

Vildagliptin-induced bullous pemphigoid

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In New Zealand, vildagliptin became fully subsidised by PHARMAC on 1 October 2018. Bullous pemphigoid is an autoimmune blistering disorder that typically affects the elderly. Dipeptidyl peptidase-four inhibitors (DPP4is, or gliptins) are a cause of drug-induced bullous pemphigoid.

Case presentation

A 69-year-old Caucasian man with type two diabetes mellitus (T2DM) and no known dermatological conditions presented with a one-month-old, widespread pruritic blistering rash. This rash developed nine months after the addition of vildagliptin to his diabetic medication regimen. The Naranjo algorithm score of causality was five, indicating a 'probable' adverse drug reaction.

There were widespread crusted erosions with scattered tense bullae over the scalp, trunk and limbs, and mucosal erosion on the lower lip (Figures 1 and 2). The diagnosis of bullous pemphigoid was confirmed by histology, which showed a subepidermal split with increased numbers of dermal eosinophils and positive anti-basement membrane antibody of 1:1280 titre. Direct immunofluorescence staining was not possible. Vildagliptin was ceased and oral doxycycline (200mg daily) initiated.¹ Re-epithelialisation on doxycycline monotherapy progressed slowly, therefore oral prednisone (40mg daily) was added, resulting in rapid re-epithelialisation. Blood glucose levels were monitored closely and managed with metformin and correctional scale insulin while the patient was taking prednisone.

Discussion

Bullous pemphigoid is an autoimmune condition. Autoantibodies target hemidesmosomes in basal keratinocytes, causing loss of adhesion between the epidermis and dermis.² It is characterised by localised or generalised bullae with preceding and/or

accompanying pruritus. Bullous pemphigoid is most commonly observed in the seventh to ninth decade of life and is associated with neurological diseases, including cerebrovascular accidents.³ The mainstay of treatment is steroid therapy. However, high-dose systemic corticosteroid treatment (prednisolone equivalent >40mg daily) is associated with significantly higher mortality during the first year.⁴ A randomised controlled trial comparing the efficacy and safety profile of doxycycline and oral prednisolone concluded non-inferiority of high-dose doxycycline (200mg oral daily) as a first-line treatment for bullous pemphigoid.¹

Figure 1: Bullous pemphigoid on the back, consisting of vesicles, erosions from ruptured bullae and an erythematous urticated rash.



Figure 2: Mucosal involvement.

DPP4is have become a popular second-line treatment in T2DM as they do not cause weight gain and have a lower adverse effect profile than sulphonylureas. However, in the last decade an increasing number of case reports and epidemiological studies have been published suggesting there is a relationship between bullous pemphigoid and DPP4is.⁵⁻⁷ The latency time between the initiation of DPP4is and onset of bullous pemphigoid ranges from 1 to 37 months in case reports.^{5,6} The association between bullous pemphigoid and DPP4is was first described in 2011.⁸ There are several hypotheses about the pathogenesis of DPP4i-induced bullous pemphigoid, but the

exact mechanism remains unknown.³ Five cases of bullous pemphigoid in patients who had been on dual metformin and DPP4i therapy for 2 to 13 months prior to disease onset were described, and two cases were resistant to immunosuppressive therapy but later achieved stable remission upon cessation of DPP4is.⁸ A meta-analysis of case-control studies further supported this association and found that vildagliptin had a higher degree of association with bullous pemphigoid compared to sitagliptin and linagliptin.⁹ The other available oral hypoglycaemic agents available in New Zealand do not cause blistering as a common adverse effect.

In New Zealand, vildagliptin became fully subsidised by PHARMAC on 1 October 2018. Before then, no cases of DPP4i-associated bullous pemphigoid had been reported to the Centre for Adverse Reactions Monitoring (CARM). Eight cases were reported between October 2018 and September 2020.¹⁰ There were six females, and the average age was 75 years (standard deviation \pm 10 years). The Australian Database of Adverse Event Notifications has recorded three cases of suspected vildagliptin-related pemphigoid. This increased incidence reflects the wider use of vildagliptin in the community since subsidisation. Bullous pemphigoid should be suspected in a patient on vildagliptin who develops an inflammatory rash with blisters.

Competing interests:

Nil.

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