Rituximab for Acquired Hemophilia A in the Setting of Bullous Pemphigoid

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PRACTICE **POINTS**

- Physicians must be aware of the potential for acquired hemophilia A in patients with bullous pemphigoid (BP).
- Rituximab is an effective therapy for BP and should be considered for patients in this cohort.

To the Editor:

Bullous pemphigoid (BP) is an autoimmune blistering disease characterized by the formation of antihemidesmosomal antibodies, resulting in tense bullae concentrated on the extremities and trunk that often are preceded by a pruritic urticarial phase.[1] A rare complication of BP is the subsequent development of acquired hemophilia A. We report a case of BP with associated factor VIII–neutralizing antibodies in a patient who improved with prednisone and rituximab therapy.

A 78-year-old woman presented with red-orange pruritic plaques on the right heel that spread to involve the arms and legs, abdomen, and trunk with new-onset bullae over the course of 2 weeks (Figure 1). Dermatology was consulted, and a diagnosis of BP was confirmed via biopsy and direct immunofluorescence.

Despite treatment with prednisone 40 mg/d and clobetasol ointment 0.05%, she continued to develop extensive cutaneous bullae and new hemorrhagic bullae on the buccal mucosae (Figure 2), necessitating hospital admission. She clinically improved after prednisone was increased to 60 mg/d and mycophenolate mofetil 500 mg twice daily was added; however, she returned 8 days after discharge from the hospital with altered mental status, new-onset hematomas of the abdomen and right leg, and a hemoglobin level of 5.8 g/dL (reference range, 14.0–17.5 g/dL). Activated prothrombin time was prolonged without correction on mixing studies, raising concern for coagulation factor inhibition. Factor VIII activity was diminished to 9% and then 1% three days later. Mycophenolate mofetil was discontinued, and the patient was acutely stabilized with blood transfusions, intravenous immunoglobulin, tranexamic acid, and aminocaproic acid. Rituximab was initiated at 1000 mg and then administered again 2 weeks later. At 7-week follow-up, coagulation studies normalized, and there was no evidence of blistering dermatosis on examination.

Bullous pemphigoid generally is seen in patients older than 60 years, and the incidence increases with age. The disease course follows formation of IgG antibodies against BP180 or BP230, leading to localized activation of the complement cascade at the basement membrane zone.[1] Medications, vaccinations, UV radiation, and burns have been implicated in disease induction.[2]

Identification of antihemidesmosomal antibodies on lesional biopsy via direct immunofluorescence is the gold standard for diagnosis, though indirect antibodies measured via enzyme-linked immunosorbent assay may provide information regarding disease severity.[1] Patients with milder disease may be treated with topical corticosteroids, doxycycline, and nicotinamide; however, severe disease

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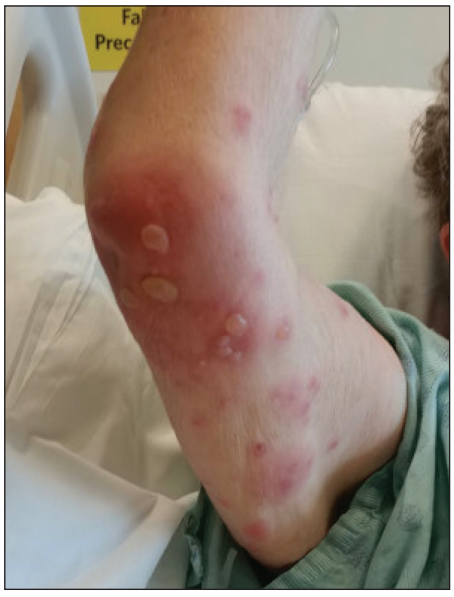

FIGURE 1. Bullous pemphigoid bullae on the arm with underlying urticarial plaques.

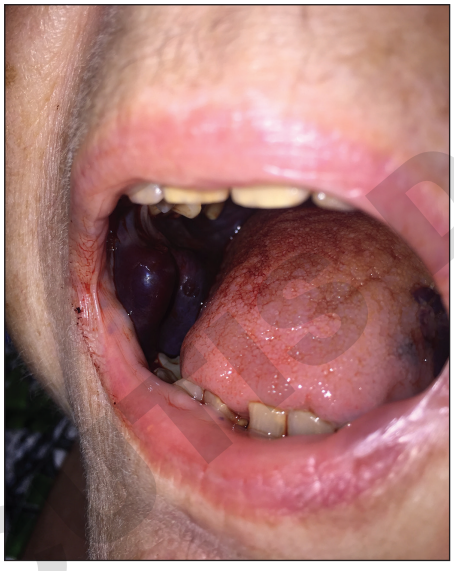

FIGURE 2. Hemorrhagic bullae of the buccal mucosae.

requires treatment with systemic glucocorticoids and steroid-sparing agents.[3] Rituximab initially was approved by the US Food and Drug Administration for the treatment of pemphigus vulgaris, and mounting evidence for the use of rituximab in BP is promising. Although data are limited to retrospective studies, rituximab has shown notable remission rates and steroid-sparing effects in those with moderate to severe BP.[4]

Acquired hemophilia A (AHA) is caused by the production of IgG autoantibodies, which block physiologic interactions between factor VIII and factor IX, phospholipids, and von Willebrand factor.[5] Acquired hemophilia A often is diagnosed by prolonged activated prothrombin time and decreased factor VIII activity after a previously unaffected patient develops severe bleeding. Treatment involves re-establishing hemostasis and the use of corticosteroids and immunosuppressive agents to diminish autoantibody production.[4]

Bullous pemphigoid–associated AHA likely is due to antigenic similarity between BP180 and factor VIII, leading to concomitant neutralization of factor VIII with the production of BP-associated autoantibodies.[5] Bullous pemphigoid–associated AHA has been reported with manifestations of bleeding concurrent with or after the development of dermatologic disease. Rituximab use has been reported with clinical efficacy in several cases, including our patient.[6] Continued hematologic monitoring is recommended, as recurrences are common within the first 2 years.[5]

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