

Lichen planus pemphigoides limited to the oral cavity: A case report and literature review

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(Submitted: 19 November 2017 – Revised version received: 11 January 2018 – Accepted: 17 February 2018 – Published online: 26 June 2018)

Lichen planus pemphigoides (LPP) is a rare autoimmune vesiculobullous disorder and its exclusive presentation in the oral cavity is an even more remote occurrence. We describe an 85-year-old woman with a symptomatic soft palatal erosion, which compromised her ability to wear a maxillary prosthesis. She had been diagnosed with and treated for lichen planus affecting her buccal mucosa 3 years prior to the onset of the lesion on palate. Persistence of the palatal lesion and its lack of response to local steroid therapy prompted a repeat biopsy for histopathological and direct immunofluorescence examination both of which confirmed LPP diagnosis. In oral lichen planus pemphigoides treatment is empirical. In this patient, a combination of systemic and topical steroids was effective in resolving the palatal ulceration. This case report highlights the importance of monitoring patient's response to therapy and appropriate diagnostic workup when signs and symptoms persist or change character.

Keywords oral lichen planus pemphigoid, lichen planus, direct immunofluorescence, bullous lichen planus, mucous membrane pemphigoid

Introduction

Lichen planus pemphigoides (LPP) is a rare mucocutaneous condition of autoimmune etiology which is characterized by a combination of clinical, histopathological, and immunological features of both lichen planus (LP) and bullous/mucous membrane pemphigoid (BP/MMP).¹⁻⁴ To date, only about 90 cases of cutaneous LLP and 35 cases of oral LPP have been reported.^{1,2,5} Lichen planus pemphigoides has a female predilection and often occurs in the fourth decade of life. Occurrence of LPP in children is very rare with fewer than 20 cases in the literature.² Cutaneous manifestations include pruritic erythematous patches with or without bullae and erosions often affecting the extremities.³ Oral lesions of LPP are variable and include white reticular plaques to erosive, ulcerative components, vesicular eruptions, and desquamative gingivitis.⁴ The most commonly affected site in the oral cavity is buccal mucosa.⁶ Histopathologic features of LPP resembles LP and when bullae are present, also bullous pemphigoid (BP).⁴ Microscopic features include hyperkeratosis, acanthosis, band-like lymphocytic infiltration, colloid bodies typical of LP, as well as subepidermal blisters expected in BP.⁶ Direct immunofluorescent (DIF) studies show linear deposits of IgG and/or C3 along the basement membrane. In LP, DIF shows granular deposition of fibrinogen and C3 along the basement membrane zone (BMZ).¹

Nature and pathogenesis of LPP have been subject to controversy. While previous studies considered LPP as simultaneous presentation of LP with BP or MMP, more recent studies suggest LPP as a variant of BP.^{3,7} The latter consideration is supported by the difference in mean age of affected patients and severity of manifestations between LP and BP. The mean age of patients with LP (40–50) is lower than those affected by BP (70–80).^{1,8} In addition, patients affected by BP generally experience more severe manifestations and have less favorable response to therapy. Furthermore, circulating auto-antibodies in LPP and bullous pemphigoid share similarities,⁴ and are

directed against BP180 domain.⁴ More specifically, anti-collagen XVII auto-antibodies in LPP react to region 4 within BP180 noncollagenous-16a domain whereas in BP auto-antibodies are directed against regions 2 and 3 within the same domain.⁴ Some authors postulate that pathogenesis of LPP and development of BP/MMP from an immunologically unrelated disorder oral lichen planus (OLP) may be explained by epitope spreading.^{3,9,10} It is thought that lichen planus-induced disruption of BMZ may lead to exposure of BMZ proteins, production of auto-antibodies against them and clinical presentations of pemphigoid.³ There are also reports of an association between LPP and phototherapy, hepatitis B infection and internal malignancies such as lymphoma, colon cancer and Castleman's disease in the literature.¹¹ In addition, a number of medications such as calcium channel blocker, NSAIDs, interferon, ribavirin, therapeutic hormones, infertility medications^{12,13} and weight reduction drugs have been implicated in the onset of LPP.^{14,15} Therefore, a thorough medical and medication history is a necessary part of work up process.

Case History

An 85-year-old woman was presented to the Oral Medicine Department of the Tehran University of Medical Sciences with the complaint of oral erosions of 5-year duration. She reported pain and burning sensation in the soft palate and inability to use her maxillary prosthesis. Her past medical history was significant for hypertension (HTN) controlled with atenolol. Review of systems was negative for cutaneous lesions. Intraoral exam revealed a superficial ulcer of about 2 cm on soft palatal midline where patient reported prior vesicular eruptions (Fig. 1).

There were also white reticular striations with associated erythema on her buccal mucosa bilaterally. Histopathological examination of an incisional specimen from the buccal

mucosa, the initial site of her symptomatic oral erosions 3 years prior to onset of soft palatal lesion, had revealed stratified squamous mucosa with mild epithelial acanthosis, diffuse vacuolar degeneration of basal layer and individual cell apoptosis. Microscopic features were consistent with lichen planus and administration of topical steroids (triamcinolone acetonide in orabase) alleviated her symptoms until palatal erosion developed. Persistence of palatal erosion and its failure to respond to topical therapy prompted tissue sampling. Histopathological examination demonstrated subepithelial separation and infiltration of inflammatory cells specially eosinophils in the area (Fig. 2A).

Direct immunofluorescence showed linear deposits of IgG and C3 in the BMZ (Fig. 2B). Both microscopic features and DIF were compatible with MMP. Following consultation with the physician regarding the status of her HTN, she was started on 5 mg of prednisone daily.² We opted to use systemic steroids because topical therapy was ineffective and patient could not tolerate intralesional injections. One month later, the lesion had improved significantly and she was able to use her denture. The lesion was fully resolved on 3 month follow-up and systemic steroid was tapered. The timeline for development of LPP from LP in this patient is illustrated (Fig 3A). In this patient, combination of systemic and topical steroids was effective in resolving the palatal ulceration (Fig. 3B).

Discussion

Pathogenesis of LPP is controversial. While some authors consider LPP and pemphigoid as two distinct conditions,³ others suggest LPP as a variant of pemphigoid^{16,17} because clinically blisters develop in association with lichen planus lesions. Evolution of LP to BP or MMP caused by epitope spreading has also been suggested.^{5,3} Table 1 summarizes the features of LPP with oral involvement in six patients one of whom is our patient. All six patients were female and the time line for development of lichen planus to BP or MMP ranged from simultaneous to 17 years.^{3,18–21}

Development of LPP in the context of OLP within 3 years as seen in our patient resembles the case reported by Maceyko et al.¹⁸ Both microscopic and DIF findings in the palatal specimen confirmed MMP, but indirect immunofluorescence (IIF) was negative. These findings are compatible with other studies^{4,5,7,16} as only 10% of MMP patients demonstrate positive IIF for circulating anti-basement membrane zone antibodies.²² Exclusive presentation of LPP in the oral cavity as seen in this patient is rare and only a few cases are reported in the literature.^{20,21}



Fig. 1 Clinical presentation of soft palatal erosion at the initial presentation.

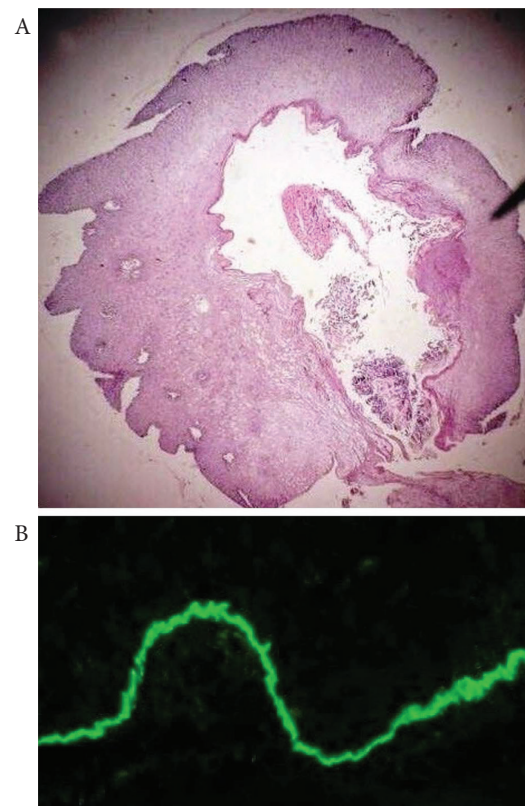


Fig. 2 (A) Low power histopathological photomicrograph of the palatal specimen demonstrating subepithelial separation at the BMZ and infiltration of inflammatory cells including lymphocytes and eosinophils. (H and E, $\times 10$). (B) Direct immunofluorescent photomicrograph of the palatal specimen illustrating linear deposition of IgG autoantibodies along the BMZ.

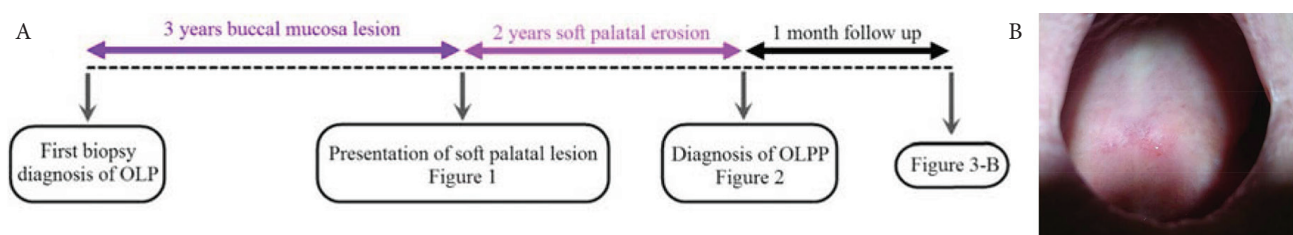


Fig. 3 (A) Timeline diagram of the patient's diseases. (B) Clinical presentation of the healed soft palatal lesion during 3 months follow-up.

Table 1. Clinical, histopathology and therapeutic features of six patients with LLP

Author	Age and sex	Time LP to LPP	Histopathology				DIF	
			Description of lesions		1 - Dense band-like lymphohistiocytic inflammatory infiltrate, 2 - colloid bodies		(Linear C3 and IgG deposition along BMZ)	
			Skin	Oral	Skin	Oral	Skin	Oral
Maceyko et al. ¹⁸	65 F	3 years	Pruritic papules and blisters on trunk, extremities	Oral erosions and bullae	✓, + subepidermal blister	–	✓	–
Zhu et al. ¹⁹	69 F	3 weeks	Pruritic rash on the entire body	Superficial oral ulcers	✓	–	✓	–
Mignogna et al. ³	72 F	1 year	No skin lesion	Erosive, vesicular and keratotic oral lesions	–	✓	–	✓
Zaraa et al. ²⁰	51 F	17 years	Erythematous plaques, bullae and lichenoid lesions	Combination of white and erosive lesions	✓	–	✓	–
Solomon et al. ²¹	63 F	simultaneous	No skin lesion	Desquamative gingivitis and bullae	–	✓	–	✓
Present case	85 F	2 years	No skin lesion	Oral erosions and ulcers	–	✓	–	✓

Involvement of LPP limited to oral mucosa is difficult to differentiate from erosive lichen planus or subepithelial vesiculating mucositis such as pemphigoid or linear IgA disease. Correct diagnosis of LPP relies on biopsy for histopathological examination and DIF studies and the latter helps differentiate between LP and subepithelial diseases one of which is LPP.²¹ When warranted, presence of lichenoid changes and additional tests can help separate LPP from other subepithelial conditions. This patient had been diagnosed with buccal mucosa lesions of LP and later developed LPP lesions on her soft palate. She could have had LPP without bullae affecting buccal mucosa but since DIF study was not performed, it was not diagnosed until soft palatal lesion appeared. This highlights the importance of proper diagnostic approach. This scenario could also depict occurrence of LPP in an anatomical site different from the initial LP as previously reported in the literature.^{23,24} Differentiation of LPP from bullous lichen planus (BLP) can be challenging. In BLP, bullae arise on pre-existing lichen planus lesions whereas in LPP, bullae appear before, during or after lichenoid lesions. Also, in BLP, subepithelial bullae are main features while in LPP, bullae may or may not be present and histopathological features of BP together with lichenoid lesions and eosinophilic spongiosis are prominent findings. In addition, unlike BLP, degeneration of basal cells is absent in LPP. Moreover, DIF study of BLP shows patchy or globular deposition of IgM, IgG, IgA, C3 and fibrinogen but in LPP there is linear deposition of IgG, IgA and C3 that is similar to BP. Furthermore, IIF study for BLP is negative but in LPP it is positive in <50% of cases. LPP is usually less severe than BP and the course of BLP is similar to lichen planus.²³

A number of triggers for the onset of LPP eruptions are reported in the literature. These include hepatitis B infection or drugs such as simvastatin, ramipril, captopril, furosemide, ibuprofen and paracetamol. Formation of auto-antibodies against BMZ components has been suggested as the underlying mechanism for medication-induced bullous eruptions.¹³ This patient was not taking any of the medications reported to induce LPP^{11,16} and the likelihood of an etiological role for atenolol is very low.

Management of LPP involves using topical and systemic corticosteroids with or without steroid-sparing agents such as

dapsone, azathioprine, tetracycline or isotretinoin.^{4,25} Recommended dosage of systemic steroids, the most commonly used agent for cutaneous LPP in adults is 0.5 mg/kg daily or 40–60 mg daily.³ Dapsone, an anti-microbial agent used in management of many immunologic conditions has also proven effective for skin lesions of LPP although high rate of recurrence have been noted.²⁴ Furthermore, tetracycline and combination of nicotinamide and erythromycin are reported to be efficacious in treatment of LPP in adults and children, respectively.³ Moreover, severe cases of cutaneous LPP have been managed with immunosuppressive agents such as cyclosporine or methotrexate.^{3,24}

Oral lesions of LPP tend to improve with treatment directed at the skin disease.²¹ However, treatment of oral lesions, depending on severity of involvement, may be individualized.²¹ In mild cases treatment include topical corticosteroid and in more severe cases systemic corticosteroid with or without steroid sparing agents is indicated.^{2,24}

Conclusion

Lichen planus pemphigoides is a rare immunobullous disease that has clinical and histopathologic manifestations of MMP or BP and OLP. The interval for development of LPP in the context of LP is variable. When the nature and character of lesions change and lesions do not respond to routine treatment, it is imperative to suspect LPP and repeat tissue biopsy for confirmation. Since there are cases of oral lichen planus pemphigoides (OLPP) which do not present with intact bullae, immunofluorescent studies are essential for differentiating between OLPP and OLP when warranted by clinical findings. LPP is a systemic disease that may affect larynx, conjunctivae, skin and esophagus causing severe complications such as dysphagia, respiratory distress and blindness with significant impact on quality of life. This case report highlights the importance of close monitoring of patient's response to therapy and appropriate workup when signs and symptoms persist or change character. This approach would help facilitate timely diagnosis, improve outcome and reduce likelihood of complications.

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