Case report

Linagliptin-associated bullous pemphigoid treated with rituximab

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SUMMARY

Dipeptidyl peptidase 4 (DPP-4) inhibitors are increasingly used these days in management of diabetes. There has been reported in a few case reports of increasing association between DPP-4 inhibitor use and bullous pemphigoid (BP). We report a case of association between linagliptin use and BP and subsequent treatment with rituximab.

BACKGROUND

Pemphigoid disorders are an uncommon, chronic, autoimmune, subepithelial, blistering disease that occurs more frequently among older adults and are characterised by the presence of inflammatory, blistering, and/or erosive mucocutaneous lesions.¹ They include a heterogeneous group of diseases such as bullous pemphigoid (BP) and mucous membrane pemphigoid. Immunohistopathologically, it is characterised by subepithelial cleavage and deposit of linear IgG and/or complement C3 deposits at the epidermal basement membrane zone.¹

BP is characterised by a humoral and cellular response from autoantibody development to two well-characterised hemidesmosomal proteins of the basement membrane necessary for dermoepidermal junction. BPAG1 or BP antigen 230 (BP230) is a cytoplasmic protein of the plakin family. The BPAG2 or BP antigen 180 (BP180) is a type XVII transmembrane protein with a large extracellular domain that is usually targeted by the autoantibody. Patients with BP typically present with a pruritic bullous eruption on the trunk and limbs.²

In contrast, pemphigus disorders have flaccid bullae resulting from autoantibodies to cell surface proteins within the epithelium of keratinocyte such as the transmembrane glycoproteins desmoglein 1 and desmoglein 3.³ BP has an incidence of 4–22 in a million individuals per year with an increasing incidence. It primarily affects adults aged over 60 years.⁴ Proposed causes include genetics, infection and drugs.^{5–7} There has been increasing support for the association between dipeptidyl peptidase 4 (DPP-4) inhibitors and BP, especially use of vildagliptin and linagliptin but not sitagliptin.⁸

CASE PRESENTATION

A 73-year-old Caucasian man with diabetes mellitus presented to the clinic with crusty, pruritic, erythematous macules on his extremities, and no mucosal involvement noticed. His other medical problems included ischaemic heart disease, cardiomyopathy,

coronary artery bypass graft, implantable cardioverter defibrillator placement, atrial fibrillation, chronic kidney disease, dyslipidaemia and hypothyroidism. His medications included atorvastatin, carvedilol, dofetilide, furosemide, levothyroxine, lisinopril, linagliptin, metformin, glipizide, multivitamin (over-the-counter (OTC)), naproxen, omega-3 fatty acid and rivaroxaban. He had been started on linagliptin approximately 56 months earlier. Histopathological examination of the skin biopsy showed subepidermal blisters with dermal eosinophils ([figure 1](#)), and direct immunofluorescence of the perilesional skin showed linear C3 deposits in the dermal-epidermal junction ([figure 2](#)), confirming BP lesions. There was absence of IgG/IgA/IgM. He was managed with topical application of corticosteroid clobetasol propionate 0.05% twice a day. He was in remission until 9 months later when he presented back to the dermatology clinic with a 2-week history of worsening pruritic lesions and BP flare. Physical examination revealed several red indurated plaques, papules and brown well-circumscribed macules prominent on his upper extremities, back and thighs along with hypopigmented patches over his lower legs. Tense bullae were present on the medial upper arms. No oral aphthae or erosions of scalp or symblepharon noticed. He was treated with oral prednisone 40 mg/day and minocycline 100 mg two times per day along with continuing topical steroids clobetasol 0.05% twice a day. Furosemide (started 32 months back) was initially suspected to be associated with BP and was switched to torsemide.

After 2 weeks of treatment, his BP continued to flare with intense pruritus and more plaques and bullae. The patient's BP180 level through ELISA was elevated at 15.6 (reference range <9) and BP230 level through ELISA was higher at 56.6 (reference range <9). The patient was treated with weekly rituximab therapy for 4 weeks along with prednisone. His BP180 and BP230 improved to 10.48 and 36.28, respectively. He had a 2-week drug holiday. He was treated with a second cycle of rituximab along with prednisone 40 mg/day. BP180 and BP230 improved further to 9.68 and 31.72, respectively.

OUTCOME AND FOLLOW-UP

After 2 weeks of completing the second cycle of rituximab, the patient started noticing recurrence of BP rashes in the axilla and knees. He was started on a third cycle of weekly rituximab along with prednisone 40 mg/day and azathioprine 100 mg/

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Figure 1 Subepidermal blister formation with an inflammatory cell infiltrate containing eosinophils (H&E staining).

day. It was recognised that his linagliptin (Tradjenta) could be associated, so it was stopped at that time. The patient finished 4 weekly rituximab treatments, and his BP rashes have improved with no recurrence of new rashes. He continues on 20 mg prednisone and azathioprine 100 mg/day dosage. His BP continues to be in remission, and his BP180 and BP230 serology also show improvement at 8 (reference range <9) and 23 (reference range <9), respectively.

DISCUSSION

There is little data on DPP-4 inhibitor use or on its long-term (more than 3 years) safety, complications and mortality data. Also, dipeptidyl peptidase substrates are ubiquitous in our body, and residual cross-over with other substrates of DPP-4, particularly with respect to immune function, remains a concern, although this has not been reported in short-term clinical trials. A likely explanation is the cross-reactivity of auto antibodies targeted against the drug. DPP-4 inhibitors have previously been reported to be associated with immune diseases such as nasopharyngitis, inflammatory bowel disease, pancreatitis, hepatitis, myalgia and hypersensitivity skin reactions such as anaphylaxis, angioedema and Steven Johnson syndrome.^{9–14}

Multiple drugs have been associated with BP including antibiotics, captopril, enalapril, hydrochlorothiazide, and ibuprofen, although the strength of these associations is unclear.⁷ More

recently, further associations have been evident among DPP-4 inhibitor use and BP.^{8 15–23} One case-control study published in 2018 of 82 diabetic patients with BP and 328 age-matched and sex-matched controls with diabetes without BP showed stronger association between DPP-4 inhibitors and BP. Vildagliptin and linagliptin showed stronger association than sitagliptin. Discontinuing DPP-4 inhibitors had better outcomes in those patients than standard therapies.⁸

In our case, the patient's home medication included atorvastatin, carvedilol, dofetilide, lisinopril, linagliptin, metformin, glipizide, multivitamin (OTC), naproxen, omega-3 fatty acids and rivaroxaban. The chronological order of starting medication was as follows: tikosyn, 24 months before presentation; furosemide, 32 months before presentation; linagliptin, 56 months; rivaroxaban, 5 years; glipizide, 6.5 years; and metformin and rest of medications, started more than 10 years back. Furosemide was stopped with no response. Tikosyn was not reported to cause BP in previous case reports. The closest possibility would be linagliptin. There is a chance that other medications could have caused the BP, but they were not previously reported to cause BP. Another possibility is idiopathic BP, but it is hard to establish a causal relationship at this point. There is no confirmatory test for drug-induced side effects/complications for medication available.

According to previous reports, the period before onset after receiving DPP-4 inhibitors ranges widely from 1 to 36 months.²¹ In our case, the onset of symptom was 56 months. Previous case reports were all treated with either topical steroids or prednisone, and none with intravenous rituximab.^{19–23}

Our patient had remission of BP for 9 months with topical corticosteroids, being on linagliptin until he relapsed. Subsequent treatment of relapses with oral steroids and then two cycles of rituximab of 4 weeks each while on linagliptin were met with temporary remission and relapses. Intravenous immunoglobulins and rituximab are treatments reserved for refractory cases of BP.

Direct immunofluorescence remains the gold standard in diagnosing BP.²⁴ ELISA for BP180 is positive in 80%–90% of BP, and BP230 is positive in approximately 60%–70% of affected patients. BP180 and BP230 are used to strengthen the diagnosis of BP.^{6 25} Also, BP180 levels correlate with disease activity, and many clinicians use it not only to diagnose BP but also to follow disease activity.²⁶

The direct immunofluorescence findings, along with BP180 and BP230 levels, in linagliptin-associated BP remain consistent with conventional BP. Our patient had a good response with a drop in BP180 and BP230 levels with each cycle of rituximab therapy.

The pathogenesis of DPP-4 inhibitors is not well understood. DPP-4 is expressed in many organs including several cell types in the skin such as keratinocytes, fibroblast and T-cells. DPP-4 activation modulates the production of eotaxin, which impacts the recruitment of eosinophils implicated in bullae formation.²⁷ A decrease in transforming growth factor beta 1 and procollagen has also been associated with DPP-4 activity.²⁸ Furthermore, DPP-4 acts as a cell-surface plasminogen receptor that facilitates the production of plasmin from plasminogen. Plasmin is a serine protease involved in cleavage of the extracellular domain of BP180.²⁹

This, along with previous case reports with similar use with linagliptin and other DPP-4 inhibitors, suggests the association between linagliptin and BP. Further work needs to be done with clinical surveillance and studies to understand this association.

Figure 2 Direct immunofluorescence showed basement membrane zone deposition of IgG.

Learning points

- ▶ Dipeptidyl peptidase 4 (DPP-4) inhibitors, especially linagliptin, could be a potential cause of bullous pemphigoid (BP).
- ▶ ELISA BP180 and BP230 could be used to diagnose and follow disease activity in linagliptin-induced BP.
- ▶ Clinicians should caution patients about potential symptoms to watch for BP and discontinue medication if diagnosed.
- ▶ More studies are needed to prove causal association between DPP-4 and BP.

Contributors All authors contributed equally to the care of the patient and writing of the report. HM performed the initial evaluation of the patient. PS and AAO were consulted and evaluated the patient for additional diagnosis and treatment. HM, PS and AAO were responsible for the conception and design of the case report, acquisition of data and interpretation of patient data and outcomes. HM drafted the initial report. PS and AAO critically evaluated and revised the report. All authors approved the final version.

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