Generalized pruritic blisters and bullous lesions

In a patient with no history of skin disease, a recent change provided a clue to his condition.

A 62-YEAR-OLD MAN presented to our skin clinic with multiple pruritic, tense, bullous lesions that manifested on his arms, abdomen, back, and upper thighs over a 1-month period. There were no lesions in his oral cavity or around his eyes, nose, or penile region. He denied dysphagia.

The patient had multiple comorbidities, including diabetes, hypertension, recent stroke, and end-stage renal disease. He was being prepared for dialysis. His medications included torsemide, warfarin, amiodarone, metoprolol, pantoprazole, atorvastatin, and nifedipine. About 3 months prior to this presentation, he was started on oral linagliptin 5 mg/d, an oral antihyperglycemic medication. He had no history of skin disease or cancer, and his family history was not significant.

Physical examination showed multiple 5-mm to 2-cm blisters and bullae on the flexural surface of both of his arms (FIGURE), back, lower abdomen, and upper thighs. His palms and soles were not involved. The lesions were nontender, tense, and filled with clear fluid. Some were intact and others were rupturing. There was no mucocutaneous involvement. Nikolsky sign was negative. There were no signs of bleeding.

The family physician (FP) obtained a 4-mm punch biopsy at the edge of a 6-mm blister for light microscopy and a 3-mm perilesional punch biopsy for direct immunofluorescence (DIF) microscopy.

WHAT IS YOUR DIAGNOSIS?

HOW WOULD YOU TREAT THIS PATIENT?

FIGURE

Intact tense bullae of varying sizes and stages over forearm (A) and upper arm (B)
**Dx: Bullous pemphigoid secondary to linagliptin use**

DIF of the biopsy sample demonstrated linear deposition of complement 3 (C3) and immunoglobulin (Ig) G along the basement membrane zone. Indirect immunofluorescence on salt-split skin demonstrated linear deposition of IgG and C3 on both the roof and floor of the induced blisters. These findings and the patient’s clinical presentation met the criteria for bullous pemphigoid (BP), which is the most common autoimmune skin-blasting disease.1

BP is associated with subepidermal blistering, which can occur in reaction to a variety of triggers. Pathogenesis of this condition involves IgG anti-basement membrane autoantibody complex formation with the hemidesmosomal antigens BP230 and BP180—a process that activates C3 and the release of proteases that can be destructive to tissue along the dermo-epidermal junction.1

- **Growing incidence.** BP usually occurs in patients > 60 years, with no racial or gender preference.1 The incidence rate of BP ranges from 2.4 to 21.7 new cases per 1 million individuals among various worldwide populations.2 The incidence appears to have increased 1.9- to 4.3-fold over the past 2 decades.2

**What you’ll see, who’s at risk**

- **Symptoms of BP** include localized areas of erythema or pruritic urticarial plaques that gradually become more extensive. A patient may have pruritis alone for an extended period prior to developing blisters and bullae. The bullae are tense and normally 1 to 7 cm in size.1 Eruption is generalized, mostly affecting the lower abdomen, as well as the flexural parts of the extremities. The palms and soles also can be affected.

FPs should be aware of the atypical clinical variants of BP. In a review by Kridin and Ludwig, variants can be prurigo-like, eczema-like, urticaria-like, dyshidrosiform type, erosive type, and erythema annulare centrifugum-like type.2 At-risk populations, such as elderly patients (> 70 years), whose pruritis manifests with or without bullous formation, should be screened for BP.1,3

- **Risk factors for BP.** Certain conditions linked to developing BP include neurologic disorders (dementia and Parkinson disease) and psychiatric disorders (unipolar and bipolar disorder).4 Further, it is important to note any medications that could be the cause of a patient’s BP, including dipeptidyl peptidase-4 (DPP-4) inhibitors, psychotropic medications, spironolactone, furosemide, beta-blockers, and antibiotics.3 This patient was taking a beta-blocker (metoprolol) and a DPP-4 inhibitor (linagliptin). Because he was most recently started on linagliptin, we suspected it may have had a causal role in the development of BP.

**The association of DPP-4 inhibitors and BP**

FPs are increasingly using DPP-4 inhibitors—including sitagliptin, vildagliptin, and linagliptin—as oral antihyperglycemic agents for type 2 diabetes mellitus. Therefore, it’s important to recognize this medication class’s association with BP.5 In a case-control study of 165 patients with BP, Benzaquen et al reported that 28 patients who were taking DPP-4 inhibitors had an associated increased risk for BP (adjusted odds ratio = 2.64; 95% confidence interval [CI], 1.19-5.85).3

**The pathophysiology of BP associated with DPP-4 inhibitors** remains unclear, but mechanisms have been proposed. The DPP-4 enzyme is expressed on many cells, including keratinocytes, T cells, and endothelial cells.3 It is possible that DPP-4 inhibition at these cells could stimulate activity of inflammatory cytokines, which can lead to enhanced local eosinophil activation and trigger bullous formation. DPP-4 enzymes are also involved in forming plasmin, which is a protease that cleaves BP180.3 Inhibition of this process can affect proper cleavage of BP180, impacting its function and antigenicity.3,6

**Other conditions that also exhibit blisters**

There are some skin conditions with similar presentations that need to be ruled out in the work-up.

- **Bullous diabeticorum** is a rare, spontaneous, noninflammatory condition found in patients with diabetes.1 Blisters usually manifest as large, tense, asymmetrical, mild-
Depending on the severity of disease, treatment can include the use of potent topical corticosteroids alone or in combination with systemic corticosteroids and anti-inflammatory antibiotics.

**Management focuses on steroids**

The offending agent should be discontinued immediately. Depending on the severity of disease, treatment can include the use of potent topical corticosteroids alone or in combination with systemic corticosteroids and anti-inflammatory antibiotics (eg, doxycycline, minocycline, erythromycin). For patients with resistant or refractory disease, consider azathioprine, methotrexate, dapsone, and chlorambucil. Exceptional cases may benefit from the use of mycophenolate mofetil, intravenous immunoglobulin, or plasmapheresis.

**For this patient**, initial treatment included discontinuation of linagliptin and introduction of topical clobetasol 0.05% and oral prednisone 40 mg/d for 7 days, followed by prednisone 20 mg for 7 days. He was also started on oral doxycycline 100 mg bid and oral nicotinamide 500 mg bid.

**References**

3. Benzaquen M, Borradori L, Berhis F, et al. Dipeptidyl peptidase...


