Localized bullous pemphigoid after knee replacement surgery

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Abstract

Bullous pemphigoid (BP) most commonly presents as widespread, itchy, tense blisters in older patients. Localized bullous pemphigoid is a less common form of BP that can be more difficult to diagnose because of its similarity to more common conditions such as allergic contact dermatitis or bullous cellulitis. Prompt recognition of localized BP is important so that appropriate treatment can be started. We present a 57-year-old woman who presented with pruritic tense bullae overlying the surgical scar from a knee replacement 6 months prior on her anterior right knee. This case illustrates the potential for localized BP to be triggered by surgical procedures.

Keywords: bullous pemphigoid, trauma-induced, autoimmunity, bullous, skin diseases, medical dermatology

Introduction

Bullous pemphigoid (BP), the most common autoimmune blistering disorder, is a chronic disease of older adults characterized by an intensely pruritic eruption of widespread tense bullae, with spontaneous flares and remissions [1]. It is caused by autoantibodies against hemidesmosomal proteins of the skin and mucous membranes [2], including BP antigen 180 (BP180, BPAG2 or type XVII collagen) and BP antigen 230 (BP230 or BPAG1), [3]. Although most cases are generalized, localized BP accounts for 16% to 29% of all cases [4]. Rarely, trauma has been reported as an inciting factor in the development of BP. In these cases, a localized distribution is seen in over 50% [5].

Case Synopsis

A 57-year-old woman presented 6 months after a right total knee replacement complaining of a 3-month history of a very itchy blistering rash overlying the surgical scar on her right anterior knee. After her surgery, she had received one dose of vancomycin for a Methicillin-resistant Staphylococcus aureus

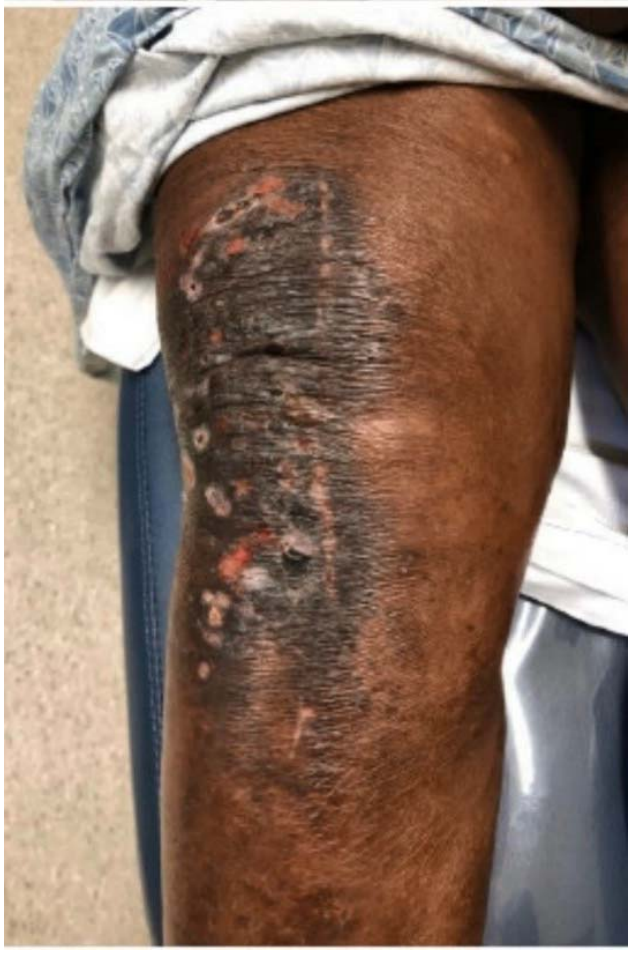

Figure 1. *Hyperpigmented, lichenified bullous eruption on the right lateral knee at initial presentation.*

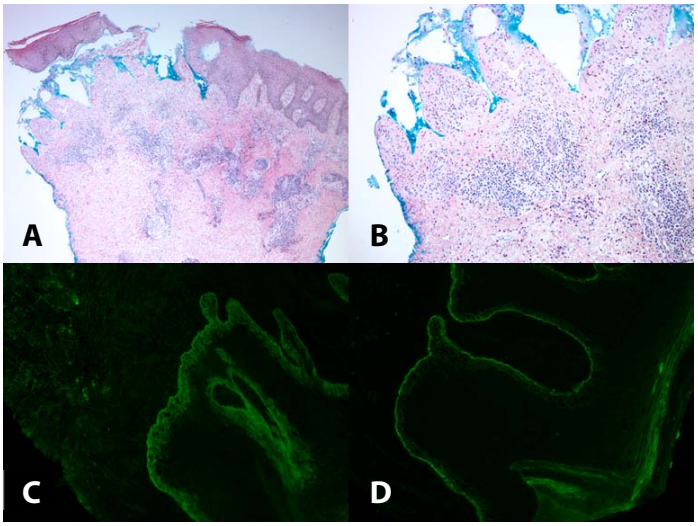

Figure 2*: Histologic sections stained with H&E show a subepidermal vesicular dermatitis with abundant eosinophils.* ***A)*** *4x,* ***B)*** *10×.* ***C)*** *Direct immunofluorescence shows strong linear deposition of IgG, and* ***D)*** *C3 at the dermoepidermal junction.*

(MRSA)-positive nares swab. Her other medications were albuterol, aspirin, furosemide, gabapentin, lisinopril-hydrochlorothiazide, omeprazole, and nortriptyline. Approximately two months after her knee replacement, she was seen in the orthopedics department for mild persistent drainage from the wound and treated with doxycycline for possible wound infection. She had gastrointestinal intolerance to the doxycycline and it was changed to trimethoprim-sulfamethoxazole. The wound healed without further drainage, but while on the second antibiotic, she developed a generalized itchy red rash believed to be a drug eruption. This rash resolved without treatment over the next few weeks, but she then developed severe itching and blisters localized to her right knee surgical site. Other than the antibiotics, there were no new medications and the patient was not applying anything to the right knee that was not being used elsewhere on her body. She tried hydrocortisone 1% and triamcinolone 0.1% creams without improvement. Review of systems was negative for fevers, chills, and night sweats.

Physical examination revealed a hyperpigmented, irregular, lichenified plaque with multiple tense bullae and several linear erosions directly overlying the surgical scar on the right lateral knee (**Figure 1**). The remainder of the examination was unremarkable. The differential diagnosis included consideration of allergic contact dermatitisl to the metal prosthesis in her knee, allergic contact dermatitis to a topical antibiotic or corticosteroid, bullous cellulitis, BP, linear IgA bullous dermatosis, and epidermolysis bullosa acquisita. A punch biopsy stained with hematoxylin and eosin showed a subepidermal vesicular dermatitis with abundant eosinophils. Direct immunofluorescence showed linear IgG and C3 deposition at the dermal-epidermal junction, consistent with a diagnosis of BP (**Figure 2**). She responded well to betamethasone dipropionate 0.05% ointment twice daily, which she used until the bullae cleared. At follow up three months later, she had no bullae, though mild pruritus had returned after discontinuing topical corticosteroids (**Figure 3**).

Case Discussion

Although most cases of BP are idiopathic and generalized, there are reports of BP triggered by various external factors. These triggers include trauma, surgery, burns, radiation treatment, and other skin eruptions such as cellulitis, lichen planus, insect bites, and prurigo nodularis [5-9]. There are also reports of localized BP occurring following psoralen plus ultraviolet A therapy, numerous drugs including angiotensin-converting-enzyme (ACE) inhibitors, loop diuretics, gabapentin, iodine, dithranol, and tar [5,10-15]. Our patient was on furosemide, a known trigger of BP, but she had been on this for at least 10 months prior to her surgery and 13 months prior to development of blisters on her knee. In addition, her bullae resolved with use of topical betamethasone even though she remained on this drug, so it is unlikely to be causative in her case.

Although the pathogenesis of localized BP is not completely understood, one proposed mechanism is that an inflammatory process at the dermal-epidermal junction results in the exposure of antigens to autoreactive T lymphocytes, leading to a secondary immune response via an epitope-spreading phenomenon. Another hypothesis is that patients with BP already have low levels of anti-basement membrane autoantibodies, which are not

pathogenic until an insult recruits inflammatory cells including granulocytes which are activated by autoantibodies, resulting in release of enzymes and tissue injury [5]. Localized BP occurring in the setting of a previous skin disorder such as cellulitis may be considered a form of "Wolf isotopic response," in which a second skin condition occurs at the site of a healed dermatosis [16]. However, in the case of our patient and others who develop BP at the site of trauma, we believe this would more correctly be considered an example of the Koebner or isomorphic phenomenon. This type of reaction, in which a dermatosis preferentially occurs in areas of skin trauma, is well known to occur in psoriasis, lichen planus, and vitiligo, among other diseases [17].

Though there is little data available about the risk of progression of localized BP to generalized BP, one study reported that approximately 37% (7/19) of localized cases ultimately developed generalized BP within three years of diagnosis [18]. Identifying localized BP is important so that it can be treated appropriately, which would hopefully decrease the risk of progression to generalized BP. Localized BP often has a delay in diagnosis versus generalized BP. A prospective nationwide cohort study of 117 patients in Switzerland revealed a mean time to diagnosis for generalized bullous pemphigoid patients of 6.1 months after the first symptoms presented [19]. In this study, localized disease (only affecting one area of the body) was found to be significantly associated with an increased diagnostic delay (defined as >4 months), though this had no bearing on the patient's survival after one year. Numerous morphologies were reported in the localized forms in this study including excoriated, eczematous, or urticarial lesions, some lacking blisters, which contributed to this diagnostic delay.

Distinguishing localized BP from other conditions can be difficult because of similar appearance and symptoms. Contact dermatitis can also present as a localized erythematous, edematous, vesiculobullous eruption with associated pruritus [20]. The patient history is critical, as contact dermatitis occurs after exposure to an allergen or irritant. Bullous cellulitis can also appear similar, with erythema and blistering in a localized area, but it is typically painful and bacterial cultures would usually be positive [21]. Linear IgA bullous dermatosis, a subepidermal bullous disease, is also in the differential of bullous pemphigoid, but classically has an annular appearance and shows linear deposition of IgA at the basement membrane zone on biopsy [22]. Epidermolysis bullosa acquisita may likewise have localized tense blisters, typically healing with milia and scarring [23]. Epidermolysis bullosa acquisita can be distinguished from BP by immunofluorescence showing antibody binding to the dermal side of salt-split skin [22].

Conclusion

Although localized BP is rare, this diagnosis should be considered in patients presenting with a localized blistering eruption at the site of prior cutaneous trauma. Once the diagnosis is made, prompt

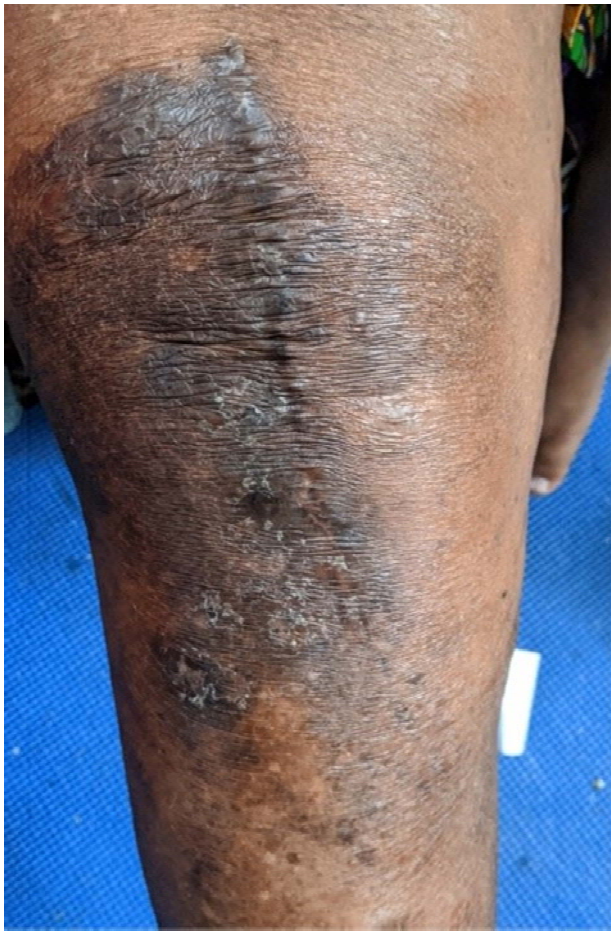

Figure 3. *Follow up after three months of treatment with ultrapotent topical steroid showed complete resolution of the bullae with residual hyperpigmentation and lichenification.*

treatment and close follow-up are important for symptom management and potentially minimizing the risk of developing generalized BP [18].

Potential conflicts of interest

The authors declare no conflicts of interests.

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