# Gliptin-Associated Bullous Pemphigoid – A Series of 3 Cases

Dear Editor,

Bullous pemphigoid (BP) is an autoimmune blistering disease commonly affecting elderly individuals.[1] It presents as tense bullous lesions filled with sero-sanguineous fluid, usually preceded by itchy, eczematous, urticarial, and excoriated plaques.[2] Studies have shown that bullous pemphigoid affected patients have autoantibodies against BP 180 protein and BP 230 protein, which are components of hemidesmosomes in basal keratinocytes.[3] Recently, there are case reports of bullous pemphigoid in type 2 diabetes mellitus (T2DM) patients who are being treated with DPP4 inhibitors/gliptins. The exact pathophysiological mechanism that drives the association between gliptins and bullous pemphigoid is not clearly understood.[1] Studies have found that there is no marked difference between "regular" bullous pemphigoid and gliptin-associated bullous pemphigoid (GABP) with respect to immunological reaction.[4] Probable mechanisms are epitope sharing, tissue remodelling, regulation of inflammatory cells, such as T lymphocytes, and triggering inflammatory response and immune-mediated reactions which result in bullous pemphigoid.[4] We are reporting three cases of T2DM being treated with gliptins who developed bullous pemphigoid.

## *Case 1*

A 64-year-old female, a known patient of T2DM, hypertension, chronic kidney disease, hypothyroidism, and anemia, developed tense hemorrhagic bullae for the past one month, with no mucosal or oral lesions [Figure 1]. She had been taking tablet vildagliptin 50mg once daily for the past six weeks. Other concomitant medicines were tablet amlodipine 5mg once daily, thyroxine sodium tablet 50 mcg once daily, capsule aspirin 75 mg and atorvastation 10 mg fixed-dose combination once daily before bed, tablet metformin 500 mg and gliclazide 80 mg fixed-dose combination twice daily, and tablet metoprolol 50 mg once daily for the last two years.

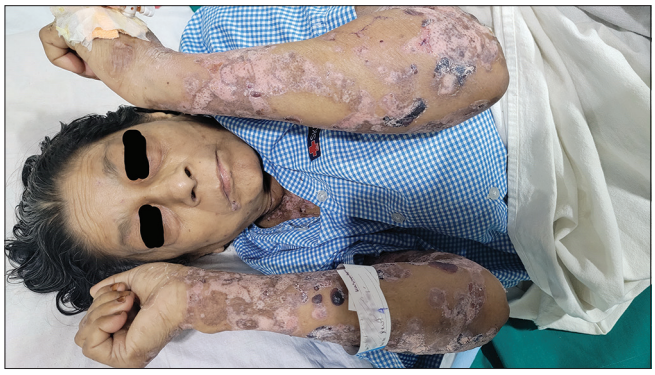

**Figure 1: Case 1 showing generalized tense bullae with sero-sanguinous fluid on the extremities and trunk, many of them healing without scarring**

She was clinically diagnosed with bullous pemphigoid due to vildagliptin. The WHO Uppsala monitoring centre (UMC) causality assessment scale showed a "probable" causality of the drug. The Naranjo scale also showed a score of 5, that is indicative of "probable" Adverse drug reaction (ADR). The preventability was assessed using the modified Schumock and Thornton scale and was found to be "not preventable." Hartwig's severity assessment scale showed that the reaction was moderately severe (Level 4). The suspected drug vildagliptin was withdrawn immediately and methotrexate was started (15 mg/week) with folic acid. Other drugs were continued.

The ADR was reported to the Pharmacovigilance Program of India (PvPI, partner of the WHO Program for International Drug Monitoring managed by Uppsala Monitoring Center, Sweden) with the worldwide unique ID of IN-IPC-300772607. The patient started recovering with weekly methotrexate (15 mg/week) from the sixth week onward. At present, the patient is doing well without any immunosuppressive therapy.

## *Case 2*

A 75-year-old gentleman presented with hemorrhagic tense bullae involving palms, soles, and oral mucosa, clinically mimicking generalized fixed drug eruption. The patient stated that the reaction started 45 days back [Figure 2]. Histopathological examination showed subepidermal bullae with fibrin, lymphocytes, and eosinophil and direct immunofluorescence (DIF) showed C3 along the basement membrane zone; however, it was negative for IgG, IgA, and IgM. The diagnosis was

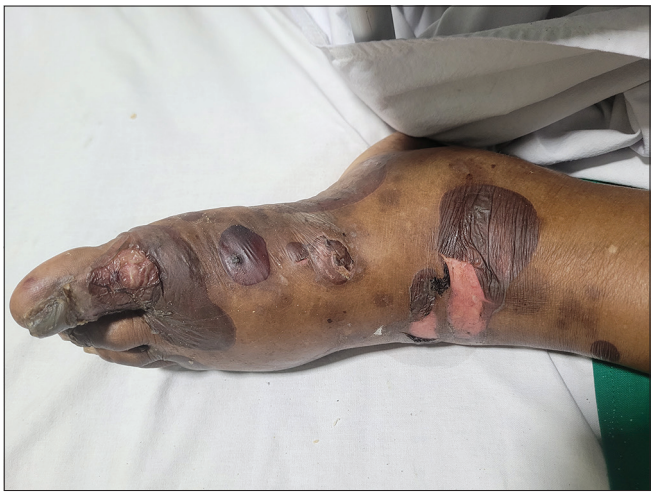

**Figure 2: Case 2 showing tense bullae on left foot and ankle mimicking generalized fixed drug eruption**

confirmed as bullous pemphigoid on clinicopathological correlation.

Further, it was revealed that he has been taking vildagliptin 100 mg once daily for T2DM for the past two years. He was diagnosed with bullous pemphigoid due to vildagliptin. The WHO UMC causality assessment scale showed a "probable" causality of the drug. Naranjo scale showed a score of 5, that is indicative of "probable" ADR. The preventability was assessed using the modified Schumock and Thornton scale and was found to be "not preventable." Hartwig's severity assessment scale showed that the reaction was moderately severe (Level 3). The suspected drug was withdrawn immediately.

Treatment was started with cyclosporine A (100mg twice daily) along with topical clobetasol propionate. Lesions resolved in seven days, and recovery was uneventful.

The ADR was reported to the PvPI with the worldwide unique ID of IN-IPC-300805131.

### *Case 3*

A 70-year-old gentleman presented with tense bullae filled with serous fluid over limbs and body for the last 6 months. Mucosa was not involved [Figure 3]. History revealed that he was suffering from T2DM and was on tablet linagliptin (a DPP 4 inhibitor) 5mg once daily for nearly a year.

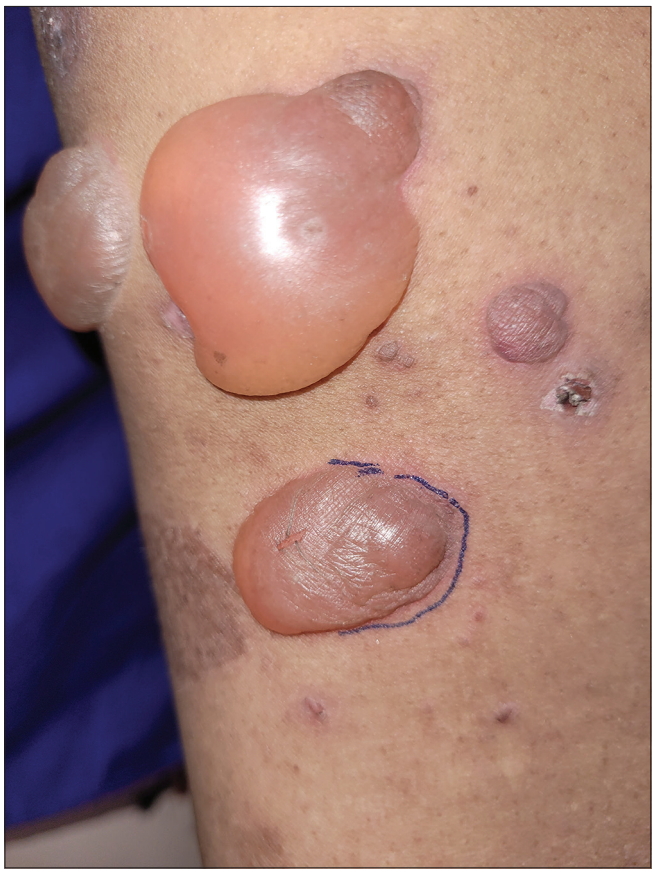

**Figure 3: Case 3 showing tense bulla filed with serous fluid**

Histopathological examination showed the presence of subepidermal bullae with scattered mild perivascular aggregates of lymphocytes along with mild spongiosis suggestive of bullous pemphigoid. However, there was paucity of eosinophilic infiltrates. It was diagnosed as bullous pemphigoid due to linagliptin [Figure 4].

The WHO UMC causality assessment scale showed a "probable" causality of the drug. The suspected drug was withdrawn immediately. The Naranjo scale showed a score of 5, that is indicative of "probable" ADR. The preventability was assessed using the modified Schumock and Thornton scale and was found to be "not preventable". Hartwig's severity assessment scale showed that the reaction was moderately severe (Level 3). Treatment started with mycophenolate mofetil 500 mg two times daily and topical clobetasol, and the patient recovered within three weeks of therapy.

The ADR was reported to the PvPI with the worldwide unique ID of IN-IPC-300813987. The patient recovered after 20 days.

## Discussion

Bullous pemphigoid typically manifests itself as tense blisters filled with serous or sero-sanguineous fluid with histopathology revealing subepidermal bulla with an eosinophil-rich infiltrate. DIF reveals linear deposition of IgG and C3 complement at the dermo-epidermal junction in perilesional skin.

DPP4 protein is a member of prolyl oligo-peptidase superfamily, which cleaves a wide range of bioactive peptides. The DPP4 protein/CD26 is expressed in various kinds of cells, including T lymphocytes, and is upregulated in bullous pemphigoid patients but independently of gliptins. One recent study has found that in GABP, the IgG reactivity

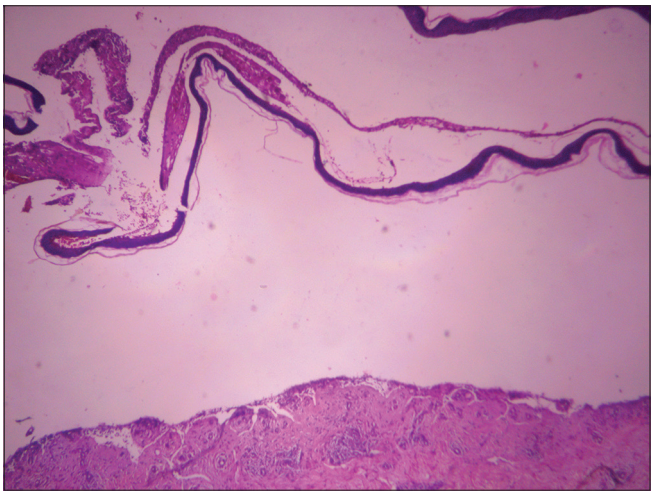

**Figure 4: Histopathology (case 3) of the bullous lesion showing sub-epidermal split with perivascular lymphocytic infiltrate and paucity of eosinophils (H and E, 40 ×)**

targets multiple BP180 epitopes which can play a possible role in the pathogenesis.[5] The same study also reports that GABP shows a low amount of eosinophils and IgG, IgA, and IgM in comparison to idiopathic bullous pemphigoid, which is evident in case 2 where DIF showed a deposit of only C3 without IgG, and in case 3, the histopathology did not contain eosinophils, as expected in "classical" variant.

DPP4 inhibitors are gaining increasing popularity recently due to their unique mechanism, and very little probability of causing hypoglycaemia, making them more preferred among physicians and patients.

It needs to be noted that continuous blockade of DPP4 may lead to exacerbation of inflammatory process. Pasmatzi *et al*.[6] and Skandalis *et al*.[7] first reported cases of BP occurring in T2DM patients receiving a gliptin (mostly vildagliptin) in conjunction with metformin. Since then, case reports, case series, and observational studies have shown similar association.[8,9] Bullous pemphigoid has been associated with all DPP-4 inhibitors, suggesting a class effect. The latency period of development of bullous pemphigoid and intake of gliptins varies between 8 days and 6.5 years.[1] In our case series, the latency period varied from six weeks in case 1, two years in case 2, and two months in case 3.

A high index of suspicion on the part of the treating physician is required to recognize and diagnose GABP, since the interval between the onset of GABP and start of intake of gliptins is variable. The treating physicians need to be aware that in GABP, there may be paucity of eosinophils in the dermal infiltrate and even the absence of IgG in DIF, in contrast to "classical" bullous pemphigoid, which can be a tale-tell sign of GABP.

## *Declaration of patient consent*

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## *Conflicts of interest*

There are no conflicts of interest.

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## References

1. Chouchane K, Di Zenzo G, Pitocco D, Calabrese L, De Simone C. Bullous pemphigoid in diabetic patients treated by gliptins: The other side of the coin. J Transl Med 2021;19:520.
2. Di Zenzo G, Della Torre R, Zambruno G, Borradori L. Bullous pemphigoid: From the clinic to the bench. Clin Dermatol 2012;30:3-16.
3. Cozzani E, Marzano AV, Caproni M, Feliciani C, Calzavara-Pinton P, Cutaneous Immunology group of SIDeMaST. Bullous pemphigoid: Italian guidelines adapted from the EDF/EADV guidelines. G Ital DermatolVenereol 2018;153:305-15.
4. Tasanen K, Varpuluoma O, Nishie W. Dipeptidylpeptidase-4 inhibitor-associated bullous pemphigoid. Front Immunol 2019;10:1238.
5. Salemme A, Fania L, Scarabello A, Caproni M, Marzano AV, Cozzani E, *et al*. Gliptin-associated bullous pemphigoid shows peculiar features of anti-BP180 and -BP230 humoral response: Results of a multicenter study. J Am Acad Dermatol 2022;87:56-63.
6. Pasmatzi E, Monastirli A, Habeos J, Georgiou S, Tsambaos D. Dipeptidyl peptidase-4 inhibitors cause bullous pemphigoid in diabetic patients: Report of two cases. Diabetes Care 2011;34:e133.
7. Skandalis K, Spirova M, Gaitanis G, Tsartsarakis A, Bassukas ID. Drug-induced bullous pemphigoid in diabetes mellitus patients receiving dipeptidyl peptidase-IV inhibitors plus metformin. J Eur Acad Dermatol Venereol 2012;26:249-53.
8. García-Díez I, Ivars-Lleó M, López-Aventín D, Ishii N, Hashimoto T, Iranzo P, *et al*. Bullous pemphigoid induced by dipeptidyl peptidase-4 inhibitors. Eight cases with clinical and immunological characterization. Int J Dermatol 2018;57:810-6.
9. Attaway A, Mersfelder TL, Vaishnav S, Baker JK. Bullous pemphigoid associated with dipeptidyl peptidase IV inhibitors. A case report and review of literature. J Dermatol Case Rep 2014;8:24-8.



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