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Oral Lichen Planus: An Overview

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Introduction

Oral lichen planus (OLP) is an inflammatory disorder of the oral mucosa with a prevalence of 0.5% to 2.2% among adults.[1,2] Disease onset tends to occur between the ages of 30 to 60 years and is observed more frequently among females than males.[2-4] In contrast to the cutaneous lesions of lichen planus, OLP is often chronic and patients are plagued with relapses and remissions.[5] OLP also often causes substantial morbidity, as it is considered to be a precancerous lesion owing to its associations with oral squamous cell carcinoma.[4,6] Rates at which OLP undergoes malignant transformation range from 0.4% to 1.4%, and these rates are highest for the atrophic and ulcerative clinical subtypes of OLP.[7]

Clinical Manifestations

While a bilateral, symmetrical pattern on the buccal mucosa is the most classic presentation of OLP,[4] there are six clinical subtypes that can be observed individually or in combination: reticular, erosive/ulcerative, plaque-like, papular, bullous, and atrophic (also known as erythematous).[5] The most recognized form of OLP is reticular lesions, which are frequently asymptomatic and can appear as multiple papules, plaque-like formations, or lacy patterns (Wickam striae).[4,5] Symptoms associated with OLP include pain, burning, swelling, irritation, and bleeding, especially with tooth brushing or eating. Symptoms are most common with the erosive or atrophic forms of OLP and are reported in approximately two thirds of patients.[2,4] Most patients with OLP experience "isolated" OLP, meaning they lack an associated cutaneous lichen planus or lichen planus affecting other mucosal sites.[8] Among OLP patients, approximately 15% report cutaneous lesions and 20% will have concomitant lesions in the genitalia. OLP may also involve the esophagus and lead to significant dysphagia.[2,9]

Diagnostic Criteria

Two main challenges have been identified in making the diagnosis of OLP: **1)** numerous other disorders either clinically and/or histopathologically resemble OLP, and **2)** the histopathologic features of OLP exist on a spectrum that is directly associated with the stage of disease at the time of biopsy, the clinical subtype, and the anatomic site.[2]

OLP shares overlapping features with oral lichenoid drug reaction, chronic ulcerative stomatitis, and lichenoid contact hypersensitivity reaction.[10] Erosive disease, especially erosive gingivitis,

Clinical Criteria	Histological Criteria
Presence of lesions that are bilateral and more or less symmetrical	Presence of a well-defined bandlike zone of cellular infiltration that is confined to the superficial part of the connective tissue, consisting mainly of lymphocytes
Presence of a lacelike network of slightly raised grey-white lines (reticular pattern)	Signs of liquefaction degeneration in the basal cell layer
Erosive, atrophic, bullous, and plaque-type lesions are accepted only as a subtype in the presence of reticular lesions elsewhere in the oral mucosa	Absence of epithelial dysplasia

Table 1. Modified WHO Criteria[11,12]; *courtesy of Benoit M. Cyrenne, MD.*

Clinical Criteria	Histological Criteria
Multifocal symmetric distribution of lesions	Band-like or patchy, predominately lymphocytic infiltrate that is found in the lamina propria and is confined to the epithelium–lamina propria interface
White and red lesions exhibiting one or more of the following forms: reticular/papular, atrophic (erythematous), erosive (ulcerative), plaque, bullous	Basal cell liquefactive (hydropic) degeneration
Lesions are not localized exclusively to the sites of smokeless tobacco placement	Lymphocytic exocytosis
Lesions are not localized exclusively adjacent to and in contact with dental restorations	Absence of epithelial dysplasia
Lesion onset does not correlate with the start of a medication	Absence of verrucous epithelial architectural change
Lesion onset does not correlate with the use of cinnamon-containing products	

Table 2. Cheng *et al.* Criteria[2]; *courtesy of Benoit M. Cyrenne, MD.*

may present with symptoms and features that are identical to other inflammatory dermatoses such as pemphigus vulgaris or mucous membrane pemphigoid.[2] Given the diverse features and anatomic specifications of OLP, its management and treatment is intrinsically multidisciplinary, involving professionals such as dentists, dermatologists, gastroenterologists, gynecologists, otolaryngologists, and ophthalmologists.[6]

The original World Health Organization (WHO) criteria for diagnosing OLP were proposed in 1978 and underwent subsequent modifications in 2003 (**Table 1**) owing to an absence of correlation between the clinical and histopathological criteria.[11,12] In 2016, a new set of criteria were proposed by the American Academy of Oral and Maxillofacial Pathology (**Table 2**).[2]

The severity of OLP can be measured using validated scoring systems such as the oral disease severity score (ODSS).[13] The ODSS provides a composite measure of the extent of disease intraorally as well as disease activity and degree of pain with high inter- and intra-rater reliability.

Treatments

Behavioural

Given the significant overlap in both the symptoms and histological features of OLP, oral lichenoid hypersensitivity reaction, and oral lichenoid drug reactions, the proper management of any patient with OLP should include a careful review of their medication and exposure history to ensure the correct identification of any modifiable factors. This thorough review may lead to a reduction in symptoms.

Oral lichenoid drug reactions can be caused by a number of different medications and may present with or without cutaneous lesions. The most common medications that may cause a reaction include anti-convulsants such as phenytoin, antibiotics, antihypertensives, antimalarials, and non-steroidal anti-inflammatory drugs (NSAID)s. Onset of symptoms after initiation of an offending medication ranges from weeks to over a year.[2] The most common causes of oral lichenoid hypersensitivity reaction include metals, flavouring agents such as cinnamon or peppermint, as well as dental restorative materials such as acrylates.[2]

Topical Therapies

Topical Corticosteroids

Topical corticosteroids are the first line treatment for all forms of OLP and are used widely to reduce pain and inflammation in the form of ointments and mouth rinses. Oral suspensions of triamcinolone have been demonstrated to be effective.[14] High-potency steroid mouth washes, which are of particular value for patients with widespread disease or posterior oropharyngeal lesions, may be used but care should be taken to avoid pituitary-adrenal axis suppression.[8]

Clobetasol propionate, the most potent topical steroid, is effective at treating OLP and has demonstrated superior efficacy compared to medium potency steroids such as fluocinonide or triamcinolone.[8] While steroid injections have demonstrated efficacy, due to the pain of administration and the association with atrophy, their utility in the treatment of OLP is limited.

Topical Calcineurin Inhibitors

Tacrolimus, a powerful immunosuppressive agent and calcineurin-inhibitor, has been found to have equal or greater efficacy in reducing pain and other symptoms compared to clobetasol,[7,15] and equal efficacy to topical pimecrolimus.[7] Further, despite warnings regarding the risk of carcinogenesis with topical and systemic tacrolimus, there is no evidence of an increased malignant potential of lesions treated with tacrolimus versus clobetasol.[15] Furthermore, tacrolimus is associated with lower rates of oral candidiasis.

Cyclosporine has been evaluated as a topical treatment for OLP in the form of both a mouth rinse and gel with good effect; however, it has failed to demonstrate superior or equal efficacy in comparison with topical corticosteroids, which has limited its clinical use.[16]

Systemic Therapy

Hydroxychloroquine

Commonly used for cutaneous lichen planus or lichen planopilaris, there is limited evidence for the use of hydroxychloroquine in the treatment of OLP. However, some evidence suggests that erosive OLP can be effectively treated with hydroxychloroquine at doses ranging from 200–400 mg.[4] A recent retrospective case series demonstrated that 79% of patients who received hydroxychloroquine experienced a reduction of 25% or more in their ODSS, and that the median time to achieve this level of reduction was 6 months.[13]

Systemic Corticosteroids

Systemic corticosteroids are viewed as the most effective treatment for patients experiencing recalcitrant or erosive OLP, and are recommended as a first line therapy for extensive and/or erosive lichen planus in European guidelines.[16] While they induce rapid resolution of symptoms, the use of systemic corticosteroids is associated with a high rate of relapse, especially in comparison to other therapies.[17] Furthermore, a comparative treatment study did not observe differences in the response to systemic prednisone at a dose of 1 mg/kg/day compared to topical clobetasol; thus, systemic corticosteroids tend to be relied on when topical approaches are ineffective, when OLP is widespread, recalcitrant, erosive, or erythematous, or when other regions are exhibiting lichen planus.[5] While systemic prednisone can be used to treat ulcers and erythema in OLP, it has not demonstrated superiority to treatment with topical triamcinolone acetonide.[8]

Mycophenolate Mofetil

Mycophenolate mofetil is an immunosuppressive agent that has demonstrated effectiveness in treating recalcitrant erosive OLP.[5] Improvements in severe cases are typically observed over an extended period of many months and the treatment is generally well-tolerated.[4]

Azathioprine

Azathioprine is a purine analog that inhibits T-cell activation. The use of azathioprine treatment for OLP has been rarely reported; it is mainly used in predominantly severe or recalcitrant cases, especially when long-term corticosteroid use is contraindicated.[4] Its efficacy was demonstrated in an open-label single arm study in which seven of nine patients experienced a complete clearance of cutaneous and oral lesions after 12 weeks of therapy.[18]

Methotrexate

Methotrexate is an immunosuppressant that exerts its effects by inhibiting folic acid metabolism, which subsequently impedes DNA and cell replication. It has demonstrated efficacy in large case series. For instance, Torti *et al* included a series of 18 patients with erosive lichen planus who were treated with low dose (<12.5 mg/week) oral methotrexate. Ten of these patients demonstrated a 75% reduction in symptoms.[19] The efficacy of methotrexate was further supported in a randomized trial comparing its efficacy with oral prednisone. In this trial, an 8-week course of methotrexate exhibited superior efficacy with a complete response rate of 73.3% compared to a 60% response rate with an 8-week course of prednisone.[16,17]

Janus Kinase Inhibitors

Janus kinase inhibitors (JAKi) are potent and broad-acting immunosuppressive medications that have

been approved for a variety of inflammatory diseases including atopic dermatitis and psoriatic arthritis. They represent a promising new treatment modality for severe cases of OLP. Case reports have demonstrated several successful treatments of recalcitrant erosive OLP using either upadacitinib or tofacitinib.[9] The success of these treatments is attributed to the upregulation of JAK1 and JAK3 levels within OLP lesions.[9]

Systemic Retinoids

Systemic retinoids are vitamin A analogs that exert their effect through the activation of retinoic acid receptors, regulating epidermal proliferation and the cutaneous inflammatory milieu. Studies have examined the use of various systemic retinoids including acitretin, alitretinoin, isotretinoin, and etretinate. Both alitretinoin and etretinate have demonstrated success in treating OLP. Remission was observed in 64% of patients who received these medications orally at a dose of 30 mg daily, compared to the 13% remission rate in patients receiving a placebo at a dose of 30 mg per oral intake daily.[4] A trial comparing topical corticosteroid monotherapy with a combination of topical corticosteroids and acitretin demonstrated significantly improved response rates at 28 weeks. Furthermore, 88% of the combination treatment group achieved an ODSS reduction of 75% (ODSS75) compared to 47% in the group receiving topical triamcinolone alone.[20]

Cyclosporine

Cyclosporine is an immunosuppressant and calcineurin inhibitor that downregulates nuclear factor Kappa B (NF-κB). Most studies have examined its use as a topical formulation with demonstrated efficacy in erosive and atrophic forms of OLP.[21,22] The use of cyclosporine as a systemic agent has been shown to be effective in case reports and case series.[22]

Apremilast

Apremilast is an oral phosphodiesterase type 4 inhibitor that is approved for the management of psoriasis, psoriatic arthritis, and oral ulcers associated with Behçet's disease. Apremilast has demonstrated effectiveness in the treatment of OLP. After 12 weeks of therapy, 55% of the patients treated with apremilast showed improvement.[23] Crushed apremilast has been used to successfully treat OLP in a recent case report.[10]

Anti-psoriasis Biologics

Evidence regarding the efficacy of interleukin (IL)-17 and IL-23 blockade for treatment of oral or cutaneous lichen planus is limited; however, several case reports and small case series have demonstrated evidence of efficacy.[23] Solimani *et al* published a series that included 5 patients in which significant improvement in mucosal ulcerations was observed following the administration of secukinumab, ustekinumab, and or guselkumab.[24] Results of a phase II randomized placebo-controlled trial that evaluated secukinumab for the treatment of lichen planus including mucosal lichen planus (which includes OLP) demonstrated efficacy in the reduction of clinical symptoms, in which 37.5% of patients treated with secukinumab experienced a reduction of symptoms compared to 23.1% of patients treated with a placebo.[25] Of note, within the same trial, patients with cutaneous lichen planus did not demonstrate any improvement with secukinumab treatment.[25]

Light-Based Therapies

Laser Therapy

Low-level laser therapy has been used to effectively treat patients with symptomatic OLP. The following have all been used, with complete epithelialization within three weeks: 308 nm excimer laser radiation, 980 nm diode lasers, and CO_2 laser evaporation.[8] It appears to be an effective treatment when no further improvement is observed with steroids alone.

Photodynamic Therapy

Photodynamic therapy (PDT) uses photosensitizing compounds that, when activated by a specific wavelength of laser light, can destroy targeted cells using strong oxidizers. PDT has been shown to reverse the hyperproliferation and inflammation observed in OLP.[26]

Ultraviolet Irradiation

Photochemotherapy with long-wave ultraviolet light (PUVA) and 8-methoxypsoralen have been effective in treating recalcitrant OLP.[8] Photosensitization with topical 0.01% trioxsalen is recommended to avoid PUVA side effects. Erosive OLP may benefit from photochemotherapy especially if it has not responded effectively to conventional therapies, however, future research into this field would be valuable.[8]

Conclusion

OLP is a chronic, potentially debilitating disease which, in its severe form, requires treatment and clinical monitoring. Despite the high prevalence of this disease, there is a lack of high-quality clinical studies on treatment modalities, which limits our ability to rank treatment options among the myriad available. New treatments with novel mechanisms of action continue to be developed, suggesting substantial promise for the future management of OLP.

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