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CASE REPORT

A case of anti-BP230 antibody-positive dyshidrosiform bullous pemphigoid secondary to dipeptidyl peptidase-4 inhibitor in a 65-year-old Filipino female

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ABSTRACT

INTRODUCTION Bullous pemphigoid (BP) is a chronic, relapsing autoimmune blistering disorder commonly found in adults older than 60 years of age. It is mediated by autoantibodies directed against the hemidesmosomal proteins BP180 and BP230, which trigger an inflammatory cascade leading to blister formation. BP may present with pruritus, followed by an erythematous plaque or urticaria, and subsequently by bullae formation with or without mucosal involvement. It develops sporadically but can also be triggered by ultraviolet light exposure, radiation therapy, and medications such as dipeptidyl peptidase-4 inhibitor (DPP4i). Since 2006, the increasing use of DPP4i (also known as gliptins) for their good safety profile in treating Type II Diabetes Mellitus has led to a further increase in the incidence of bullous pemphigoid.

CASE REPORT This is a case of a 65-year-old hypertensive and diabetic elderly Filipino female presenting DPP4i (linagliptin)-induced bullous pemphigoid with an atypical dyshidrosiform pattern, negative direct immunofluorescence (DIF), and Enzyme-linked immunosorbent assay (ELISA) that is negative for anti-BP180 antibodies but positive for anti-BP230 antibodies.

CONCLUSION The increasing use of DPP4i for diabetes mellitus for its good safety profile may be an essential contributing factor to the increasing incidence of BP in elderly hypertensive and diabetic patients with a simultaneous increasing incidence of atypical BP presentations such as the dyshidrosiform variant. Inability to recognize these factors carries significant therapeutic implications, including prolonged multidrug immunosuppression and increased patient morbidity and mortality.

KEYWORDS Bullous pemphigoid, gliptin, ELISA

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INTRODUCTION

Bullous pemphigoid (BP) is a chronic, relapsing, autoimmune blistering disorder common in adults older than 60 years.[1] The incidence of classic BP has increased after the Food and Drug Administration (FDA) approved dipeptidyl peptidase-4 inhibitor (DPP4i) for diabetes mellitus in 2006.[2] Due to misdiagnosis of atypical (non-bullous) BP, such as dyshidrosiform BP (DBP), characterized by blisters on the palms and soles of a patient diagnosed with or suspected of having BP, the true incidence of BP is unknown.[3] BP is characterized by an autoimmune response against the hemidesmosomal proteins BP180 and BP230.[1] Anti-BP230 antibody-positive BP accounts for only 5%–8% of all BP cases.[4] Direct immunofluorescence (DIF) can be negative due to improper sampling or subthreshold levels of immune complexes.[5] The annual cumulative incidence of BP was estimated to range from 2.4 to 23 per million in different populations worldwide, with an increasing incidence of 1.9- to 4.3-fold.[2] From 2011 to 2019, the Philippine Dermatological Society Health Information System (PDS-HIS) documented 905 BP cases, of which only 13 were drug-induced, and none were DPP4i-induced.[6] A 10-year retrospective prevalence study from 2000 to 2019 found that 58 (14.6%) out of 397 BP cases were DPP4i-associated.[7] Although DBP incidence is unknown, retrospective studies have revealed a 3.5 to 45% (median, 28%) incidence.[3] Diagnostic dilemmas and delays in treatment were noted due to missed associations of BP with medications such as DPP4i, and an increase in atypical BP presentations. To the author's knowledge, there is still no reported case of anti-BP230 antibody-positive dyshidrosiform DPP4i-associated BP worldwide and locally.

CASE REPORT

A 65-year-old hypertensive, diabetic, Filipino woman presented with pruritus on her right leg four months after empagliflozin plus linagliptin

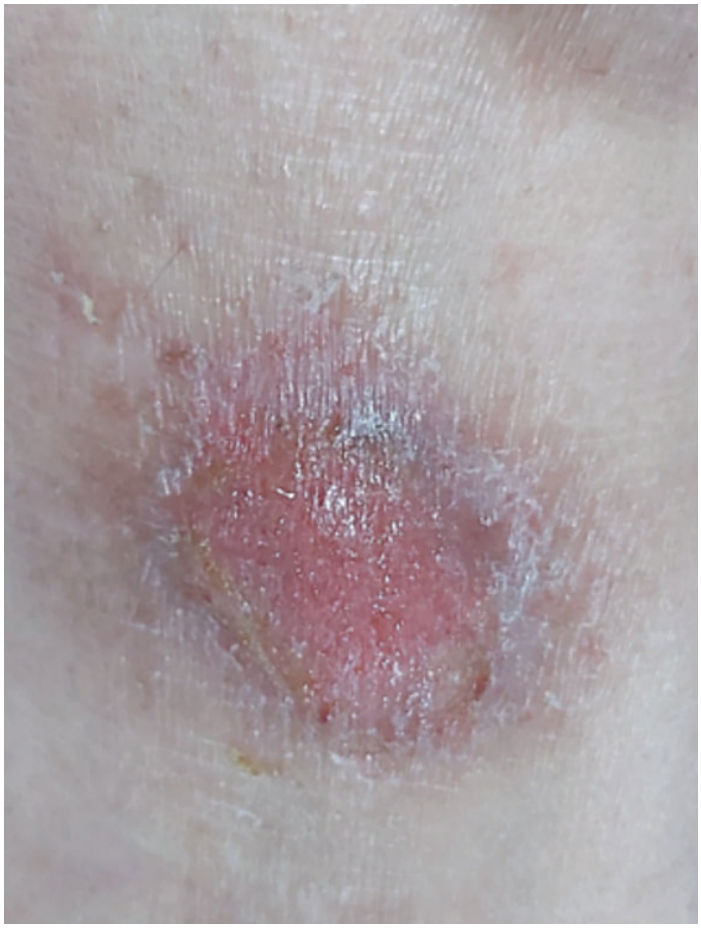

Figure 1. Pruritic, erythematous nummular plaque on the anterodistal left leg of a patient with dyshidrosiform BP secondary to DPP4i.

was started. Four months after, a gradually enlarging (from 2 to 6 cm) pruritic, erythematous, and edematous plaque with erosions and serous to purulent discharge (Figure 1) was noted with subsequent appearance of multiple pruritic, tense, tapioca-like vesicles and bullae on the hands (Figure 2A) feet, arms, and legs (Figure 2B). She was diagnosed by a dermatologist with recalcitrant eczema unresponsive to topical corticosteroids, topical and oral antibiotics, and topical antifungal medications. Drug-induced BP was considered, and she was started on prednisone (20 mg/day, tapered), lymecycline (300 mg/day), cetirizine (20 mg/day), and clobetasol cream (twice a day) with 90% improvement after three months. Linagliptin was discontinued by an endocrinologist as suggested by the dermatologist. Biopsy was done (11 months after empagliflozin plus linagliptin was started), which revealed subepidermal blister formation with eosinophils lining along the dermal-epidermal junction and surrounding the superficial blood vessels of the papillary dermis (Figure 3). Direct immunofluorescence (DIF) study was negative for IgG, IgM, IgA, C3, and fibrinogen. Enzyme-linked immunoassay was negative for anti-BP180 antibody (2.686 RU/ml; normal value: <20 RU/ml), but positive for anti-BP230 antibody (>200 RU/ml; normal value <20 RU/ml), clinching the diagnosis of BP. Currently, the patient occasionally develops 1 to 2 new lesions that would spontaneously resolve within the day or after applying clobetasol cream twice a day.

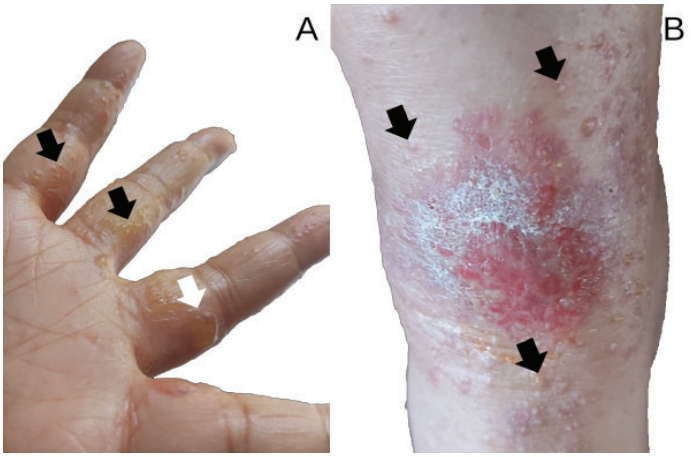

Figure 2. **A.** Multiple pruritic tense tapioca-like vesicles (black arrows) and bullae (white arrows) on the hand, and **B.** around a pruritic, erythematous nummular plaque on the anterodistal left leg of a patient with dyshidrosiform BP secondary to DPP4i.

DISCUSSION

Bullous pemphigoid targets the NC16A domain of BP180 in approximately 85-90% of cases, and BP230 in about 5-8% of all BP cases. In contrast to BP180, the pathogenic relevance of autoantibodies against BP230 is unclear. Anti-BP230 antibody-positive BP has a non-inflammatory and milder clinical

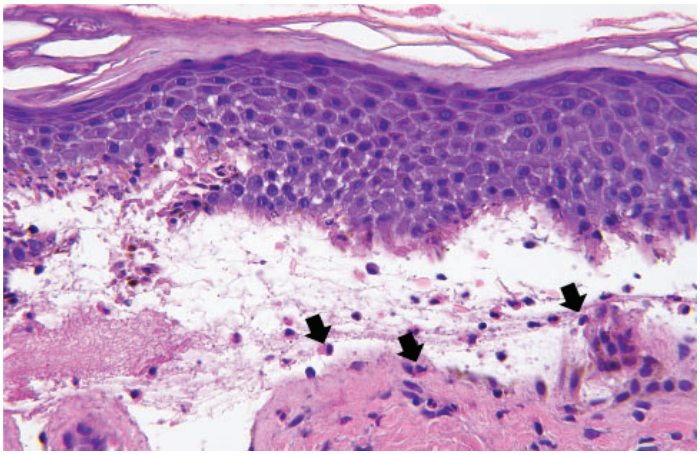

Figure 3. Subepidermal blister formation with eosinophils (black arrows) lining along the dermal-epidermal junction and surrounding the superficial blood vessels of the papillary dermis in a patient with dyshidrosiform BP secondary to DPP4i.

presentation with a typical initial presentation of edematous erythemas rather than tense bullae.[4,8] In a small percentage of cases, DIF will initially be negative due to either improper specimen sampling from lesional skin or a subthreshold quantity of immune complexes on the skin.[5] BP was associated with a 6-44% first-year mortality rate. The causes of mortality can be multifactorial and include heart disease, infection, neurologic disease, and adverse effects of medications.[9] Aside from the classic presentation of tense bullae, BP can also present with atypical forms, including dyshidrosiform BP, pemphigoid vegetans, pemphigoid nodularis, vesicular pemphigoid, large erosive toxic epidermal necrolysis-like lesions, erythrodermic pemphigoid, and lichen planus pemphigoides.[1] Dyshidrosiform BP has been reported in at least 84 cases and is characterized by blisters on the palms and soles. Blisters can present on both the palms and soles (67%), on the soles (30%), or the palms only (3%). The diagnosis of this BP subtype is often delayed because it is misdiagnosed as pompholyx or repeatedly treated for recurrent or persistent dermatitis. Some presented with prodromal symptoms such as eczematous, papular, and urticarial eruptions prior to the appearance of blisters.[8] Bullous pemphigoid can also be triggered by DPP4i. DPP4i is a second or third-line drug for type 2 diabetes mellitus that has been associated with an approximately 3-fold increased risk for BP. The mean latency period between the introduction of the DPP4i and confirmation of BP is approximately 22.6 months. Among the DPP4i, vildagliptin had the strongest association with an approximately 11-fold increased risk of BP, followed by linagliptin with about 7-fold increased risk. The pathogenesis is uncertain, but an alteration in the correct cleavage of BP180 resulting in modification of its antigenicity and function was postulated as a potential mechanism.[2] Studies have shown that DPP4i-induced BP has a better prognosis with a good response to therapy after drug withdrawal than classic BP.[8] DPP4i is preferred for its neutral effects on body weight and good atherosclerotic cardiovascular safety compared to other antidiabetic drugs. A 2021 multicenter retrospective study, which included 320 BP cases, revealed that among the cases, 77.5% were idiopathic, 9.7% were potentially drug-induced, and 12.8% had new medications missed by dermatologists. In addition, 39% of the missed cases presented with non-bullous eruptions.[10]

CONCLUSION

The increasing use of DPP4i for diabetes mellitus for its good safety profile may be an essential contributing factor to the increasing incidence of BP in elderly hypertensive and diabetic patients with a simultaneous increasing incidence of atypical BP presentations such as the dyshidrosiform variant. Anti-BP230 is an important additional serologic marker for BP, especially if the anti-BP180 antibody and DIF are negative. Dermatologists must be aware of known BP-associated medications and atypical BP presentations, especially in cases with recalcitrant eczemas. Inability to recognize these factors carries significant therapeutic implications, including prolonged multidrug immunosuppression and increased patient morbidity and mortality.

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