

Lichen Planus Pemphigoides Treated With Ustekinumab



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PRACTICE POINTS

- Lichen planus pemphigoides (LPP) is a rare autoimmune subepidermal blistering disease with few cases reported in the literature.
- Because tumor necrosis factor α (TNF- α) and other inflammatory cytokines are involved in the pathogenesis of bullous pemphigoid and lichen planus, it is feasible that they also may be involved in the pathogenesis of LPP.
- Ustekinumab may be used to treat LPP as a potential corticosteroid-sparing agent because it indirectly blocks TNF- α , as well as other proinflammatory cytokines such as IFN- γ , IL-17, and IL-22.

A 71-year-old woman presented with pink to violaceous, flat-topped, polygonal papules on the volar wrists, extensor elbows, and bilateral lower legs of 3 years' duration. She also had erythematous, violaceous, infiltrated plaques with microvesiculation on the bilateral thighs of several months' duration. She reported pruritus, burning, and discomfort. Her medical history included type 2 diabetes mellitus, hypertension, and asthma with no history of skin rashes. Workup revealed lichen planus pemphigoides (LPP), a rare papulosquamous and vesiculobullous dermatosis that shares features of both lichen planus (LP) and bullous pemphigoid (BP). Despite multiple traditional therapies, her disease continued to progress, further developing mucosal disease. After a review of the literature on LP, BP, and LPP, it was noted that tumor necrosis factor α (TNF- α), along with other cytokines, plays a pivotal role in all 3 diseases. After several conventional systemic therapies failed, we treated our patient with ustekinumab with favorable results.

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Case Report

A 71-year-old woman presented with pink to violaceous, flat-topped, polygonal papules consistent with lichen planus (LP) on the volar wrists, extensor elbows, and bilateral lower legs of 3 years' duration. She also had erythematous, violaceous, infiltrated plaques with microvesiculation on the bilateral thighs of several months' duration (Figure 1). She reported pruritus,



FIGURE 1. Lichen planus pemphigoides presentation with erythematous, violaceous, infiltrated plaques with microvesiculation on the thigh.

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burning, and discomfort. Her medical history included type 2 diabetes mellitus, hypertension, and asthma with no history of skin rashes. A complete physical examination was performed. Age-appropriate screening for malignancy was negative. Hepatitis B and C antibody serologies were negative. Her medications at the time included risedronate and atenolol, which she had been taking for several years.

Punch biopsies from perilesional skin were submitted for hematoxylin and eosin staining and direct immunofluorescence (DIF). Histopathology showed a subepidermal blistering disease with tissue eosinophilia consistent with lichen planus pemphigoides (LPP)(Figure 2); direct immunofluorescence was positive for IgG, C3, and type IV collagen at the dermoepidermal junction. Serum BP180 was positive at 51 U/mL (reference range, <14 U/mL) and BP230 was negative. She was then started on tetracycline (500 mg twice daily), nicotinamide (500 mg twice daily), prednisone (5 mg daily), and dapsone (100 mg daily).

After 3 months without improvement, tetracycline and nicotinamide were discontinued, prednisone was increased to 10 mg daily, and dapsone was continued. A repeat biopsy was taken from a new area of involvement on the left lower leg, which revealed a psoriasiform dermatitis with interface changes. The DIF was positive for IgG and C3 along the basement membrane. A serum indirect immunofluorescence for BP180 also was positive.

The patient developed mild hemolytic anemia on dapsone; the medication was eventually discontinued. Subsequent treatments included adequate trials of azathioprine, mycophenolate mofetil, and hydroxychloroquine. Azathioprine (150 mg daily) and hydroxychloroquine (400 mg daily) treatment failed. She initially improved on mycophenolate mofetil (500 mg in the morning and 1000 mg in the evening) with flattening of the papules on the arms and legs and decreased erythema. However, mycophenolate mofetil eventually lost its efficacy and was discontinued.

Because several medications failed (ie, tetracycline, nicotinamide, prednisone, dapsone, azathioprine, mycophenolate mofetil, hydroxychloroquine), she was started on ustekinumab (45 mg) initial loading dose by subcutaneous injection (patient's weight, 63 kg). At 4 weeks, the patient was given the second subcutaneous injection of ustekinumab (45 mg). She experienced marked improvement with no new lesions. The prior lesions also had decreased in size and were only slightly pink. The prednisone dose was tapered to 5 mg daily.

She had near-complete resolution of the skin lesions 12 weeks after the second dose of ustekinumab. Since then, she has had some recrudescence of the papulosquamous lesions but no vesicles or bullae. With the exception of occasional scattered pink papules on the forearms, her condition greatly improved on ustekinumab. She is no longer taking any of the other medications with the exception of prednisone (down to 1 mg daily) with a plan to gradually taper completely off of it.

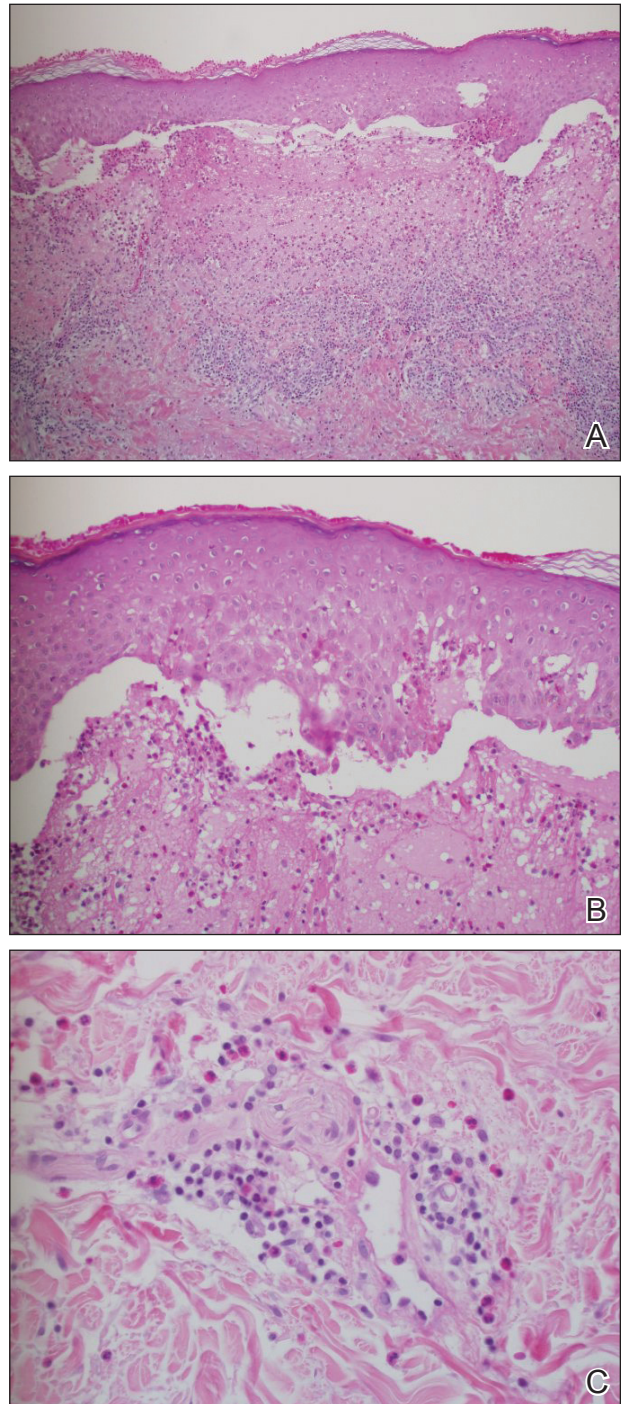


FIGURE 2. Histopathology revealed a brisk inflammatory infiltrate with a subepidermal split (A)(H&E, original magnification $\times 4$) with multiple eosinophils (B)(H&E, original magnification $\times 20$). A perivascular infiltrate was present with marked eosinophils (C)(H&E, original magnification $\times 40$).

Comment

Clinical Presentation—Lichen planus pemphigoides is a rare autoimmune subepidermal blistering disease with few cases reported in the literature. It is considered a

clinical variation of bullous pemphigoid (BP) or a coexistence of LP and BP.^{1,2} It is characterized by bullous lesions developing on LP papules as well as on clinically uninvolved areas of the skin. It has been reported that LPP is provoked by several medications including cinnarizine, captopril, ramipril, simvastatin, psoralen plus UVA, and antituberculous medications (eg, isoniazid, rifampin, ethambutol, pyrazinamide).¹ Risedronate or atenolol have not been reported to cause LPP, LP, or BP; however, according to Litt,³ a lichenoid drug eruption has been associated with atenolol. Furthermore, some cases of LPP demonstrate overlapping characteristics with paraneoplastic pemphigus and have been associated with internal malignancy. Hamada et al⁴ described a case of LPP coupled with colon adenocarcinoma and numerous keratoacanthomas. The earliest depiction of the coexistence of a case of mainstream LP complicated by an extensive bullous eruption was by Kaposi⁵ in 1892. He coined the term *lichen ruber pemphigoides*.⁵

Compared to BP, LPP is believed to affect a younger age group and have a less serious clinical course. The mean age of onset of LPP is in the third to fourth decades of life, while BP typically presents in the sixth decade. When comparing the location of bullae in LPP versus BP, the lesions of LPP tend to occur on the limbs, while BP tends to occur on the trunk.⁶

Clinically, LPP is distinguished by the existence of bullous lesions developing atop of the lesions of LP as well as on normal skin, with the latter being more commonplace. A classic example of LPP is characterized by an initial episode of traditional LP lesions often having severe pruritus, with or without patches of erythema, with the sudden eruption of tense bullae. These bullae commonly appear on the extremities and can appear over the normal skin, erythematous patches, or preexisting papules.⁷ In the atypical clinical presentations of this dubious skin condition, the bullae may only be seen on the lesions of LP.⁸ There also could be a lichenoid erythrodermic manifestation of a bullous eruption.⁹

Oral lesions of LPP have been described but had not been studied immunopathologically until Allen et al¹⁰ portrayed a 59-year-old man with cutaneous and oral lesions of LPP. They performed biopsies on the oral lesions and examined them by routine light microscopy and immunofluorescent techniques. The fine keratotic striae on the anterior buccal mucosal lesions were clinically consistent with oral LP. Perilesional tissue in conjunction with ulceration of the posterior buccal mucosa demonstrated histologic and immunopathologic alterations consistent with BP.¹⁰

Histopathology—Histopathologically, the lesions of LP show a bandlike lymphohistiocytic infiltrate, colloid bodies in the dermis, irregular acanthosis with saw-toothed rete ridges, orthokeratosis, wedge-shaped hypergranulosis, and liquefaction degeneration of the basal layer. Direct immunofluorescence shows mainly IgM and C3 deposited on colloid bodies, fibrin, and fibrinogen.¹¹ The

histopathology of the bullous lesion of LPP depicts a subepidermal bulla with variable diffuse or sparse lymphohistiocytic infiltrate and frequent eosinophils with or without neutrophils in the upper dermis. The existence of C3 alone or with IgG along the dermoepidermal junction gives confirmation on DIF.⁷

Autoantibodies—The expression of IgG autoantibodies directed against the basement membrane zone distinguishes LPP from bullous LP.² IgG autoantibodies to either one or both the 230-kDa and 180-kDa BP (type XVII collagen) antigens has been demonstrated with LPP.^{4,12-14} Hamada et al⁴ described a histologic pattern more consistent with paraneoplastic pemphigus. It has been suggested that injury to the basal cells in LP or damage due to other courses of therapy such as psoralen plus UVA unveil suppressed antigenic determinants or produce new antigens, leading to antibody development and production of BP.^{12,15}

Zillikens et al² performed a study to identify the target antigen of LPP autoantibodies. They used sera from patients with LPP (n=4) and stained the epidermal side of salt-split human skin in a configuration identical to BP sera. In BP, the autoimmune response is directed against BP180, a hemidesmosomal transmembrane collagenous glycoprotein. They demonstrated that sera from BP patients largely reacted with a set of 4 epitopes (MCW-0 through MCW-3) grouped within a 45 amino acid stretch of the major noncollagenous extracellular domain (NC16A) of BP180. By immunoblotting and enzyme-linked immunosorbent assay, LPP sera also were compellingly reactive with recombinant BP180 NC16A. Lichen planus pemphigoides epitopes were additionally mapped using a series of overlapping recombinant segments of the NC16A domain. The authors demonstrated that all LPP sera reacted with amino acids 46 through 59 of domain NC16A, a protein portion that was previously shown to be unreactive with BP sera. In addition, they showed that 2 LPP sera reacted with the immunodominant antigenic region related to BP. Furthermore, they identified a unique epitope within the BP180 NC16A domain—MCW-4—which was distinctively recognized by sera from patients with LPP.²

Pathogenesis—The pathogenesis of both LP and BP has been linked to multiple cytokines that induce apoptosis in basal keratinocytes. Implicated cytokines include IFN- γ , tumor necrosis factor α (TNF- α), IL-1, IL-6, and IL-8, as well as other apoptosis-related molecules, such as Fas/Apo-1 and Bcl-2 in LP.¹⁶⁻¹⁸ Soluble E-selectin, vascular endothelial growth factor, IL-1 β , IL-8, IL-5, transforming growth factor β 1, and TNF- α were found to be elevated in either blister fluid or sera of BP patients.¹⁵⁻¹⁷

Management—Lichen planus pemphigoides usually responds well to traditional therapies, with systemic steroids being the most efficacious treatment of extensive disease.^{12,13} Other options include tetracycline and nicotinamide, isotretinoin, dapsone, and

immunosuppressive drugs such as systemic corticosteroids.¹² Demirçay et al¹² described a patient with skin lesions that rapidly cleared after the administration of oral methylprednisolone (48 mg/d) and oral dapsone (100 mg/d). The methylprednisolone and dapsone were withdrawn after 12 and 16 weeks, respectively. There was no recurrence during the 1-year follow-up period.¹² Kolb-Mäurer et al¹⁹ described a patient who was treated with pulsed intravenous corticosteroids and continued to develop new papular and vesicular skin lesions. However, when oral acitretin was added to the patient's regimen, the skin lesions cleared.¹⁹ There are several case reports of the successful use of hydroxychloroquine in LP.^{20,21}

Cutaneous, nail, and oral LP also can be treated with TNF- α inhibitors (eg, adalimumab, etanercept) with resolution of lesions.²²⁻²⁵ However, we have not been able to find any reports of treating LPP with biologic medications in a search of PubMed articles indexed for MEDLINE using the terms *lichen planus pemphigoides* and *biologic treatments/therapies*. Given the fact that TNF- α and other inflammatory cytokines are involved in the pathogenesis of BP and LP, it is feasible that they also may be involved in the pathogenesis of LPP.

In our patient with cutaneous LPP, we chose to use ustekinumab instead of a primary TNF- α inhibitor because ustekinumab indirectly blocks TNF- α , as well as other proinflammatory cytokines such as IFN- γ , IL-17, and IL-22, which also could have played a role in the patient's disease. Our goal was to use ustekinumab as a potential corticosteroid-sparing agent. Ustekinumab greatly improved her skin condition and allowed us to discontinue other medications.

REFERENCES

- Harting MS, Hsu S. Lichen planus pemphigoides: a case report and review of the literature. *Dermatol Online J*. 2006;12:10.
- Zillikens D, Caux F, Mascaro JM, et al. Autoantibodies in lichen planus pemphigoides react with a novel epitope within the C-terminal NC16A domain of BP180. *J Invest Dermatol*. 1999;113:117-121.
- Litt J. *Litt's Drug Eruptions and Reactions Manual*. 18th Ed. London, England: Informa Healthcare; 2011.
- Hamada T, Fujimoto W, Okazaki F, et al. Lichen planus pemphigoides and multiple keratoacanthomas associated with colon adenocarcinoma. *Br J Dermatol*. 2004;151:252-254.
- Kaposi M. Lichen ruber pemphigoides. *Arch Derm Syph*. 1892;343-346.
- Swale VJ, Black MM, Bhogal BS. Lichen planus pemphigoides: two case reports. *Clin Exp Dermatol*. 1998;23:132-135.
- Okochi H, Nashiro K, Tsuchida T, et al. Lichen planus pemphigoides: case reports and results of immunofluorescence and immunoelectron microscopic study. *J Am Acad Dermatol*. 1990;22:626-631.
- Mendiratta V, Asati DP, Koranne RV. Lichen planus pemphigoides in an Indian female. *Indian J Dermatol*. 2005;50:224-226.
- Joly P, Tanasescu S, Wolkenstein P, et al. Lichenoid erythrodermic bullous pemphigoid of the African patient. *J Am Acad Dermatol*. 1998;39:691-697.
- Allen CM, Camisa C, Grimwood R. Lichen planus pemphigoides: report of a case with oral lesions. *Oral Surg Oral Med Oral Pathol*. 1987;63:184-188.
- Rapini RP. *Practical Dermatopathology*. Philadelphia, PA: Mosby Elsevier; 2005.
- Demirçay Z, Baykal C, Demirkesen C. Lichen planus pemphigoides: report of two cases. *Int J Dermatol*. 2001;40:757-759.
- Sakuma-Oyama Y, Powell AM, Albert S, et al. Lichen planus pemphigoides evolving into pemphigoid nodularis. *Clin Exp Dermatol*. 2004;28:613-616.
- Hsu S, Ghohestani RF, Uitto J. Lichen planus pemphigoides with IgG autoantibodies to the 180kd bullous pemphigoid antigen (type XVII collagen). *J Am Acad Dermatol*. 2000;42:136-141.
- Kuramoto N, Kishimoto S, Shibagaki R, et al. PUVA-induced lichen planus pemphigoides. *Br J Dermatol*. 2000;142:509-512.
- Ameglio F, D'Auria L, Cordiali-Fei P, et al. Bullous pemphigoid and pemphigus vulgaris: correlated behaviour of serum VEGF, sE-selectin and TNF-alpha levels. *J Biol Regul Homeost Agents*. 1997;11:148-153.
- Ameglio F, D'auria L, Bonifati C, et al. Cytokine pattern in blister fluid and serum of patients with bullous pemphigoid: relationships with disease intensity. *Br J Dermatol*. 1998;138:611-614.
- D'Auria L, Mussi A, Bonifati C, et al. Increased serum IL-6, TNF-alpha and IL-10 levels in patients with bullous pemphigoid: relationships with disease activity. *J Eur Acad Dermatol Venereol*. 1999;12:11-15.
- Kolb-Mäurer A, Sitaru C, Rose C, et al. Treatment of lichen planus pemphigoides with acitretin and pulsed corticosteroids. *Hautarzt*. 2003;54:268-273.
- Eisen D. Hydroxychloroquine sulfate (Plaquenil) improves oral lichen planus: an open trial. *J Am Acad Dermatol*. 1993;28:609-612.
- James WD, Berger T, Elston D. *Andrews' Diseases of the Skin*. 11th ed. Philadelphia, PA: Mosby Elsevier; 2011.
- Holló P, Szakonyi J, Kiss D, et al. Successful treatment of lichen planus with adalimumab. *Acta Derm Venereol*. 2012;92:385-386.
- Yarom N. Etanercept for the management of oral lichen planus. *Am J Clin Dermatol*. 2007;8:121.
- Chao TJ. Adalimumab in the management of cutaneous and oral lichen planus. *Cutis*. 2009;84:325-328.
- Irla N, Schneiter T, Haneke E, et al. Nail lichen planus: successful treatment with etanercept. *Case Rep Dermatol*. 2010;2:173-176.