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CASE REPORT

Alogliptin-induced bullous pemphigoid

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Introduction

A 70-year-old Caucasian woman presented to the accident and emergency department with a 3-day history of sudden onset intensely pruritic erythematous eruption with widespread blister formation all over her body. The patient had recently been switched from sitagliptin to alogliptin by her GP as a result of her poor glycaemic control. Skin biopsy showed bullous pemphigoid, clinically thought likely to be caused by alogliptin. Withdrawal of alogliptin and treatment with oral prednisolone, doxycycline and antihistamines resolved her rash. She was discharged on a tapering dose of oral prednisolone and an increased dose of metformin. The onset of bullous pemphigoid is a potential side effect of all dipeptidyl peptidase-4 (DPP-4) inhibitors. Clinicians should be aware of the possibility of DPP-4 inhibitor-induced bullous pemphigoid in patients who are switched from one member of this drug class to another, even if there was no reaction with prolonged use of a previous DPP-4 inhibitor.

Case report

A 70-year-old woman with a history of type 2 diabetes mellitus, which had been treated with metformin and sitagliptin for about a decade, had been switched from sitagliptin to alogliptin 6 weeks earlier by her GP to improve her glycaemic control. She presented to the accident and emergency department with an intensely painful and itchy rash, and tense blisters all over her body, predominantly on her trunk, but with no involvement of her mouth. Examination of her skin showed tense blisters of varying shapes and sizes surrounded by patches of denuded skin and erythema (Figures 1 and 2).

Her systemic examination was otherwise unremarkable. Her chest X-ray showed no abnormalities and her blood counts were within normal limits with white blood cell count 7.28×10^9/litre (normal range 4–11×10^9/litre), neutrophils 4.57×10^9/litre (normal range 1.7–6.1×10^9/litre) and eosinophils 0.42×10^9/litre (normal up to 0.4×10^9/litre). Her urine/albumin creatinine ratio was below the level of detection. The dermatology team was consulted, and skin biopsy was performed. Standard light microscopy showed a subepidermal vesicle. Immunofluorescence microscopy of the skin biopsy sample showed complement-mediated, C3 linear basement deposits, confirming the diagnosis of bullous pemphigoid (Figures 3 and 4).

The clinical presentation, and histopathology with direct immunofluorescence, suggested bullous pemphigoid, likely as a result of alogliptin. Withdrawal of alogliptin and treatment with oral prednisolone, doxycycline and antihistamine resolved her skin eruption. The patient was discharged home with a tapering dose of prednisolone and an increased dose of metformin. The need for pain control and antihistamine before her discharge was minimal.

Discussion

Bullous pemphigoid is the most commonly occurring autoimmune skin condition, especially in the elderly population. Lever (1953) first described it as subepidermal bullous formation disease (Douros et al, 2019). The annual incidence of bullous pemphigoid in the UK is 42.8 cases per million population (Hübner et al, 2016). Drug-induced bullous pemphigoid is reported more commonly in the elderly population, notably linked to dipeptidyl peptidase-4 (DPP-4) inhibitors (Liu, 2003; Kridin and Bergman, 2018).

Alogliptin is an oral antidiabetic drug in the DPP-4 inhibitor class. Alogliptin inhibits DPP-4 and increases the amount of active plasma incretins which helps with glycaemic control. The National Institute for Health and Care Excellence (2014) recommends considering adding a DPP-4 inhibitor as second-line therapy to first-line metformin when control of blood glucose remains or becomes inadequate. Bullous pemphigoid is not a listed side effect of the drug. Béné et al (2016) analysed the French Pharmacovigilance Database for reports of spontaneous adverse drug reactions between April 2008 and August 2014, and found that 1297 patients were exposed to DPP-4 inhibitor class and

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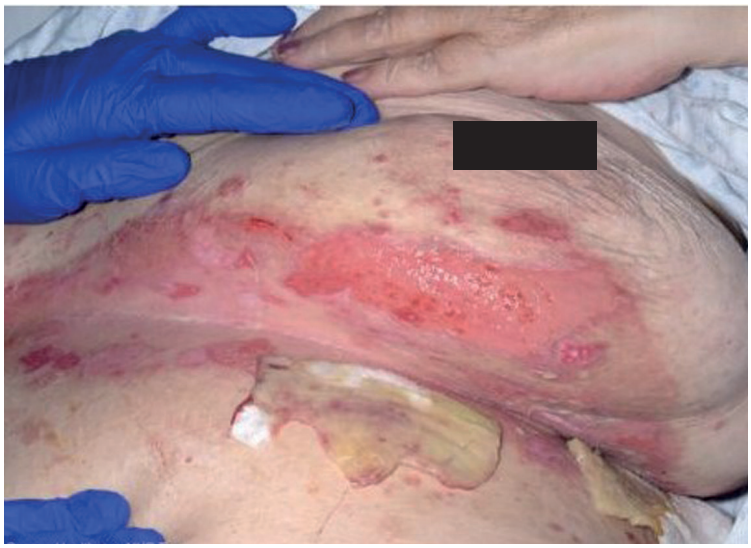

Figure 1. Blisters of varying shapes and sizes surrounded by patches of denuded skin and erythema on the patient's upper abdomen and both breasts.

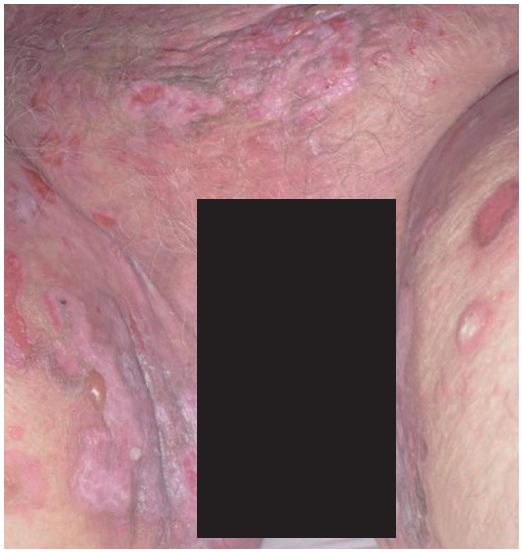

Figure 2. Florid bullous pemphigoid erythematous rash with blisters affecting the patient's lower abdomen, thighs, groin and genitals.

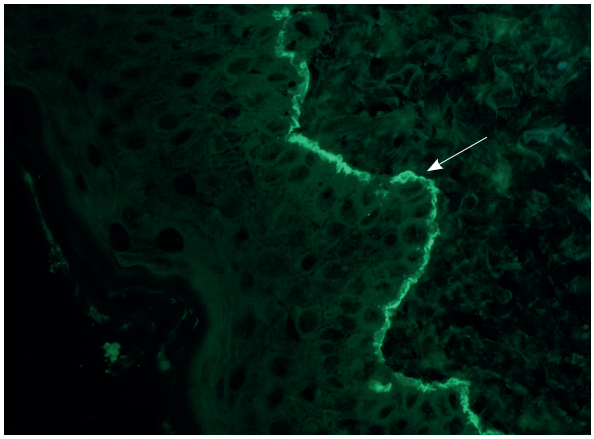

Figure 3. Immunofluorescence with linear complement-mediated C3 (C3-HP×200) deposition in the subepidermal basement membrane (arrow), characteristic of bullous pemphigoid.

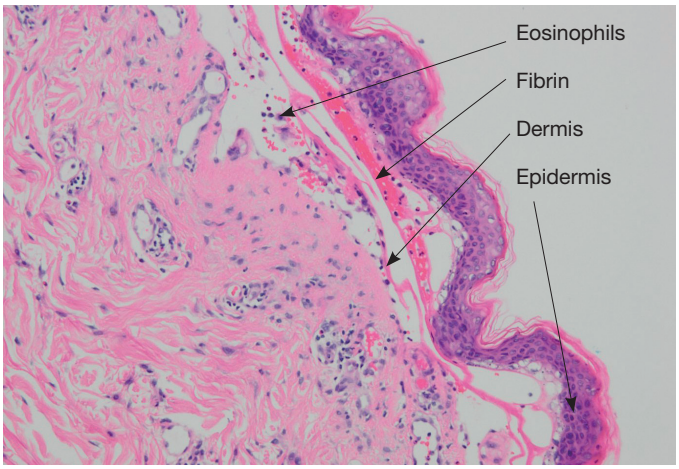

Figure 4. Skin biopsy (haematoxylin and eosin×100) showing a subepidermal vesicle with fibrin and eosinophils between the epidermis and dermis, characteristic of bullous pemphigoid.

42 developed bullous pemphigoid, most commonly caused vildagliptin, saxagliptin or sitagliptin. Vildagliptin-induced bullous pemphigoid was reported by Skandalis et al (2012), who suggested the possibility of a general association of all gliptins with the development of bullous pemphigoid as a drug-induced reaction. The patient in the present case report had been taking sitagliptin (also a DPP-4 inhibitor) for about a decade with no adverse reactions. She developed bullous pemphigoid within 6 weeks of switching to alogliptin, another member of the same class. To the best of the authors' knowledge this is the first reported case of bullous pemphigoid developed upon initiation of a DPP-4 inhibitor in a patient who had a history of prolonged use of another DPP-4 inhibitor before the switch.

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Learning points

- The induction of bullous pemphigoid can be a potential side effect of all dipeptidyl peptidase-4 (DPP-4) inhibitors.
- Clinicians should not exclude the possibility of DPP-4 inhibitor-induced bullous pemphigoid in patients who are switched from one member of the drug class to another, even if there was no reaction with prolonged use of the former one.
- Patients should be educated about the possibility of bullous pemphigoid with DPP-4 inhibitors in order to identify and treat any cases in a timely fashion.

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