Adalimumab-associated bullous pemphigoid in a patient with ulcerative colitis

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Key words: Adalimumab; bullous disease; drug reaction; ulcerative colitis.

INTRODUCTION

Bullous pemphigoid (BP) is an uncommon skin condition in which erythematous, urticarial papules and plaques progress to form tense bullae, typically in elderly men and women.[1] In this disease, IgG autoantibodies are directed against hemidesmosome proteins, resulting in the formation of subepidermal vesicles.[1] At least 50 drugs have been associated with BP, including the anti–tumor necrosis factor (TNF)-α drugs etanercept, infliximab, and adalimumab.[2-5] Here we describe a case of suspected adalimumab-induced BP in a patient with ulcerative colitis.

Abbreviations used:

BP: bullous pemphigoid
TNF: tumor necrosis factor

CASE REPORT

A 49-year-old white man with ulcerative colitis and primary sclerosing cholangitis presented to the emergency department with diffuse, pruritic papules and vesicles involving the trunk, extremities, hands, and feet. He reported a stable, several-year history of metoprolol, pantoprazole, levothyroxine, and ursodiol use and denied use of herbal medications and supplements. He did admit to occasional ibuprofen use; however, he did not take ibuprofen before the onset of his symptoms. He denied recent colonoscopy and kidney dysfunction, dehydration, strenuous physical activity, and vaccinations. Biopsy performed by dermatology found subacute dermatitis with focal eosinophilic spongiosis. He was prescribed topical corticosteroids and advised to follow up if he failed to improve.

One week later, the patient returned to the clinic with numerous, coalescing, pink, edematous papules, some with a targetoid appearance (Fig 1). Vesicles and pustules on an erythematous base involved the superior forehead bilaterally, scalp, trunk, hands and feet. No oral involvement was noted. Thorough medication review was significant for a 1.5-year history of adalimumab use. Hematoxylin-eosin staining of a skin biopsy specimen showed eosinophilic spongiosis with subepidermal clefts and numerous eosinophils. Direct immunofluorescence found discontinuous linear basement membrane zone IgG and continuous linear basement membrane zone C3 with scattered inflammatory cells in the dermis. Results of serum testing for indirect immunofluorescence were negative (including salt-split skin). Laboratory evaluation was remarkable for an elevated BP180 of 126.3 (reference range, <9.0 U). He was subsequently given prednisone, 60 mg daily, for presumed BP.

Two weeks later, he again reported worsening symptoms although still receiving prednisone, 60 mg daily, with appropriate compliance. Large red bullae with significant weeping saturated his clothing (Fig 2). Adalimumab was held owing to concerns for drug-induced disease, and prednisone was increased to 80 mg daily. He was admitted to the hospital for topical steroid wet dressings (acetic acid solution) and azathioprine, and intravenous immunoglobulin infusions were initiated after consultation with the gastroenterology department.

To date, the patient is maintained on azathioprine, 150 mg daily, and prednisone as a slow taper. He has no active lesions and reports no further complaints. He has received 2 rounds of intravenous

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Funding sources: None.
Conflicts of interest: None declared.
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JAAD Case Reports 2017;3:339-41.
2352-5126
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http://dx.doi.org/10.1016/j.jdcr.2017.03.008

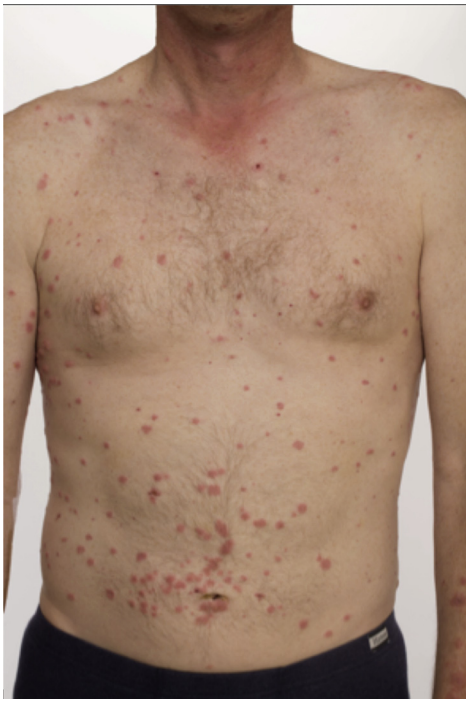

Fig 1. One week after initial presentation, the patient had numerous pink, edematous papules and vesicles, especially prominent on the trunk and extremities.

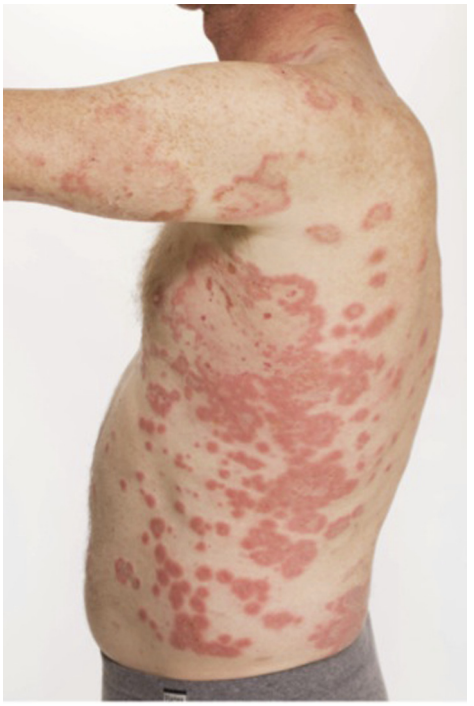

Fig 2. The patient presented with large, erythematous, weeping bullae despite therapy with 60 mg prednisone daily for 2 weeks.

immunoglobulin. BP180 antibody titers have normalized, and the patient has markedly improved.

DISCUSSION

The development of unprecedented autoimmune disease after administration of certain medications is well established in the literature. Although use of metoprolol, pantoprazole, levothyroxine, and ursodiol has not been reported in the literature to induce BP specifically, anti—TNF-α agents are well-established culprits. Anti—TNF-α—induced BP has been reported in the literature in patients who have required such medications for psoriasis or rheumatoid arthritis, and although ibuprofen has been associated with this phenomenon, our patient was not taking this medication.[2-5]

The time course for development of autoimmune disease after administration of anti—TNF-α agents may be quite variable and is perhaps underestimated in some cases. For instance, studies performed by the Mayo Clinic found anti—TNF-α—induced lupuslike syndrome, new-onset or worsening of psoriasis, and vasculitis an average of 16.2, 17.1, and 34.5 months, respectively, after initiation of therapy.[6-8]

Autoantibody production is also increased in patients receiving anti—TNF-α therapy; however, it remains unclear how this correlates with the development of disease. The prevalence of antinuclear antibody and anti-dsDNA antibodies induced by anti—TNF-α agents can range from 23% to 57% and 9% to 33%, respectively.[9] It is not unusual to measure antinuclear antibody and anti-dsDNA antibody titers in our patients, whereas anti-BP180 antibody titers are rarely measured at all unless there is suspicion for immunobullous disease. Therefore, induction trends of anti-BP180 antibody titers after anti—TNF-α therapy have not been documented. One patient receiving etanercept for rheumatoid arthritis, however, did have anti-BP180 antibody—positive BP, and in this case the investigators concluded a likely drug-induced adverse event.[4]

Autoimmune bullous disease has been associated with inflammatory bowel disease in the literature. It is not uncommon for epidermolysis bullosa acquisita, a bullous disorder in which antibodies are formed against type-VII collagen, to present in a patient with inflammatory bowel disease. Although this disease may clinically mimic BP, elevated anti-BP180 antibody titers along with the clinical scenario helped to differentiate the 2 in our patient. The salt split technique may be considered to better differentiate subtypes of subepidermal immune bullous disease and represents an integral component of a dermatologist's armamentarium for diagnosis; however, in our patient's case this was noncontributory and anti-BP 180 antibody titers

proved more revealing. The exact incidence of BP in patients with inflammatory bowel disease is unknown, although one case series does report a patient with an ulcerative colitis flare and concomitant cutaneous bullous eruption.[10] Our patient's ulcerative colitis was stable before his symptoms. In contrast to reports of patients with idiopathic BP, patients with drug-induced BP tend to be younger with tense bullae that may be accompanied by erythema-multiforme–like lesions on the palmar/plantar surfaces. Direct immunofluorescence shows linear basement membrane zone IgG and C3 in 90% of these patients.[2] We think that the young age of our patient, elevated anti-BP180 antibody titer, histopathologic findings, clinical examination, and disease resistance to appropriate therapy with high-dose steroids for 2 consecutive weeks with worsening symptoms before discontinuation of adalimumab are suggestive of drug-induced BP rather than incident idiopathic BP. Although a direct cause-and-effect relationship cannot be established with complete certainty in patients with prior, chronic autoimmune disease such as ulcerative colitis, the possibility of a drug-induced reaction should not be ignored, as prompt cessation may induce remission of disease.

REFERENCES

1. Schiavo AL, Ruocco E, Brancaccio G, et al. Bullous pemphigoid: etiology, pathogenesis, and inducing factors: facts and controversies. *Clin Dermatol*. 2013;4:391-399.
2. Stavropoulos PG, Soura E, Antoniou C. Drug-induced pemphigoid: a review of the literature. *J Eur Acad Dermatol Venereol*. 2014;9:1133-1140.
3. Altindag O, Aydeniz A, Gursoy S. A Case with anti TNF-α induced bullous pemhigoid. *Turk J Rheumatol*. 2010;25:214-216.
4. Bordignon M, Belloni-Fortina A, Pigozzi B, et al. Bullous pemphigoid during long- term TNF-α blocker therapy. *Dermatology*. 2009;4:357-358.
5. Stausbol-Gron B, Deleuran M, Sommer Hansen E, et al. Development of bullous pemphigoid during treatment of psoriasis with adalimumab. *Clin Exp Dermatol*. 2009;7:285-286.
6. Wetter DA, Davis MD. Lupus-like syndrome attributable to anti–tumor necrosis factor α therapy in 14 patients during an 8-year period at Mayo Clinic. *Mayo Clin Proc*. 2009;84(11):979-984.
7. Shmidt E, Wetter DA, Ferguson SB, et al. Psoriasis and palmoplantar pustulosis associated with tumor necrosis factor-α inhibitors: The Mayo Clinic experience, 1998 to 2010. *J Am Acad Dermatol*. 2012;67(5):179-185.
8. Sokumbi O, Wetter DA, Makol A, et al. Vasculitis associated with tumor necrosis factor-α inhibitors. *Mayo Clin Proc*. 2012;87(8):739-745.
9. Mongey AB, Hess EV. Drug insight: autoimmune effects of medications: what's new? *Nat Clin Pract Rheumatol*. 2008;4(3):136-144.
10. Sotiriou MC, Foo CW, Scholes CT, et al. Immunobullous disease and ulcerative colitis: a case series of six patients. *Br J Dermatol*. 2015;173(3):792-796.