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Commentary: Systemic Therapy for Mucosal Lichen Planus with a Focus on Oral Lichen Planus: Update and Review of Challenges and Successes

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Introduction

Lichen planus (LP) is a chronic inflammatory dermatosis of the skin, mucosa, hair, and nails. The sites of mucosal involvement include oral, genital, esophageal, ocular, otic, and less frequently bladder, nasal, laryngeal, and anal surfaces[1]. The skin and oral cavity are the two most common sites affected.

Oral lichen planus (OLP), a mucosal variant, tends to be chronic, sometimes involving multiple extra-oral sites, therapeutically challenging, and an oral potentially malignant disease (OPMD)[1-4]. The prevalence of OLP is estimated at 1-2%[5]. OLP is typically more chronic than cutaneous LP. Disease presenting primarily on the gingivae, known as desquamative gingivitis, affects approximately 10% of patients with OLP[3,6].

No curative treatment for LP is available. Therapeutic approaches are directed at reducing inflammation and pain and improving the quality of life. As OLP is considered to be a T cell-mediated disease, therapeutic interventions have targeted the inflammatory pathways underlying OLP[7].

Cutaneous LP may resolve spontaneously over several years, but spontaneous remission of mucosal LP is rare. Periodic follow-up of patients with OLP is indicated. If active disease persists, the patient should be monitored every 3-6 months. At the time of diagnosis of OLP, patients should be counseled about the increased risk of oral cancer and understand the need for periodic examinations even if they are asymptomatic, or if their symptoms are well-controlled[2,4,8].

Mucosal Lichen Planus

The most common extra-oral location of mucosal lichen planus (MLP) is the genital mucosa[1,3,9]. Some patients have multiple mucosal sites involved simultaneously. Patients seldom associate oral symptoms of OLP with symptoms involving cutaneous, genital, or other mucosal sites and may feel uncomfortable when talking about these with their provider. Orogenital LP can affect both women and men[1,10-12]. Gingival involvement is a major component in these patients with the vulvovaginal-gingival and peno-gingival syndromes. As a consequence of chronic erosive and ulcerative mucosal LP scarring may cause major anatomic and functional problems including stenosis of the introitus and obstruction of the urethra. Patients may suffer intense pain with dysuria and dyspareunia[1]. Other mucosal surfaces such as esophageal,

conjunctival, and otic tissues may be involved. Involvement in these areas causes great morbidity[13-15].

The coexistence of OLP and vulvar lichen sclerosus (LS) is under-recognized. Both OLP and vulvar LS are common in older women. Janovska et al reported 86 women with both OLP and vulvar LS[16]. The preferred treatment was topical corticosteroids. Some patients with recalcitrant disease required systemic therapy. Drugs including hydroxychloroquine, doxycycline, metronidazole, methotrexate, and mycophenolate mofetil benefitted these patients. The use of systemic agents reduced the disease activity of both conditions and was thought to decrease the risk of developing oral and/or vulvar squamous cell carcinoma[16].

Treatment of Mucosal Lichen Planus

Those LP patients with involvement of multiple mucosal sites are the most challenging to treat[1,10-19]. Multidisciplinary management with dermatologists, dentists and dental specialists, gastroenterologists, gynecologists, otorhinolaryngologists, and ophthalmologists involved in the ongoing care of patients with MLP may be necessary.

The main goal of therapy for MLP is the control of inflammation allowing healing and remission of the disease. Ancillary goals are control of symptoms of pain and the restoration of mucosal health. Treatment should be directed at eliminating atrophic, erosive, and ulcerative lesions and potentially lessening the likelihood of malignant transformation[8,16,19].

Topical therapy is satisfactory for many patients with mild to moderate but limited mucosal disease[7,9,17-20]. Systemic therapy is indicated for those whose disease cannot be controlled with topical therapy, those whose disease is extensive and not amenable to topical therapy, and those whose disease involves multiple mucosal surfaces compromising organ function such as severe oral, esophageal, conjunctival, otic or genital involvement with scarring and chronic ulceration[1,9,13-15,18,19].

Treatment of Mucosal Lichen Planus – Focus on Oral Lichen Planus

Therapy for OLP should begin with supportive measures such as gentle oral hygiene, control of gingivitis and oral candidiasis, smoking cessation, and limitation of alcohol intake, under the care of the patient's dental practitioner. Topical therapy with fluorinated corticosteroids and calcineurin inhibitors, singly or in combination is the mainstay of treatment[7,9,17-19].

The administration of systemic corticosteroids alone or as a bridge to other anti-inflammatory immunomodulating agents is an effective short-term treatment option. Systemic corticosteroids are used to control acute exacerbations and to achieve control of severe disease activity. Prednisone administered as a tapering 3-week course in a dose of 0.5 mg/kg in a single, daily dose for 1 week, tapered by 50% per week for the next two weeks is an effective starting point for systemic therapy of refractory MLP. Doses such as prednisone 40 mg/day for week 1, 20 mg/day for week 2, and 10 mg/day for week 3 would be appropriate for most patients[7,18,19].

At the same time the systemic corticosteroid regimen is started, an anti-inflammatory immunomodulatory agent should be initiated to allow the agent time to exert its effect before corticosteroids are discontinued. Immunomodulatory therapies are numerous. There are no consensus treatment guidelines for systemic immunomodulatory therapy. We propose a treatment algorithm based on the review of existing evidence, recent literature, and the authors' personal experience[7,9,16-19,21]. *Fig.1*

The first level of immunomodulatory agents are drugs that exert an anti-inflammatory effect in addition to their primary indication. Medications such as hydroxychloroquine, doxycycline, dapsone, and other antibiotics such as metronidazole and griseofulvin constitute these first-level systemic agents which should be started concomitantly to systemic corticosteroids.

Of these, hydroxychloroquine would be the first choice. Several trials with 10 patients[22], 21 patients[23], and a retrospective review[24] support the use of hydroxychloroquine in MLP. A trial of 3-6 months should be undertaken. The clinician should expect that up to 65% of patients will achieve complete remission and the rest will have moderate to marked improvement with doses of 200-400 mg daily for 6 months. If improvement is not complete, a second first-level immunomodulatory agent such as doxycycline or metronidazole may be added for a 3-month trial[16,25].

Treatment of Patients with Recalcitrant Mucosal Lichen Planus

Clinicians should expect that many patients with MLP who have been refractory to excellent oral hygiene, ongoing dental management, and supportive care, plus a tapering course of systemic corticosteroids and a 3–6-month trial of a first-level systemic immunomodulatory agent, will be challenging to treat. These are the most intractable cases requiring patience and dedication.

• Short-term course of systemic corticosteroids, second or third level immunomodulatory agent (methotrexate, biologic agent, etc.)
• Short-term course of systemic corticosteroids, second level immunomodulatory agent (mycophenolate mofetil, etc.)
• Short-term course of systemic corticosteroids, first level immunomodulatory agent (hydroxychloroquine, etc.)
• Topical therapy with corticosteroids and calcineurin inhibitors
• Supportive measures, continuing care of dental practitioner, control of candidiasis

Figure 1:

If the MLP is not controlled with first-level immunomodulatory agents, the clinician should seek improvement with second-level drugs[19]. Antimetabolites such as methotrexate (MTX), mycophenolate mofetil (MMF), or azathioprine are second-level options[21,25-30]. In this group, MMF would be our first choice. A 3–6-month trial with MMF in doses of 1000-3000 mg per day is appropriate.

The third level of immunomodulatory therapy includes biological agents such as rituximab, adalimumab, and etanercept[19]. Experience with these agents is limited to case reports and small case series. Despite the reports of certain biologic agents causing drug-induced lichenoid tissue reactions[31-33], we consider biologics a new and emerging therapeutic option for MLP that will likely replace the older immunomodulatory drugs. The same way that some biologics are useful in treating inflammatory bowel disease while others may trigger it, a similar effect may be observed with biologics and MLP. These contradictory responses may reflect a balance of different immunity pathways. Recently, the therapy with an oral JAK-inhibitor, tofacitinib, resulted in complete remission in a patient with intractable MLP with severe esophageal involvement[34].

Summary and Conclusions

MLP is a chronic debilitating, painful, and distressing disease. At this time, no curative treatment regimen exists. The current literature is replete with case reports, small series, and non-randomized trials of therapy. The goal of treatment is to provide comfort for the patient. Therapy should focus on controlling inflammation, halting the development of new lesions, and providing the opportunity for established lesions to heal. In the face of this chronic and scarring disease, effective therapy is mandatory. Our treatment algorithm begins with supportive measures under the care of the dental practitioner. This must be maintained throughout the time it may take to gain complete remission.

We recommend a treatment algorithm of escalating intensity of management beginning with a 3-week course of systemic corticosteroids at which time the first level immunomodulatory agent is initiated. The corticosteroid in a pulse fashion reduces the intensity of inflammation and permits the immunomodulator to start controlling disease activity.

Gaining and sustaining remission is challenging. However, the clinician should expect marked or moderate improvement if not complete remission in 3-6 months in many patients. Maintaining remission for 3 additional months before tapering the immunomodulatory agent is essential. Long-term, low-dose immunosuppressive therapy may be necessary.

Clinicians should be aware that flares while undergoing immunosuppressive therapy may represent an episode of acute candidiasis rather than an exacerbation of the MLP.

Refractory MLP may require second and third immunomodulatory agents for 3–6-month trials. We have suggested our preference for each level based on our review of the current literature and our personal experience in managing MLP patients.

As the old drugs (corticosteroids, hydroxychloroquine, MTX, and MMF) get gradually replaced by the newer and more targeted ones (JAK-inhibitors and biologics), the future of therapeutics in MLP becomes more promising. We believe that oral JAK-inhibitors such as tofacitinib and the new emerging biological agents will increase our therapeutic arsenal to manage this debilitating condition.

Conflicts of Interest

The authors have no conflicts of interest and no financial interest to report.

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