CASE REPORT

A case of bullous pemphigoid uniquely associated with dipeptidyl peptidase-4 (DPP-4) inhibitor

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ABSTRACT

Bullous pemphigoid (BP) is a chronic autoimmune blistering disease mainly affecting the elderly population. While the pathogenesis has not yet been fully elucidated, it has been suggested that there is a correlation observed with certain groups of medications. Among drugs correlated with bullous pemphigoid, the group of dipeptidyl peptidase-4 inhibitors (-gliptins) used in the treatment of diabetes mellitus has been one of the most strongly associated. This is a case of a 64-year-old female on regular maintenance medications including linagliptin who developed generalized pruritus followed a week after by appearance of localized fluid-filled vesicles and bullae on the right lower leg. BP associated with dipeptidyl peptidase-4 inhibitors is characterized as "non-inflammatory" – lesions are localized and associated with less erythema compared to the classic presentation. Serum eosinophilia was absent, and serum autoantibody against BP180 was positive. Histopathologic and immunohistologic results revealed characteristics similar to classic bullous pemphigoid. The association of dipeptidyl peptidase-4 inhibitors to the development of BP was observed to have a long latency period between initiation of drug to onset of lesions. There was significant improvement after both withdrawal of the drug and standard steroids and doxycycline. Unlike other drug-induced BP, dipeptidyl peptidase-4 inhibitor-associated BP was found to have similar prognosis with the classic manifestation as the patient noted recurrence one month after remission despite withdrawal of inciting drug.

Keywords: DPP-4 inhibitor-associated bullous pemphigoid, drug-associated bullous pemphigoid, dipeptidyl peptidase-4 inhibitor, bullous pemphigoid, gliptins

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INTRODUCTION

Bullous pemphigoid (BP) is a chronic, autoimmune blistering disease occurring primarily in the elderly population. The pathogenesis of this condition has been strongly linked to the presence of circulating and tissue-bound autoantibodies against the basement membrane antigens BP180 and BP230. In most cases, the causative agent remains unidentified, but in a selected few, certain medications have been implicated in the pathogenesis of the disease. Dipeptidyl peptidase-4 inhibitors (-gliptins), in particular, which are used primarily in the treatment of diabetes mellitus, have been increasingly suspected to be a prime aggravating drug in the incidence of BP.

Case Report

This is a case of a 64-year-old Filipino-Chinese female, hypertensive and diabetic with chronic lacunar infarct, who consulted for "blisters" on the lower extremities. 2 weeks prior to consult, she noted severely pruritic erythematous papules predominantly on the right lower leg, which she also noted 3-4 days after on her trunk, abdomen and lower back. 1 week prior to consult, she noted appearance of clear serous fluid-filled vesicles and bullae, the largest measuring around 2 centimeters localized to the right lower leg. She also noted progression of pruritic erythematous papules on the flexor surface of upper extremities.

The patient recalls an allergy to an unrecalled antibiotic which presented as morbiliform rash and managed with oral betamethasone/dexchlorphenamine maleate (Celestamine). Current medications of the patient include the following maintenance medications taken since 40 months prior to consult: Nebivolol 5 mg OD, Linagliptin 2.5 mg + Metformin 500 mg (Trajenta Duo) OD, Clopidogrel 75 mg OD and Apixaban 2.5 mg BID. Four months prior to consult, she was also given sultamicillin 1.5 g IV every 6 hours for 7 days and oral levofloxacin 500 mg OD for 7 days for an infected non-healing wound. She currently only takes ascorbic acid 500 mg + zinc sulfate monohydrate 27.5 mg OD as supplement and has no history of herbal drug intake.

Upon consult, physical examination revealed few well-defined tense, firm-topped round to oval bullae filled with serous to hemorrhagic fluid, some flattened and few topped with yellowish crust with an erythematous background on the right anterior lower leg (Figure 1a). There are also several erosions topped with hemorrhagic crusts and excoriations on bilateral flexor aspects of forearms, abdomen and back due to pruritus. The patient does not have any oral lesions.

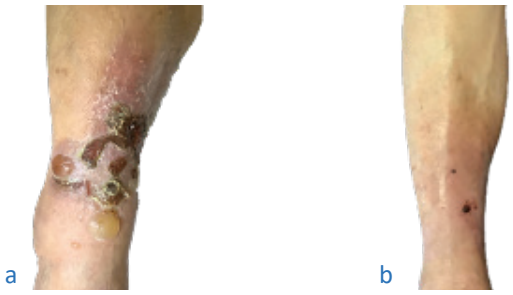

Figure 1. (a). Few well-defined tense oval bullae filled with serous to hemorrhagic fluid localized to the right anterior lower leg. (b). Resolution of lesions one month after treatment with tapered prednisone, short-term doxycycline and withdrawal of linagliptin.

Laboratory tests were done – patient had slightly low hematocrit but white blood count and eosinophil count were normal at 8,350 and 6%, with increased neutrophil count at 79% (normal range 40-74%). Blood sugar was normal. Blister fluid culture and sensitivity revealed few S. aureus sensitive to all tested antibiotics (azithromycin, penicillin, clindamycin, erythromycin, linezolid,oxacillin, rifampicin, trimethoprim-sulfamethoxazole, tetracycline, tigecycline and vancomycin). Serum ELISA for antibodies against BP180 was positive.

Histopathology revealed moderately diffuse spongiosis with few necrotic keratinocytes. There is a subepidermal blister containing eosinophils and neutrophils (Figure 2). In the dermis, there is a moderately dense superficial and deep perivascular and interstitial mixed inflammatory infiltrate of eosinophils, neutrophils, lymphocytes and histiocytes with dilated blood vessels. Direct

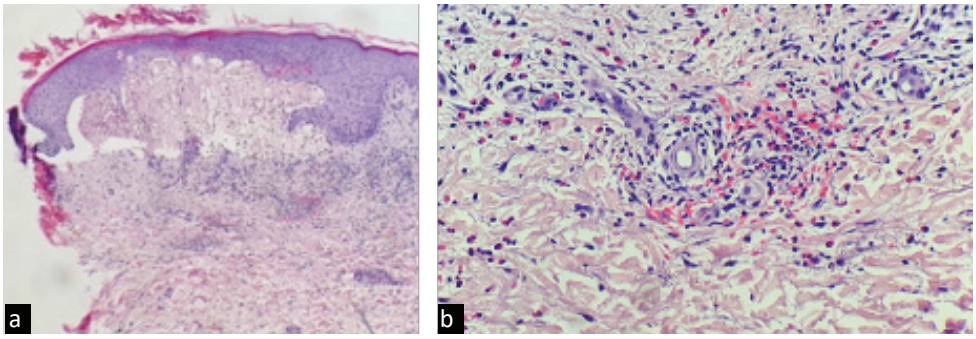

Figure 2. (a). Routine histopathology from the edge of a bulla revealed a subepidermal blister containing eosinophils and neutrophils (haematoxylin-eosin stain; magnification x100). (b). Dermis revealed a moderately dense superficial and deep perivascular and interstitial mixed inflammatory infiltrate of eosinophils, neutrophils, lymphocytes and histiocytes with dilated blood vessels.

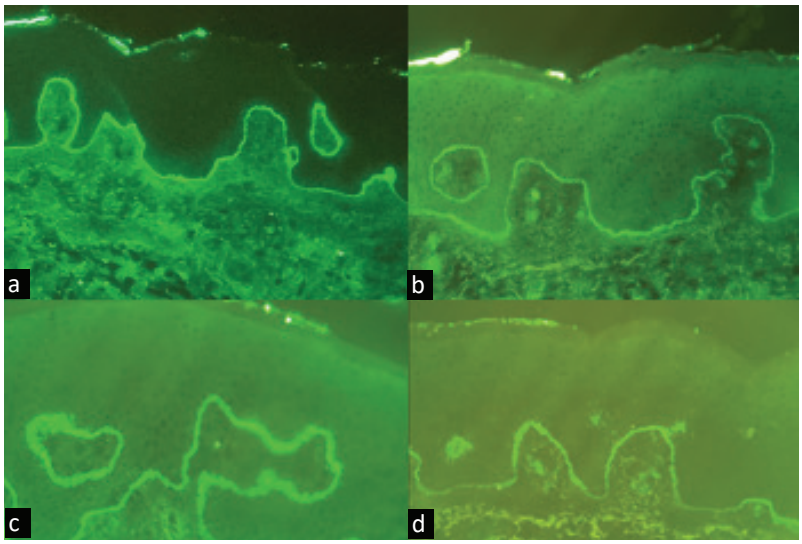

Figure 3. (Clockwise from top right): Direct immunofluorescence shows (a). Strong linear deposits of IgG on the basement membrane zone (BMZ). (b). Granular deposits of C3. (c). Positive linear deposits for IgA. (d). Positive linear deposits for IgM

immunofluorescence was positive for the following: strong linear deposits on the basement membrane zone for IgG, positive granular deposits for C3, positive linear deposits for IgA and positive granular deposits for IgM (Figure 3).

The initial assessment was bullous pemphigoid and because of the increasing incidence of association with DPP-4 inhibitor, management included standard treatment for BP as well as shifting the patient's metformin + linagliptin to pure metformin. Medications are as follows: oral prednisone 20 mg once daily for one week shifted to methylprednisolone 16 mg once daily for another week with slow tapering, and one week of oral doxycycline 100 mg twice daily for one week. Pruritus improved and lesions cleared after one month (Figure 1b). The final assessment was DPP-4 inhibitor-associated BP.

Discussion

Several drugs are associated with bullous pemphigoid. Two types have been documented in literature; the first type is the proper drug-induced type, with a clinical course similar to a typical drug hypersensitivity reaction, while the second type is a drug-triggered or drug-aggravated type, which has a more chronic presentation and resembles classic BP in its course.[1] The group of DPP-4 inhibitors (gliptins), in particular, are documented to have strong correlation with BP onset, inciting the drug-associated or drug-aggravated type of BP.[2] A long latency period has been documented between the intake of DPP-4 inhibitors and onset of lesions, with durations ranging from months to years (up to 48 months in documented cases).[3] DPP-4 inhibitors are incretin-based drugs used to treat diabetes by prolonging glucagon like peptides. The pathophysiology in its contribution to BP has been linked to the drug acting as a hapten triggering autoantibodies against BP180 through epitope spreading.[3] It was found that DPP-4 inhibitor-associated BP had positive serum antibodies for BP180 but negative for the specific antigenic epitope BP180 NC16A. Additionally, 86% of these patients taking DPP-4 inhibitors that presented with non-inflammatory BP were positive for HLA DQB1*0301, suggesting a genetic risk factor as well.[4]

DPP-4 inhibitor-associated BP would present with a non-inflammatory presentation characterized by a more localized distribution, less erythema and smaller blisters.[5] In the case presented, bullae were localized to the right lower leg. For DPP-4 inhibitor-associated BP, serum eosinophilia is less common. ELISA would reveal that serum IgG is positive for BP180, but negative for NC16A. However, histology and DIF findings has been documented less, and most case reports would indicate that the findings are similar to classic BP, and some with fewer eosinophils.[4]

For treatment of DPP-4 inhibitor-associated BP, withdrawal of the DPP-4 inhibitor is recommended however, while majority report a favorable impact and faster remission, few report no difference in outcome as compared to a typical drug induced BP. Standard

treatment protocol was applied in most case reports and the prognosis for future relapse rates are similar to classic BP. This further strengthens the hypothesis that DPP-4 just aggravates and increases the risk the disease but it is not the sole cause. [6] Most were treated with steroids, and some more extensive cases with oral steroids and dapsone. Oral corticosteroids in these cases were given as prednisone 15 mg/day for a mild case and up to 30 mg/day as monotherapy,and in more severe cases, given with dapsone starting at 25 mg/day.[6] Remission was achieved for all cases, some as fast as 1 week but others took several months, and all cases had relapse after a certain number of months.[6] In the case of this patient, remission was achieved after one month however prognosis is similar to the waxing-waning course of classic BP as the patient experienced recurrence of pruritus and few fluid-filled blisters one month after remission.

Conclusion

There has been increasing incidence in DPP-4 inhibitor-associated BP. Though its clinical course is similar to classic BP, a non-inflammatory and more localized presentation would prompt suspicion of association with drug. The long latency in DPP-4 inhibitor and lesion onset suggests that rather than being simply an adverse reaction to treatment, DPP-4 inhibitor-associated BP should be viewed as a drug-associated or drug-aggravated disease.

Determining the association of BP to DPP4-inhibitors is significant as the management for these patients not only entails standard management of BP but also withdrawal of the suspect drug, which in this case was found to significantly improve the patient's lesions after one month. Unlike other drug-induced BP, however, DPP-4 inhibitor associated BP was found to have the same prognosis with classic BP as the patient noted recurrence one month after remission.

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