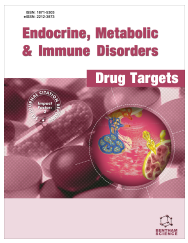
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CASE REPORT

The Liraglutide-Induced Pemphigus Vulgaris: A First Case Report Highlighting Autoimmune Risks of GLP-1 Receptor Agonists



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Abstract: ***Introduction*:** Pemphigus vulgaris (PV) is a rare autoimmune blistering disorder that primarily affects the skin and mucous membranes. Drug-induced pemphigus (DIP) is an uncommon variant that is triggered by certain medications. The introduction of novel hypoglycemic agents, such as glucagon-like peptide-1 receptor agonists (GLP-1RA), has been associated with an increase in drug-induced bullous diseases. However, reports of pemphigus induced by these agents remain exceedingly rare.

***Case Presentation*:** We report the first case of liraglutide-induced PV in a 40-year-old female patient with type 2 diabetes mellitus. The patient developed erosive lesions on the palatal and buccal mucosa three months after initiating liraglutide therapy. Histopathological examination confirmed the diagnosis of PV. The temporal association with liraglutide use, combined with positive results from *in vitro* gamma-interferon release assays, supports the diagnosis of DIP. The patient showed partial remission after liraglutide discontinuation and topical glucocorticoid therapy, but lesions recurred when liraglutide was reintroduced.

***Conclusion*:** The precise mechanism behind liraglutide-induced pemphigus is not yet fully understood. Potential mechanisms include interference with immune modulation or direct effects on keratinocytes. This case underscores the importance of careful monitoring for autoimmune reactions in patients treated with GLP-1RAs and highlights the need for further research into the underlying mechanisms and management strategies for DIP.

Keywords: Case report, pemphigus vulgaris, drug-induced pemphigus, liraglutide, GLP-1 receptor agonists, diabetes mellitus, immunomodulation, pharmacovigilance.

1. INTRODUCTION

As the global prevalence of diabetes continues to rise, there is an increasing demand for safer and more effective glucose-lowering therapies. Several novel glucose-lowering agents, such as dipeptidyl peptidase 4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1RA), and sodium-glucose transporter 2 inhibitors (SGLT-2i), have been developed to meet this need. Among these, GLP-1RAs have garnered significant attention due to their unique mechanism of action and favorable tolerability profile. GLP-1 is an incretin hormone that effectively stimulates insulin secretion, gene expression, and β-cell growth. GLP-1RAs mimic the physiological activity of endogenous GLP-1, leading to substantial improvements in glucose control [1, 2]. However, with the increased use of GLP-1RAs, there have also been growing reports of potential side effects.

Drug-induced pemphigus (DIP) is a rare autoimmune skin disorder characterized by clinical, histologic, and immunologic features that are indistinguishable from idiopathic pemphigus. The development of DIP is closely linked to the administration of certain medications [3, 4]. While sever-

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al drugs can induce pemphigus, no GLP-1RA-related cases have been reported, though pemphigoid cases associated with GLP-1RAs exist.

In this study, we present the first reported case of pemphigus vulgaris (PV) induced by liraglutide, a GLP-1RA. By analyzing this case, we aim to explore the potential association between GLP-1RA use and DIP, highlighting the importance of early recognition of DIP, which will facilitate timely treatment modifications and minimize potential complications. Additionally, we review relevant literature and case reports to delve into the pathogenesis of GLP-1RA-induced pemphigus in order to provide clinicians with valuable insights into the selection of glucose-lowering treatment regimens and facilitate further research into the mechanisms underlying drug-related side effects.

2. CASE REPORT

Informed consent was obtained from the patient for participation in this case report, and the study was approved by the Medical Ethics Committee of West China Stomatological Hospital, Sichuan University (Approval ID: WCHSIR-B-D-2024-309).

A 40-year-old woman with a 1-year history of diabetes presented with 3 months of painful palatal and buccal mucosal erosions. Six months prior, she started metformin (0.5 g twice daily) and gliclazide (1 tablet daily). Due to poor glycemic control, her regimen was adjusted 3 months before presentation to metformin (0.5 g three times daily), dapagliflozin (10 mg daily), and liraglutide (1.2 mg subcutaneously daily). She had no history of infections, drug allergies, or hereditary diseases.

Intraoral examination Fig. (**1A**) showed multiple superficial erosions on the labial, buccal, lingual, and palatal gingiva, as well as the posterior hard palate and soft palate, with peripheral keratinization (Figs. **1A-D**). Nikolsky's sign was positive. No skin blistering was observed.

Laboratory tests showed elevated fasting blood glucose (6.861 mmol/L; normal <6.1 mmol/L) and glycosylated hemoglobin (7.11%; normal <6%). Other tests, including blood routine, stool routine, coagulation, liver and kidney function, specific infections, tuberculin test, bone density, and chest/abdominal CT, revealed no significant abnormalities.

Histopathologic examination of the gingival mucosa demonstrated intra-epithelial blister formation, which was consistent with PV (Figs. **2A**, **B**). Direct immunofluorescence was negative. Antibody tests showed elevated anti-Dsg1 (55.9 U/mL; normal <20 U/mL), with normal anti-Dsg3 and anti-BP180 levels. An *in vitro* gamma-interferon release assay indicated a 53% increase in interferon-gamma release with liraglutide stimulation (Supplementary Table **1**), while dapagliflozin and metformin yielded negative results [5].

Based on the patient's history, clinical presentation, laboratory findings, and pathologic results, a diagnosis of liraglutide-induced PV was established.

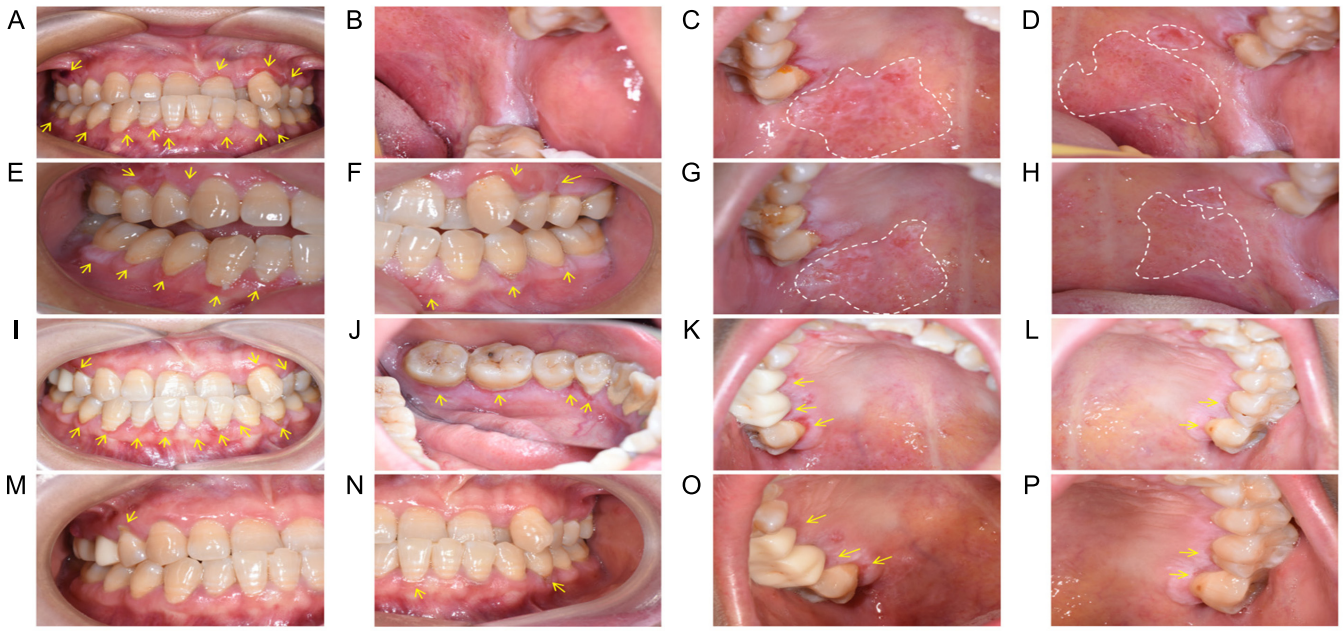


Fig. (1). Intraoral photographs documenting treatment progression (white dotted lines and yellow arrows representing palatal and gingival erosions, respectively). **(A-D)** Scattered erosions on the gingiva and palate were observed at the initial visit. **(E-H)** Improvement in erosions was observed after 3 weeks of discontinuing liraglutide and 6 weeks of topical treatment. **(I-L)** Recurrence of mild erosions in the original lesion area following 2 years of liraglutide reintroduction. **(M-P)** Further improvement of erosion lesions 3 months after liraglutide discontinuation. *(A higher resolution / colour version of this figure is available in the electronic copy of the article)*.

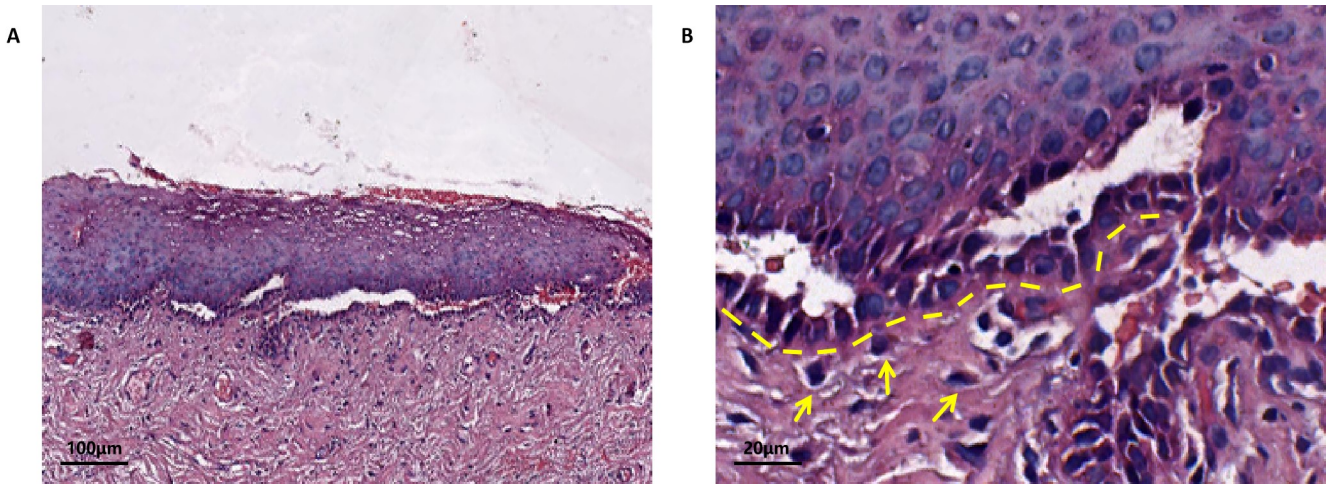


Fig. (2). Histopathologic examination of gingival tissue. **(A)** 4× magnification showing intraepithelial blister formation. **(B)** 20× magnification showing the formation of a suprabasal blister, with a layer of fence-like basal cells (yellow dotted line) attached to the connective tissue and scattered infiltration of lymphocytes (yellow arrows) in the submucosa. *(A higher resolution / colour version of this figure is available in the electronic copy of the article)*.

According to the treatment guidelines for DIP, immediate discontinuation of liraglutide and initiation of combined systemic and topical glucocorticoid therapy were recommended. However, systemic glucocorticoids were contraindicated due to the patient's poor glycemic control as per endocrinology consultation. The treatment plan included topical glucocorticoids, chlorhexidine gargle, and epidermal growth factor. After six weeks of treatment and three weeks off liraglutide, oral lesions improved but did not fully heal (Figs. **1E-H**). Due to significant glycemic fluctuations, the endocrinologist recommended resuming liraglutide at 1.2 mg per day alongside the topical regimen.

After two years of follow-up, mild erosions recurred in the original lesion area (Figs. **1I-L**). Antibody levels showed increased anti-Dsg1 (104.2 U/mL; normal <20 U/mL). Liraglutide was discontinued again for three months under endocrinologist supervision, leading to improved gingival eruptions (Figs. **1M-P**) and a decrease in anti-Dsg1 to 74.8 U/mL.

3. DISCUSSION

Traditional hypoglycemic agents have rarely been associated with pemphigus, with only one reported case of glibenclamide-induced PV in 1993 [6]. However, new hypoglycemic agents like DPP-4i, GLP-1RA, and SGLT-2i have seen increased reports of bullous diseases. This study presents the first documented case of PV induced by liraglutide, a GLP-1RA.

After three months of treatment with dapagliflozin and liraglutide for poor glycemic control, the patient developed multiple oral erosions, with a biopsy confirming PV. The temporal link between medication adjustment and PV onset suggests DIP. Therefore, we conducted a literature review on GLP-1RA- and SGLT-2i-induced autoimmune bullous diseases, primarily PV and bullous pemphigoid (BP), both of which can be induced by specific drugs. To date, only one case of SGLT-2i-related BP induced by empagliflozin has been reported [7], with no documented cases of dapagliflozin-induced pemphigus. In contrast, GLP-1RAs have been linked to five cases of BP (three with dulaglutide, one with liraglutide, and one with semaglutide) (Table **1**) [8-12]. No case of GLP-1RA-induced pemphigus has been previously reported.

A search of the FDA Adverse Event Reporting System (FAERS) database revealed 7 cases of pemphigus and 51 cases of pemphigoid associated with GLP-1RAs as of April 2024, including three pemphigus cases linked to liraglutide. Additionally, *in vitro* interferon-gamma release assays indicated a significant increase in interferon-gamma release upon stimulation of liraglutide, suggesting a likely causal relationship. The Naranjo scale score of 5 further supports this association. Due to the limited number of cases of GLP-1RA-induced pemphigus, high-powered epidemiological studies are needed to clarify the relationship.

The mechanism by which GLP-1RAs induce pemphigus remains unclear, but it may involve interfering with immunomodulatory functions or directly acting on cutaneous keratinocytes. GLP-1R is expressed on various immune cells, including innate immune cells (macrophages, neutrophils, and eosinophils), cells linking innate and adaptive immunity (invariant natural killer T cells, dermal γδ T cells), and adaptive immune cells (T/B lymphocytes) [13, 14]. Numerous studies have demonstrated that GLP-1RAs exhibit anti-inflammatory and immunomodulatory effects in systemic diseases, such as promoting M2 macrophage differentiation, inhibiting eosinophil activation, reducing pro-inflammatory cytokines, and enhancing Treg cell function [15, 16]. GLP-1RAs are also believed to have therapeutic roles in certain autoimmune diseases, such as type 1 diabetes mellitus, psoriasis, and inflammatory bowel disease [17]. However, the immunomodulatory function of GLP-1RAs appears to be detrimental in the context of pemphigus development.

Table 1. Summary of reported cases of bullous pemphigoid induced by GLP-1 receptor agonists.

Author, Year	Patient's Age and Gender	Drug and Dose	Related Disease	Onset Latency (weeks)	Management	Prognosis	References
Fukuda, 2019	62, M	Dulaglutide; 0.75 mg, once a week	BP	12	Withdrawal of dulaglutide with prednisolone and minocycline	Complete remission with no recurrence	[5]
Schwager, 2019	64, M	Dulaglutide; dose not specified	BP	6	Withdrawal of dulaglutide with topical corticosteroids	Complete remission	[6]
Collins, 2021	75, M	Liraglutide; 1.2 mg, once a day	BP	2	Withdrawal of liraglutide with doxycycline	Partial remission, pigmentary changes remained	[7]
Buruss, 2021	61, F	Semaglutide; dose not specified	BP	4	Withdrawal of semaglutide	Complete remission with no recurrence	[8]
Sonego, 2023	84, F	Dulaglutide; 1.5 mg, once a week	BP	8	Withdrawal of dulaglutide with prednisone, doxycycline, and topical treatment	Partial remission	[9]

Note: M: male; F: female; BP: Bullous pemphigoid.

Investigating the mechanism of BP induced by DPP-4i, another class of incretin hormone-related drugs, may provide insights into GLP-1RA-associated pemphigus. DPP-4i enhance GLP-1 levels *in vivo* by inhibiting its hydrolysis, exerting hypoglycemic effects. Several large-scale epidemiological studies have confirmed a strong correlation between DPP-4i and BP [18-20]. The mechanism by which DPP-4i induce BP involves immune modulation and direct effects on keratinocytes. Immunologically, DPP-4 is expressed in numerous immune cells [21] and regulates various immune functions [22-26]. DPP-4i suppress inflammatory immune responses and show therapeutic potential in diseases, such as Alzheimer's disease, obesity-associated inflammation, and myocarditis [27-29]. However, the relationship between DPP-4i and autoimmune diseases is complex. An epidemiological study on an Asian population found that DPP-4i treatment was significantly associated with a reduced prevalence of overall autoimmune diseases [30]. Nevertheless, specific autoimmune diseases, including BP, inflammatory bowel disease, and autoimmune joint disease, have been linked to DPP-4i usage [31]. It has been demonstrated that DPP-4i may induce BP by affecting Treg cell function, which is crucial for peripheral immune tolerance. In patients with idiopathic BP, total peripheral blood Treg cells and all Treg cell subsets are increased compared to healthy individuals, and effector Treg cells correlate positively with disease severity. In contrast, in DPP-4i-induced BP, total Treg cells and all Treg cell subsets are not increased, but naive Treg cells positively correlate with disease area index [32, 33]. This suggests that DPP-4i may cause immune dysregulation, leading to autoimmune diseases. Given the similar hypoglycemic and immunomodulatory functions of GLP-1RAs and DPP-4i, it is hypothesized that GLP-1RAs might also induce autoimmune diseases. A search of the FAERS database for cases associated with GLP-1RAs in 21 common autoimmune diseases indicated that GLP-1RAs are closely linked to the development of several autoimmune diseases, including inflammatory bowel disease, rheumatoid arthritis, and pemphigoid. Among these, liraglutide accounted for 22.7% of the cases (Figs. **3A**, **B**).

GLP-1RAs, including liraglutide, might induce pemphigus by affecting the physiological activities of keratinocytes. GLP-1R has been identified in various organs, but its role in the skin is not well understood. Some studies show mRNA and protein expression of GLP-1R in keratinocytes and inhibition of cell proliferation by liraglutide [34-36]. However, some argue that GLP-1R expression in the skin might be due to immune cell infiltration rather than keratinocytes themselves [37]. Therefore, further research is needed to confirm these findings.

Genetic susceptibility, particularly in relation to HLA class II alleles, plays a crucial role in autoimmune blistering diseases. In general, PV is associated with HLA-DRB1*04:02, DQB1*05:03, and DQB1*03:02, while BP is linked to HLA-DQB1*03:01 [38]. A study identified HLA class II alleles in six patients with DIP and found that all carried the DRB1*04:02 allele [39]. Furthermore, studies on patients with DPP-4i-induced BP revealed that most carried the DQB1*03:01 allele [40]. This suggests that both drug-induced and idiopathic bullous diseases may share the same susceptible HLA alleles, with both exogenous factors and genetic susceptibility contributing to disease development. Therefore, extensive research on the HLA genotypes of patients with autoimmune bullous diseases is needed to predict the risk of drug-induced cases, identify high-risk populations, and develop personalized treatment plans to mitigate adverse reactions.

There are common autoimmune mechanisms between BP and PV, focusing on autoantibodies against different adhesion proteins. Literature on cases of BP and PV occurring sequentially or simultaneously suggests that immune dysregulation and epitope spreading are potential factors for their coexistence or progression [41-43]. Drug-induced cases,

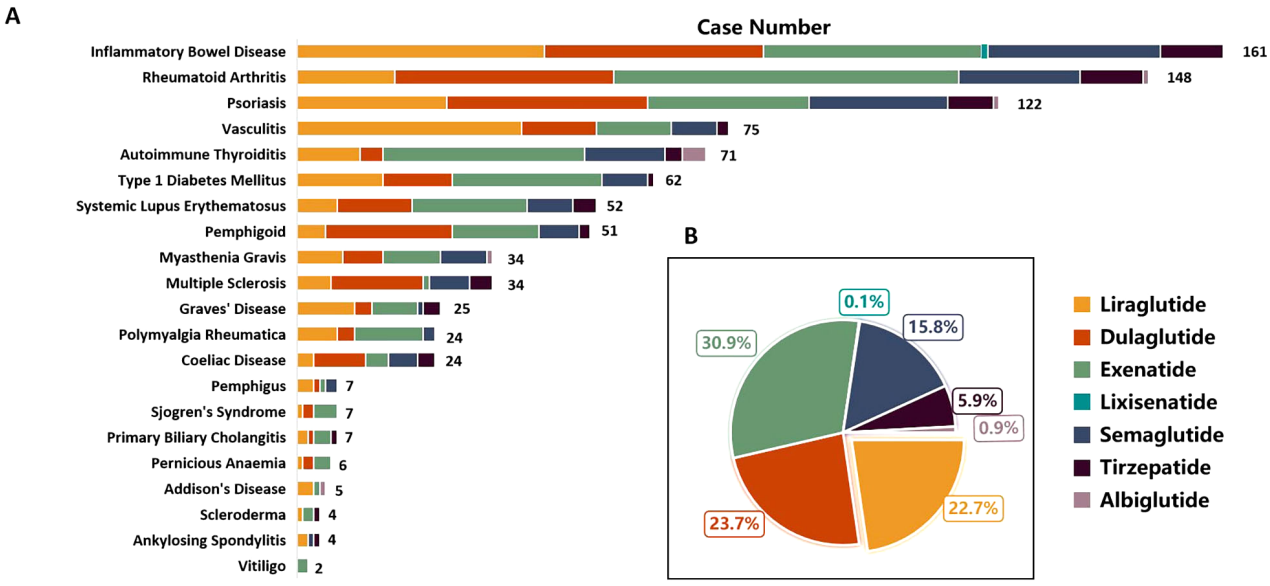


Fig. (3). FAERS database analysis: reported cases of GLP-1 receptor agonists-induced autoimmune diseases. **(A)** Number of cases of common autoimmune diseases induced by GLP-1 receptor agonists. **(B)** Percentage of cases induced by different types of GLP-1 receptor agonists. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

such as those triggered by DPP-4 inhibitors or immunotherapies (*e.g.*, PD-1/PD-L1 inhibitors), may play a role in the transition between BP and PV. Clinical differentiation between BP and PV is mainly based on a comparison of their characteristics, including age at onset, blister appearance, mucosal involvement, Nikolsky's sign, and differences between pruritus and pain. These distinctions are crucial for clinical differentiation, especially in drug-induced blistering diseases.

We acknowledge that a negative DIF result is uncommon in PV but not unprecedented. Several factors may explain this, including sampling issues, where the biopsy site influences DIF positivity, particularly if the lesion is in the early stage or minimally involved. DIF sensitivity is lower in early or mild PV cases, with some studies showing transient negative results in localized stages [44]. Intermittent immune complex deposition may also lead to variable DIF results as autoantibody levels fluctuate. Additionally, technical factors, such as tissue handling, can affect the outcome. Despite negative DIF, positive anti-Dsg1 antibodies from ELISA testing support the diagnosis of PV, reinforcing the clinical and histopathological findings. In the current study, the patient had an elevated anti-Dsg1 titer (55.9 U/mL) but was negative for anti-Dsg3, which is atypical in oral mucosa-limited PV [45, 43]. This could be explained by desmoglein compensation, where anti-Dsg1 alone may cause lesions due to variations in desmoglein expression [46, 47], early disease where anti-Dsg1 appears first, epitope spreading, or the involvement of non-desmosomal autoantibodies contributing to PV pathogenesis [48, 49].

Early detection and prompt discontinuation of the offending drug are essential in managing DIP. Due to the limited number of cases of GLP-1RA-associated pemphigus, identifying a generalized pattern is challenging. The time of onset varies. In this case, PV developed three months after starting liraglutide. Previous reports of BP induced by GLP-1RAs showed onset times ranging from one to twelve weeks. In addition, GLP-1RA-induced PV appears to have milder inflammation, limited erosion, and better prognosis, similar to the "non-inflammatory" properties observed in DPP-4i-associated BP [36]. Differentiating DIP from other oral erosive lesions in diabetic patients remains a clinical challenge. For example, poorly controlled diabetes can lead to increased dental caries and residual roots, increased risk of oral candidiasis, viral ulcers (*e.g.*, herpes simplex virus) and bacterial infections, autoimmune diseases (*e.g.*, oral lichen planus), and secondary systemic complications, such as diabetic nephropathy and anemia, all of which could present as oral mucosal erosions. In this case, clinical examination, negative fungal cultures and viral PCR tests, normal results of blood routine, liver and kidney function tests, along with a classic PV histopathologic pattern, can help to exclude the above conditions.

Clinicians should implement comprehensive monitoring regimens for patients on new hypoglycemic agents, particularly GLP-1RAs, with regular follow-up, detailed medical history records, and skin and mucosal examinations to detect early signs of adverse effects. The early symptoms of autoimmune diseases are often atypical. If patients experience unexplained fatigue, weight changes, low-grade fever, joint and muscle pain, rash, or digestive discomfort after starting medication, they should be treated with caution and undergo immunological screening, particularly if there is a family history of autoimmune diseases. Multidisciplinary consultation

may be necessary for early identification. Patients on GLP-1RAs should be informed about potential side effects, such as skin and mucosal lesions, and educated on recognizing symptoms for early detection and intervention. Clear guidelines for adjusting or discontinuing GLP-1RAs in cases of suspected DIP are essential, requiring collaboration with endocrinologists to balance glycemic control and manage adverse effects. In cases where drug discontinuation is not feasible or symptoms are mild, symptomatic treatment can be considered. However, for more severe cases, management strategies should include drug withdrawal, alternative glucose-lowering agents, and immunosuppressive therapy. Regular dermatologic and endocrinologic follow-up, skin and mucosal examinations, antibody titer monitoring, and periodic DIF testing are necessary to assess disease progression and therapy response. Further studies are needed to develop standardized monitoring protocols for drug-induced autoimmune diseases.

CONCLUSION

This first documented case of liraglutide-induced PV highlights the potential for GLP-1RAs to trigger autoimmune blistering diseases. This underscores the need for increased vigilance among clinicians prescribing GLP-1RAs, particularly in patients presenting with unexplained mucocutaneous lesions. Further studies, including *in vitro* models using human keratinocytes to assess immune activation, animal models to study immune-mediated blistering, and longitudinal studies to monitor autoantibodies and clinical outcomes in patients using GLP-1RAs, are essential to establish a definitive causal relationship, elucidate the immunopathogenesis, and optimize management strategies for DIP.

AUTHORS' CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: Data collection: CW and SZ; visualization: ZZ, WD, ZS, XQ, and FH; draft manuscript: XF, LJ, and SC. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

PV	=	Pemphigus Vulgaris
DIP	=	Drug-induced Pemphigus
GLP-1RAs	=	glucagon-like Peptide-1 Receptor Agonists
DPP-4i	=	dipeptidyl Peptidase 4 Inhibitors
SGLT-2i	=	sodium-glucose Transporter 2 Inhibitors
BP	=	bullous Pemphigoid
FAERS	=	FDA Adverse Event Reporting System

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the ethics committee (Medical Ethics Committee of West China Stomatological Hospital, Sichuan University)(WCHSIRB-D-2024-309).

HUMAN AND ANIMAL RIGHTS

All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committee and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

The study obtained informed consent of the patient.

STANDARDS OF REPORTING

CARE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author, Lu Jiang, on special request.

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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