# A Case of Recalcitrant Erosive Oral Lichen Planus with an Excellent Response to Topical Tacrolimus

## Topikal Takrolimus Tedavisine Mükemmel Yanıt Veren İnatçı Eroziv Oral Liken Planus Olgusu

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**ABSTRACT** Erosive oral lichen planus (EOLP) is a rare form of mucosal lichen planus characterized by intractable symptoms and complications that significantly impact patients' quality of life. It usually results in pain which can lead to severe problems in daily activities such as eating, drinking, speech, and interpersonal relationships. EOLP usually has a chronic course and spontaneous remissions are scarce. Although there are many treatment options for EOLP including both topical and systemic immunosuppressive agents, therapeutic results are frequently disappointing and effective treatment modality remains elusive. It is often resistant to topical steroid and the use of systemic agents is limited by side effects. Tacrolimus is a new non-steroidal topical immunomodulator agent approved for the treatment of atopic dermatitis. In recent years, it is shown to be effective in other persistent inflammatory skin and mucosal diseases as well as atopic dermatitis. Herein, we report on a 76-year-old male with recalcitrant EOLP of the lower lip who had a excellent improvement of his lesion following a four-week course of topical 0.1% tacrolimus ointment.

**Key Words:** Lichen planus, oral; therapy; tacrolimus

**ÖZET** Eroziv oral liken planus (EOLP) hastanın yaşam kalitesini önemli ölçüde etkileyen inatçı semptom ve komplikasyonlarla karakterize nadir görülen mukozal liken planus formudur. EOLP'de lezyonlar genellikle ağrılı olup yeme, içme, konuşma gibi günlük aktivitelerde ve kişisel ilişkilerde ciddi problemlere yol açabilmektedir. Sıklıkla kronik bir seyir gösteren EOLP'de spontan gerileme oldukça nadirdir. EOLP'de topikal ve sistemik birçok tedavi alternatifi bulunmasına rağmen tedaviye yanıt çoğu zaman yüz güldürücü değildir ve hali hazırda etkili bir tedavi ajanı bulunmamaktadır. Sıklıkla topikal steroid tedavisine dirençlidir ve sistemik ajan kullanımı ise yan etkileri yüzünden kısıtlıdır. Takrolimus atopik dermatit tedavisinde onay almış yeni non steroidal immünmodulator ajandır. Son yıllarda atopik dermatitin yanı sıra diğer inatçı inflamatuvar deri ve mukozal hastalıkların tedavisinde de etkili olduğu gösterilmiştir. Bu yazımızda, alt dudak yerleşimli inatçı EOLP'si olan ve dört hafta süreyle uygulanan %0.1 topikal takrolimus tedavisine mükemmel yanıt veren 76 yaşındaki erkek hasta sunulmuştur.

**Anahtar Kelimeler:** Liken planus, oral; tedavi; takrolimus

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Oral lichen planus (OLP) is one of the most common chronic oral mucosal diseases of unknown etiology, characterized by relapses and remissions. Its prevalence in the general population is estimated between 0.5% and 2%, with a female predilection and a peak of incidence in the fourth-fifth decades.[1,2] It is generally divided into six clinical subtypes: reticular, papular, plaque-like, atrophic or erythematous, erosive

and/or ulcerative and finally bullous. More than one form may be present at the same time and in the same location.[3] Reticular OLP, the most common presentation of the OLP, is usually asymptomatic and can be present as white keratotic lines (Wickham striae), with an erythematous border involving the buccal mucosa, tongue, and gingiva. Erosive oral lichen planus (EOLP), a severe form of mucosal lichen planus, is characterized by small or large areas of well-defined erosions and ulcers covered by pseudomembrane. Patients with the EOLP are typically symptomatic with pain being the most common complaint, along with burning, swelling, irritation, and dysgeusia.[1-4] Many topical and systemic immunomodulator agents are currently available for off-label use in this disorder, but an effective treatment modality remains elusive.[3-5]

Tacrolimus, a new non-steroidal topical immunomodulator, is increasingly favoured in the management of recalcitrant inflammatory skin and mucosal disease. Recently, some reports and open trials have demonstrated that topical tacrolimus therapy, which was approved as a safe treatment for atopic dermatitis, is effective for EOLP as well.[2-4,6-12]

## CASE REPORT

A 76-year-old male with a 6-year history of plaque type OLP on the buccal mucosa admitted to our clinic for painful lip ulcer. He had previously been treated for symptomatic whitish buccal lesions with various therapeutic agents including topical and intralesional corticosteroid, topical cyclosporine, systemic steroid, acitretin and fluconasole without significant improvement. As it was concluded from his history, the lip ulcer occurred 8 months ago and persisted despite intralesional corticosteroid, topical application of triamsinolon acetonid orabase cream and mupirocin cream. In the last 3 months, he had lost 6 kg in weight due to eating difficulties. The patient did not have history of tobacco or alcohol use and his medical history included hypertension and 25-year history of type 2 diabetes mellitus requiring oral antidiabetics. He had undergone complete thymoma resection two years ago. Routine laboratory examinations were within normal limits except for moderate hypercholesterolemia and hyperglycemia. Serologic markers for hepatitis B and C virus were negative. Oral examination revealed bilateral extensive whitish plaques on the buccal mucosa and 1x2.5 cm superficial, non-indurated ulcer covered with yellowish exudate and hemorrhagic crust on his right side of the lower lip (Figure 1). No cutaneous or genital lesions and nail involvements were present or reported. Histological examination of a biopsy taken from ulcerated lesion with presumptive diagnosis of EOLP and squamous cell cancer revealed a band-like submucosal lymphomononuclear infiltrate with lichenoid damage of the basal layer and necrotic keratinocytes (Figure 2). The histopatho-

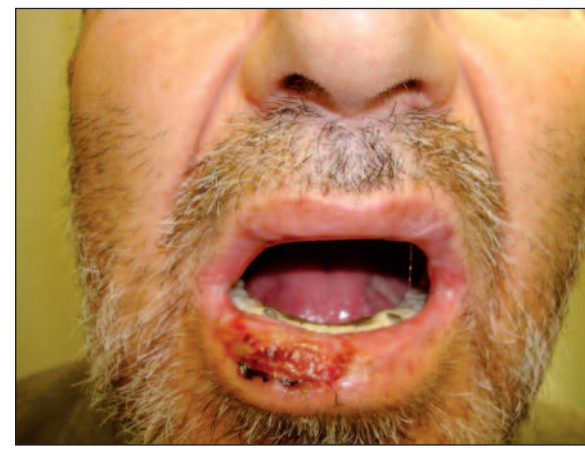

**FIGURE 1:** Clinical appearance of the erosive lip lesion prior to initiation of topical tacrolimus therapy.

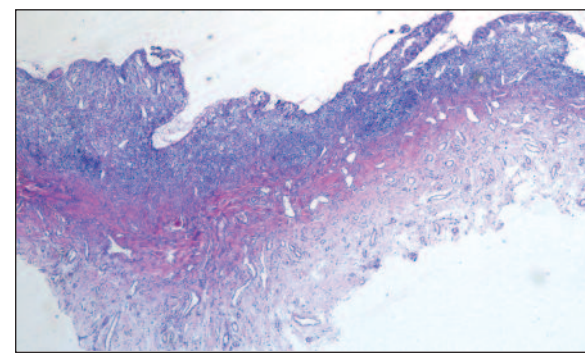

**FIGURE 2:** Dermal band-like infammatory infltration underlying an extensive ulceration of the mucosa (Hematoxylin-eosin stain; original magnification X40).

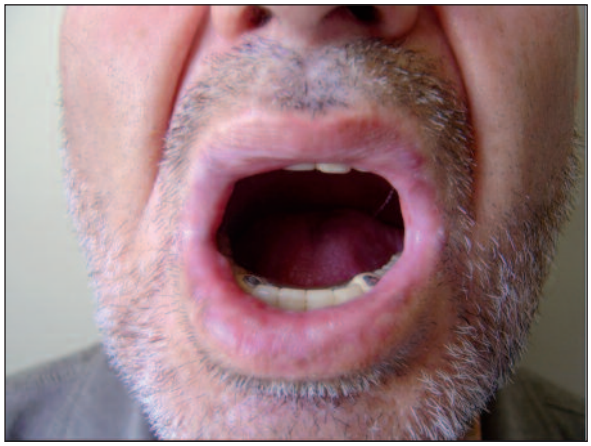

**FIGURE 3:** Complete resolution after 4 weeks of treatment with twice-daily 0.1% tacrolimus ointment.

logical findings of the lesion were consistent with a diagnosis of EOLP. Because of his poor response to previous topical corticosteroid therapy, the patient was started on tacrolimus (Protopic) 0.1% ointment to be applied twice a day to the affected area. Two weeks after the topical tacrolimus therapy, both buccal lesions and lip ulcer dramatically improved and symptoms such as burning and pain disappeared. The ulcerated lip lesion completely healed within the four weeks (Figure 3). No significant irritation was observed during the 2 months of treatment period and no recurrence was noted during our one-year follow-up.

## DISCUSSION

EOLP poses a particular therapeutic challenge because, in contrast to cutaneous lesions, it is usually resistant to treatment and typically runs a chronic course with most patients requiring long-term maintenance treatment.[1] It is characterized by painful erosions, ulcerations and whitish streaks in a lacy or fern-like pattern on the oral mucosa. Although the exact pathogenesis of EOLP is still unknown, cytotoxic T cell-mediated autoimmune reactions directed against basal keratinocytes are thought to play a central role. EOLP requires treatment when associated symptoms of burning pain and irritation interfere with eating, speech and, consequently, the quality of life.[6-9,13] Treatment of EOLP is difficult and lack of randomized controlled trials makes evaluation of therapies challenging. Topical corticosteroids are widely used as first-line treatment, but response is often incomplete. Systemic therapy should only be considered when topical therapy does not achieve adequate improvement. Long-term systemic steroids are usually effective but are associated with a well-known spectrum of side-effects and dramatic relapses following steroid withdrawal. Other systemic therapies including acitretin, antimalarials, dapsone, cyclocporine, PUVA therapy and thalidomide have also been reported with variable successes rate but these have adverse effects that may limit their long-term use.[3,6,10,11]

Tacrolimus was isolated in 1984 from the Japanese soil fungus *Streptomyces tsukubaensis*. It was initially introduced as a systemic immunosuppressant for the prevention of allograft rejection in solid organ transplantation. It was then formulated as an immunosuppressant ointment and used in the treatment of atopic dermatitis.[11] In the recent literature, successful treatment and management of recalcitrant inflammatory skin and mucosal disease with topical tacrolimus have been reported in several cases and studies.[4,6-9] Tacrolimus, a calcineurin-inhibitor, has also been shown to be effective in treating lesions of EOLP that are recalcitrant to topical steroid therapy.[2,3,6,7,9]

The action mechanism of the topical tacrolimus in treating EOLP is not fully known. Tacrolimus has powerful immunosuppressive activities by inhibiting T-cell production of proinflammatory cytokines. The immunosuppressive action of tacrolimus is similar to that of cyclosporine, although it has a greater capacity to penetrate the mucosa, and is 10-100 times more potent than the latter drug. Tacrolimus, by binding to lymphocyte cytosolic FK-binding proteins, interferes with $Ca^{+2}$/calmodulin-dependent phosphatase calcineurin. This leads to the inhibition of interleukin 2 gene transcription resulting in decreased activation and proliferation of T-lymphocytes to foreign antigens.[2,7-9,12] Topical application of tacrolimus may induce a rapid improvement in EOLP via blocking the activation of T-lymphocytes by targeting calcineurin, an important activator of T-lymphocyte.

In contrast to the systemic therapy options mentioned above, topical tacrolimus is safe and effective and has relatively low side effects The most common side effects of topical tacrolimus are transient burning and pruritus at the site of application. These side effects may be more tolerable than the side effects of other therapies, including first-line topical corticosteroids.[5,6,8,9]

In conclusion, topical use of tacrolimus is a safe, well tolerated, and effective therapy for EOLP lesions recalcitrant to traditional therapies. We suggest that following an unsuccessful response to treatment with moderate/potent topical corticosteroids, topical tacrolimus can be considered as a management option before commencing systemic immunosuppresion.

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