Dipeptidyl-Peptidase 4 Inhibitor-Induced Variants of Bullous Pemphigoid: A Case Series of Four Patients

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Abstract
Bullous pemphigoid is the most common acquired bullous disease with an autoimmune basis and a tendency to involve mostly old people. By rising incidence of diabetes all over the world, consumption of antidiabetes medications has also increased. One of the most used antidiabetes drugs is gliptin family (dipeptidyl-peptidase 4 inhibitor). Recently, this class of oral antidiabetic agents showed a correlation with the occurrence of bullous pemphigoid and its subtypes, including mucous membrane pemphigoid and pemphigoid nodularis. We are reporting a case series of 4 diabetes patients that we diagnosed with bullous pemphigoid subtypes (mucous membrane pemphigoid, pemphigoid nodularis, and its rarest subtype, linear IgA bullous dermatosis) after taking different drugs of gliptin family.

Introduction
Bullous pemphigoid (BP) is the most common acquired autoantibody blistering disease that is idiopathic and has shown a great tendency to develop in older adults [1–4]. The characteristic of the disease is that it mainly affects the trunk and the extremities, which can appear as several pruritic tense bullae and erythematous plaque [5]. The increasing number of BP cases is shown to be related to the increasing rate of senility, stimulated by different drugs like antibiotics and antidiabetic agents, and the ability of better diagnosis as a result of
more attention paid to rare types of disease [1, 6]. From an immunological viewpoint, the disease is specified by circulating autoantibodies against hemidesmosomal proteins at the dermal-epidermal junction (DEJ), known as BP180 and BP230 [7, 8].

Recent studies have revealed that the new class of oral antidiabetic agents named dipeptidyl-peptidase 4 inhibitor (DPP-4 inhibitor) or gliptins play a significant role in increasing the risk of BP [9–11]. However, slight differences have been reported between typical BP and DPP-4-induced BP. For instance, the involvement of the mucous membrane, noninflammatory lesions, non-erythematous erosions, and decreased eosinophil infiltration in bullae are mainly seen in DPP-4-induced BP. The other significant difference is related to epitope involvements; in typical BP, NC16A domain is commonly involved, while other epitopes of BP180 take part in pathogenesis of DPP-4-induced BP [6, 12].

The first case report of the association between gliptins and the occurrence of BP was diagnosed in 2011 by Skandalis et al. [13]. Recently, few articles have been published about the impact of DPP-4 inhibitors on rare variants of BP such as mucous membrane pemphigoid (MMP, cicatricial pemphigoid) and pemphigoid nodularis [12, 14, 15]. This case series aimed to report a possible association of rare forms of BP: MMP, pemphigoid nodularis, and linear IgA bullous dermatosis (LABD), with gliptins use. In our knowledge, there are no previous reports of such associations.

Case Presentation

Case 1

A 58-year-old woman with a previous history of diabetes, hypertension, and ischemic heart disease was referred to the clinic with complaints of severe generalized pruritus and blisters, which had started 2 months prior to her visit. She also had poorly controlled diabetes mellitus, whereas she was taking empagliflozin, gliclazide, and Zipmet (sitagliptin + metformin). So, she was recommended to get hospitalized in the dermatology department for more investigations.

The clinical examination showed multiple scattered vesicles with erythematous nodules and necrotic, ulcerative centers on the trunk and limbs. The involvement of the face and neck was milder and manifested as erythematous patches with excoriation and crusts on the scalp. The mucosal membrane was intact. Initial laboratory tests were normal (including BP180: 4.8) except for BP230: 102. Direct immunofluorescence (DIF) report revealed a linear deposit of IgG and C3 in DEJ, which was concluded as being a pemphigoid group. Histopathological examination revealed mild acanthosis and spongiosis with focal parakeratosis and rare eosinophilic exocytosis. The dermis was infiltrative by quite a significant number of eosinophils. The epidermis was markedly acanthosis, associated with dermis fibrosis. All the features were compatible with pemphigoid nodularis.

Based on the diagnosis, treatment was started. The patient was first prescribed 2 tubes of clobetasol ointment daily, cap doxycycline 100 mg daily, and then mycophenolate mofetil 2 g daily was added. Besides the treatment, oral antidiabetic agents were changed according to consultation with the endocrinologist. Zipmet was omitted, and insulin was added to the diet. After discharge, the lesions improved, and there were no more signs of new lesions.

Case 2

A 58-year-old woman with a known case of DM showed signs of severe pruritus. The problem had begun 6 months prior and was associated with prurigo lesions and PIH all over the trunk and limbs, but there were no signs of involvement in the mucosal membrane, head, and neck.

Histopathological examination revealed that skin tissue had acanthosis, parakeratosis, severe focal excoration, and ulceronecrotic in the epidermis. The papillary dermis showed
inflammatory infiltrate, mainly composed of lymphocytes and neutrophils. DIF showed linear deposition of anti-total immunoglobulin and anti-C3 along the DEJ, both 2+, which was compatible with the pemphigoid groups. The final diagnosis suggested nodular BP (nonbullous) based on the histopathology and DIF.

There were no abnormalities in routine laboratory tests, but BP indicators were high (BP180 200, BP230 200). The patient was under treatment with an oral antidiabetic agent: Zipmet 100 mg daily. After the diagnosis of pemphigoid nodularis was established, the medication was modified to metformin 1,000 mg BD and pioglitazone 30 mg daily. She was also treated with topical agents (ointment clobetasol) 1/2 tube and cap doxycycline 100 mg daily for 2 months. The disease improved, and there were no new involvements except for the PIH of previous lesions.

Case 3
A 59-year-old man with a previous case of diabetes mellitus was referred to the clinic with a history of scattered bullous lesions, which had developed 2 months prior to the visit. The lesions were mostly located in the neck, limbs, trunk, and genitalia. There was no other disease in the previous medical history except for DM, and he had been taking Linagliptin for 4 months. Examination showed small bullae and vesicles on a clean basis without any crust or ulcer. All laboratory findings, including BP180 and BP230, were normal, but mild anemia was seen (Hb: 11.6).

A biopsy was performed, and histopathology revealed a subepidermal bullous reaction with eosinophilic predominance. DIF revealed IgA2+ and IgG 1+ deposition and confirmed the diagnosis of LABD.

Immediately after diagnosis, linagliptin was ceased, and a topical steroid (clobetasol) was started. One month after therapy, the patient went through complete remission, and no sign of the disease has been observed since then.

Case 4
A 64-year-old man was referred to the clinic with complaints of ulcerative bullous lesions that have developed on the scalp since last year. He was a known case of type 2 diabetes mellitus and had been taking Melijent (metformin 500 mg + linagliptin 2.5 mg) twice a day for 2 years.

Clinical examination revealed scattered ulcerative bullous lesions on the scalp with erythema, and some lesions had left scars. There were no signs of hair loss around the lesions, and no other body parts were involved. Laboratory examinations, including BP180 and BP230, were reported to be in the normal range.

The pathology report showed diffuse dermo-epidermal separation producing subepidermal blisters containing extravasated RBCs with an intact epidermal roof. No vacuolar degeneration of basal keratinocytes and no Civatte body formation were seen. The dermis showed some vascular ectasia, mild interstitial edema, some solar elastosis, and mild perivascular infiltrate of lymphoplasmacytic inflammatory cells. No perifollicular or interfollicular dermal scarring was seen in multiple sections.

Although DIF had not been done, the final diagnosis suggested MMP (cicatricial pemphigoid) based on the clinical and histopathological findings. Based on a consult with an endocrinologist, Melijent was ceased, and a topical steroid (clobetasol) was started. After 2 months, the patient had improved completely, and in the 1-year follow-up, no bullous lesions were observed.

Discussion
The increasing rate of diabetes and the growing size of the senile community have increased the potential of exposure to DPP-4 inhibitors and susceptibility to BP disease [16]. The most probable medications that are thought to be involved in the development of BP are...
gliptins, programmed cell death protein 1, programmed death-ligand 1 inhibitors, loop diuretics, penicillin, NSAID, thiazides, and psoralen with UVA light. Studies have also shown that in comparison with other drugs, DPP-4 inhibitors have the most substantial connection with the incidence of BP. It is also claimed that BP is the most probable side effect of DPP-4 inhibitors [3, 16].

A study by Stander et al. [17] revealed that patients with BP induced by DPP-4 inhibitors are characterized by a dominant involvement of trunks, more intense bullous eruptions, and markedly lower serum levels of BP180 NC16a and anti-BP230 autoantibodies. Among AIBDs, BP, and LABD are the most drug-induced variants, but few cases of MMP induced by drugs have been seen. MMP and BP both share the same immunity and are differentiated by clinical features such as more frequent mucous membrane lesions and scarring lesions in MMP. To the best of our knowledge, two cases of MMP induced by DPP-4 inhibitors have been reported, but no cases of gliptin-induced LABD could be found in the literature [12, 14]. Vildagliptin seems to be the most probable gliptin to induce BP among DPP-4 inhibitors. In a study by Kridin et al. [9], it was shown that linagliptin has a role in the progress of the disease. In another study by Stander et al. [17], which compared vildagliptin and sitagliptin, sitagliptin had a higher seropositivity rate and higher levels of autoantibodies. It also has been found that metformin has no association with increasing the risk of BP (prescribed alone or in combination) [1, 9, 12, 17].

Autoantibodies mainly target the NC16a domain of BP180 in conventional BP. However, in BP and its subtypes that are induced by DPP-4 inhibitors, it is different, and autoantibodies also work against other domains of BP (e.g., LAD1) [14, 15].

Although the true mechanism of DPP-4 inhibitor-induced BP is still vague, there is an immunological theory behind it. DPP-4 is a plasminogen receptor that is found extensively on most cell surfaces, including T cells and keratinocytes. This protease turns plasminogen into plasmin (a serine protease) and cleaves BP180 into other ectodomains like 120 KDa and 97 KDa. Hence, the inhibition of DPP-4 may lead to disrupted cleavage and formation of neoepitopes with different antigenicity in BP180, and it may also increase cytokine release, which is both responsible for blister formation and tissue damage [3, 4, 11, 18].

In the present study, all 4 patients experienced remission after gliptin withdrawal plus taking anti-inflammatory treatment (topical or oral). Meanwhile, there is no definite study to show whether the immediate withdrawal of gliptins after diagnosis plays a significant role in remission.

Some previous studies have approved complete remission after rapid discontinuation of drug with a different median time from 10 to 35 days, while others have seen no major change in remission between the group who continued gliptins and the group with discontinuation. However, it is generally suggested that ceasing the drug would be effective in complete remission because, based on a study, ongoing drug administration and long exposure might lead to neoepitope formation and a more complicated disease cycle [1, 4, 5, 19].

**Conclusion**

Overall, due to the increasing number of BP cases following gliptin intake, the probability of the occurrence of rare subtypes should be taken into account. This topic needs to be evaluated in larger dimensions (from the aspect of population, type of study, and longer follow-up) to prove if the possible association between DPP-4 inhibitors and rare forms of pemphigoid really exists. We have also followed all the patients for more than a year, and to this date, there is no sign of relapse in any of them to be reported. *The CARE Checklist has been completed by the authors for this case report and attached as supplementary material.*
Statement of Ethics

The study is done base on the established guidelines by the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). This paper is exempt from the Ethics Committee approval. Study protocol was reviewed, and the need for approval was waived by the Ethics Committee of Razi Hospital on January 10th, 2022. Written informed consent was obtained from the patients for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Diagnosis of the patients and revision of data were done by Professor Kamran Balighi. Data collecting, manuscript writing, and consent obtaining were done by Sama Heidari and Mohammadreza Kavyani. Dr. Kambiz Kamyab Hesari was responsible for pathology and DIF approval. The last review and manuscript editing were done under the supervision of Dr. Nasim Tootoonchi.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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