Lower Extremity Salvage in the Setting of Bullous Pemphigoid Exacerbation: A Case Report

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Bullous pemphigoid (BP) is the most common autoimmune blistering disease, where patients suffer from painful bullae and erosions often covering large portions of the skin and mucosae. Without timely treatment, it can cause significant morbidity and even death.1 Skin lesions are caused by autoantibody attack and subsequent loss of function of the hemidesmosome proteins, which attach the epidermis to the underlying dermis. Immune-suppression is required to prevent sloughing, scarring, and adhesions of the skin.2 In most cases, no clear precipitating factor is identified; however, cases have been reported secondary to drug exposure, trauma, radiotherapy, and surgical procedures.3 After initial onset, BP may develop a chronic course with periods of partial remission and acute relapse triggered by the factors discussed.

**CASE**

A 71-year-old woman presented to the dermatology clinic with a nonhealing wound of the left distal leg. History was significant for epidermal growth factor receptor positive (EGFR+) metastatic lung adenocarcinoma on erlotinib therapy for 1 year prior. Physical examination revealed a superficial 6 cm × 6 cm ulcer on the leg, with biopsy demonstrating infiltrative nodular basal cell carcinoma (BCC). One month later, she returned with severely pruritic, tense bullae on the bilateral lower legs, upper arms, and cheeks (Fig. 1). Punch biopsy with immunofluorescence revealed linear IgG immunoreactivity along the basement membrane (BM) consistent with BP. Due to concern for induction of BP by erlotinib, this medication was discontinued; IVIG and methotrexate were initiated, with eventual resolution of bullous lesions.

With the patient’s BP apparently well-controlled, radiotherapy was undertaken for treatment of her BCC, with the patient completing 28 sessions over a period of 7 weeks. Three months after completion of radiotherapy, she developed radiation-induced necrosis of the site, with adjacent tense bullae consistent with recurrent BP (Fig. 2). She resumed topical steroids, IVIG, and methotrexate for 3 months with resolution of BP; however, the wound remained open.

While continuing IVIG, the patient’s wound was debrided (Fig. 3) without evidence of residual malignancy on pathology, and she eventually underwent closure of the postradiation lower extremity wound using a free rectus abdominis muscle flap with split-thickness skin graft. The postoperative course was complicated by reactivation of her BP presenting with superficial necrotic skin graft overlying the flap. BP-antibody titers were elevated, and biopsy of the free flap revealed active BP and myositis, requiring partial debridement; however, large portions of the muscle were healthy and left intact. Therapy was reinitiated with a combination of IVIG, methotrexate, and an oral steroid taper, and subsequently laboratory markers stabilized. The remaining muscle was covered with allograft that firmly adhered to the wound bed, indicating viability, followed by split-thickness skin grafting and wound closure. IVIG was discontinued and weekly rituximab was initiated for a total of four cycles, during which...
no new bullae formed. Ultimately, the patient achieved wound closure; with interdisciplinary management, the site healed, and her condition stabilized (Fig. 4).

**DISCUSSION**

Bullous pemphigoid is a challenging clinical problem, where, in the setting of tissue damage and inflammation, certain antigens are “unmasked” and exposed to the immune system, breaking immune tolerance to host antigens and triggering an autoimmune response. In drug-induced cases, it is thought that mechanically or chemically altered skin may uncover antigens (eg, hemidesmosome proteins) within the BM with resultant autoantibody binding, complement activation, and blister formation. Several reports describing this phenomenon have been published.

In cases of erlotinib-induced BP, the drug is thought to act as a hapten, binding and altering the antigenic properties of proteins in the BM of the skin, inducing autoantibody binding. We theorize treatment with erlotinib was the triggering event in this patient, whereby tolerance was broken and autoimmunity to the hemidesmosome proteins in the skin developed. The patient thus remained susceptible to reactivation of BP with further skin insults even after complete cessation of erlotinib, as the immune system recognized the hemidesmosome proteins (eg, BP antigen 180) and mounted an immune response when
these proteins were exposed. Our patient not only had recurrence of BP after cessation of erlotinib, but also had been on erlotinib for 1 year before developing BP, prompting consideration that erlotinib-induced BP may not always appear early in treatment and may require additional skin injury or a second triggering factor. Thus, erlotinib should be considered as a potential cause in any patient developing BP while undergoing treatment.

After resolution of erlotinib-induced BP, our patient had recurrence in the setting of radiotherapy and surgical intervention. Microvascular free-flap procedures are complex and often required to close irradiated wounds; however, radiotherapy can promote BP, affecting the subsequent success of the surgical procedure. Both radiotherapy and the surgical procedure (free-flap harvest and split-thickness skin graft) alter structures in the BM of the skin and increase local vessel permeability, amplifying the potential for deposition of antibodies at the site of injury.\(^5,7,11\)

This patient likely developed BP in the setting of erlotinib therapy with high levels of circulating auto-antibodies to which the surgically manipulated and radiotherapy-treated tissues were more susceptible. This reactivated BP then spread to previously healthy skin in a patient who was insufficiently immunosuppressed. From a surgical standpoint, it would seem counter-intuitive to treat a postoperative patient with systemic steroids, given their role in suppressing wound healing. Furthermore, treatment with methotrexate in a microsurgical procedure would also be avoided due to its prothrombotic effects. However, as evidenced by this complex case, in patients with autoimmune diseases affecting the surgical site, controlling the autoimmune response is paramount to allow for wound healing. Because immune-related inflammation was the greatest barrier to flap salvage, control of the disease with steroids and methotrexate is ultimately what allowed for flap survival.

**CONCLUSIONS**

Surgical procedures and radiotherapy should be carefully considered in patients with a history of BP due to the risk of reactivation, even if the disease has been quiescent for some time. As free-flap procedures may be required to close wounds in the setting of previously irradiated tissues, and increasingly in patients on the EGFR class of chemotherapeutics which can trigger autoimmune conditions as seen in this patient, consideration of these co-morbid conditions and interdisciplinary perioperative management with appropriate immune-suppression may be required to ensure successful outcomes of surgical procedures.

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**REFERENCES**