Case Report

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Cutaneous Adverse Reactions Associated with Dipeptidyl Peptidase-4 Inhibitors in Diabetes: A Case Series

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ABSTRACT

Dipeptidyl peptidase-4 (DPP-4) inhibitors are effective glucose-lowering agents for type 2 diabetes mellitus but may cause dermatological adverse effects ranging from mild to severe. This case series highlights various skin reactions to DPP-4 inhibitors, aiming to enhance clinicians' awareness for early recognition and management, and to underscore the need for further research and pharmacovigilance to ensure patient safety.

Keywords

Dipeptidyl peptidase-4 (DPP-4), type 2 diabetes, DPP-4 inhibitors, Dermatology, Hypoglycemia risk.

Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors are oral antihyperglycemic agents that block the DPP-4 enzyme, preventing degradation of glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP) [1]. This action enhances incretin activity, thereby promoting insulin secretion, suppressing glucagon release, and improving glycemic control without increasing hypoglycemia risk [2]. Among the reported adverse effects, bullous pemphigoid—termed DPP-4 inhibitor-associated bullous pemphigoid (DPP4i-BP) or gliptin-associated bullous pemphigoid (GABP)—is a notable dermatological manifestation [3]. This case series describes patients with type 2 diabetes mellitus who developed various skin reactions among the DPP-4 inhibitor therapy. Awareness of such reactions is crucial for timely recognition and management.

Case Series

This study presents a retrospective review of a case series examining DPP-4 inhibitor–induced skin manifestations among patients with type 2 diabetes mellitus attending the Diabetes Center at Grand Hantha International Hospital between 2022 and 2024.

A total of 64 patients who had been prescribed any DPP-4 inhibitor—sitagliptin, linagliptin, vildagliptin, or teneligliptin—and subsequently developed pruritic skin lesions were included. Only patients whose skin manifestations resolved spontaneously following discontinuation of the DPP-4 inhibitor were enrolled. In selected cases, skin biopsies were performed for histopathological analysis.

The mean age of the cohort was 61 ± 9.3 years (range: 40–80 years). Of these, 41 patients (64.1%) were female and 23 (35.9%) were male. The most frequently used agent was sitagliptin (62.5%), followed by linagliptin (23.4%), reflecting local prescribing practices and drug availability. Vildagliptin accounted for 6.3%, and teneligliptin for 3% of cases. Additionally, two patients (3.2%) developed recurrent skin reactions after switching from one DPP-4 inhibitor to another.

The median latency period between drug initiation and onset of skin lesions was 24 months (IQR 12-36), ranging from 1 month to 100 months. In most cases, both patients and healthcare providers initially failed to attribute the dermatologic symptoms to DPP-4 inhibitor use, leading to a delay in drug discontinuation. The medium duration of delay drug withdrawal after the appearance of the skin lesion was 3 months (IQR 1-6). Eleven patients (17%)

had consulted dermatologists, but the reactions were not initially recognized as being drug-related.

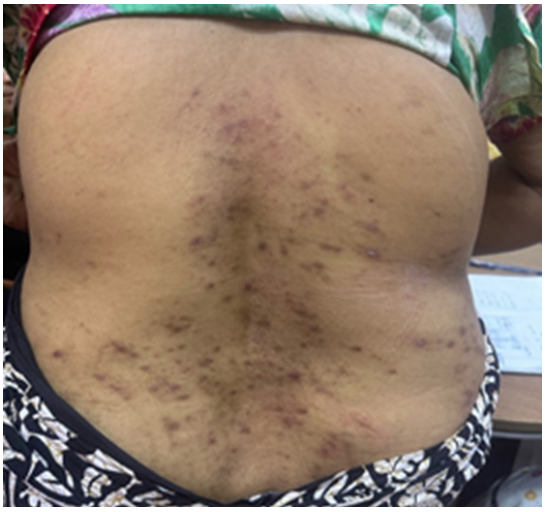

Figure 1: Numerous pruritic lesions leaving hyperpigmented plaques and macules on the back.

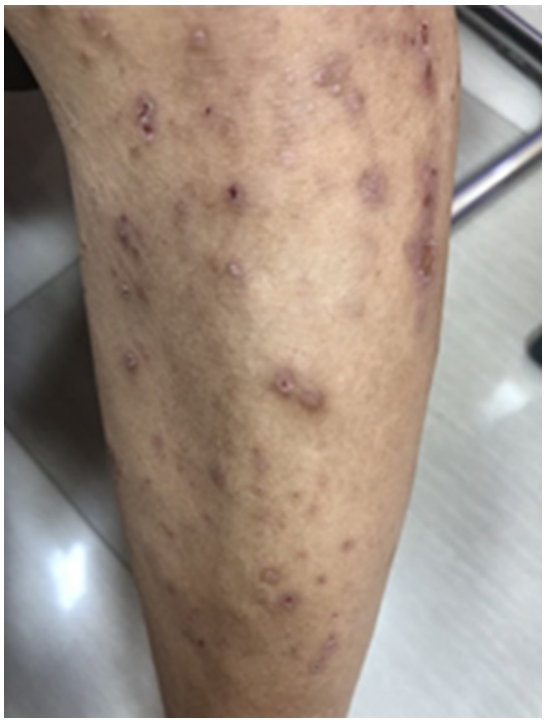

Figure 2: Numerous pruritic lesions leaving hyperpigmented plaques and macules on the extensor surface of the leg.

All affected patients presented with intense pruritus. No vesicular lesions were observed; instead, the lesions showed excoriations, erythematous bases, and hyperpigmented plaques or macules secondary to scratching. The distribution typically involved the trunk and extremities, sparing the face and palms. The extensor surfaces of the forearms were most commonly affected, followed by the lower limbs, thighs, upper back, and abdomen. Unlike fungal infections, the axillae and groins were rarely involved.

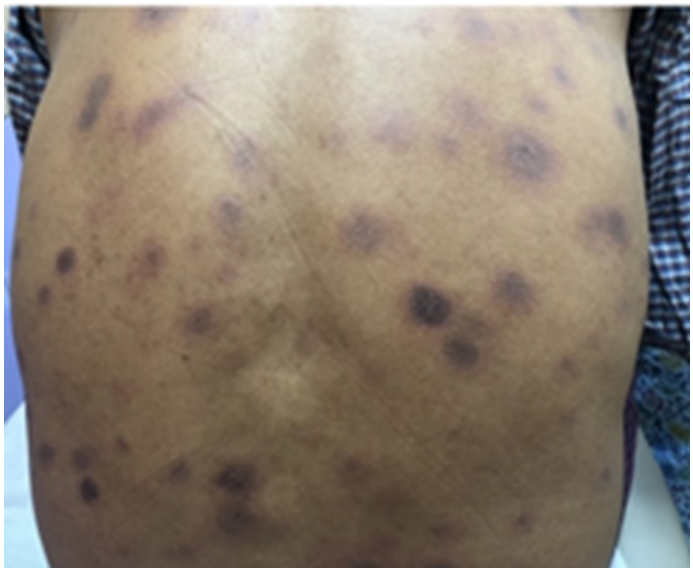

Figure 3: No obvious vesicles leaving marked pigmentation after withdrawal of the drug

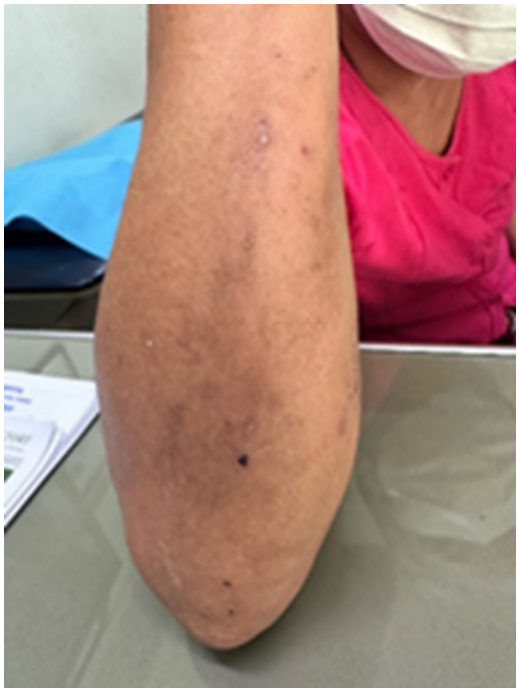

Figure 4: Milder form may have scratch marks only leaving few scars.

Among the 64 patients, 9 (14%)—including 5 males and 4 females—underwent skin biopsy. Histopathological findings commonly revealed hyperkeratosis, mild acanthosis, focal spongiosis, and perivascular interstitial infiltration by lymphocytes and plasma cells. Scattered eosinophils were occasionally observed, and one case demonstrated granuloma formation. The biopsy findings were generally consistent with noninfectious inflammatory dermatosis, with one case showing intraepidermal bullae containing a few pemphigus-like cells.

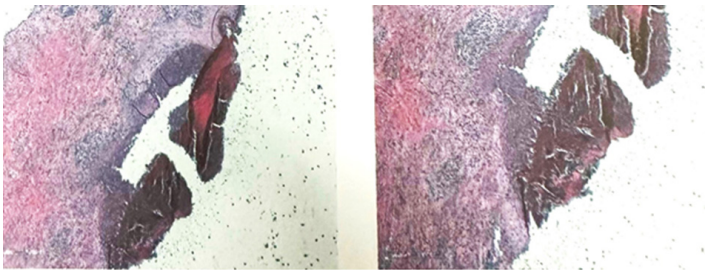

Figure 5: Acantholysis of stratum spongiosum, intraepidermal bulla containing a few pemphigus cells.

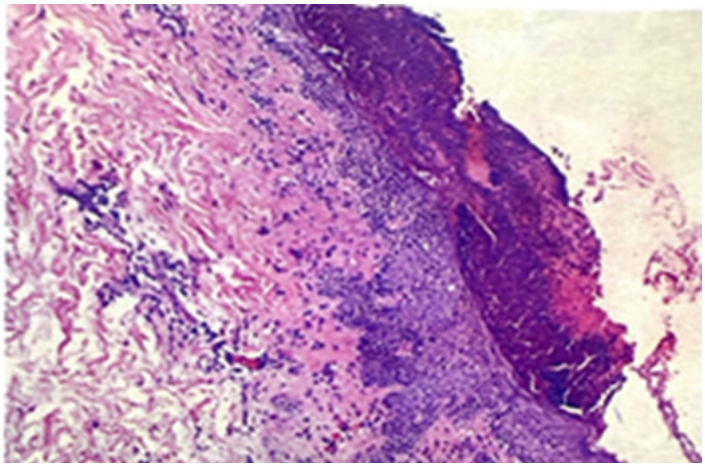

Figure 6: Intra epidermal abscess.

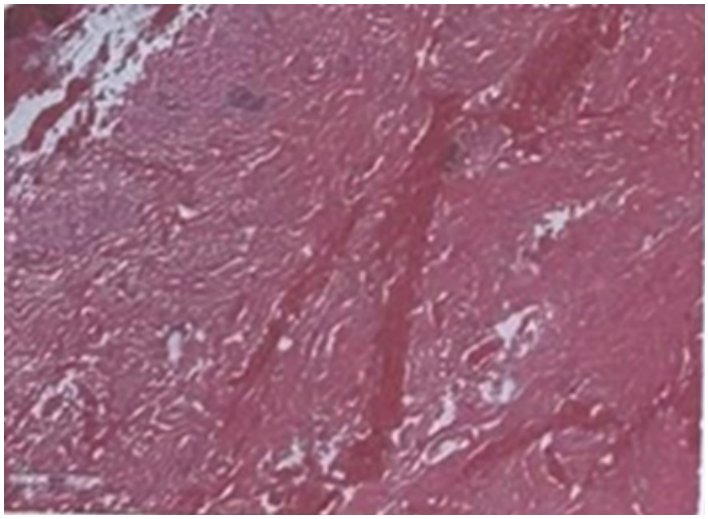

Figure 7: Hyperkeratosis, mild acanthosis, focal spongiosis.

Results Summary and Key Observations

DPP-4 inhibitor–related skin manifestations were most frequently observed with sitagliptin and linagliptin, likely reflecting their greater clinical use. The wide variability in latency periods suggests an idiosyncratic and immune-mediated mechanism rather than dose dependence. Chronic pruritic eruptions primarily involved the extensor surfaces and trunk, characterized by erythematous plaques, erosions, and hyperpigmentation. Histopathology was generally consistent with non-infectious inflammatory dermatoses, with occasional features of bullous disease.

Delayed recognition and prolonged continuation of the offending drug were common, emphasizing the need for clinical vigilance, timely dermatological consultation, and early discontinuation to prevent chronic or recurrent lesions.

Discussion

Real-world data have demonstrated a significant association between dipeptidyl peptidase-4 inhibitors (DPP-4i) and cutaneous adverse drug reactions (CADRs). According to the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS), a total of 3,024 cases of skin and subcutaneous tissue disorders have been reported following DPP-4 inhibitor use, with bullous pemphigoid (BP) being the most frequent manifestation (970 cases) [4].

Dermatologic reactions associated with DPP-4 inhibitors vary widely and include bullous pemphigoid, pruritus, exanthematous drug eruptions, photosensitivity reactions, and, less commonly, angioedema [5]. Although severe cutaneous adverse reactions (SCARs) are uncommon, they can be life-threatening, involving widespread skin damage and systemic features [6].

The latency period between the initiation of gliptin therapy and onset of bullous pemphigoid symptoms has been reported to range from 8 days to 6.5 years [7], with mean latency periods of 6 to 19 months in most studies [8]. In our series, the mean latency period was 28 months, suggesting delayed recognition and underreporting of DPP-4 inhibitor–induced skin reactions in clinical practice.

The mainstay of management is discontinuation of the offending drug, with most cases showing symptomatic remission within 1–6 months. Previous studies reported partial or complete remission in 95% of patients after drug withdrawal, compared with 55% among those who continued therapy [9,10]. Consistent with these findings, all patients in our cohort achieved complete recovery following cessation of the DPP-4 inhibitor.

The pathogenesis of DPP-4 inhibitor–associated BP remains incompletely understood. Inhibition of CD26/DPP-4 expression on T-cells may disrupt immune regulation, contributing to autoimmune skin inflammation [9]. Depending on disease severity, topical or systemic corticosteroids, immunosuppressive therapy, or intervenous immunoglobulin (IVIG) may be indicated [5]. However, early recognition is often hindered by lack of biopsy or immunostaining, which limits diagnostic confirmation.

It remains unclear whether DPP-4 inhibitor therapy alone can trigger BP or whether underlying autoimmune susceptibility acts as a cofactor. Despite increasing case reports linking gliptins to dermatologic reactions, prospective and mechanistic studies are still limited. Our findings add to the existing clinical evidence supporting the association between DPP-4 inhibitor use and a spectrum of dermatologic manifestations in patients with type 2 diabetes.

Conclusion and Clinical implications

Dipeptidyl Peptidase-4 (DPP-4) inhibitors are widely used antihyperglycemic agents that are generally safe and effective in diabetes management. However, clinicians involved in diabetes care, as well as dermatologists, should remain vigilant for their potential to cause cutaneous adverse reactions. Educating patients about these possible side effects at the time of prescription and maintaining a high index of suspicion among healthcare providers are essential for early recognition. Continuous post-marketing pharmacovigilance plays a crucial role in timely detection and appropriate management of such reactions, thereby enhancing overall diabetes care and ensuring patient safety.

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