A new eruption of bullous pemphigoid within psoriatic plaques following cyclosporine withdrawal

Katerina Svigos, BA, Lauren Fried, BS, Lu Yin, BA, Nooshin Brinster, MD, Kristen Lo Sicco, MD, and Prince Adotama, MD
New York, New York

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INTRODUCTION

Psoriasis is a chronic, immune-mediated inflammatory disorder characterized by keratinocyte hyperproliferation and development of psoriatic plaques. It has 2%-4% prevalence in Western countries and is more common with increasing age.[1] Although most cases can be managed with topical treatments, more severe manifestations require systemic therapies, including phosphodiesterase type 4 inhibitors, tumor necrotic factor -alfa inhibitors, interleukin (IL)-17/IL-23 inhibitors, or immunosuppressive agents such as methotrexate or cyclosporine.[1]

There is an emerging link between psoriasis and bullous pemphigoid (BP), an autoimmune blistering disorder characterized by autoantibody formation against the basement membrane zone (BMZ) hemidesmosome components BP180 and BP230. Autoantibody complement fixation leads to dermal inflammatory infiltrate with C3 and IgG deposition in the BMZ and formation of tense blisters.[2] Multiple case-control studies have demonstrated an increased prevalence of BP in psoriasis patients compared with controls.[2,3] Although isolated BP typically presents after the age of 70, it often develops earlier in patients with a history of psoriasis.[3]

Herein, we present a case of a 64-year-old male with a history of psoriasis treated with cyclosporine who developed new-onset BP within his psoriatic plaques following a lapse in cyclosporine treatment.

Abbreviations used:

BMZ: basement membrane zone
BP: bullous pemphigoid
IL: interleukin

CASE DESCRIPTION

A 64-year-old man with a history of hypertension and psoriasis treated with cyclosporine 200 mg twice a day presented after blisters had appeared on both upper extremities 2-3 days after running out of cyclosporine. An outside dermatologist had diagnosed his psoriasis 1-2 years before and treated him with the IL-17 inhibitor secukinumab, but discontinued it 9 months prior to presentation due to cost.

Two months before presentation, the patient experienced acute worsening of his psoriasis with diffuse erythema, plaques, scaling, fissuring in his hands and knees, and chills. He presented to the emergency department, where a biopsy demonstrated erythrodermic psoriasis (Fig 1). Two weeks prior to presentation, he re-established care with dermatology and was started on cyclosporine 200 mg twice a day (2.5-3 mg/kg/day), triamcinolone 0.1% ointment twice a day to the body, and hydrocortisone 2.5% ointment twice a day to the face. He improved with a 70% reduction in body surface area involvement. Three days prior to presentation, he ran out of cyclosporine. Fifty-six hours after the last dose, he noted appearance of blisters on the upper extremities and presented to dermatology.

From the Ronald O. Perelman Department of Dermatology, New York University Grossman School of Medicine.
Authors Svigos and Fried contributed equally to this article. Authors Lo Sicco and Adotama contributed equally to this article as lead co-authors.
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Correspondence to: Prince Adotama, MD, 240 E 38th St., 11th floor, New York, NY 10016. E-mail: Prince.adotama@nyulangone.org.

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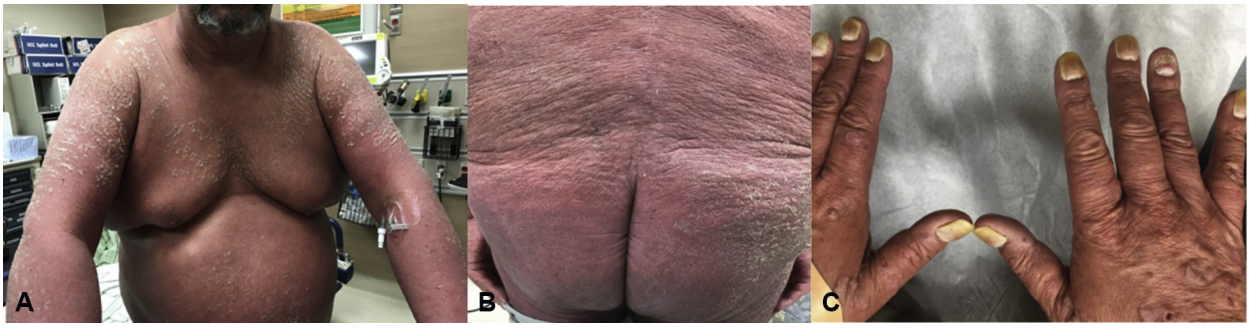

Fig 1. The patient presented to the emergency department 2 months before, demonstrating erythroderma involving (**A**) the chest and arms and (**B**) buttocks and back, with (**C**) nail involvement.

On examination, the patient had erythematous papules and scaling on his face and bilateral ears and generalized erythema and scaling on both arms. Multiple tense, fluid-filled blisters were noted on his bilateral flexor forearms and outer upper arms, some appearing to follow the lines of his psoriatic plaques (Fig 2). Eroded and flaccid blisters were also noted on his bilateral palms and plantar feet at the bases of his toes. Both lower legs were erythematous and edematous without fissures. His chest and abdomen were relatively spared with minimum erythema, though a lichenified plaque was noted on the central back.

Two biopsies were obtained from the blisters on the dorsal aspect of the left hand. Hematoxylin-eosin staining demonstrated subepidermal separation with eosinophils within the blister cavity and aligned along the adjacent dermoepidermal junction. Direct immunofluorescence revealed linear C3 deposition along the dermoepidermal junction, consistent with a diagnosis of BP. Anti-BP180 IgG was later found to be elevated at 43 units/mL serum, and salt-split skin showed an epidermal IgG staining pattern on indirect immunofluorescence. Cyclosporine was re-initiated and then gradually tapered, and methotrexate was started and up-titrated to 17.5-20 mg/week for treatment of both psoriasis and BP. No new blisters were reported on this regimen, and the psoriasis remained stable (Fig 2).

DISCUSSION

Psoriasis results from inappropriate T-cell activation and increased production of pro-inflammatory cytokines in the skin, leading to keratinocyte hyperproliferation and plaque development. Psoriasis may predispose patients to development of BP, and there is increasing evidence supporting the association between these disease processes. It is hypothesized that chronic inflammation at the dermoepidermal junction exposes BMZ antigens to autoreactive T-cells, increasing susceptibility to autoantibody formation.[2,3] Alternative theories linking psoriasis to BP have been explored, such as a shift in Th1/Th2 expression leading to decreased suppression of B-cell autoreactivity.[4,5]

A rare subepidermal autoimmune bullous subtype, p200 pemphigoid, is characterized by autoantibodies targeting recombinant laminin gamma-1 protein. p200 pemphigoid is associated with psoriasis, with 28.3% of patients in a systematic review with the evidence of concomitant disease. IgG in p200 pemphigoid localizes to the dermal side of the salt-split skin, and thereby differs from the epidermal localization of BP180, as seen in our patient. BP180 positivity is rare in p200 pemphigoid.[6]

Our patient had a first-time eruption of biopsy-proven BP in the setting of a lapse in psoriasis treatment with cyclosporine. Notably, cyclosporine can be used in the treatment of both psoriasis and BP.[7] There are previous reports of psoriasis exacerbation with cyclosporine withdrawal.[8] However, to our knowledge, an eruption of BP within psoriatic plaques following cyclosporine cessation has not been described previously.

Cyclosporine, a potent immunosuppressant, inhibits T-cell activation, decreasing transcription of IL-2.[9] Given the cyclosporine serum half-life of approximately 6-24 hours, our patient likely reached a subtherapeutic serum concentration during the period in which he developed the BP bullae. We hypothesize that withdrawal of the immunosuppressive effects of cyclosporine may have resulted in a rebound increased inflammatory response, which, following chronic psoriasis-mediated inflammation and BMZ antigen exposure, allowed for autoantibody production and development of BP.

The precise mechanism may specifically rely on a rebound in IL-2 levels, which are suppressed by cyclosporine. One study determined that 18 of 25 (72%) patients with BP had increased serum IL-2 in the earliest stages of the disease, suggesting that IL-2 may serve as a marker of BP disease activity.[10]

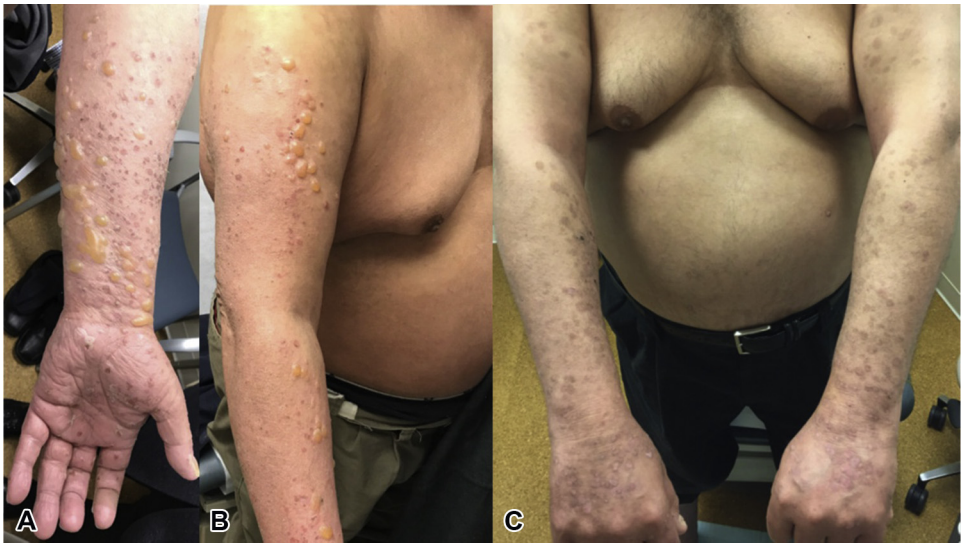

Fig 2. Initial presentation of bullous pemphigoid eruption on (**A**) the left arm and (**B**) the right arm appearing within healing psoriatic plaques upon the cessation of cyclosporine 200 mg twice a day, 2 days before. **C**, Resolving bullous eruption of the bilateral arms and hands at the 5-week follow-up following the initiation of methotrexate 17.5-20 mg weekly.

Thus, potential rebound elevation in IL-2 following cyclosporine withdrawal may have triggered BP development.

Herein, we reported a case of a 64-year-old man with a history of psoriasis who developed first-time eruption of BP within psoriatic plaques following withdrawal of cyclosporine. A potential limitation of our case presentation is that our patient's BP eruption occurred just 2 days following cyclosporine cessation. However, the short half-life of cyclosporine does suggest a subtherapeutic serum concentration by the time of his eruption. Clinicians should be aware of the potential for BP development in patients with psoriasis, particularly after cessation of high-potency immunosuppressive agents such as cyclosporine.

Conflicts of interest

None disclosed.

REFERENCES

1. Fried L, Cobos GA, Cohen D. Psoriasis. In: Alexiades M, Zubek A, eds. *Cosmetic Dermatologic Surgery*. Wolters Kluwer; 2020:682-689.
2. Phan K, Goyal S, Murrell DF. Association between bullous pemphigoid and psoriasis: systematic review and meta-analysis of case-control studies. *Australas J Dermatol*. 2019;60(1):23-28.
3. Kridin K, Bergman R. Association between bullous pemphigoid and psoriasis: a case-control study. *J Am Acad Dermatol*. 2017; 77(2):370-372.
4. Boussemart L, Jacobelli S, Batteux F, et al. Autoimmune bullous skin diseases occurring under anti-tumor necrosis factor therapy: two case reports. *Dermatology*. 2010;221(3): 201-205.
5. Nakayama C, Fujita Y, Watanabe M, Shimizu H. Development of bullous pemphigoid during treatment of psoriatic onycho-pachydermo periostitis with ustekinumab. *J Dermatol*. 2015;42(10):996-998.
6. Kridin K, Ahmed AR. Anti-p200 pemphigoid: a systematic review. *Front Immunol*. 2019;10:2466.
7. Thivolet J, Barthelemy H, Rigot-Muller G, Bendelac A. Effects of cyclosporin on bullous pemphigoid and pemphigus. *Lancet*. 1985;1(8424):334-355.
8. Van Hooff JP, Levinson KL, Stoak WVD. Cyclosporin and psoriasis. *Lancet*. 1985;1(8424):335.
9. Russell G, Graveley R, Seid J, al-Humidan AK, Skjodt H. Mechanisms of action of cyclosporine and effects on connective tissues. *Semin Arthritis Rheum*. 1992;21(6 suppl 3):16-22.
10. Schaller J, Giese T, Ladusch M, Haustein UF. Interleukin-2 receptor expression and interleukin-2 production in bullous pemphigoid. *Arch Dermatol Res*. 1990;282(4):223-226.