ISSN- O: 2458 - 868X, ISSN–P: 2458 – 8687
National Library of Medicine - ID: 101731606

International Journal of Medical Science and Innovative Research (IJMSIR)
IJMSIR : A Medical Publication Hub
Available Online at: www.ijmsir.com
Volume – 10, Issue – 6, December – 2025, Page No. : 28 – 34

Gliptin-Induced Bullous Pemphigoid: A Case Series

[1]Dr Shamoel Chauhan, Junior Resident, Department of Pharmacology, B.J. Government Medical College and Sassoon General Hospital, Pune

[2]Dr Sujeet Anant Divhare, Associate Professor; Department of Pharmacology, B.J Government Medical College and Sassoon General Hospital, Pune

Corresponding Author: Dr Shamoel Chauhan, Junior Resident, Department of Pharmacology, B.J. Government Medical College and Sassoon General Hospital, Pune

Citation this Article: Dr Shamoel Chauhan, Dr Sujeet Anant Divhare, "Gliptin-Induced Bullous Pemphigoid: A Case Series", IJMSIR - December – 2025, Vol – 10, Issue - 6, P. No. 28 – 34.

Type of Publication: Case Series

Conflicts of Interest: Nil

Abstract

Bullous pemphigoid (BP) is a chronic autoimmune blistering disorder characterised by tense bullae and intense pruritus. Dipeptidyl peptidase-4 (DPP-4) inhibitors are widely used to manage type 2 diabetes mellitus. In recent years, multiple studies have recognised DPP-4 inhibitors as causative agents for drug-induced BP.

This series includes two patients who developed BP after starting Sitagliptin therapy and a third who developed the condition following the initiation of Vildagliptin. It highlights distinct clinical courses: a 75-year-old male with Sitagliptin-induced BP who exhibited a refractory course requiring Omalizumab despite stopping the drug; a 73-year-old female with Vildagliptin-induced BP characterised by rapid onset within 15 days; and a 55-year-old female with Sitagliptin-induced BP presenting with mucosal involvement and clear dose-related worsening. Immunological profiling revealed isolated anti-BP180 positivity in all cases, with histology showing a subepidermal cleft with eosinophilic infiltrates, and direct immunofluorescence showing linear C3 and IgG deposition in one case.

Clinical improvement was observed after stopping the inciting gliptin and starting systemic therapy tailored to disease severity. All patients showed a gradual decrease in blister formation and symptomatic relief following these interventions.

This series highlights that gliptin-induced BP is not a uniform condition; it can present with variable latent periods, atypical mucosal involvement, and varying degree of reversibility. Pharmacovigilance is crucial, as early detection, discontinuation of the drug, and appropriate therapy are vital for improving clinical outcomes and preventing disease progression.

Keywords: Sitagliptin, Vildagliptin, Drug-induced, Adverse drug reaction, Bullous pemphigoid

Introduction

Bullous pemphigoid (BP) is a prevalent autoimmune blistering disorder seen in older adults, typically manifesting with tense bullae, urticarial lesions, and pronounced pruritus. Its pathogenesis is driven by autoantibodies targeting the hemidesmosomal

components BP180 and BP230, which activate complement pathways and promote eosinophil-rich inflammation, ultimately resulting in subepidermal blister formation.[1]

While most BP cases are idiopathic, a growing subset is now attributed to drugs: a phenomenon referred to as drug-induced bullous pemphigoid (DIBP).[2] Among these are DPP-4 inhibitors, also known as gliptins, widely used in the treatment of type-2 diabetes mellitus, which have emerged as a major contributor, with multiple studies demonstrating elevated BP risk in patients treated with Gliptins.[3] Vildagliptin appears to carry the highest relative risk, followed by Sitagliptin and Linagliptin, suggesting possible molecule-specific variations in immunogenic potential.[3]

The mechanism remains incompletely understood, but proposed pathways include alteration of the BP180 antigenic structure, disruption of immune homeostasis due to DPP-4 inhibition on T cells and eosinophils, and enhanced susceptibility in elderly diabetic patients with baseline immune dysregulation.[3]

Clinically, DPP-4 inhibitor-associated BP may mimic idiopathic BP but can exhibit atypical features such as milder erythema, predominant acral involvement, or localised onset that later generalises.[4]

Given the increasing global use of DPP-4 inhibitors and the ageing diabetic population, recognition of DIBP is of growing clinical importance. Early recognition is essential, as timely withdrawal of the offending drug often results in clinical improvement.

Case 1:

A 75-year-old male with long-standing type 2 diabetes mellitus, coronary artery disease, and hypertension developed recurrent, large hemorrhagic bullae predominantly over both feet and legs, later progressing to generalised distribution over several months. He had been initiated on Sitagliptin 50mg for glycemic control, and the onset of symptoms occurred approximately three months after initiation of therapy.

The bullae were tense, hemorrhagic, and associated with itching and significant discomfort. Initial treatment with oral Doxycycline and topical Corticosteroids resulted in minimal improvement. He was subsequently started on oral Prednisolone (30 mg/day, tapered over 3 months), which provided only a partial remission.

Due to persistent disease activity, he was evaluated further and initiated on injection Omalizumab 300 mg subcutaneously once monthly. The patient showed substantial clinical improvement with the biologic therapy, resulting in a marked reduction in the number and severity of lesions. After tapering and discontinuation of Omalizumab, the patient was transitioned to tablet Mycophenolate mofetil (MMF) 500 mg daily for long-term maintenance, with good disease control.

Serological evaluation for autoimmune blistering disorders revealed a positive BP180 antibody level (112.53 RU/mL) and negative BP230 antibody (10.37 RU/mL), supporting the diagnosis of bullous pemphigoid.

At the last follow-up, the disease remains quiescent.

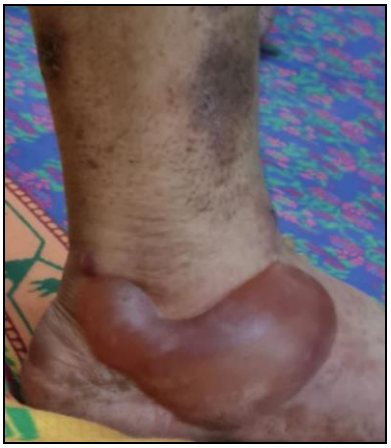

Figure 1: Showing a large tense bulla with serous fluid on the foot

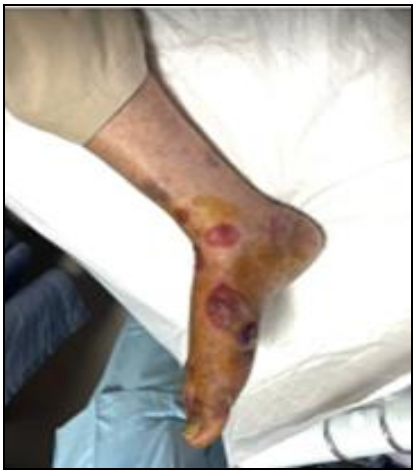

Figure 2: Showcasing multiple bullae on the foot

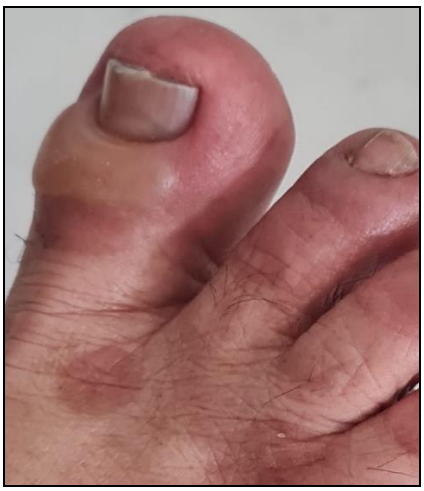

Figure 3: Lesions after maintenance therapy initiated

Case 2:

A 73-year-old female, a known case of type 2 diabetes mellitus for 15 years and a chronic smoker for more than four decades, presented with recurrent, painful, pruritic, fluid-filled lesions over the lower limbs and trunk. Her glycemic control had been suboptimal owing to a lack of dietary control or exercise, requiring multiple oral anti-diabetic agents over the years.

She was initiated on Vildagliptin 50 mg twice daily. Remarkably, within 15 days of initiation, she developed an erythematous rash over the ankles and feet. The lesions were initially managed with moisturisers. Over the following weeks, the rash progressively extended, more prominently on the left side, reaching the mid-shin to thigh region. She was then treated with tablet Fexofenadine 180 mg twice daily and Nadifloxacin (1% W/W) cream for the rash and pruritus, which provided minimal benefit.

The rash eventually evolved into tense, fluid-filled blisters that appeared over the ankle lesions, spreading proximally to involve the thighs and trunk.

A skin biopsy was performed, and histopathology demonstrated a subepidermal cleft with basal layer squamatization, accompanied by aggregates of eosinophils and fibrin within the cleft. Dermal changes included a perivascular lymphocytic infiltrate with scattered eosinophils.

Direct immunofluorescence revealed:

- C3: linear positive at dermo-epidermal junction
- IgG: faint positive at dermo-epidermal junction
- IgA, IgM, C4: Negative

A serological work-up showed positive anti-BP180 (78.03 RU/mL) and negative anti-BP230 titre (6.01 RU/mL).

These findings are consistent with bullous pemphigoid, and in the context of recent DPP-4 inhibitor exposure, a diagnosis of Vildagliptin-induced bullous pemphigoid was established.

Vildagliptin was discontinued, and the patient was initiated on Mycophenolic acid 360 mg twice daily for long-term immunosuppression. Metformin 500 mg twice daily was continued for diabetes management. At the most recent follow-up, no new lesions had appeared, and the existing lesions were gradually resolving.

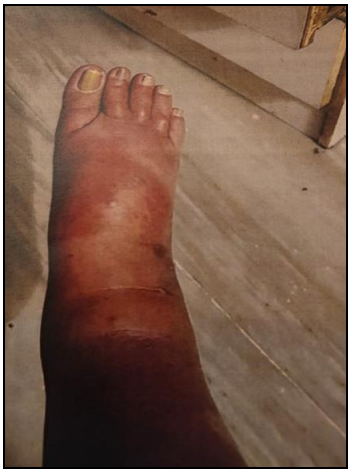

Figure 4: Rash over ankle and shin

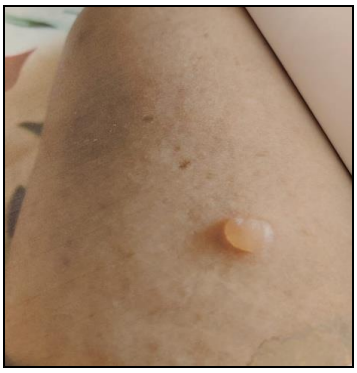

Figure 5: Fluid filled lesion on left thigh

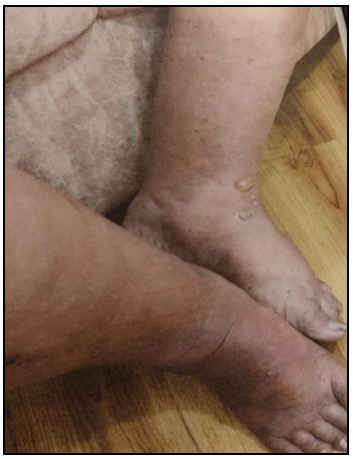

Figure 6: Fluid filled blister over left ankle

Case 3:

A 55-year-old female presented with complaints of recurrent, painful, and pruritic blisters involving the face, trunk, and extremities, with subsequent involvement of the oral and nasal mucosa.

The patient was diagnosed with type 2 diabetes mellitus 1 month before the onset of cutaneous symptoms. She was initiated on Sitagliptin 50mg daily. One month after initiating Sitagliptin, she developed localised blisters on her cheeks and chin. This was initially managed as infective or allergic aetiology with courses of antifungal creams, antihistamines and antibiotics, resulting in temporary symptomatic relief.

The dosage of Sitagliptin was increased from 50mg to 100mg for tighter glycemic control. Following this dose escalation, the disease activity worsened significantly, spreading to her arms, back, neck and new involvement of the oral cavity and nasal mucosa.

A serological work-up for vesiculobullous disorders was consistent with the first and second case; with the patient demonstrating a positive anti-BP180 (54.08 RU/mL) and negative anti-BP230 titre (<2 RU/mL).

Based on these findings and temporal correlation, a diagnosis of Sitagliptin-induced Bullous Pemphigoid was made. Sitagliptin was stopped and replaced with Tablet Voglibose 0.3mg and Metformin 500mg BD. The patient was started on a steroid-sparing regimen of Doxycycline (100mg BD) and Nicotinamide (250mg BD) along with topical Fusidic acid and corticosteroids.

At the most recent follow-up, the pain has reduced, though the patient continues to have mild persistent disease activity.

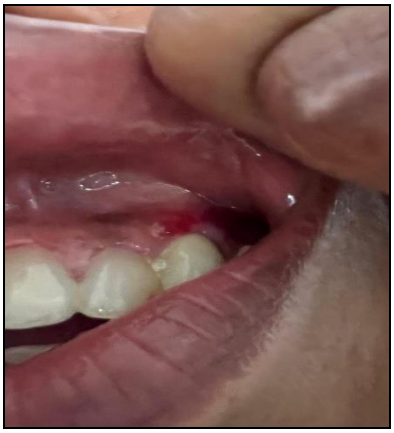

Figure 7: Mucocutaneous lesion in the mouth

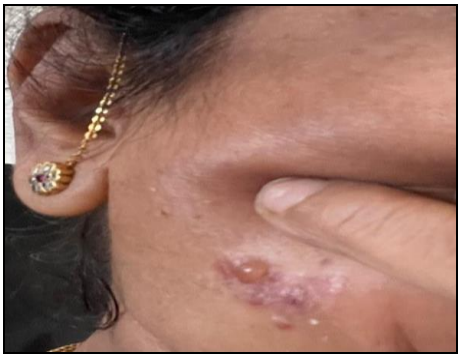

Figure 8: Multiple serous-filled lesions on the cheeks

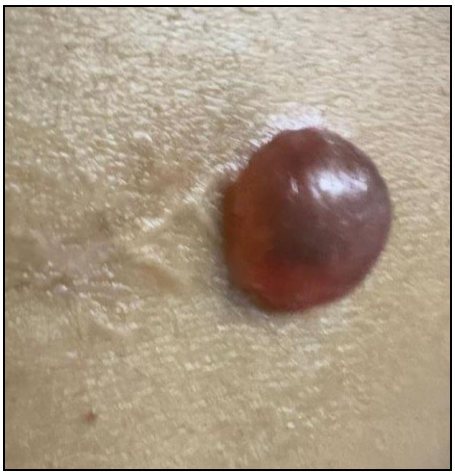

Figure 9: Tense fluid-filled blister on the chin

Discussion

Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering disorder, driven by autoantibodies targeting the hemidesmosomal proteins BP 180 and BP 230.[1]

Over the last decade, multiple pharmacovigilance studies, case-control analyses, and datasets have demonstrated an association between DPP-4 inhibitors and the development of BP. Among the various agents, Vildagliptin and Sitagliptin exhibit the strongest and most reproducible association with BP across populations.[5]

Several mechanisms have been proposed to explain this link. The exact pathophysiology of gliptin-induced BP is still under investigation. It is thought to be an immune-mediated process centred on the function of DPP-4 (also known as CD26), an enzyme expressed on various cells, including T-lymphocytes.[6] Inhibition of DPP-4 may alter T-cell signalling and promote an inflammatory state. This could disrupt immune self-tolerance, triggering an autoimmune response directed against hemidesmosomal proteins BP180 and BP230 at the dermal-epidermal junction, culminating in blister formation.[7]

The cases in this series demonstrate a clear temporal association between gliptin initiation and the onset of blistering. Consistent with the reported latency periods ranging from 8 days to more than 6 years.[8]

All patients showed BP180 antibody positivity without BP230 reactivity, aligning with previously described Gliptin-induced Bullous pemphigoid (GIBP) serological patterns.[9] The third case showed classic histopathology with subepidermal cleft, filled with eosinophils and Linear IgG/C3 deposition- consistent with BP.[9]

Management typically begins with withdrawal of the offending DPP-4 inhibitor, which has been associated with improved outcomes and reduced recurrence. Nonetheless, several studies note that GIBP may be more treatment-refractory than idiopathic BP, potentially necessitating prolonged immunosuppression or biologic therapy.[10] In the present series, cessation of Sitagliptin or Vildagliptin combined with systemic Corticosteroids, Omalizumab, or Mycophenolate derivative resulted in clinical improvement in all cases.

These observations highlight the importance of increased clinical awareness among dermatologists, endocrinologists, and primary care physicians. Prompt recognition of new onset pruritic or bullous eruptions in patients on gliptins and early discontinuation of the drug remains crucial for optimising outcomes.

Conclusion

The three cases presented add to the expanding body of literature implicating DPP-4 inhibitors as a significant trigger for bullous pemphigoid. The consistent

chronology between drug exposure and blister formation, the presence of supportive serological and histopathological markers, and the clinical improvement upon gliptin cessation collectively strengthen the causal association.

Gliptin-induced BP may present with varied clinical severities- from localised pruritic plaques to extensive hemorrhagic bullae.

As DPP-4 inhibitors continue to be extensively prescribed for type 2 diabetes mellitus both in India and globally, awareness of this potential adverse effect is imperative for dermatologists, endocrinologists, and general physicians. Implementing regular dermatologic monitoring and educating patients about early skin changes may support timely recognition.

Future research focusing on mechanistic pathways and genetic predisposition may enable risk-stratified prescribing and ultimately improve patient safety.

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