Generally these lesions are in intimate contact with a dental amalgam restoration and are unilateral and not symmetrical.

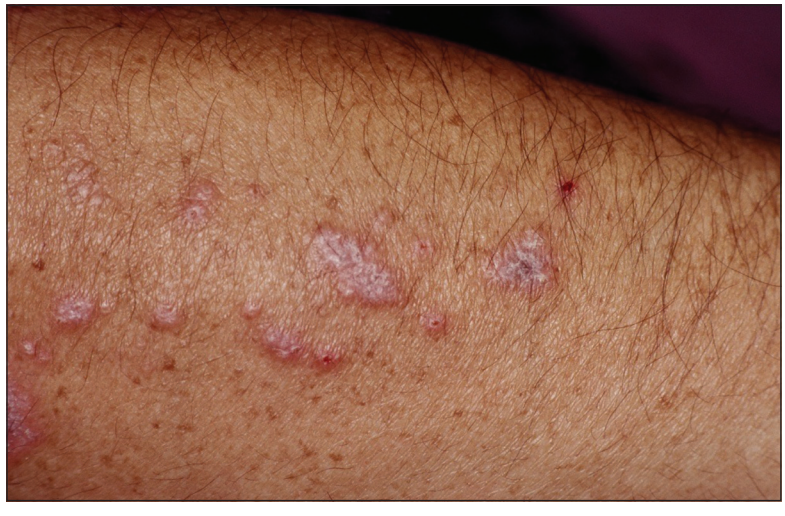
Oral lichenoid reactions also develop in up to 80% of patients with chronic graft *vs* host disease following allogenic bone marrow transplant (Schubert and Sullivan, 1990).

Among other possible extrinsic antigens for oral lichen planus weak evidence supports a role for the herpes viruses herpes simplex virus 1, Epstein–Barr virus, cytomegalovirus and human herpes virus 6 (Lodi et al, 2005).

The strongest evidence to date supports a role for hepatitis C virus in causing oral lichen planus. This evidence suggests a geographical variation (Harman et al, 2004), with individuals living in Southern Europe and Japan more likely to be affected. However, more recent meta-analyses demonstrate an association between hepatitis C and oral lichen planus without any obvious geographical variation (Petti et al, 2011).

Stress is recognized by patients to have an exacerbating effect on their oral lichen planus. However, the evidence

Figure 5. Cutaneous lichen planus.



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is conflicting (Girardi et al, 2011). It can be difficult to determine whether stress and effect on mood is as a direct consequence of the oral lichen planus or a causative factor.

Genetic background has been studied in relation to oral lichen planus and it has been considered that the HLA-DR6 allele in Italian patients may be linked to the association between oral lichen planus and hepatitis C virus (Carrozzo et al, 2001). However, no significant association with any HLA has been reported in familial lichen planus.

Histopathology

The histopathology of oral lichen planus is similar to that of cutaneous lichen planus. However, there remains both intra- and inter-individual variation in the interpretations of histopathology by pathologists (Van der Meij et al, 1999). Whether dysplastic features in the epithelium should be exclusionary in the histopathological diagnosis has also been a source of differences in the literature (Gonzalez-Moles et al, 2008) and this has made establishing a definite clinicopathological definition of oral lichen planus difficult.

Management

In the first instance, as oral lichen planus often presents as a white, red or ulcerated lesion intraorally, the priority is to obtain a definitive diagnosis through biopsy.

Once oral lichen planus has been confirmed, treatment is not given with curative intent, but for symptomatic relief.

In cases where there are few or no symptoms and a mild clinical presentation it is feasible to consider discharge to the care of a dentist for monitoring these lesions. Advice on smoking cessation should be given to patients who smoke.

Topical therapies

Asymptomatic oral lichen planus requires no intervention. The patient should be educated regarding the disease and told to report any new oral symptoms to his/her dentist. Review should be part of the patient's oral health check in primary care and if there are any suspicious lesions the patient should be referred for diagnosis to oral medicine, oral surgery or maxillofacial clinics. Individuals should maintain high levels of oral hygiene and be advised not to smoke or drink excessive amounts of alcohol. They should be advised to use toothpaste which is sodium lauryl sulphate free.

For patients with mildly symptomatic oral lichen planus treatment is largely based on topical corticosteroids, which have proven to be efficacious. Cochrane reviews of interventions to treat oral lichen planus (Thongprasom et al, 2011) and erosive lichen planus affecting mucosal sites (Cheng et al, 2012) note a lack of high quality placebo-controlled trials for treatment of oral lichen planus, with no strong evidence for the efficacy of a single treatment, including topical corticosteroid therapy. While the potent corticosteroid clobetasol is of benefit in oral lichen planus lesions (Conrotto et al, 2006), its potency and risk of adrenal suppression mean that other topical steroids are frequently used instead, including betamethasone as a mouthrinse (McGrath et al, 2003; Al-Hashimi et al, 2007), and fluticasone as both a mouthrinse and spray (Hegarty et al, 2002). These are held in the mouth for up to 5 minutes at a time before the patient spits out in order to avoid any potential side effects from these corticosteroid preparations.

Calcineurin inhibitors in the form of tacrolimus 0.1% ointment have also been effective in managing oral lichen planus and can be considered as second-line topical treatment in cases refractory to topical corticosteroids (Kaliakatsou et al, 2002). They are used with caution because of the possibility of increased risk of malignant transformation of oral lesions, which has been suggested by a single case report (Mattsson et al, 2010). Evidence for a causal link is lacking (Johani et al, 2009). Sirolimus could have advantages in this regard having both immunosuppressive and tumour inhibitory properties (Hodgson and Chaudhry, 2010).

Both topical and systemic retinoids have been used in the treatment of oral lichen planus with beneficial results. While topical retinoids are potentially effective in oral lichen planus they are likely inferior to topical corticosteroids (Al-Hashimi et al, 2007). Owing to the serious side effects associated with systemic use of retinoids and their teratogenic potential they are seldom used systemically in oral lichen planus.

Topical aloe vera use has been found to be effective in improving quality of life scores and clinical appearance in oral lichen planus compared to placebo (Salazar-Sanchez et al, 2010), although a Cochrane review found this evidence to be weak with risk of bias (Thongprasom et al, 2011).

Systemic therapies

Use of systemic steroids is reserved for recalcitrant lesions or in cases of oral lichen planus with severe widespread lesions. Steroid use is limited to short courses.

As with the use of systemic steroids in management of oral lichen planus, there is limited evidence supporting the use of steroid-sparing medications. Azathioprine has been seen to be effective in cutaneous lichen planus with indication of similar benefit in oral lichen planus (Al-Hashimi et al, 2007). Thiopurine methyltransferase levels are always checked before commencing azathioprine because of the risk of myelosuppression. If used, its dose is gradually increased to a maximum of 2 mg/kg to ensure no side effects, with weekly blood tests initially to monitor full blood count and liver function. Long-term use of azathioprine carries the risk of infection and increased risk of malignancy (Schiavo et al, 2010).

While evidence supporting use of mycophenolate mofetil in oral lichen planus is limited, as it has a better safety profile in organ transplant patients compared to

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azathioprine, it can be considered for use in refractory oral lichen planus (Al-Hashimi et al, 2007). As with azathioprine use, however, monitoring of bloods is required and increased risk of infection and malignancy should be noted.

Other treatments

Less commonly used treatment modalities include phototherapy which encompasses photodynamic therapy, ultraviolet A, ultraviolet B and laser use. Photodynamic therapy, using a photoactive dye and laser device, has immunomodulatory effects. This is considered a safe treatment option and has shown positive results in treatment of oral lichen planus (Kvaal et al, 2013). The use of both CO_2 lasers and low-level laser therapy has also shown beneficial results (Cafaro et al, 2013), although their use is limited by cost and familiarity with their use. It should also be noted that lesions treated with laser cannot be histologically examined for malignant change.

A recent review of ultraviolet A and ultraviolet B phototherapy for use in oral lichen planus found limited effects of the various treatments with no strong evidence for their effectiveness in oral lichen planus (Pavlic and Vujic-Aleksic, 2014).

Management of lichenoid reactions

Management of lichenoid reactions is dependant on whether a definitive cause, such as a dental material or medication, can be established. Patch testing to the dental series can be carried out on skin because of its higher sensitivity to establish a reaction to, most commonly, amalgam or mercury. Readings are taken after 48 and 72 hours. Late reactions up to 2 weeks after placement of the various materials should also be considered.

The combination of a positive patch test and close association between the oral lesion and amalgam restoration gives a good indication that the lesion will improve following replacement (Al-Hashimi et al, 2007). In order to determine if a drug is involved in a lichenoid reaction, cessation of that drug is required with follow-up to assess for lesion resolution. For many patients this is not a practical option as the risks involved in medication cessation may take priority over any potential benefit in resolving oral lesions.

There remains a need for large multicentre studies to further our understanding of successful treatment options in oral lichen planus. A number of therapies are available for use in the management of oral lichen planus, but for many of these, there is not sufficient evidence from the literature to support their widespread application with any deal of confidence.

Malignant risk

Oral lichen planus is classified by the World Health Organization as a potentially malignant disorder which has a significant increased risk of cancer. Defining the frequency of malignant transformation in oral lichen planus is quite difficult because of the large degree of variation in studies, which is related to the absence of universal criteria for diagnosing oral lichen planus in the first instance and also variation in these studies in patient selection, follow-up and information on exposure to other risk factors. Numerous studies report a malignant transformation rate of between 0.5 to over 2% (Gonzalez-Moles et al, 2008).

The literature fails to report a specific type of lichen transforms more commonly than others. The tongue is the most common site of squamous cell cancer development in individuals with oral lichen planus. There is no evidence suggesting a frequency of specialist review and a degree of disease ownership has to be given to the patient for self monitoring and reporting any significant symptom change.

Conclusions

Oral lichen planus is a common condition best managed in the oral medicine setting. Its clinical manifestations can vary from an asymptomatic to a severely painful disease affecting eating and speaking. There are a number of treatment options available, the most commonly used being topical corticosteroids. For severe disease, systemic medications may be warranted including corticosteroid and steroid-sparing medications. Long-term management of symptomatic oral lichen planus may be challenging and the potential for malignant change must be considered. Referral to an oral medicine department is strongly advised for the diagnosis and symptom management in many cases of oral lichen planus. BJHM

Conflict of interest: none.

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KEY POINTS

- Oral lichen planus is a chronic T-cell mediated inflammatory response to an unknown trigger.
- It has a wide spectrum of presentations but typically presents as bilateral white lesions which may be ulcerated.
- Oral lichen planus can have a negative effect on quality of life, affecting eating, drinking and speaking.
- Treatment is predominantly directed at symptomatic relief, most commonly with topical analgesics and/or immunosuppressants.
- Systemic therapies are reserved for severe recalcitrant lesions.
- Oral lichen planus is considered a potentially malignant disorder with regular monitoring required.
- Oral medicine specialists play a key role in the diagnosis and management of oral lichen planus.

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