Oral Lichen Planus Treated With Plasma Rich in Growth Factors

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PRACTICE **POINTS**

- Treating erosive oral lichen planus lesions refractory to conventional steroid treatments can be challenging for clinicians.
- Complete re-epithelialization and total pain relief could be observed after 1 to 3 weekly perilesional infiltrations with plasma rich in growth factors.
- No relapse of the lesions in the same area or other complications could be observed during the follow-up time.

The use of plasma rich in growth factors (PRGF) is a treatment for erosive oral lichen planus (OLP) resistant to steroid therapy. An anonymous database at a clinical center was reviewed to collect demographic data, lesion type, treatment protocol, number of infiltrations, pain score, and healing time of the lesions. Fifteen patients were included in this study. All patients were diagnosed with erosive OLP. The lesions in all patients were refractory to steroid therapy (topical and systemic). Results showed that the use of plasma rich in growth factors (PRGF) could be a promising alternative for the treatment of erosive OLP refractory to steroid therapy, though new prospective studies are needed to confirm these preliminary observations.

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Lichen planus is a chronic inflammatory mucocutaneous disease that usually affects the skin and/or the genital and oral mucosae.[1,2] This disease classically presents with clinical relapses or outbreaks that alternate with periods of remission or latency. Oral lichen planus (OLP) can present with or without extraoral manifestation. It sometimes is difficult to differentiate OLP from oral lichenoid reactions, which can be related to dental materials, some drugs, and systemic conditions or can be idiopathic.[1,2]

Oral lichen planus is one of the most common noninfectious diseases of the oral cavity, with a reported prevalence of 1% worldwide and marked geographical differences. In Europe, the prevalence of OLP ranges from 1% to 2%.[3,4] It is more frequent in women (1.5:1 to 2:1) and usually appears in the fourth and fifth decades of life.[1-4]

The causes of OLP have not been entirely elucidated, but it is broadly accepted that there is a deregulation on different T lymphocytes that in turn causes effects on CD8 lymphocytes in response to an external noxa. This unknown "trigger" or starting factor also produces an impact on basal keratinocytes. Therefore, the pathogenesis of lichen planus is influenced by a series of cellular events mediated by different cytokines.[2,5,6] Among these, tumor necrosis factor α and IL-1 are known to have important roles in the disease. More recently, other cytokines, such as IL-4, secreted by type 2 helper T cells, also have been related to the development and progression of the oral lesions.[5,6] In addition to the factors that generate the onset of the disease, there are others that may precipitate clinical outbreaks. Different factors have been related to the progression of the disease, influencing the initiation,

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perpetuation, and/or worsening of OLP lesions.[1,2] Exactly how these factors affect disease progression is another challenging question. The list of possible or potential factors related to disease progression is long; nonetheless, in the vast majority, a clear explanation at a molecular level has not been clearly demonstrated.[2,5]

Conventionally, 6 clinical presentations of OLP lesions divided into 2 main groups have been described in the oral cavity: white forms (reticular, papular, and plaquelike) and red forms (erythematous, atrophic-erosive, and bullous).[1,7-9]

Oral lichen planus mainly is treated with topically or systemically administered steroids based on the presence of symptoms such as pain and inability to perform daily activities (eg, eating, talking).[5,10] The treatment of choice often is based on the professional's experience, as there are no broadly accepted national or international clinical practice guidelines on steroid type, administration route, dose, vehicle for administration, or maintenance.[11] Despite this lack of unified criteria, different topical and systemic steroid administration protocols allow a reduction in the symptoms or even the disappearance of the red lesions to be achieved in many cases. Unfortunately, there are many patients with lesions refractory to standard treatments for OLP.[12] Several alternatives for these patients have been described in the literature, though on many occasions these alternatives present substantial side effects for the patient.[13] The search for an effective treatment without side effects is still challenging. One of the treatments tested under this premise has been the application of plasma rich in growth factors (PRGF) by means of infiltration or topical application, in both cases obtaining good results without side effects.[14]

We sought to analyze the information from a case series of patients treated at the Eduardo Anitua Clinic (Vitoria-Gasteiz, Spain) and describe the results and follow-up of patients with erosive OLP refractory to standard therapy who have been successfully treated by local infiltration of PRGF as the only treatment.

Material and Methods

Patients—We included data from the database of the clinical center with de-identified information of patients with erosive OLP diagnosed clinically and histopathologically who did not respond to conventional treatment (ie, topical and/or systemic corticosteroids [depending on the case]) as well as patients who presented with extensive erosive OLP with systemic involvement and whose systemic treatment was not effective in resolving oral manifestations.

Therapies Administered and Evaluations—Lesions refractory to conventional corticosteroid protocols had been previously treated for 30 days with 0.5% triamcinolone acetonide mouth rinse followed by a cycle of 1% triamcinolone acetonide mouth rinse. Subsequently, a cycle of oral corticosteroids (prednisone for 30 days: 1 mg/kg/d in a single morning dose with staged reduction after the first week) had been administered. One day after the corticosteroid treatment was suspended, the patients were treated by PRGF-Endoret (BTI Biotechnology Institute) infiltration following the protocol described by Anitua et al.[15,16]

Before starting the infiltrations with PRGF, the patient had been asked to rate the pain level on a visual analog scale (VAS) of 1 to 10, with 10 being the most intense imaginable pain. Pain score was subsequently rated and registered during every visit. An initial photograph of the lesion also was obtained to establish a starting point for further comparisons of clinical evolution of the lesions.

Prior to each infiltration, the plasma was separated into 2 fractions. The second fraction was the one that corresponded to the highest number of platelets and included the 2 mL of plasma just above the white series (or buffy coat). This fraction of plasma was the one used to infiltrate the lesions.

Plasma rich in growth factors was activated just before infiltration. The activation was done by adding 10% calcium chloride. Once activated, it was infiltrated into the active lesion using a 31-G × 1/6-in hypodermic needle and a 2-mL Luer-lock syringe. Infiltrations were performed without anesthesia. Four punctures were made for each ulcerative lesion, dividing the lesion into 4 points: upper, lower, right, and left. Plasma rich in growth factors was infiltrated until a slight blanching was observed in the surrounding tissue. At that moment, the infiltration was stopped and was carried out in the next infiltration site.

One treatment session was performed per week, with follow-up 1 week after treatment. In the control visit, the state of the lesions was re-evaluated, and it was decided whether new infiltrations were needed. The treatment was finished when complete epithelialization of the lesion was visualized or the associated symptoms disappeared. At each visit, photographs were taken, and the patient assessed the severity of pain on the VAS.

Statistical Analysis—A Shapiro-Wilk test was carried out with the obtained data to check the normal distribution of the sample. The evolution of pain during the study was compared by paired *t* test. The qualitative variables were described by means of a frequency analysis. Quantitative variables were described by the mean and the SD. The data were analyzed with SPSS V15.0 for Windows (SPSS Inc). $P<.05$ showed statistical significance.

Results

A total of 15 patients were included in the study, all with atrophic-erosive lichen planus. Two patients were male, and 13 were female. The mean age (SD) of the patients included in the study was 55.27 (14.19) years. The mean number of outbreaks per year (SD) was 3.2 (1.7), with a range of 1 to 8 outbreaks.

Healing of OLP Lesions—The number of treatment sessions to achieve complete healing varied among the

patients (Figures 1 and 2). Ten patients (66.7%) required a single session, 2 patients (13.3%) required 2 sessions, and 3 patients (20%) required 3 sessions. The mean time (SD) without lesions for the patients who required a single session was 10.9 (5.2) months (range, 6–24 months).

Pain Assessment—The mean (SD) score obtained on the VAS before treatment with PRGF was 8.27 (1.16); this score dropped to 1.27 (1.53) after the first treatment session and was a statistically significant difference (P=.006).

For those patients requiring more than 1 session, the mean (SD) pain scores decreased by 0.75 (0.97) points and 0 points after the first and second sessions of treatment, respectively. The mean (SD) amount of PRGF infiltrated in each patient in the first session was 2.60 (0.63) mL. In the second session, the mean (SD) amount was 1.2 (0.33) mL; these differences were statistically significant (P=.008). In the last session, the mean (SD) amount was 1.1 (0.22) mL.

Follow-up and Adverse Effects—The mean (SD) follow-up time was 47.16 (15.78) months. The patients were free of symptoms, and there were no adverse effects derived from the treatment during follow-up.

Comment

The primary goal of OLP treatment is to stop the outbreaks.[1,9,13] The lack of potency of corticosteroids in some patients with OLP could be due in part to the inadequate selection of the vehicle (ointment/oral rinse) for the extension and characteristics of the lesion or because of an inappropriate prescription dose, time, and/or frequency, as described by González-Moles.[17] However, even when using an appropriate protocol, some lesions are resistant to topical treatment and require other therapeutic modalities.[1,9,13] Previously proposed topical treatments include different immunosuppressants, such as the mammalian target of rapamycin, tacrolimus ointment 0.1%, pimecrolimus cream 1%, or cyclosporine A (50–100 mg/mL) formulations.[18] Nevertheless, these drugs seem to have a greater number of side effects than topical steroids, and tacrolimus has been associated with cases of oral malignancy after continuing treatment.[15]

Severe and/or recalcitrant lesions and extraoral involvement have been successfully treated with systemic prednisone (40–80 mg/d).[1,9,13] Nevertheless, systemic corticosteroid toxicity requires that these treatments should

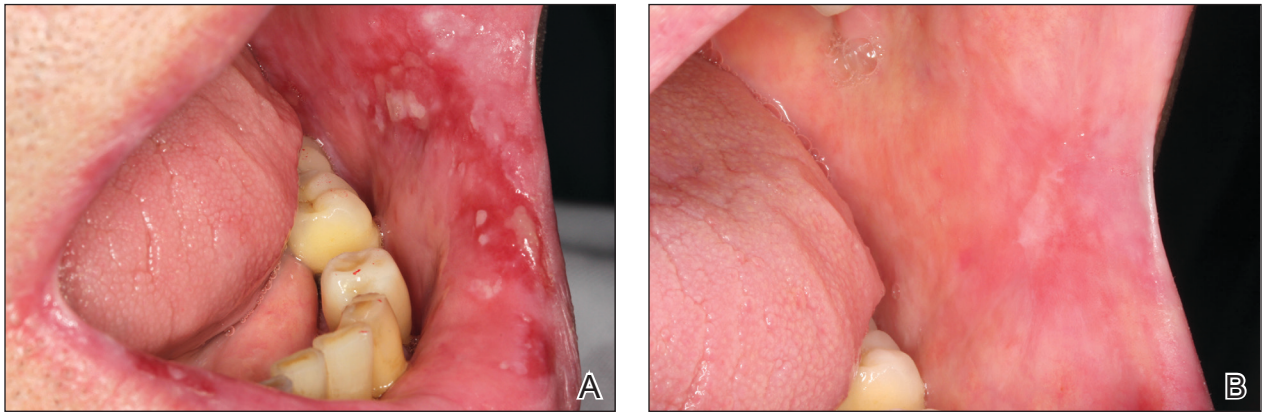

FIGURE 1. A, Atrophic-erosive and ulcerative recalcitrant lesions of oral lichen planus after topical and systemic corticosteroid administration. B, Total healing after 3 weekly perilesional infiltrations with plasma rich in growth factors.

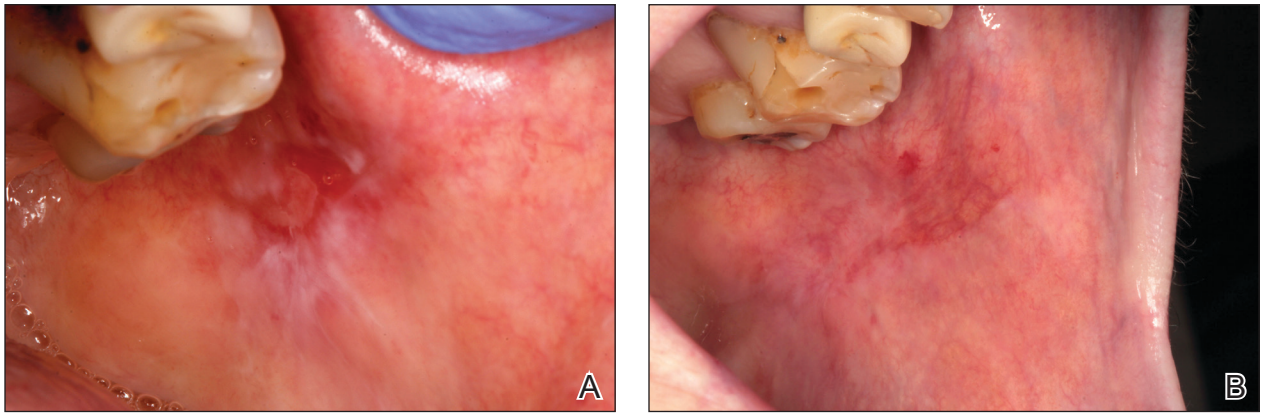

FIGURE 2. A, An oral lichen planus lesion resistant to treatment with topical and systemic corticosteroids. B, Re-epithelialization 1 week after a single perilesional infiltration with plasma rich in growth factors.

be used only when necessary at the lowest possible dose and for the shortest possible duration.[19] Other nonpharmacologic options for treatment are photodynamic, UV, and low-level laser therapy.[20,21] They have been accepted as supplementary modalities in different inflammatory skin conditions but present important technical requirements. Their effectiveness in corticosteroid-resistant cases have not been definitively assessed. Interestingly, promising results recently have been reported by Bennardo et al[22] when comparing the efficacy of autologous platelet concentrates with triamcinolone injection.

In our study, the use of PRGF stopped the lesions' evolution since the first treatment session, reducing them by 6.5-fold. The positive effects observed may have been promoted by the activity of different proteins present in PRGF (eg, platelet-derived growth factor, vascular endothelial growth factor, transforming growth factor, epidermal growth factor, fibroblast growth factor, fibronectin). These molecules contribute to collagen synthesis; angiogenesis; endothelial cell migration and proliferation; or keratinocyte cell migration, proliferation, differentiation, growth, and migration—phenomena that are essential for healing and re-epithelialization.[23-25]

Different studies also have supported an anti-inflammatory effect of PRGF mediated by an inhibition of the transcription of nuclear factor–κB and the expression of cyclooxygenase-2 and chemokine receptor type 4 produced by its high content of hepatocyte growth factor or the reduction of inflammatory marker expression, such as intercellular adhesion molecule 1. The development of an efficient 3-dimensional fibrin scaffold formation that occurs after PRGF administration also could facilitate healing, helping some cell populations to guide their position and function.[23-25]

Limitations of our study include the small number of patients and the absence of a control group. The higher number of female patients in the study did not seem to affect the results, as differences related to gender have not been reported when treating patients with OLP with autologous platelet concentrates or other modalities of treatment.

Conclusion

Results from our study indicate that the use of PRGF could be a new treatment option for OLP cases refractory to conventional therapy. No complications were observed during the treatment procedure or during the complete follow-up period. Nonetheless, new prospective studies with a greater number of patients and longer follow-up periods are needed to confirm these preliminary results.

REFERENCES

1. Al-Hashimi I, Schifter M, Lockhart PB, et al. Oral lichen planus and oral lichenoid lesions: diagnostic and therapeutic considerations. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2007;103:1-12.
2. Kurago ZB. Etiology and pathogenesis of oral lichen planus: an overview. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2016;122:72-80.
3. McCartan BE, Healy CM. The reported prevalence of oral lichen planus: a review and critique. *J Oral Pathol Med*. 2008;37:447-453.
4. González-Moles MÁ, Warnakulasuriya S, González-Ruiz I, et al. Worldwide prevalence of oral lichen planus: a systematic review and meta-analysis. *Oral Dis*. 2021;27:813-828.
5. Nosratzehi T. Oral lichen planus: an overview of potential risk factors, biomarkers and treatments. *Asian Pac J Cancer Prev*. 2018;19:1161-1167.
6. Mehrbani SP, Motahari P, Azar FP, et al. Role of interleukin-4 in pathogenesis of oral lichen planus: a systematic review. *Med Oral Patol Oral Cir Bucal*. 2020;25:E410-E415.
7. Edwards PC, Kelsch R. Oral lichen planus: clinical presentation and management. *J Can Dent Assoc*. 2002;68:494-499.
8. Gorouhi F, Davari P, Fazel N. Cutaneous and mucosal lichen planus: a comprehensive review of clinical subtypes, risk factors, diagnosis, and prognosis. *ScientificWorldJournal*. 2014;2014:742826.
9. Babu A, Chellaswamy S, Muthukumar S, et al. Bullous lichen planus: case report and review. *J Pharm Bioallied Sci*. 2019;11 (suppl 2):S499-S506.
10. Thongprasom K, Carrozzo M, Furness S, et al. Interventions for treating oral lichen planus. *Cochrane Database Syst Rev*. 2011;7:CD001168.
11. López-Jornet P, Martínez-Beneyto Y, Nicolás AV, et al. Professional attitudes toward oral lichen planus: need for national and international guidelines. *J Eval Clin Pract*. 2009;15:541-542.
12. Yang H, Wu Y, Jiang L, et al. Possible alternative therapies for oral lichen planus cases refractory to steroid therapies. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2016;121:496-509.
13. Ribero S, Borradori L. Re: risk of malignancy and systemic absorption after application of topical tacrolimus in oral lichen planus. *J Eur Acad Dermatol Venereol*. 2017;31:E85-E86.
14. Piñas L, Alkhraisat MH, Fernández RS, et al. Biological therapy of refractory ulcerative oral lichen planus with plasma rich in growth factors. *Am J Clin Dermatol*. 2017;18:429-433.
15. Anitua E, Zalduendo MM, Prado R, et al. Morphogen and proinflammatory cytokine release kinetics from PRGF-Endoret fibrin scaffolds: evaluation of the effect of leukocyte inclusion. *J Biomed Mater Res A*. 2015;103:1011-1020.
16. Anitua E, Prado R, Sánchez M, et al. Platelet-rich plasma: preparation and formulation. *Oper Tech Orthop*. 2012;22:25-32.
17. González-Moles MA. The use of topical corticoids in oral pathology. *Med Oral Pathol Oral Cir Bucal*. 2010;15:E827-E831.
18. Siponen M, Huuskonen L, Kallio-Pulkkinen S, et al. Topical tacrolimus, triamcinolone acetonide, and placebo in oral lichen planus: a pilot randomized controlled trial. *Oral Dis*. 2017;23:660-668.
19. Adami G, Saag KG. Glucocorticoid-induced osteoporosis update. *Curr Opin Rheumatol*. 2019;31:388-393.
20. Lavaee F, Shadmanpour M. Comparison of the effect of photodynamic therapy and topical corticosteroid on oral lichen planus lesions. *Oral Dis*. 2019;25:1954-1963.
21. Derikvand N, Ghasemi SS, Moharami M, et al. Management of oral lichen planus by 980 nm diode laser. *J Lasers Med Sci*. 2017;8:150-154.
22. Bennardo F, Liborio F, Barone S, et al. Efficacy of platelet-rich fibrin compared with triamcinolone acetonide as injective therapy in the treatment of symptomatic oral lichen planus: a pilot study. *Clin Oral Investig*. 2021;25:3747-3755.
23. Anitua E, Andia I, Ardanza B, et al. Autologous platelets as a source of proteins for healing and tissue regeneration. *Thromb Haemost*. 2004;91:4-15.
24. Barrientos S, Brem H, Stojadinovic O, et al. Clinical application of growth factors and cytokines in wound healing. *Wound Repair Regen*. 2014;22:569-578.
25. Anitua E. Plasma rich in growth factors: preliminary results of use in the preparation of future sites for implants. *Int J Oral Maxillofac Implants*. 1999;14:529-535.