The older patient presenting with itch and a recent medication change

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CASES
Mr D (aged 73 years) and Mr H (aged 82 years) both presented to the clinic with a history of widespread itch with blisters (bullae). Mr D had an eight-month history of multiple tense bullae over his trunk with mucosal ulceration, while Mr H had a three-month history of widespread tense, haemorrhagic blisters on his limbs and trunk, without mucosal involvement. Figures 1 and 2 demonstrate tense bullae.

Both patients had extensive medical history, including hypertension, peripheral vascular disease, ischaemic heart disease and type 2 diabetes. Both had commenced linagliptin in the past year – Mr D nine months prior, and Mr H three months prior. Both patients had no change in other medications or household cleaning or skin products.

QUESTION 1
What is the most likely diagnosis and how is medication history relevant?

QUESTION 2
What investigations would you perform?

ANSWER 1
The most likely diagnosis is drug-induced bullous pemphigoid (DIBP).

Bullous pemphigoid is the most common autoimmune blistering disease in elderly people, with an annual incidence of 2.4–23 cases per million.1 The condition is associated with increased mortality and an immune reaction against two known antigens (BP180/BP230), which results in C3 and immunoglobulin G (IgG) deposition in the subepidermal junction.1 While the defining feature is itch, the clinical presentation ranges from tense bullae, with infrequent involvement of mucosal surfaces,1 to pruritus with complete absence of lesions (20% of patients).2 Bullous pemphigoid also occurs secondary to a number of medications; however, the pathogenesis is not completely elucidated.3 Since 2011, case reports have implicated dipeptidyl peptidase-4 (DPP-4) inhibitors in DIBP, and recent observational studies have confirmed increased risk.4–6 In Australia, five DPP-4 inhibitors are currently available on the Pharmaceutical Benefits Scheme: alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin.7 Time from commencement of DPP-4 inhibitor to disease onset ranges considerably (10 days to three years), with a median of 8.2 months.1–4

ANSWER 2
The investigation of choice is a 3–4 mm punch biopsy. In suspected bullous pemphigoid, two biopsies should be taken: one from the edge of an intact blister (half blister, half surrounding skin) for histology staining (haemotoxylin and eosin [H&E]), the other from uninvolved perilesional skin (within 1 cm of a bulla) for direct immunofluorescence (DIF).8 It is important to note that while there are suggestive features on investigation, no single test can differentiate bullous pemphigoid from DIBP; rather, the medication history should draw suspicion of the latter.

Other investigations include a full blood examination (eosinophilia may be present).

CASE CONTINUED
In both cases, biopsies showed subepidermal blisters with medium-density scattered eosinophils and lymphocytes in the upper dermis when stained with H&E (Figure 3), and linear IgG and C3 deposition at the epidermal basement membrane on DIF, consistent with a diagnosis of bullous pemphigoid.8 Linagliptin was ceased immediately in both cases, with commencement of doxycycline 100 mg daily and betamethasone dipropionate 0.05% ointment three times per day to affected skin. In both patients, major disease activity diminished within two weeks of linagliptin cessation.

QUESTION 3
Is ceasing the causative medication enough? What antidiabetic agents can be used in place of linagliptin?

QUESTION 4
How common is DPP-4 inhibitor–induced bullous pemphigoid? What other medications are associated?

ANSWER 3
There are two recognised patterns of DIBP: 1) the condition resolves with
medication discontinuation, and 2) the condition persists despite cessation (drug-triggered bullous pemphigoid). While the most important action is cessation of the culprit medication, patients with severe or refractory presentations may require treatment. For limited disease, first-line therapy includes potent topical corticosteroids (betamethasone dipropionate 0.05%). Second-line treatments are frequently combined and include steroid-sparing and anti-inflammatory agents such as doxycycline or minomycin, with nicotinamide (vitamin B3), or other immunosuppressants such as mycophenolate mofetil or methotrexate. Patients should be regularly reviewed until new blisters cease forming, and doses can be slowly tapered. In severe cases, oral corticosteroids may be required; however, these should be used cautiously as they are associated with significantly more severe adverse outcomes (when compared with doxycycline) and may destabilise glycaemic control. High-risk presentations such as systemically unwell patients with mucosal involvement or extensive, generalised blistering should be referred for review by dermatology.

While more confirmatory evidence is needed, the largest case-control study to date (n = 3397) in a Finnish population found no increased risk of DIBP with sulfonylureas, sodium–glucose co-transporter 2 inhibitors, glucagon-like peptide 1 analogues, thiazolidinediones (or glitazones), heterocyclic sulfonamides or α-glucosidase inhibitors, suggesting they may be safe alternatives.

ANSWER 4

Over the past two decades, bullous pemphigoid incidence has increased between 1.9 and 4.3-fold, which is attributable to increasing life expectancy, greater predisposing neurological disease and/or increasing use of culprit medications. More than 50 medications have been implicated. These include many commonly prescribed medications – DPP-4 inhibitors, antibiotics (eg penicillins), nonsteroidal anti-inflammatory agents, diuretics, anti-hypertensive medications, anti-arrhythmic medications, disease-modifying antirheumatic medications, salicylates and anti-tumour necrosis factor alpha (TNF-α) agents.

DPP-4 inhibitors have been significantly associated with DIBP, with an overall adjusted odds ratio (OR) of 2.19–3.16. Of all DPP-4 inhibitors, vildagliptin shows the strongest association (OR 3.57–10.67), possibly due to its relatively lower selectivity, resulting in greater inhibition of other isozymes. The newer DPP-4 inhibitor linagliptin, responsible in the present cases, has not been as well studied but was recently found to have a stronger association (OR 6.65) than that of the overall DPP-4 inhibitor class (OR 3.16), suggesting it may be a more potent class member in causation.

Figure 1. Tense bullae on the dorsum of the hand
Figure 2. Bullae and surrounding erythema on the volar aspect of the wrist
Figure 3. Haemotoxylin and eosin stain of 3 mm punch biopsy of skin down to the level of the subcutis taken from a truncal lesion of Mr D
Key points
• Bullous pemphigoid causes significant morbidity and mortality and is associated with a growing number of common medications including DPP-4 inhibitors, which are increasingly used in treating diabetes for their anti-inflammatory effects and suitability in renal failure.
• Among DPP-4 inhibitors, vildagliptin is most strongly associated with DIBP.
• As bullous pemphigoid can present without overt blistering (20% of patients), the diagnosis should be considered in any patients with new-onset pruritus and any medication changes.
• While commencement of topical corticosteroids is standard treatment, DPP-4 inhibitors must be ceased immediately for patients with suspected DIBP, and the reaction well documented and explained to patients.

Resources
• Australian Medicines Handbook Online, https://amhonline.amh.net.au
• MIMS Online, www.mimsonline.com.au
• Litt’s Drug Eruption & Reaction Database, www.drugeruptiondata.com
• Pharmacovigilance teams within the sponsoring pharmaceutical company can also be contacted by medical professionals to report adverse events and request further information.

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Competing interests: None.
Funding: None.
Provenance and peer review: Not commissioned, externally peer reviewed.

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