Exacerbation of bullous pemphigoid after hand, foot, and mouth disease treated with rituximab

Alfreda F. Batt, BS, Sheila Z. Jalalat, MD, Lindsey Hunter-Ellul, MD, and Michael G. Wilkerson, MD

Galveston, Texas

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INTRODUCTION

Bullous pemphigoid (BP) is a chronic autoimmune, blistering disease typically affecting the elderly. It is the most common disorder within the pemphigoid group and represents the most frequent autoimmune blistering disease in general.1,2 The etiopathogenesis involves the induction of an inflammatory cascade that is hypothesized to include many triggering factors, one of which includes infections.2 Here we present a man with a history of stable BP and subsequent severe flaring of his disease after contracting hand, foot, and mouth disease (HFMD). We also discuss rituximab as an adequate therapy in treating refractory BP.

CASE REPORT

A 56-year-old white man with a history of asthma, chronic renal failure, and stable BP presented with complaints of worsening pruritic vesicles over the course of 2 months. These lesions developed 2 months after contracting a severe case of HFMD diagnosed by his primary care physician. His diagnosis was based on his high fevers and severe blistering on his hands, feet, and mouth, and he was confined to bed for 2 weeks amid a coxsackievirus A6 (CVA6) breakout in the summer of 2012. His primary care physician prescribed prednisone, 40 to 60 mg orally daily, which resulted in mild-to-moderate control of his blisters.

Before his CVA6 infection, his BP was in complete remission on a regimen of prednisone, 10 mg orally every other day. He presented to our dermatology clinic with his post-CVA6-induced flare, at which time his physical examination found 40% to 50% of his body surface area covered with tense bullae, erosions, and crust located on his face, neck, chest, abdomen, back, buttocks, genitalia, and bilateral upper and lower extremities, with sparing of the oral mucosa (Fig 1, A and B). In addition, his laboratory, histopathology, and direct immunofluorescence findings all supported a diagnosis of BP at that time. Results of a paraneoplastic pemphigus panel were normal, and the pemphigoid panel found an elevated BP 230 IgG antibody level (106 U; normal <9 U) and slightly elevated BP 180 IgG antibody level (25 U; normal <9 U; ARUP Laboratories, Salt Lake City, Utah).

He was prescribed prednisone, 60 mg orally daily, doxycycline, 100 mg orally twice a day, and mycophenolate mofetil, 1500 mg tablet orally daily with repeated attempts to taper prednisone. However, because of frequent flaring and inability to taper prednisone over the course of 6 months, we initiated rituximab, 1000 mg intravenously on days 1 and 15, followed by 500 mg/m² intravenously monthly for 2 doses. With this regimen, his prednisone was tapered down to 10 mg and mycophenolate mofetil down to 500 mg. In total, the patient received 4 doses of rituximab infusions (375 mg/m² per infusion). With each infusion, he experienced acute onset of pruritus followed by significant clearing of lesions over several days. Complete metabolic panel, complete blood count, and pemphigoid panels were followed up with closely. He currently remains asymptomatic with downward trending BP titers with a maintenance regimen of prednisone, 10-mg...
tablet orally daily, mycophenolate mofetil, 500-mg tablet orally twice a day, and doxycycline, 100-mg tablet orally daily (Figs 2 and 3).

**DISCUSSION**

BP is a chronic autoimmune disorder that is clinically identified by widespread tense bullae, erosions, or persistent pruritic urticarial lesions. These bullae are caused by antibodies against hemidesmosomal antigens, particularly BP antigen 1 (BP 230) and BP antigen 2 (BP 180), resulting in a characteristic autoantibody deposition at the epidermal basement membrane. BP incidence is estimated between 4.5 and 22 new cases per 1 million per year in central Europe. Yet, with more advanced ways to diagnose this condition, BP incidence appears to be increasing.

BP etiopathogenesis is not currently well understood. Overall, genetic predisposition and inducing factors are known to lead to the onset and course of BP. In fact, the human leukocyte antigen HLA-DQB1*0301 gene is reported to be a major genetic predisposing factor for BP. In addition, many physical triggers are documented to induce BP including drugs, radiotherapy, ultraviolet light, thermal and electrical burns, and even surgical procedures.

Infectious agents are triggers for autoimmune conditions, including blistering diseases. Microorganisms have been identified in patients with BP and pemphigus vulgaris, including human herpes viruses, hepatitis B and C viruses, *Helicobacter pylori*, and *Toxoplasma gondii*. A recent study reported a relationship between pemphigus vulgaris and CV but was unable to detect the viral genome in skin of affected patients. Although there was an elevated CV-IgG positivity ratio, it proved to not be statistically significant. In current literature, HFMD-induced BP exacerbation has not been reported.

HFMD is a clinical syndrome characterized by a maculopapular or vesicular viral exanthem of the hands, feet, and oral mucosa. Typically, it is caused by CVA16 and enterovirus 71, causing an acute self-resolving viral disease most commonly in children. However, CVA6 outbreaks were reported by the Centers for Disease Control and Prevention in the United States between 2011 and 2012. The reported cases were more severe resulting in higher fevers, extensive cutaneous eruptions, and hospitalizations for dehydration and severe pain in adults and children. This outbreak was around the same time that our patient had contracted HFMD.

BP’s chronic, debilitating nature results in high morbidity and mortality if not adequately treated. Treatment goals include decreasing blister formation and pruritus, promoting healing of blisters and erosions, and improving quality of life. Systemic prednisone is the first-line therapy for BP. Azathioprine, methotrexate, cyclophosphamide, and mycophenolate mofetil are corticosteroid-sparing agents and are sometimes used as adjuvant therapy. In addition, anti-inflammatory drugs including tetracyclines, nicotinamide, or dapsone.
may also be effective as monotherapy in mild disease or in combination with corticosteroids in some patients. The response to treatment depends on the extent and severity of the disease, patient age, existence of comorbidities, and previous treatments. For cases refractory to conventional therapies, rituximab, an anti-CD20 monoclonal antibody, has been used off label.

Rituximab depletes B cells in the periphery and affects T cells, ultimately resulting in immunosuppression by decreasing BP’s antibodies against the recipient’s hemidesmosomes, thereby decreasing BP’s autoimmune nature. In addition, there is evidence that there are structural and functional differences between normal B cells, malignant B cells, and B cells present in patients with autoimmune diseases. This finding may explain the improvement of our patient’s BP without worsening of his CVA6 infection. Nonetheless, future studies are required to determine specific dosing, effectiveness, and safety of using this novel agent to treat BP, as associations with increased infection and cardiotoxicity have been reported. Our patient had an impressive response to rituximab, after experiencing disease recalcitrance with other treatment modalities and has not exhibited adverse effects to date.

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