Bullous pemphigoid triggered by dulaglutide: a case report and a review of the literature

Benedetta Sonego, Enrico Zelin, Iris Zalaudek, Nicola di Meo

Dermatology Clinic of Trieste, Maggiore Hospital, University of Trieste, Italy

Abstract

Bullous pemphigoid (BP) is an autoimmune disease with a chronic relapsing course, predominantly affecting elderly people. Drugs are one of the possible triggers. A class of antidiabetic drugs often associated with the development of BP are inhibitors of dipeptidyl peptidase 4 (DPP-4 inhibitors or gliptins), while less known is the association with glucagon-like-peptide-1 receptor agonists. We describe a case of BP caused by dulaglutide and summarize the other few cases described in the literature. As a class of drugs widely used in clinical practice, it is important to know about this possible adverse event.

Correspondence: Benedetta Sonego, Maggiore Hospital, Piazza dell'Ospitale 1, 34125, Trieste, Italy.
Tel.: +39.0403992056.
E-mail: benedetta.sonego@gmail.com

Key words: bullous pemphigoid; adverse drug reaction; dulaglutide; GLP-1 receptor agonists; antidiabetic drugs.

Contributions: BS, NdM, conceptualization; BS, EZ, data curation, resources, writing; NdM, IZ, supervision, validation. All the authors approved the final version to be published.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: none.

Availability data and materials: data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Informed consent: the patients have given written informed consent for the publication of their case details.

Acknowledgments: the authors would like to thank their colleague Dr. Marco Zanette for the attention and care given to the patient described in this case report and for emphasizing the importance of sharing this clinical experience.

Received: 21 January 2023.
Accepted: 9 February 2023.
Early view: 6 June 2023.

Licensee PAGEPress, Italy
Dermatology Reports 2023; 15:9676
doi:10.4081/dr.2023.9676

Introduction

Bullous pemphigoid (BP) is an autoimmune disease with a chronic relapsing course, predominantly affecting elderly people. Different triggers have been identified such as infections, vaccines, organ transplants, and medications.[1] In drug-induced BP, although the medication can act as an initial trigger for the manifestation, the disease seems to show a multifactorial etiopathogenesis involving also individual genetic susceptibility.[1,2] One class of antidiabetic drugs frequently associated with the development of drug-induced BP are the DDP-4 inhibitors; however, the association with glucagon-like-peptide-1 (GLP-1) receptor agonists is less known.[3,4] Herein, we describe a case of BP induced by dulaglutide, a GLP-1 receptor agonist.

Case Report

An 84-year-old woman presented to our dermatology clinic for evaluation of a diffuse bullous rash. The patient reported numerous comorbidities such as chronic kidney disease, hyperthyroidism, and hypertension for which she took several medications. She had been suffering from type II diabetes mellitus for about 20 years initially treated with vildagliptin, repaglinide, and acarbose; at the last check, all oral antidiabetic drugs were replaced with weekly dulaglutide subcutaneous administrations (1.5 mg). The drug was administered for seven weeks and then discontinued after one month because the patient developed a mild erythematous rash. At observation (two months after the beginning of dulaglutide), the patient manifested numerous tense bullous lesions with serous-hematic content spread over the entire skin area, and a single blister was observed on the oral mucosa. She reported intense itching (Figure 1).

A cutaneous biopsy was taken, and histological examination showed conspicuous eosinophilic papillitis with an arrangement of eosinophils along the free border of the dermal-papillary clefts. Direct immunofluorescence demonstrated IgG and C3 deposits on the basement membrane. Blood samples showed neutrophilic leukocytosis, an important elevation of inflammatory indices, and a marked increase in total IgE. Circulating antibody titer was: BP180 positive >200 U/ml (standard value <20 U/mL), BP230 positive 31 U/ml (standard value <20 U/mL). A diagnosis of bullous pemphigoid was made.

The patient had no recent infections or vaccinations. On suspicion of a paraneoplastic form, tumor markers were evaluated, which, however, proved negative. Regarding medications, dulaglutide appeared to be the only newly introduced drug.

Table 1. Overview of literature: cases of pemphigoid induced by glucagon-like-peptide-1 receptor agonists.

Author, year	Patient's age and gender	Drug	Onset latency (weeks)
Fukuda, 2019[5]	62, M	Dulaglutide	8
Buruss, 2021[6]	61, F	Semaglutide	4
Collins, 2021[7]	75, M	Liraglutide	2

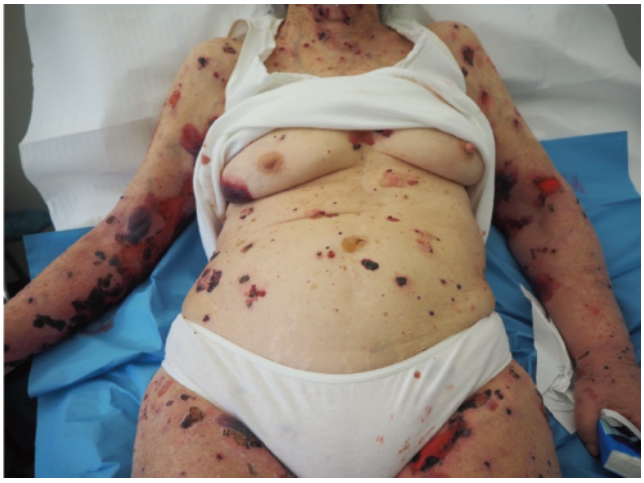

Figure 1. Clinical manifestation of dulaglutide-induced bullous pemphigoid.

Oral prednisone 25 mg/day and oral doxycycline 100 mg 2/day were prescribed. Topically, the patient was daily treated with drainage of bullous lesions and eosin touching. Regarding diabetes therapy, after discontinuation of dulaglutide, the therapy the patient was previously taking was restored with the addition of a daily subcutaneous injection of insulin glargine. At subsequent follow-ups (the patient was initially seen every month for the first three months, then every three months for the next six months, and then continued with follow-ups at six-month intervals), we noticed the absence of new lesions and gradual re-epithelialization of pre-existing erosions. Cortisone and antibiotic therapy were then gradually scaled up to discontinuation.

Discussion

Ours is one more case of dulaglutide-induced BP. Reviewing the literature we found other three cases of BP induced by GLP-1 analogs (Table 1): Fukuda *et al*. described a case of drug-induced BP occurring two months after the start of dulaglutide antidiabetic therapy.[5] In addition, Clayton *et al*. observed a case developed one month after the introduction of semaglutide.[6] Instead, Collins *et al*. described a case of BP liraglutide-induced that occurred two weeks after the introduction.[7] These reports seem to confirm that GLP-1 analogs can trigger BP, with latency from 2 weeks up to 2 months after the introduction of the therapy. Although the mechanism by which GLP-1 analogs cause BP is not already known, the hypothesis is that the drug binds to its receptor on skin keratinocytes and fibroblasts causing damage and consequently the development of BP.[5]

Conclusions

Patients suffering from BP are often elderly individuals with many comorbidities, who perform poly-pharmacotherapy. Understanding the cause of BP is not always trivial and aside from excluding a possible paraneoplastic form, it is important to look for a possible pharmacological cause, especially when reviewing all newly introduced medications. GLP-1 analogs are antidiabetic drugs with an important positive effect on the prevention of cardiovascular events and they are likely to be widely prescribed in the future. However, it is important to remember that in some cases they can induce the development of BP, even several weeks after their introduction.

References

1. Moro F, Fania L, Sinagra JLM, et al. Bullous pemphigoid: Trigger and predisposing factors. Biomolecules 2020;10:1-29.
2. Ujiie H, Muramatsu K, Mushiroda T, et al. HLA-DQB1*03:01 as a Biomarker for Genetic Susceptibility to Bullous Pemphigoid Induced by DPP-4 Inhibitors. J Invest Dermatol 2018;138:1201-4.
3. Tasanen K, Varpuluoma O, Nishie W. Dipeptidyl peptidase-4 inhibitor-associated bullous pemphigoid. Front Immunol 2019;10:1-10.
4. García Castro R, Godoy Gijón E, González Pérez AM, Román Curto C. Bullous pemphigoid and DPP4 inhibitors. Med Clin (Barc) 2019;153:368-71.
5. Fukuda G, Yoshida T, Hirayama A, et al. Dulaglutide-related bullous pemphigoid in a patient with type 2 diabetes: A case report. Geriatr Gerontol Int 2019;19:1289-90.
6. Burruss CP, Jones JM, Burruss JB. Semaglutide-associated bullous pemphigoid. JAAD Case Reports 2021;15:107-9.
7. Collins MK, Choudhary S, Ho J, Bunimovich YL. Bullous pemphigoid triggered by liraglutide. Cutis 2021;107:E9-E11.