SKIN

BRIEF ARTICLE

Remission of Bullous Pemphigoid in a Patient Treated with Upadacitinib: A Case Report

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ABSTRACT

Bullous pemphigoid (BP) is a chronic autoimmune blistering disorder that often requires complex medical management. Cases of recalcitrant BP that do not respond to first line agents pose a therapeutic dilemma. Herein, we present a case of recalcitrant BP successfully treated with an oral janus kinase inhibitor, upadacitinib, after limited response with prednisone tapering, doxycycline, dupilumab and omalizumab. We observed substantial improvement following the initiation of upadacitinib after two months, complete remission after six months, and sustained remission one-year post-therapy. This case highlights the emerging potential of JAK inhibitors in managing refractory BP.

INTRODUCTION

Bullous pemphigoid (BP) is a chronic autoimmune blistering disorder characterized by tense bullae and generalized pruritus. BP treatment can be challenging, and first-line therapy often consist of systemic corticosteroids as gold standard. Given relapse occurs in approximately half of patients, second-line therapy with immunosuppressive agents is common, including azathioprine, mycophenolate mofetil, methotrexate, chlorambucil and cyclophosphamide, showing variable efficacy.[1] There is also evidence for use of doxycycline for BP and literature has found doxycycline 200 mg daily to be comparable to prednisolone 0.5 mg/kg daily for short-term blister control].[1-3] Further, combination therapy is often used to optimize efficacy. One study compared the combined use of methylprednisolone 0.5 mg/kg daily with either azathioprine 1.5-2.5 mg/kg daily or dapsone 1.5 mg/kg daily with comparable outcomes in each group.[4] Biologics, including rituximab, IVIG, omalizumab, and dupilumab, are increasingly being used in refractory cases.[1,2,5]

Janus kinase (JAK) inhibitors, including baricitinib and upadacitinib, have been reported as potential therapeutic options for refractory BP.[6-8] Associated adverse effects of JAK inhibitors, including venous thromboembolism, malignancy, and infections, can pose a therapeutic challenge.[9] To date, there has only been two reports of BP successfully treated with upadacitinib.[7,8] Herein, we present a case of refractory BP, highlighting significant improvement with upadacitinib.

CASE PRESENTATION

A 72-year-old man presented to an outside dermatologist for blistering lesions concerning for a bullous disorder prompting biopsy (**Figure 1**).

Clinical Findings

Biopsy of lesional skin on the first web space of the left hand revealed subepidermal vesicular dermatitis with neutrophils and eosinophils leading towards the diagnosis of bullous pemphigoid, but could not exclude other autoimmune bullous diseases. The patient was evaluated in our clinic through a televisit as the patient was wintering out of state. Since repeat biopsies weren't possible, indirect immunofluorescence (IIF) was ordered.

Diagnostic Assessment

IIF revealed bullous pemphigoid 180 IgG antibodies at 14.1 U/ml (Reference Range < 9) and bullous pemphigoid 230 IgG antibodies at 2.0 U/ml (Reference Range <9). Although BP 180 was only slightly elevated, this finding combined with the histopathology led to the diagnosis of bullous pemphigoid.

Therapeutic Intervention

The patient was trialed on a prednisone taper, doxycycline and niacinamide with limited improvement. He was then treated with dupilumab and omalizumab therapy, each for six-month periods, without disease control. Although he was initially responsive to prednisone, the patient would continue to flare when weaning down. Since he failed multiple systemic therapies, upadacitinib was selected as the next therapeutic option. Within two months of treatment, the patient had significant improvement in BP lesions on upadacitinib 15 mg every other day, with global improvement of all BP lesions after six months.

Follow up and Outcomes

After six months, the patient weaned down to upadacitinib 7.5 mg every other day. He was then weaned off completely after a total of one year on upadacitinib. To date, there has been no recurrence of BP for 18 months total following cessation of any treatment.

DISCUSSION

Bullous pemphigoid (BP) can present significant treatment challenges, often can be refractory to traditional therapies, and requires innovative management approaches.[1] Our case underscores the diagnostic limitations and unpredictable clinical nature involved in the management BP. Given reports of its efficacy in BP, and other dermatologic diseases that share similar pathophysiology, the initiation of the selective JAK-1 inhibitor upadacitinib was trialed in this case. Upadacitinib, originally FDA-approved for rheumatoid arthritis, has seen off-label use in various inflammatory conditions.

A recent literature review found 57 cases of alopecia areata, 218 cases of psoriasis, 68 cases of hidradenitis suppurativa, 13 cases of vitiligo and 9 cases of palmoplantar pustulosis with upadacitinib leading to effective disease control via decreased inflammatory response.[10] Further, many other inflammatory skin conditions have few reported cases of successful disease management with upadacitinib, including erythema multiforme, granuloma annulare, lichen planus, pyoderma gangrenosum, pityriasis rubra pilaris and BP.[10]

Given the heightened expression of JAK/STAT proteins and increased number of T-helper type 2 cytokines, such as IL-4 and IL-13, in BP pathogenesis, the introduction of JAK inhibitors represents a promising direction for refractory BP.

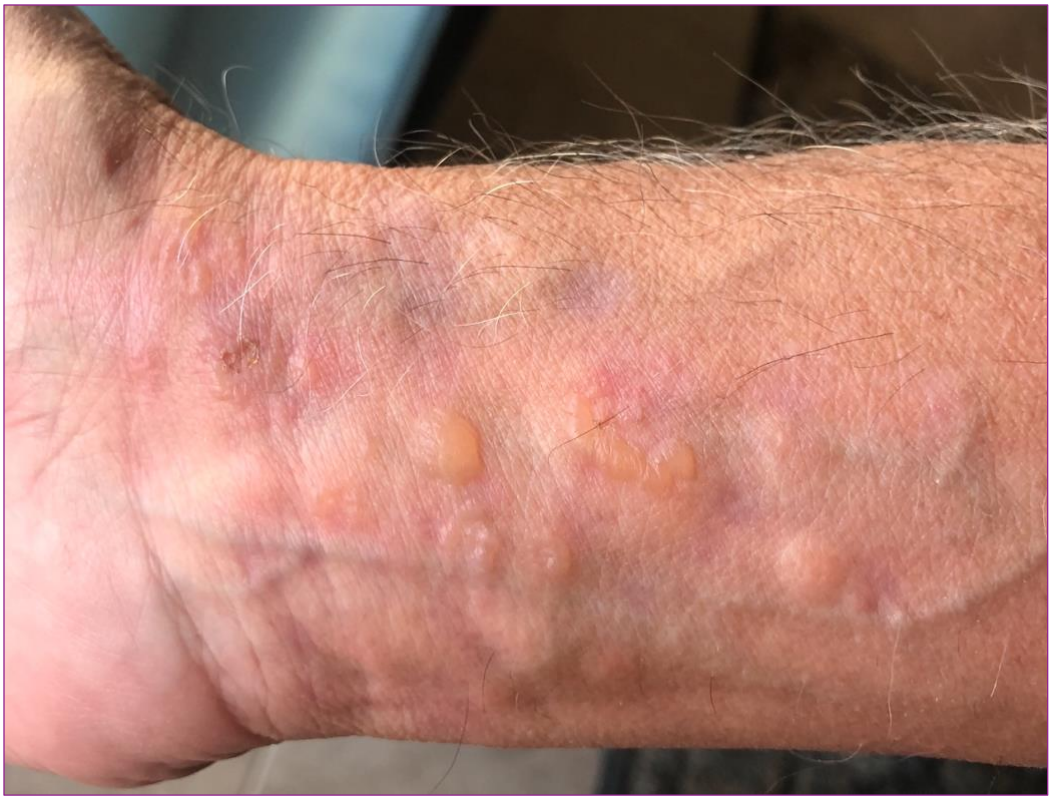

Figure 1. Multiple, tense vesicles filled with yellow fluid surrounded by erythema was noted on the left forearm. Hyperpigmented papules with overlying thin crust were also noted.

Xiao et al. reported a case in 2022 of severe BP with comorbid psoriasis successfully treated with baricitinib, a JAK-1/2 inhibitor, with complete remission following 24-weeks of treatment.[6,10,11] Since then, there have been two cases of recalcitrant BP successfully treated with upadacitinib, a more selective JAK-1 inhibitor.[7,8] One case achieved complete disease remission following two months on upadacitinib.[7] Another case of drug-induced BP from immunotherapy (MK-4830 with pembrolizumab) for active metastatic cancer was reported to have clinical improvement following one month on upadacitinib prior to passing away two months after therapy initiation.[8]

Our patient with BP who was refractory to more standard BP treatments, not only cleared on a JAK inhibitor, but appears to be in remission for 18-months without any therapy. Upadacitinib, as a selective JAK-1 inhibitor, could be particularly beneficial by reducing cytokine activity without broader effects on other JAK pathways.[10] This targeted inhibition could potentially reduce disease activity and improve clinical outcomes for patients with BP.

CONCLUSION

This case adds to existing literature suggesting selective JAK inhibitors may be promising in the management of challenging, treatment-resistant BP. Further research is warranted to expand on the usage of JAK inhibitors in the treatment of this condition.

Conflict of Interest Disclosures: None

Funding: None

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