MMJ

Malta Medical Journal, 33 (1): Pages (2021)
http://mmsjournals.org/index.php/mmj

CASE REPORT

Dipeptidyl Peptidase-4 Inhibitor-Associated Bullous Pemphigoid in Malta: A case report and clinical series

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Bullous pemphigoid (BP) is an autoimmune blistering disease associated with a number of predisposing factors including age, neurological disease, diabetes mellitus and drugs. Over the past few years, dipeptidyl peptidase-4 inhibitors (DPP4-Is), referred to as gliptins, have been increasingly associated with the development of this blistering disease.

Locally, since the introduction of gliptins into the national formulary, we have noted a surge in the number of cases of presumed gliptin-induced BP. We present a local case report, followed by a short case series which highlights the typical characteristics of patients with gliptin-induced BP and shows the surge in the number of local cases.

Patients with drug-induced BP, as opposed to conventional BP, tend to respond quicker upon cessation of the culprit drug. Therefore physicians should be aware of this association and have a low threshold for investigating diabetics who present with unexplained pruritus, erythema and bullae, especially if these patients are on DPP4-Is.

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Introduction

Bullous pemphigoid (BP) is a sub-epidermal blistering skin disease mediated by autoantibodies to hemidesmosome proteins BP180 and BP230, which are crucial for stable adhesions between the epidermis and dermis.[1]

Risk factors associated with this disease include age, neurologic disease, diabetes mellitus and various drugs. Over 60 different drugs have been associated with BP in the literature. However, in a recent systematic review only aldosterone antagonists, dopaminergic drugs, anticholinergics and dipeptidyl peptidase-4 inhibitors (DPP4-Is), have been shown to be statistically associated with BP.[2]

DPP4-Is, widely referred to as gliptins, are oral hypoglycaemic agents used in type 2 diabetes. They were first introduced into the market in 2006 and since then there has been evidence to suggest an association between the use of DPP4-Is and development of BP.[1,3]

We report a case of an elderly diabetic man with presumed gliptin-induced BP. Moreover, we report a surge in the number of cases of BP in diabetic patients at our outpatient clinic a few months following the introduction of DDP4-Is into the national formulary.

Case Presentation

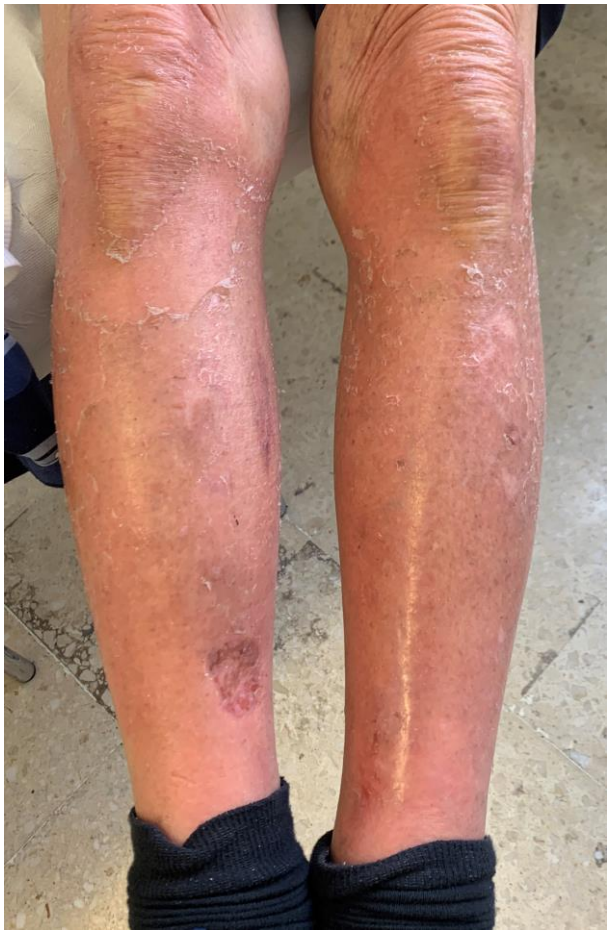
An 85-year old male presented with a one-month history of large, pruritic, tense bullae on the lower aspect of both legs. The patient's medical history included type 2 diabetes, hypertension and ischaemic heart disease, for which he was on a number of drugs which included vildagliptin, metformin, gliclazide, perindopril, aspirin, simvastatin, isosorbide dinitrate and omeprazole. Amlodipine had been stopped a few weeks prior to presentation in view of worsening of lower limb oedema.

On examination, oedematous legs with bullae and some excoriation marks were visible. Initially the differential diagnosis included bullae associated with lower limb oedema, bullous diabeticorum and bullous pemphigoid. The former diagnosis was favoured at the outset in view of the incidental worsening of the lower limb oedema and the fact that the bullae only affected the legs. Thus the patient was commenced on a loop diuretic.

A few days later the patient re-presented to clinic, this time having new bullae on the forearms. A punch biopsy was taken from the forearm and this revealed a subepidermal blister. Direct immunofluorescence showed linear deposits of IgG and C3 in the basement membrane zone which was consistent with a diagnosis of BP. He was treated with clobetasol propionate ointment applied onto the blisters, nicotinamide 500mg t.i.d and doxycycline 500mg b.i.d. The bullae initially healed without formation of new blisters but the patient complained of persistent pruritus. Eight months from the initial presentation, the patient presented urgently to clinic complaining of worsening pruritus, erythema and desquamation (Figure 1). After ensuring compliance to current treatment of BP a review of other possible triggers was done. Of note, the patient was on vildagliptin for diabetes which was the most recent drug added to his list. This had been started two years prior to this presentation. Keeping in mind the association of BP with DPP4-Is, vildagliptin was omitted following liaison with his diabetologist for alternative management. In the meantime, topical clobetasol propionate ointment was continued. There was complete resolution of his symptoms within three months from discontinuing vildagliptin,

suggesting a final diagnosis of BP that was triggered by DPP4-I use.

Figure 1 Legs showing erythema and desquamation



Discussion

Drug-induced BP very often has the same clinical and histological features as classical BP. In its established form patients typically present with pruritus and formation of bullae. However, in the pre-bullous phase, the clinical picture of BP may be misleading and may only include pruritus with possibly vague erythematous and urticated areas. In drug-induced BP patients very often respond well after the drug is stopped and have little or no relapses while patients with classical BP tend to have a more chronic course and very often require long term systemic therapy. Nevertheless, a small cohort of patients with drug-induced Bullous Pemphigoid who initially respond to stopping the culprit drug later on develop classical BP.

Our patient had many risk factors for BP including age, DM and was taking a statin, ACE-I and DPP4-I, all of which have been associated. Initially he was thought to have classic BP. However, as the patient complained of persistent pruritus and worsening erythema despite systemic therapy, a thorough review of his drug history confirmed that the most

recently added medication was Vildagliptin prompting us to a possible association.

In classical BP, autoantibodies typically target specific portions of the hemidesmosomal proteins of the basement membrane, BP180 and BP230, which are normally crucial for maintaining adhesion between the epidermis and dermis. In 85% of cases these antibodies target the non-collagenous region 16A (NC16A) of BP180 (collagen XVII). Antibodies to BP230 are also found but to a lesser extent.[4]

In drug-induced BP, the antibody target is similarly BP180 but the portion targeted may be different.[4] In DPP4I-associated BP, the gliptin is thought to alter the antigenicity of BP180 making it more amenable to attack by antibodies. In this case they tend to target the mid-portion of BP180 rather than the NC16A domain as in classical BP[5].

DPP4-Is are a relatively new class of drugs which have been introduced into the market in 2006. These drugs are used to treat type 2 diabetes mellitus and act by competitively inhibiting the enzyme DPP4 which is normally found in various organs including the skin. DPP4 normally inactivates glucagon like peptide (GLP-1) and glucose-dependant insulinotropic polypeptide (GIP). DPP4-Is thus prevent inactivation of these incretins thereby increasing insulin levels and inhibiting glucagon production.[6]

The first licensed gliptin was sitagliptin in 2006 and this was followed by vildagliptin, saxagliptin, linagliptin and alogliptin.[7] Since their introduction into the market there have been various case-reports, case-control trials and pharmacovigilance database studies which have confirmed an association between the use of gliptins and the development of BP. Moreover, a systematic review and adjusted meta-analysis by Phan et al. has positively suggested a significant association between DPP4-I use and development of BP. The strongest association was found with vildagliptin while sitagliptin did not seem to be associated with development of BP.[3]

Locally, the DPP4-I vildagliptin was introduced into the national formulary in April 2016. Between 2017 and 2019 we have seen a surge in bullous pemphigoid amongst the diabetic community with a good proportion of these patients taking gliptins. We therefore retrospectively analysed the data of patients presenting to the department of dermatology at Sir Paul Boffa Hospital between 2017 and 2019 with a known diagnosis of gliptin-induced BP (Table 1).

The above findings are similar to the published data on the subject, which confirm that patients developing gliptin-induced BP were more likely to be male and elderly. The latency period between drug initiation and the development of symptoms also appeared to be quite variable in our findings (6-28 months) when compared to various pharmacovigilance reports which report a mean latency period that can vary between 6 to 19 months.[3] Clinical symptoms appeared to resolve in a number of weeks to months, and 13 out of the 15 patients have remained symptom-free. The gliptin associated in all but one of the cases was vildagliptin, which is the only DPP4-I in the government formulary.

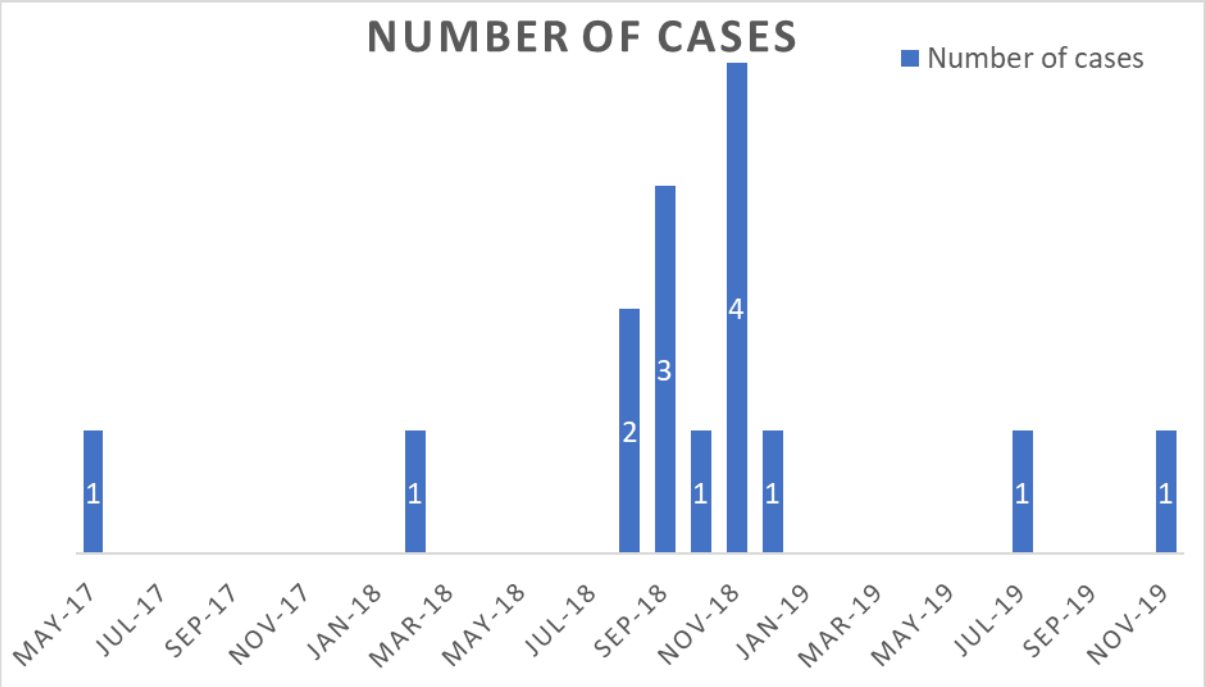
Table 1 Summary of data

Number of Patients	15 (1 patient deceased)
DPP-IV inhibitor	93% Vildagliptin (14/15) 7% Linagliptin (1/15)
Sex (M/F)	60% M (8/15) 40% F (6/15)
Average age (yrs)	76 (59-87)
Latency period before onset of bullous pemphigoid (in months)	Mean 14 months (range: 6-28 months)
Symptoms	Pruritus and bullae13/15 Pruritus without bullae 2/15
Treatment (topical vs oral vs other)	Topical steroids alone: 6/15 Oral agents added: 9/15
Outcome (sustained or not)	Sustained:13/15 Refractory: 2
Gliptin Stopped **Gliptin not stopped**	14/15 0/15

Stopping the drug in conjunction with short term application of topical steroids is usually sufficient to treat DPP4I-associated BP. However, few cases have been reported where, due to a phenomenon referred to as 'epitope spreading' after cessation of the drug and initial improvement, patients may then develop conventional BP.[5] Two of our patients had initially responded to treatment and later started complaining of re-emerging symptoms, possibly due to development of classical BP. These have been started on systemic drugs.

Locally, the numbers of cases of presumed gliptin-induced BP have been notably high when compared to the current literature.[3] Between 2017-2019 we had 15 patients presenting with this diagnosis with 11 of these patients presenting in the second half of 2018 (Figure 2). These findings could be explained by the initiation of gliptins in a large cohort of diabetic patients once introduced into the formulary in 2016. The surge in 2018, could be explained by the long latency period and reflects the bulk of patients that were started. Moreover, some patients might have been misdiagnosed as gliptin-induced BP rather than classical BP due to the increasing awareness of this association. Confirmation of drug-induced BP can only be done upon re-challenge of the drug, which is not ethically correct.

Figure 2 Bar graph showing the number of new cases presenting with a diagnosis of gliptin-induced bullous pemphigoid between May 2017 and November 2019.



Conclusion

This case highlights the importance of keeping drugs in mind as potential culprits for skin disease. Many drugs may have a long latency period, so a thorough drug history including the time when the drugs were started is relevant. Physicians should be aware of the association between BP and DPP4-I and have a low threshold for investigating patients on gliptins who present with non-specific pruritus with or without the presence of bullae.

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