# Methotrexate in Lichen Planus Pemphigoides – A Case Report and Review of the Literature

Dear Editor,

Lichen planus pemphigoides (LPP) is a rare sub-epidermal autoimmune blistering disorder that appears to be a combination of lichen planus (LP) and bullous pemphigoid (BP). It is characterized by the presence of tense fluid-filled lesions in a background of lichenoid changes that develop due to autoantibodies targeting an epitope within the C-terminal NC16A domain of the 180 kDa BP antigen.

A 55-year-old lady presented to us with a chief complaint of hyperpigmented itchy lesions over the body of eight months' duration. Multiple violaceous to hyperpigmented macules and papules initially appeared over the limbs, and subsequently increased to involve other body sites including the lower abdomen, and back [Figure 1]. A week later, the patient developed multiple, tense, itchy, fluid-filled blisters over the hyperpigmented lesions and over normal skin. Histopathological examination from a violaceous papule was consistent with lichenoid tissue reaction, and biopsy from a blister revealed a subepithelial cleft with eosinophils, fibrin, and occasional keratinocytes. Direct immunofluorescence revealed linear C3 deposit at the dermo-epidermal junction, but IgA and IgG were negative [Figure 2]. ELISA and IIF could not be done due to financial constraints and non-availability at our center.

Based on the clinical and histopathological findings, a diagnosis of LPP was made, and the patient was started on oral prednisolone (1 mg/kg body weight) along with topicals. However, there was an inadequate response to the treatment that led to an eruption of new lesions after three weeks of therapy. The oral steroid was tapered and stopped over a week, and the patient was then switched to oral methotrexate 7.5 mg once a week which was later increased to 15 mg. Patient responded well as new lesions ceased and old lesions resolved with hyperpigmentation [Figure 3]. Methotrexate was given for a total duration of five months. There was no recurrence in the six months of follow-up.

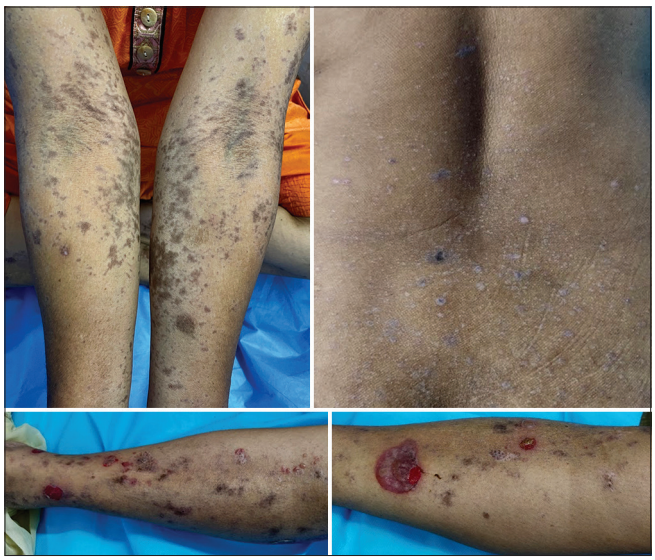

**Figure 1: Lichenoid lesions over upper limbs, back; fluid filled blisters involving lesional and uninvolved skin**

LPP is an acquired autoimmune dermatosis characterized by the development of blisters on pre-existing lichenoid lesions and normal skin.[1] A widely accepted hypothesis on its pathogenesis states that LP, as a primary inflammatory process, initiates exposure of a previously sequestered antigen leading to a secondary autoimmune response against the newly released antigen. The basement membrane zone damage leads to the formation of autoantibodies against BP180 antigen through "epitope spreading".[2]

The classical clinical picture of LPP comprises tense blisters along with lichenoid papules and plaques. Blisters usually emerge after the development of the lichenoid skin changes. LPP, bullous LP, and BP are a group of disorders that may present with cutaneous blisters and a background of lichenoid lesions. In bullous LP, the blisters are confined to the LP lesions but in LPP, they appear on normal skin and over lesions.

Most available data regarding treatment is in the form of case reports with maximum literature on the use of systemic corticosteroids in varying doses (0.5 mg/kg to 2 mg/kg).[3] However, considering the adverse effect profile of corticosteroids, these are not always the ideal choice. Other frequently used treatment modalities include topical corticosteroids, dapsone, azathioprine, acitretin, cyclosporine, intravenous immunoglobulin, methotrexate, and rituximab.[3] We chose to treat our patient with oral methotrexate due to its affordability and favorable safety profile.

Methotrexate inhibits dihydro-folate reductase and acts as a folate antagonist. Its efficacy in autoimmune dermatoses is due to the inhibition of aminoimidazole-carboxamide ribonucleotide transformylase enzyme which decreases *de novo* purine synthesis and leads to an increase in intracellular adenosine, both of which have anti-inflammatory properties. The use of methotrexate for LPP has been infrequently reported in the literature and with varying success. Table 1 summarises the available case reports on the use of methotrexate in LP pemphigoides.

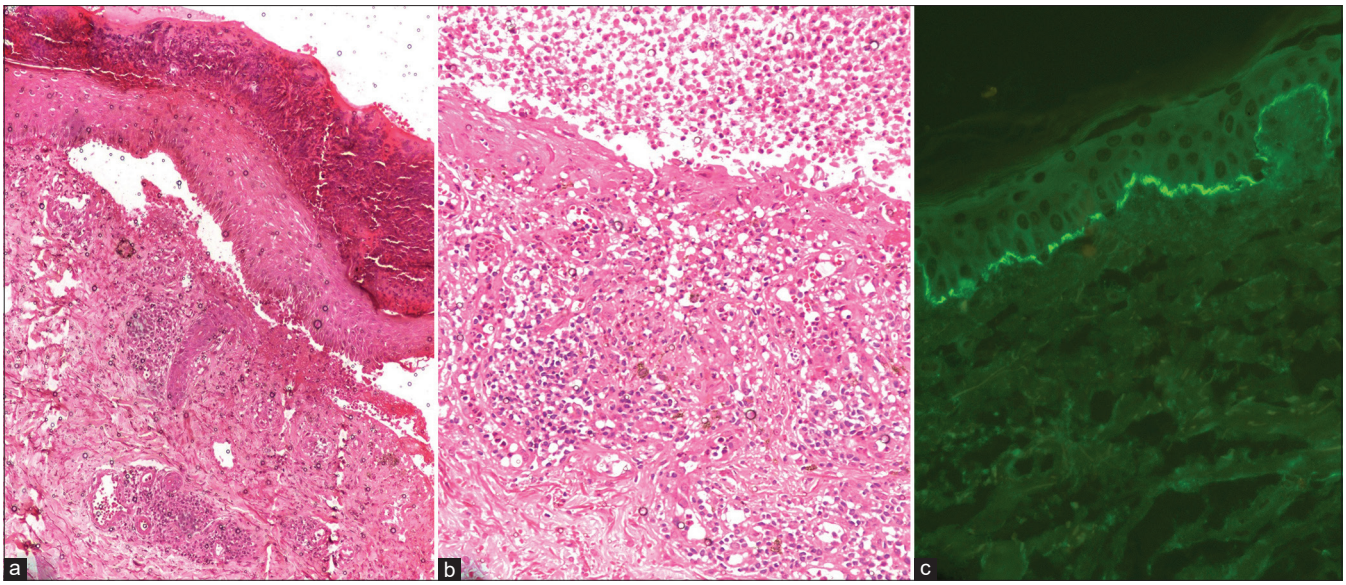


**Figure 2: (a) Histopathology of a blister showing subepithelial cleft with necrotic keratinocytes, eosinophils and fibrin. Upper dermis shows dense inflammation. (H&E 10×). (b) Histopathology of a lichenoid lesion showing interface dermatitis with upper dermis showing perivascular moderately dense mixed inflammatory infiltrate comprising of eosinophils and neutrophils along with fibrin deposition along with basophilic degeneration of collagen. (H&E 20×). (c) Direct immunofluorescence showing C3 (2+) linear deposits at the dermo-epidermal junction (IgG, IgA -ve) (D.I.F. 10×)**

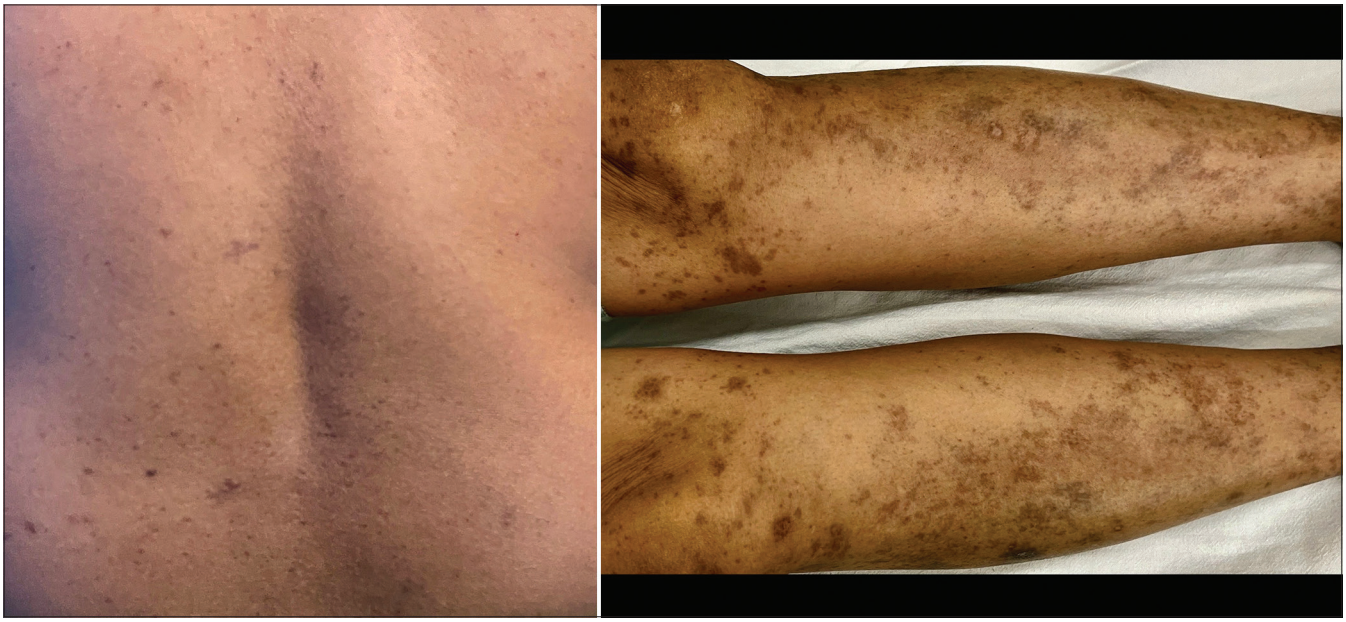

**Figure 3: Healed lesions after 3 months on methotrexate**

Adequate data supports its use in LP and BP and hence by extrapolation, it should be useful in LP pemphigoides considering the overlapping pathogenesis. It possesses both immunomodulatory and anti-inflammatory properties. Further, it suppresses inflammatory cell chemotaxis, inhibition of monocyte / macrophage activation, and inhibition of histamine release from basophils. It is a good option to explore in recalcitrant cases of LP pemphigoides requiring high-dose corticosteroids for control and in children due to the plethora of experience of its use in childhood dermatosis and favorable side effect profile. Further, the treatment response can be monitored with the help of anti-BP180 autoantibodies titers. In the present case, they could not be performed due to financial constraints.

To conclude, our report highlights the clinical and histopathological features of this rare autoimmune bullous disorder that appears to be an overlap of LP and BP. We have also underscored the importance of methotrexate as a good treatment option in this condition.

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Nil.

**Table 1: Reported literature on use of methotrexate in LP pemphigoides**

| Case report | Age/ Sex | Disease duration | Findings |
|---|---|---|---|
| Malakar and Saha 2016[4] | 35 yr/ Male | 8 months | Initially started on oral prednisolone (40 mg/day) then combination of prednisolone and methotrexate 15 mg/ week (as adjuvant); partial improvement after 2 months. Patient then switched to cyclosporine and responded well |
| Duong *et al*. 2011[5] | 2 yr/ Female | 3 weeks | Oral prednisolone 2 mg/kg/day; response was good but disease flared on tapering; weekly oral methotrexate 0.5 mg/kg/dose was added and prednisolone withdrawn over 8 weeks. Serial decrease in circulating BP180 autoantibodies corresponding to clinical improvement . |
| Lamberts *et al*. 2020[6] | 62 yr/ Male | 2 years | Known case of diabetes and COPD, presented with clinical and histological findings suggestive of LPP but lacked blisters clinically (non-bullous LPP). Initially started on topical corticosteroids but relapsed. Switched to methotrexate 7.5 mg/week which led to complete remission. Discontinued after 9 months but remained in remission. |
| Current case | 55 yr/ Female | 8 months | Initially developed lichenoid lesions followed by blisters (lesional and non-lesional). Initially started on oral prednisolone 1mg/kg but poor response. Switched to methotrexate 15 mg/week. Well-controlled after 5 months of therapy. |

COPD- chronic obstructive pulmonary disease

## *Conflicts of interest*

There are no conflicts of interest.

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