Lichenoid drug eruption after treatment with ixekizumab for plaque psoriasis

Neda Ghiam[1,2] MD, Oben Ojong[3] DO, Gabriella Vasile[3] DO, Paolo Romanelli[2] MD, Francisco Kerdel[1] MD

Affiliations: [1]Florida Academic Dermatology Centers, Coral Gables, Florida, USA, [2]Dr Phillip Frost Department of Dermatology and Cutaneous Surgery, University of Miami, Miller School of Medicine, Miami, Florida, USA, [3]Larkin Community Hospital-Palm Springs Campus, Hialeah, Florida, USA

Corresponding Author: Neda Ghiam MD, Florida Academic Dermatology Centers, 475 Biltmore Way, Suite 207, Coral Gables, FL 33134, Tel: 305-324-2110 ext. 2950, Email: NGhiam@FADCresearch.com

Abstract

Lichen planus, the prototype of lichenoid dermatoses, is an idiopathic, T cell-mediated, autoimmune, inflammatory disease. It may affect the skin, hair, nails, and mucous membranes. Many clinical variants of lichen planus have been described, including lichenoid drug eruption or drug induced lichen planus, associated with a myriad of culprit medications. We describe a 63-year-old woman with longstanding psoriasis effectively controlled with ixekizumab, who developed lichenoid drug eruption. Her lichen planus lesions improved after treatment discontinuation and the patient was started on an IL23 inhibitor to treat her psoriasis through an alternative mechanism of action. Our report adds to the literature and provides insight into the complex pathophysiology of lichen planus.

Keywords: psoriasis, lichen planus, ixekizumab

Introduction

The advent of monoclonal antibodies has revolutionized the treatment of many inflammatory diseases, particularly psoriasis. Available biologics specifically target the relevant inflammatory pathways leading to psoriasis production with high efficacy and desirable safety profiles. Ixekizumab is a humanized IgG4 monoclonal antibody against IL17A that blocks the production of chemokines, cytokines, antimicrobial peptides, and beta-defensins from keratinocytes [1]. We report a case of lichenoid eruption after treatment with Ixekizumab for plaque psoriasis.

Case Synopsis

A 63-year-old woman with a history of psoriasis for 15 years presented to the clinic complaining of an intensely pruritic rash for two days that interfered with her sleep. The eruption was diffuse over her abdomen, upper and lower extremities, chest, back, and pelvis. The patient had received nine months of therapy with ixekizumab and had injected her thirteenth dose of ixekizumab one week before the onset of the rash. The patient denied any systemic symptoms including joint pain. Previous treatments for psoriasis included narrow band UVB for one month and adalimumab for six months. Adalimumab therapy was stopped owing to inadequate response.

She had a past medical history positive for Meniere disease, hypothyroidism, and hyperlipidemia and negative for hepatitis C. Concurrent medications at the time of eruption were folic acid, triamterene, and Senna-Time. Patient had been on these medications for years without any adverse side effects.

On physical examination, multiple, generalized, purple, polygonal papules and plaques were noted on the skin. Lesions were most aggregated over the back, buttocks, anterior upper thigh, posterior thighs, posterior legs, and lower abdomen. Linear erosions were noted on the back and on the upper extremities. No scaling, erythema, or induration were noted, ruling out a psoriasis flare (**Figure 1**). The

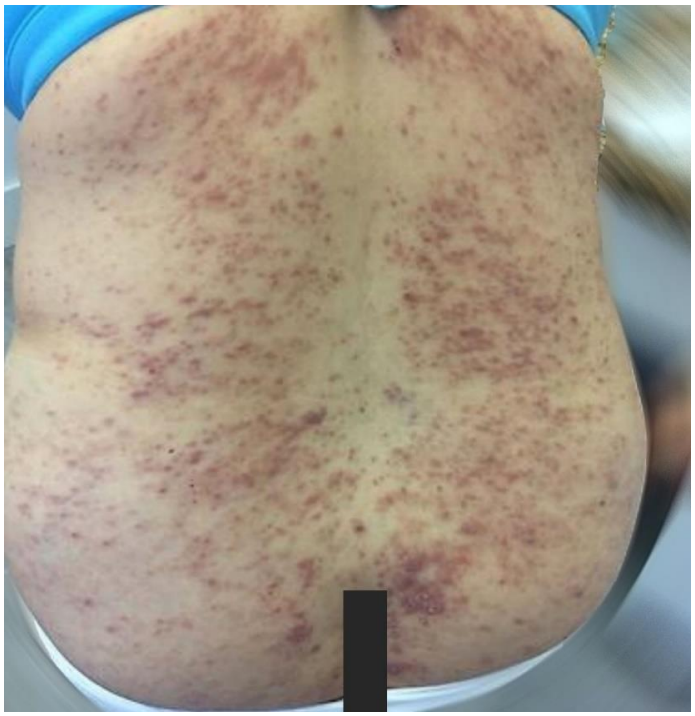

Figure 1. *Multiple, generalized, purple, polygonal papules and plaques on the patient's back. Note the lesions being eczematous and not scaly, consistent with lichen planus.*

mucous membranes and flexural areas were spared (**Figure 2**).

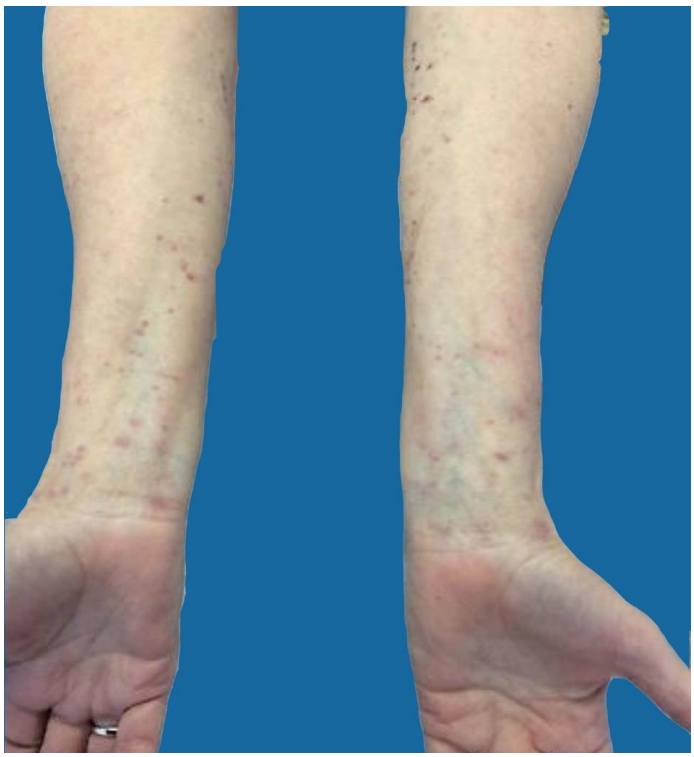

Figure 2. *Lesions sparing classic flexural areas commonly involved in lichen planus, suggestive of lichenoid drug eruption.*

A four-millimeter punch biopsy was performed on one of the lesions on the left infrascapular back and was sent for histopathologic analysis. Histopathologic result of the punch biopsy showed hyperkeratosis and focal wedge-shaped hypergranulosis, irregular acanthosis with vacuolar alteration of the basal layer, scattered necrotic keratinocytes, and band-like superficial inflammatory lymphocytic infiltration. These changes were consistent with lichen planus (**Figure 3**).

Our patient was advised to stop ixekizumab and was prescribed triamcinolone acetonide 0.1% topical cream for the body and clobetasol 0.05 % solution for

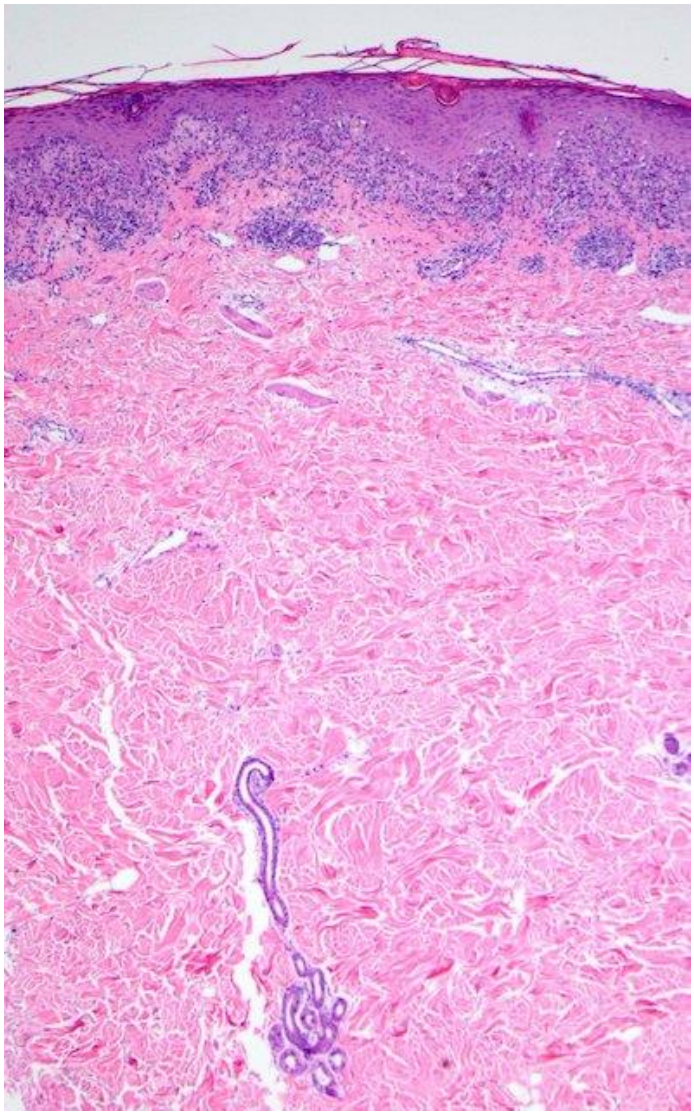

Figure 3. *Punch biopsy showing hyperkeratosis, focal wedge-shaped hypergranulosis, vacuolar alteration of the basal layer, and band like superficial inflammatory lymphocytic infiltration, consistent with lichen planus. H&E, 10×.*

the scalp. At the two-week follow-up visit, she had partial resolution of the pruritus and skin lesions. At the six-week follow-up visit, her skin had almost cleared and the pruritus had substantially diminished. Therapy with guselkumab, an IL23 inhibitor, was initiated to treat her psoriasis through an alternative mechanism of action. At the five-month follow up visit, her psoriasis was clear and the LP lesions had resolved with residual hyperpigmentation.

Case Discussion

Lichen planus (LP) or lichen ruber planus is an idiopathic, inflammatory, T cell mediated autoimmune disease. Many clinical variants of LP have been described, including hypertrophic, atrophic, actinic, bullous, annular, linear, ulcerative, lichen planopilaris, lichen planus pigmentosus, and drug induced lichen planus or lichenoid drug eruption (LDE), [2]. Lesions in idiopathic LP typically present as purple, pruritic, polygonal, planar, and violaceous papules or plaques [3]. The eruption tends to be symmetric and favor the flexural areas of the wrists, forearms, and ankles and is more common in adult women [3].

There are no pathognomonic clinical or histological features to distinguish LDE from idiopathic cutaneous LP, but some distinguishing features have been proposed. Lichenoid drug eruptions tend to present as generalized and more desquamative and eczematous with sparing of classic flexural areas of LP, as observed in our patient. The mean age for LDE is 65 years whereas it is 50 years for idiopathic LP [2]. Mucosal involvement is less common and Wickham striae are not seen [4]. Our patient was 63 years old and did not have mucosal involvement or Wickham striae.

Histologically, features believed to be more common in LDE are prominent necrotic keratinocytes in clusters, eosinophils, and plasma cells [5]. The presence of lymphoid cells in the upper dermis and in the deeper perivascular infiltrate are also proposed to more frequently occur [4]. However, the absence of eosinophils or any of the mentioned features cannot reliably rule out a lichenoid drug eruption. Focal parakeratosis and focal interruption of granular layer are common in LDE while parakeratosis is uncommon in idiopathic LP [2]. In our case, plasma cells but no eosinophils were seen. Focal parakeratosis and focal interruption of the granular layer were observed (**Figure 4**) and mid-dermis perivascular lymphocytic infiltrates were present on higher magnification (**Figure 5**).

Histologic criteria in general are not solely sufficient to make a distinction between lichenoid drug eruption and conventional idiopathic LP [2]. Therefore, a careful history, showing evidence of the emergence of lesions after treatment and subsequent improvement or resolution after treatment discontinuation is a more prudent consideration when differentiating between the two conditions. Our patient developed LP lesions after treatment with ixekizumab, showing a temporal relationship, and lesions subsided after treatment discontinuation. We did not re-administer ixekizumab to our patient because of ethical reasons. Furthermore, recurrence of LDE after drug re-challenge is reportedly uncommon [6].

A large number of medications have been associated with lichenoid drug eruptions, although recurrence after drug re-challenge is generally rare [6]. Diuretics, ACE inhibitors, non-steroidal anti-inflammatory drugs, metals, antihypertensives, antimalarials, and

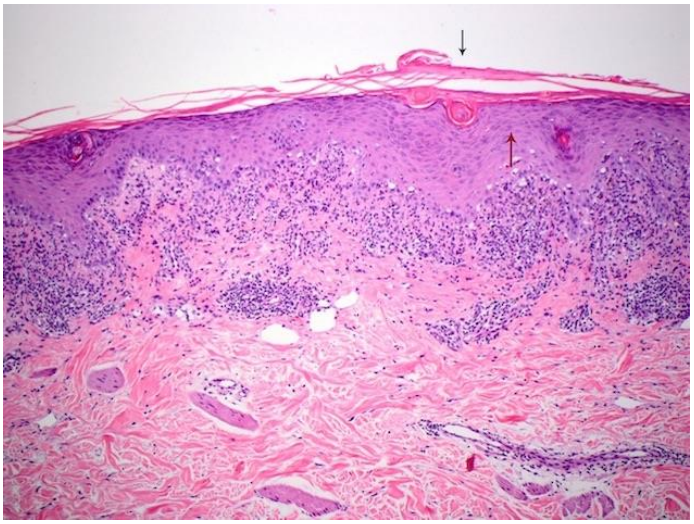

Figure 4. *Focal parakeratosis (black arrow) and focal interruption of the granular layer (red arrow) were seen, features more common in lichenoid drug eruption than idiopathic lichen planus. H&E, 25×.*

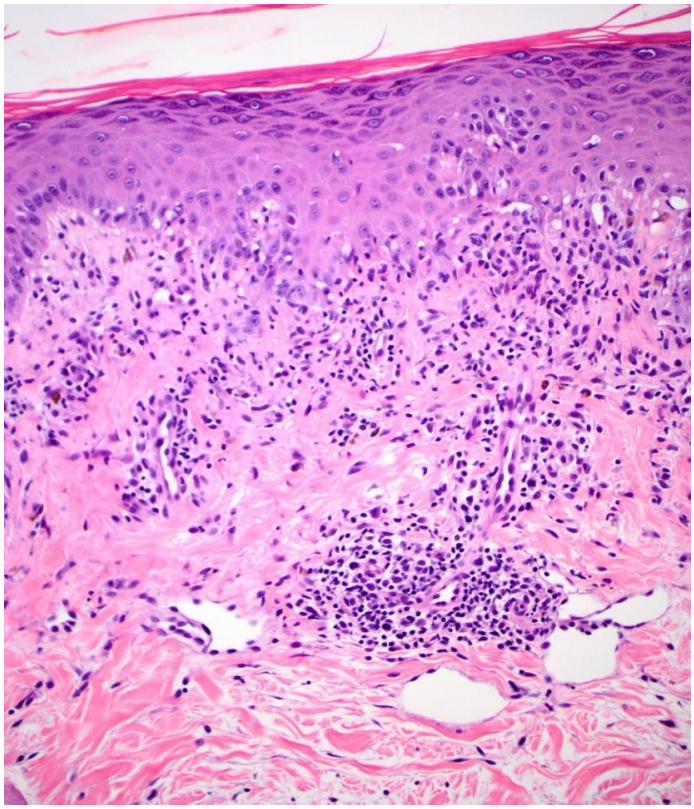

Figure 5. *Higher magnification of the lesions demonstrating inflammatory lymphocytic infiltration in the mid-dermis, H&E, 100×.*

antimicrobials, and others have been implicated in causing lichenoid drug reactions [2]. Some vaccines have been reported to cause LP, including hepatitis B, HPV, DTaP, influenza, and rabies vaccines [7, 8,9,10]. Anti-PD1 therapies have also been reported to cause lichenoid drug eruptions [11, 12]. Other cancer treatments such as the tyrosine kinase inhibitor crizotinib and epidermal growth factor receptor inhibitor olmutinib have also been reported to cause lichen planus like eruptions [13, 14].

Lichenoid reaction patterns have been reported with systemic psoriasis treatments, namely methotrexate and biologics [15]. Amongst systemic biologic psoriasis treatments, lichenoid drug eruptions secondary to TNF inhibitors have been reported, including adalimumab and an infliximab biosimilar [16-19]. Ulcerative lichenoid mucositis associated with secukinumab, an IL17A inhibitor, has been reported [20]. Both IL17 and TNF are believed to be implicated in the pathogenesis of lichen planus, although the exact mechanisms are not yet fully established [16, 21-23]. Therefore, the emergence of lichenoid reactions to anti-TNF and anti-IL17 medications is unexpected. However, a paradoxical psoriatic reaction to TNF inhibitors is seen despite the role of TNF in the development of psoriasis lesions. This reaction is hypothesized to relate to the elimination of the inhibitory effect of TNF on IFNα, therefore promoting hyperproliferation of the keratinocytes [24]. Additionally, there is a synergistic effect proposed for TNF and IL17 in psoriasis and the therapeutic effects of TNF inhibitors are presumed to be indirectly through suppression of the IL23/Th17 pathway [25]. Therefore, considering the elevated presence of both IL17 and TNF in lichen planus, it could be inferred that through some mechanism, TNF inhibitors promote lichenoid drug eruptions. The same hypothesis could be applied to lichenoid reactions to IL17 inhibitors. However, until the clear role of TNF and IL17 is established in the pathophysiology of lichen planus, these hypotheses cannot be examined and confirmed appropriately.

Conclusion

We report a case of new onset, biopsy proven lichenoid eruption after nine months of treatment with ixekizumab, which resolved after treatment discontinuation. Our report adds to the emerging evidence regarding the complex interactions of different pathways in the pathophysiology of psoriasis and lichen planus.

Potential conflicts of interest

Dr. Francisco Kerdel has served as a speaker for Eli Lilly and Company, has been on their advisory board and has received research funds from them. No funds have been received for this manuscript. Other authors have no relevant conflict of interest to disclose.

References

1. Ren V, Dao Jr H. Potential role of ixekizumab in the treatment of moderate-to-severe plaque psoriasis. *Clin Cosmet Investig Dermatol*. 2013;6:75 [PMID: 23515267].
2. Bolognia J, Schaffer JV, Cerroni L. Dermatology. Fourth edition. ed. [Philadelphia, Pa.]: Elsevier, Philadelphia, Pa.]; 2018.
3. Weston G, Payette M. Update on lichen planus and its clinical variants. *Int J Womens Dermatol*. 2015;1:140-9 [PMID: 28491978].
4. Tziotzios C, Lee JY, Brier T, et al. Lichen planus and lichenoid dermatoses: clinical overview and molecular basis. *J Am Acad Dermatol*. 2018;79:789-804 [PMID: 30318136].
5. Lage D, Juliano PB, Metze K, et al. Lichen planus and lichenoid drug‐induced eruption: a histological and immunohistochemical study. *Int J Dermatol*. 2012;51:1199-205 [PMID: 22416968].
6. Arnold DL, Krishnamurthy K. Lichen, Planus. In: StatPearls [Internet]. StatPearls Publishing; 2018. [PMID: 30252382].
7. Jones J, Marquart JD, Logemann NF, DiBlasi DR. Lichen striatus-like eruption in an adult following hepatitis B vaccination: a case report and review of the literature. *Dermatol Online J*. 2018;24(7). [PMID: 30261572].
8. Laschinger ME, Schleichert RA, Green B. Lichenoid drug eruption after human papillomavirus vaccination. *Pediatr Dermatol*. 2015;32:e48-9. [PMID: 25690057].
9. Brennan C, Davis L. Lichenoid drug reaction following influenza vaccination in an HIV-positive patient: a case report and literature review. *J Drugs Dermatol*. 2014;13:873-5 [PMID: 25007374].
10. An I, Demir V, İbiloğlu İ, Akdeniz S. Lichen planus secondary to rabies vaccination. *Dermatol Online J*. 2017;23(3) [PMID: 28329523].
11. Coscarart A, Martel J, Lee MP, Wang AR. Pembrolizumab-induced pseudoepitheliomatous eruption consistent with hypertrophic lichen planus. *J Cutan Pathol*. 2020;47:275-279 [PMID: 31589773].
12. Kaunitz G, Kim RH. Lichen Planus Follicularis Tumidus Associated With PD1 Blockade. *JAMA Dermatol*. 2019;155:1197-8 [PMID: 31365028].
13. Ho YH, Chen CL. Crizotinib-induced lichenoid drug eruption in a patient with lung cancer. *Cutis*. 2018;102:403-6 [PMID: 30657798].
14. Oh SH, Byun HJ, Oh SJ, et al. Olmutinib Induced Lichen Planus Like Eruption. *Ann Dermatol*. 2018;30:451-3 [PMID: 30065585].
15. Ferguson NN, Asarch A, VanBeek M, Swick BL. Acute mucocutaneous methotrexate toxicity associated with interface dermatitis and numerous eosinophils. *Am J Dermatopathol*. 2013;35:e63-e6 [PMID: 23221488].
16. Asarch A, Gottlieb AB, Lee J, et al. Lichen planus-like eruptions: an emerging side effect of tumor necrosis factor-alpha antagonists. *J Am Acad Dermatol*. 2009;61:104-11. [PMID: 19539844].
17. Inoue A, Sawada Y, Yamaguchi T, et al. Lichenoid drug eruption caused by adalimumab: a case report and literature review. *Eur J Dermatol*. 2017;27:69-70. [PMID: 27777187].
18. El Habr C, Meguerian Z, Sammour R. Adalimumab-induced lichenoid drug eruption. *J Med Liban*. 2014;103:1-3 [PMID: 25807724].
19. Gonzalez N, Patel P, Han G. A dissimilar biosimilar? Lichenoid drug eruption induced by an infliximab biosimilar. *Br J Dermatol*. 2018;178:965-8 [PMID: 28556906].
20. Thompson JM, Cohen LM, Yang CS, Kroumpouzos G. Severe, ulcerative, lichenoid mucositis associated with secukinumab. *JAAD case rep*. 2016;2:384 [PMID: 27752531].
21. Shen Z, Gao X, Ma L, et al. Expression of Foxp3 and interleukin-17 in lichen planus lesions with emphasis on difference in oral and cutaneous variants. *Arch Dermatol Res*. 2014;306:441-6 [PMID: 24292092].
22. Speeckaert R, Lambert J, Grine L, et al. The many faces of interleukin‐17 in inflammatory skin diseases. *Br J Dermatol*. 2016;175:892-901 [PMID: 27117954].
23. Erdem MT, Gulec AI, Kiziltunc A, et al. Increased serum levels of tumor necrosis factor alpha in lichen planus. *Dermatology*. 2003;207:367-70 [PMID: 14657628].
24. Succaria F, Bhawan J. Cutaneous side‐effects of biologics in immune‐mediated disorders: A histopathological perspective. *J Dermatol*. 2017;44:243-50 [PMID: 28256759].
25. Chiricozzi A, Guttman-Yassky E, Suárez-Farinas M, et al. Integrative responses to IL17 and TNFα in human keratinocytes account for key inflammatory pathogenic circuits in psoriasis. *J Invest Dermatol*. 2011;131:677-87 [PMID: 21085185].