# A case of irritant contact dermatitis and suspected linagliptin-induced koebnerized bullous pemphigoid

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***Key words:*** dipeptidyl peptidase-4 inhibitor; irritant contact dermatitis; koebnerized bullous pemphigoid; linagliptin.

## INTRODUCTION

Linagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor used in the treatment of type 2 diabetes mellitus. Numerous case reports and a recent Korean population-based case-control study have identified DPP4 inhibitors as a trigger for the development of bullous pemphigoid (BP).[1-5] Unique clinicopathologic characteristics have been described in DPP-4–induced BP, which include generalized blisters lacking edematous erythema, scant infiltration of eosinophils in the perilesional skin, and negative autoantibodies against BP180-NC16A.[1] The diagnosis of BP is challenging, as it can mimic a variety of other inflammatory conditions. We report a case of koebnerizing BP suspected secondary to linagliptin.

*Abbreviations used:*

BP: bullous pemphigoid
DPP-4: dipeptidyl peptidase-4

## CASE PRESENTATION

A 68-year-old white man with history of heart failure and type 2 diabetes mellitus was admitted to the hospital with an erythematous, eroded, intensely pruritic and painful eruption, developing 5 months after his first dose of linagliptin. The eruption was localized to the back, buttocks, groin, scrotum, and penis (Fig 1, *A* and *B*). Irritant contact dermatitis was the initial diagnosis because of the patient's history of frequent episodes of incontinence and use of absorbable undergarments. Allergic contact dermatitis was also considered, however, no patch testing was performed. The patient was treated with triamcinolone 0.1% ointment and zinc oxide ointment with minimal improvement. The patient continued to complain of pruritus and pain, and the eruption continued to spread, primarily in intertriginous sites and areas of friction over the following 7 days. Herpes simplex virus superinfection was excluded by viral polymerase chain reaction. Blood cultures were negative. Given the recalcitrant nature of the eruption, punch biopsies were obtained from the genital region. The specimens demonstrated subepidermal bulla formation with eosinophils on hematoxylin-eosin staining (Fig 2, *A* and *B*) and linear IgG and C3 along the dermoepidermal junction on direct immunofluorescence. The histopathologic and immunophenotypic features supported a diagnosis of BP. Linagliptin was held at this time for consideration of linagliptin-induced BP, and the patient began a prednisone taper, doxycycline, 100 mg twice daily, and niacinamide, 500 mg twice daily. The patient's bumetanide was also withheld; however, given that bumetanide-associated BP has only been reported in a single case, which occurred 2 weeks after initiation of the medication, linagliptin was thought to be the more likely culprit.[6] Medication reconciliation was unremarkable for any additional sources or drug-drug interactions. The patient had multiple subsequent hospital admissions for heart failure and was rechallenged with furosemide and/or bumetanide during these admissions with no recurrence of his immunobullous lesions. Ultimately, he

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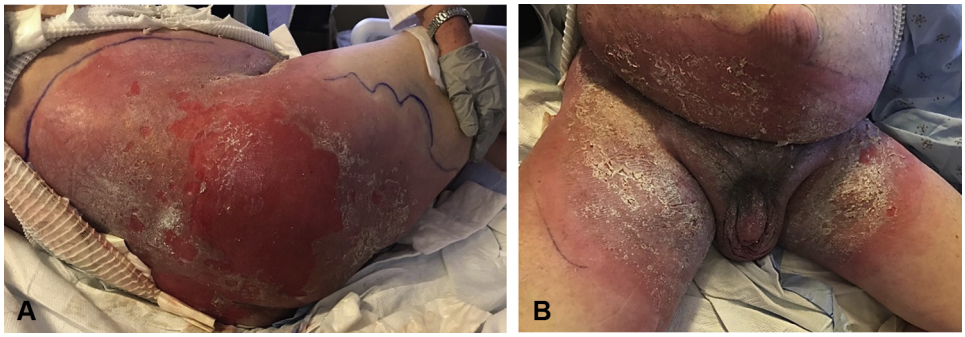


**Fig 1.** **A**, Diffuse, erythematous, scaly, eroded plaques with areas of re-epithelization on the right lower abdomen, lower back, hip, and buttock. **B**, Diffuse, erythematous, scaly, eroded plaques with areas of re-epithelization on the lower abdomen, bilateral groin, scrotum, and penis.

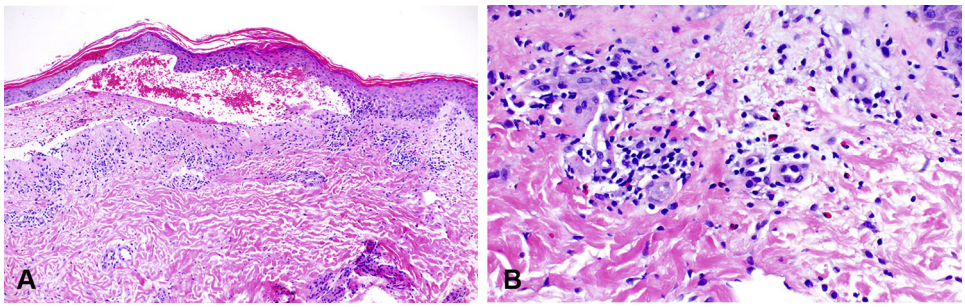


**Fig 2.** **A**, A punch biopsy found a prominent subepidermal cleft containing eosinophils in the blister cavity as well as tagging the dermo-epidermal junction (hematoxylin and eosin stained tissue sections, original magnification ×100). **B**, Within the dermis is an eosinophil-rich perivascular and interstitial infiltrate. (**A** and **B**, Hematoxylin and eosin stain. original magnifications: **A**, ×100; **B**, ×400.)

had been off prednisone, doxycycline, and niacinamide for at least 1 month without recurrence of his BP rash, prior to his final hospitalization, after which he was transitioned to hospice care and died of heart failure. Bullous amyloidosis as a rare cutaneous manifestation of systemic amyloidosis was considered given the cardiac death; however, no additional serologic studies were performed because there was no protein gap, calcium levels were normal, and no IgM was deposited on direct immunofluorescence. Although the case unfortunately did not offer a long-term follow-up, the lack of recurrence after greater than 30 days off prednisone suggests that linagliptin-induced BP may not recur after discontinuation of the medication and control with corticosteroid taper.

## DISCUSSION

BP is a rare blistering disease characterized by tense subepithelial blisters arising from normal-to-erythematous skin in a confined distribution.[7] Although DPP-4 inhibitor exposure is a well-established cause of BP, localized forms of disease are not well documented. The onset of new bullous lesions is delayed and ranges from 2 to 13 months after the first dose of linagliptin.[1-3] The cause is largely unknown; however, DPP-4 inhibitors may induce BP de novo or accelerate the development of BP in susceptible individuals. Keratinocytes, endothelial cells, and lymphocytes are known to express DPP-4 receptors. Inhibition of these receptors may enhance pro-inflammatory chemokines that promote eosinophil activation in the skin, tissue damage, and blister formation. DPP-4 inhibition may also prevent keratinocyte proliferation and collagen synthesis.[8] The diagnosis can be challenging, as it can mimic other vesiculobullous diseases. Our patient's history and localized lesional distribution initially favored robust irritant contact dermatitis; however, the lack of response to traditional treatment, as well as the discovery of tense bullae near the primary eruption site, made the consideration for BP more likely. The localized lesional distribution observed was attributed to koebnerization and has been described to occur with BP.[7] Because of the temporal relationship of the disease onset and improvement observed

following drug withdrawal, linagliptin was thought to be the most probable cause of BP in this case. Irritant contact dermatitis has not been reported as a predisposing factor for BP; however, it may have contributed to the initiation of BP. We hypothesize that pre-existing epidermal inflammation may have predisposed the patient to the development of autoantibodies. We present a case of suspected linagliptin-induced BP to highlight a unique phenotypical characteristic not previously described. We also use this case to draw attention to the temporal relationship of drug-induced BP among various medications to aid in the search of causality.

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