Two cases of bullous pemphigoid effectively treated with oral tofacitinib

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Key words: bullous pemphigoid; JAK inhibitor; Janus kinase inhibitor; tofacitinib; treatment efficacy.

INTRODUCTION

Bullous pemphigoid (BP) is the most common subepidermal autoimmune blistering disease,[1] chiefly affecting elderly patients in their eighth decade of life.[2] BP pathogenesis is thought to be instigated by an autoantibody response toward hemidesmosomal proteins (BP180 and BP230)[3] and currently has no cure. There is growing data on the positive role of oral tofacitinib, a Janus kinase inhibitor (JAKi), for the treatment of autoimmune cutaneous diseases.[4,5] We herein retrospectively report 2 cases of BP seen at Columbia University Medical Center's Dermatology clinic, and treated with 10 milligrams (mg) of off-label oral tofacitinib twice daily. Given the side effect profile of JAKis,[6] baseline and follow-up laboratory surveillances were done (complete blood count, complete metabolic panel, glucose, lipid panel, and tuberculosis screening). Clinical images were retrieved through chart review for use in this publication (Figs 1 and 2).

Abbreviations used:

BP:	bullous pemphigoid
JAK:	Janus kinase
JAKi:	Janus kinase inhibitor
STAT:	signal transducers and activators of transcription

CASE REPORT

Case 1

A 65-year-old woman presented for an itchy rash on her right knee that started after a right patellar tendon rupture arthroplasty. Frequent scratching worsened her rash and caused it to spread proximally and distally to the knee. No prescription creams were tried. She had a history of hypothyroidism, hypercholesterolemia, hypertension, obesity, osteoarthritis, and a 5-year history of seronegative spondyloarthropathy treated with adalimumab and sulfasalazine. On physical examination, her right anterior lower leg and bilateral arms displayed linear hemorrhagic crusty excoriations with hyperpigmentation. Over a 2-year period, the patient failed oral antihistamine (cetirizine hydrochloride), topical steroids (triamcinolone acetonide and fluocinonide), gabapentin, and 1 dose of ivermectin. A neurology referral ruled out small fiber neuropathy. An extensive autoimmune workup (celiac, monoclonal antibody, and lupus) also came back negative. She had no history of immunobullous disorders. She presented for a 2-month follow-up with consistently severe pruritus. On inspection, there were numerous excoriations and erythematous lichenified plaques across her bilateral arms, legs, chest, neck, and abdomen, and a single bulla was noted on her right palm. Her presentation was consistent with BP and was confirmed by biopsy and elevated serum BP180 and BP230 immunoglobulin G autoantibodies. The patient's rheumatologist was contacted to discuss stopping sulfasalazine for possible drug-induced BP. A month later, she presented with BP refractory to prednisone, doxycycline, and niacinamide. Bilateral arms and legs were covered with hyperpigmented patches, small areas of erythema and scale, and many areas of linear hemorrhagic crust, without bullae.

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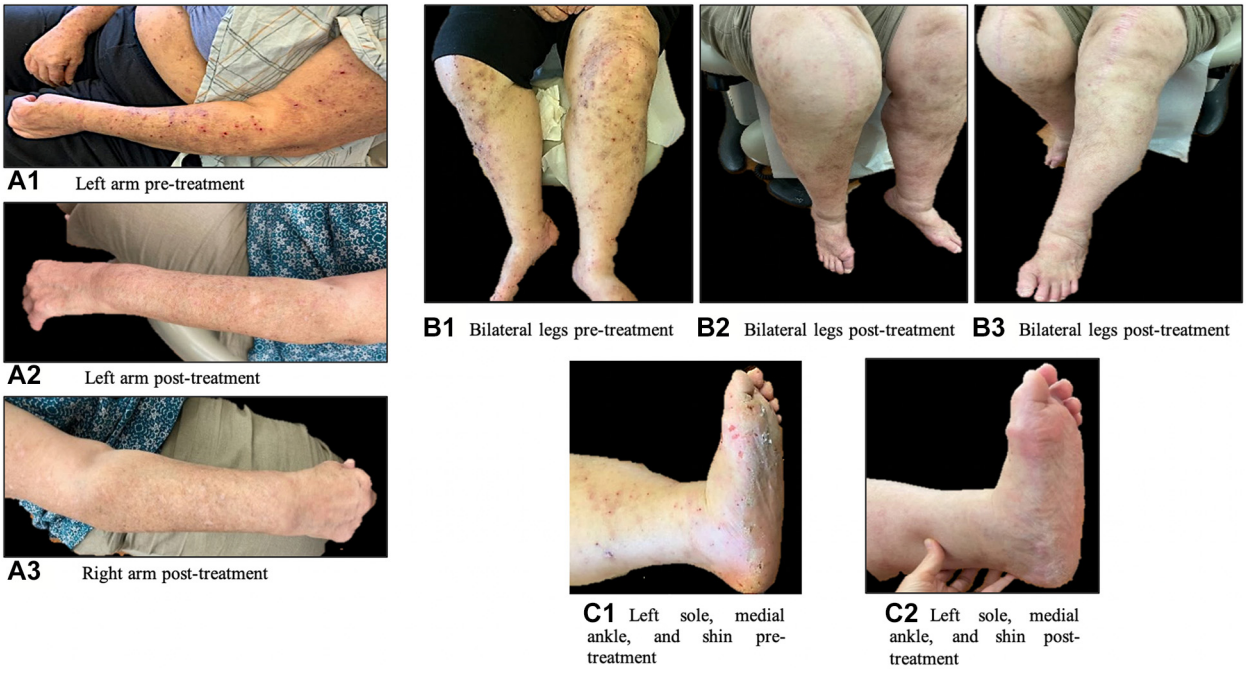

Fig 1. Clinical images of the extremities of a female patient with bullous pemphigoid before (**A1**, **B1**, and **C1**) and after 3 months (**A2**, **A3**, **B2**, **B3**, and **C2**) of oral tofacitinib therapy.

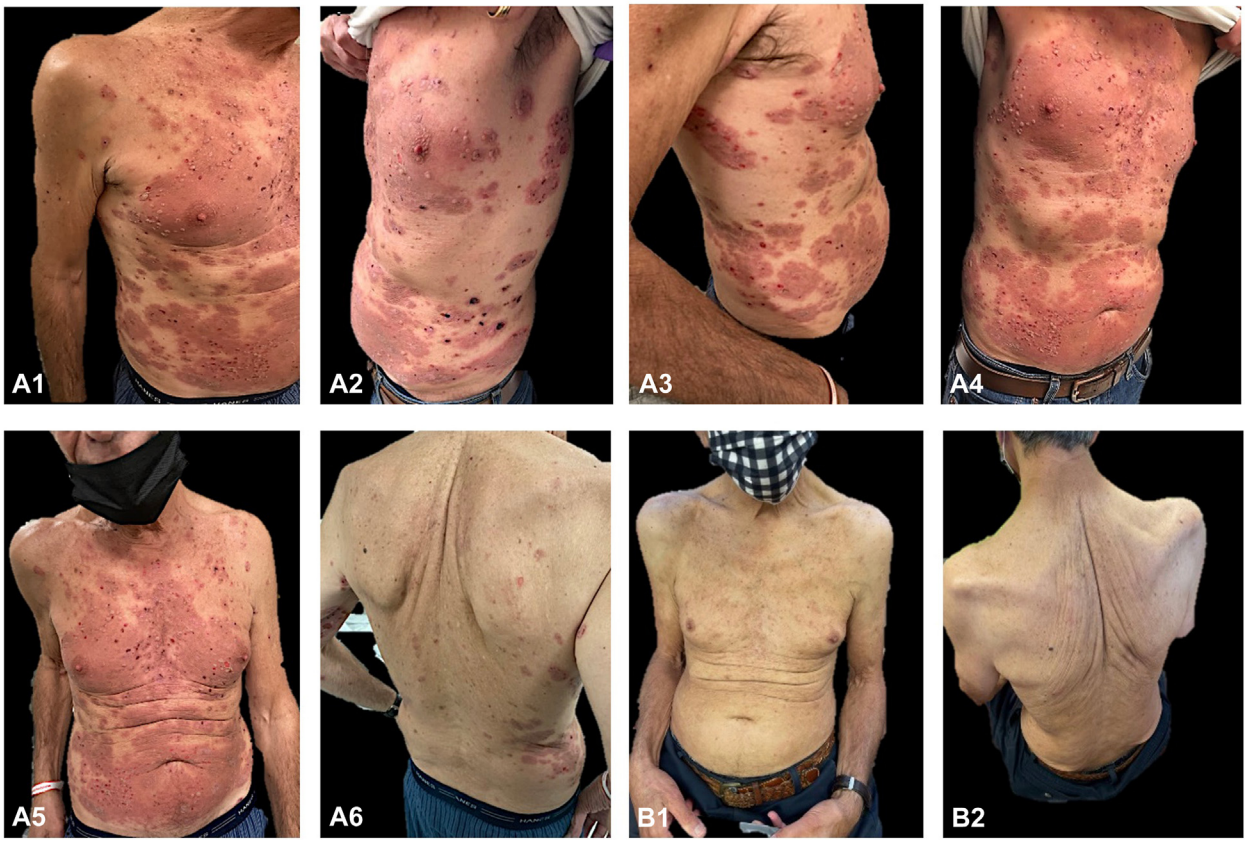

Fig 2. Clinical images of the trunk of a male patient with bullous pemphigoid before (**A1-A6**) and after (**B1** and **B2**) 3 weeks of oral tofacitinib therapy.

She was, therefore, prescribed 10 mg of oral tofacitinib twice daily. A week later, her BP dramatically improved. She suffered sinus pain that persisted after a course of antibiotics. Her tofacitinib dose was hence cut in half (5 mg twice daily) as a precaution. She presented after a week with recurrent pruritus and was consequently put back on 10 mg twice daily. After 3 months of oral tofacitinib, the sinus pain had resolved, she had no side effects or laboratory abnormalities, and her skin had cleared (Fig 1, *A2*, *A3*, *B2*, *B3* and *C2*). She is presently doing well and being followed up for medication tolerance and efficacy.

Case 2

A 76-year-old man presented for a 1-month history of severe itch on his chest. His pruritus was previously attributed to notalgia paresthetica and alleviated by steroid injections to his back. He had a history of moderate to severe degenerative disc disease. Physical examination showed erythematous patches, bullae, and erosions over his chest, abdomen, and anterior thighs (Fig 2, *A*). He was treatment-naïve and denied any history of cancer. A punch biopsy established a diagnosis of BP. Multiple trials of prednisone were ineffective and mycophenolate exacerbated his skin. He developed steroid-induced atrial fibrillation that was managed by cardiology. His trunk, proximal thighs and arms had many erythematous patches with overlying erosions, hemorrhagic crust, and bullae. Dupilumab was initiated a month later with only slight improvement. Two months later, he presented for rapidly worsening BP while on mycophenolate and dupilumab. His entire trunk, proximal arms and legs exhibited many dusky plaques with surrounding erythema-early bullous lesions. His BP deteriorated after 3 rituximab infusions. He was thus prescribed 10 mg oral tofacitinib twice daily and kept on dupilumab pending the appeal process approval of tofacitinib. After starting oral tofacitinib, he experienced complete clearance of his skin and pruritus as early as 3 weeks of treatment (Fig 2, *B1* and *B2*). He is currently tolerating the tofacitinib well and continues to be monitored symptomatically and laboratory-wise.

DISCUSSION

BP is a chronic and highly debilitating disease with a paucity of effective treatments. Treatment goals involve reducing blisters and pruritis, promoting healing, and improving quality of life. These aims are met by a therapeutic strategy that dampens autoantibody production and antibody-driven inflammation, while curtailing the risk for medication-induced adverse events. Topical corticosteroids, systemic corticosteroids, and doxycycline constitute first line treatment. Nonetheless, our 2 patients failed topical and systemic corticosteroids, immunosuppressive corticosteroid-sparing agents for extensive BP (mycophenolate, doxycycline), and alternative options for recalcitrant BP (rituximab, dupilumab). A recent case report suggested a potential for the use of barcitinib, another JAKi, as a novel alternative therapy for concomitant plaque psoriasis and BP, or either condition.[7] Moreover, tofacitinib demonstrated antipruritic effects in other autoimmune skin diseases (atopic dermatitis, psoriasis).[8,9] Noteworthily, Juczynska et al found significantly greater expression of JAK/STAT proteins in skin lesions of BP patients compared to controls,[10] which connotes a favorable outcome in targeting this signaling pathway for the treatment of BP. In fact, systemic JAKis (eg oral tofacitinib) successfully fulfill the treatment objectives of BP while sparing patients the side effects of mainstay therapies. Indeed, case 2's blisters and pruritus only improved after instituting oral tofacitinib, with a relatively fast response (3 weeks). Furthermore, case 1's BP, which did not remit following sulfasalazine discontinuation, nor with other therapies, only resolved after 3 months of tofacitinib. This report is the first of its kind looking into the benefit of oral tofacitinib for BP. In light of the scarcity of effective BP treatments and higher level of evidence data, more elaborate studies are needed to confirm our promising findings and investigate the long-term, efficacious, and safe dosage of oral tofacitinib for the treatment of BP.

Conflicts of interest

None disclosed.

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