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Case Report

Association of Dipeptidiyl Peptidase-4 Inhibitors and Bullose Pemphigoid: A Report of Four Cases

Dipeptidil Peptidaz-4 İnhibitörleri ve Büllöz Pemfigoid Arasındaki İlişki: Dört Olgu Raporu

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ABSTRACT

Dipeptidyl-peptidase 4 inhibitors (DPP4i) are commonly used as antidiabetic medications. Although these drugs are generally recognized for their favorable clinical safety profile, emerging evidence points to the potential for adverse events associated with DPP4i. Notably, cases of bullous pemphigoid (BP) linked to DPP4i therapy have recently been documented in the medical literature. This report presents four cases of BP in elderly patients resulting from DPP4i treatment, involving two cases with ligandliptin and two with vildagliptin use. Successful remission was achieved in all cases through discontinuation of the implicated medication and implementation of topical corticosteroid therapy. It is imperative for clinicians to be vigilant about the potential risk of BP development when employing DPP4i drugs, particularly in the context of elderly patients with diabetes.

Keywords: Bullose pemphigoid, DPP4i, dipeptidyl peptidase 4 inhibitors

ÖZ

Dipeptidil-peptidaz 4 inhibitörleri (DPP4i) yaygın olarak kullanılan antidiyabetik ilaçlardandır. Bu ilaçlar sıklıkla güvenli olarak bilinse de DPP4 inhibitörlerinin yan etki potansiyelini gösteren kanıtlar bulunmaktadır. Özellikle, DPP4i tedavisine bağlı büllöz pemfigoid (BP) olguları son zamanlarda tıbbi literatürde belgelenmiştir. Bu raporda, yaşlı hastalarda DPP4i tedavisine bağlı olarak gelişen, ikisi linagliptin ve ikisi vildagliptin kullanımını içeren dört BP olgusu sunulmaktadır. Tüm olgularda, söz konusu ilacın kesilmesi ve topikal kortikosteroid tedavisinin uygulanmasıyla başarılı bir remisyon elde edilmiştir. Klinisyenlerin özellikle diyabetli yaşlı hastalarda DPP4i ilaçlarını kullanırken, potansiyel BP gelişimi riski konusunda dikkatli olmaları gerekmektedir.

Anahtar kelimeler: Bülloz pemfigoid, DPP4i, dipeptidil peptidaz 4 inhibitörleri

INTRODUCTION

Bullous pemphigoid (BP) is a chronic blistering dermatological disease that predominantly affects elderly individuals. Characterized by the development of autoimmunity against hemi-desmosomal proteins such as BP180 (collagen XVII) and BP230, BP commonly presents as tense blisters, causing pruritic urticarial and eczema-like lesions[1]. The recent literature has highlighted a connection between dipeptidyl-peptidase 4 inhibitors (DPP4i) and drug-induced BP. Notably, differences exist between the classic and DPP4i-induced variants of BP; while the former involves antibodies against the non-collagenous (NC16A) domain, the latter targets another region of NC16A. This report discusses four cases of DPP4i drug-induced BP, involving two cases linked to ligandliptin and two cases linked to vildagliptin.

CASE REPORTS

Patient consent form was obtained.

Case 1

A 77-year-old man presented to our clinic with a 1-week history of erythematous bullous lesions. The patient, previously diagnosed with type 2 diabetes mellitus, sought medical attention because of uncontrolled glucose levels despite intensive insulin

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and metformin treatment. Linagliptin was subsequently added to the patient's regimen. Six months later, the patient developed erythematous bullous skin lesions following the introduction of DPP4i therapy. Blisters initially appeared on his legs and later spread across his body. The patient had no history of allergies. Physical examination and differential diagnosis were performed in the dermatology clinic. A skin lesion biopsy confirmed the clinical diagnosis of BP. Upon discontinuation of the DPP4i drug and initiation of topical corticosteroid therapy (klobetasol propionate), the dermatological lesions resolved.

Case 2

A 77-year-old man with a 10-year history of type 2 diabetes mellitus and chronic renal failure due to diabetes was referred to our clinic with a 2-month history of erythematous bullous lesions. The lesions initially presented as pruritic rashes before developing into bullous formations (Figure 1a,b). Linagliptin was the sole medication he had used over the past 6 months. Physical examination and differential diagnosis were performed in the dermatology clinic. A skin lesion biopsy confirmed the clinical diagnosis of BP. Following diagnosis confirmation, linagliptin was discontinued, and treatment with topical corticosteroids (clobetasol propionate) and antihistamine drugs was initiated, resulting in the healing of skin lesions.

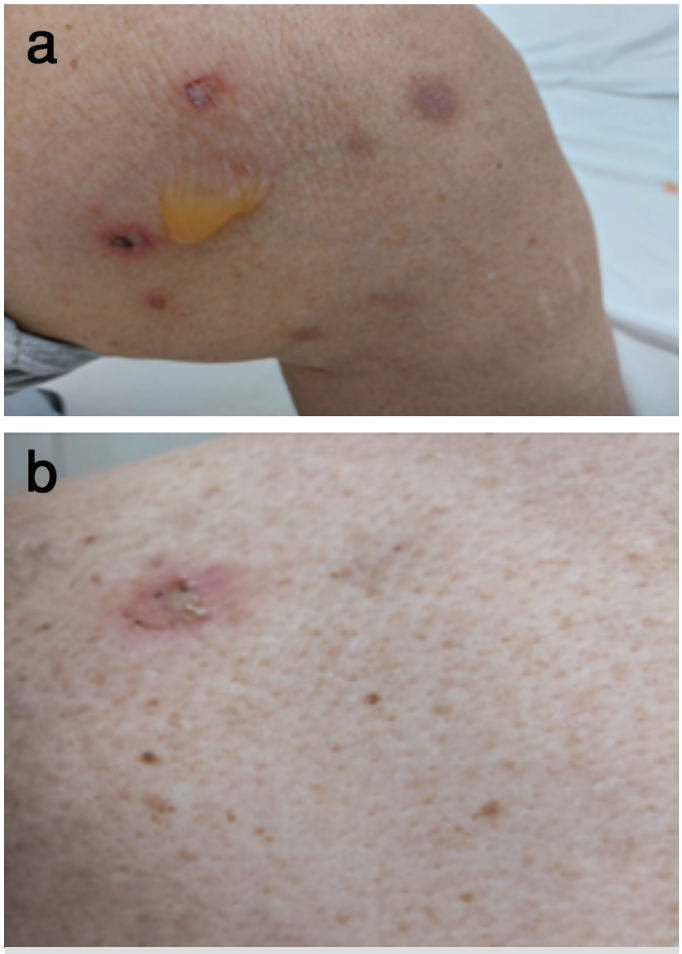

Figure 1a, b. Newly developed and healing erythematous bullous lesions in case 2

Case 3

A 78-year-old woman presented to our clinic with an itchy rash that had appeared on her back a month earlier. Diagnosed with type 2 diabetes mellitus for 5 years, she was on metformin and vildagliptin treatment. Allergy history was negative. Clinical assessment led to a diagnosis of BP attributed to the DPP4i drug vildagliptin. Physical examination and differential diagnosis were performed in the dermatology clinic. A skin lesion biopsy confirmed the diagnosis, prompting the discontinuation of vildagliptin treatment. Topical corticosteroids (clobetasol propionate) and antihistamine drugs were prescribed, resulting in the regression of skin lesions after 1 month and complete healing during the follow-up period.

Case 4

A 71-year-old woman with pruritic lesions on her back was referred to our outpatient clinic from the dermatology clinic. The patient was diagnosed with type 2 diabetes mellitus for 15 years and had been on vildagliptin treatment for 6 months. The itchy erythematous bullous lesions had presented 2 months previously. Allergy history was negative. Physical examination and differential diagnosis were performed in the dermatology clinic. Skin lesion biopsy confirmed the diagnosis, and vildagliptin treatment was discontinued. Corticosteroids and antihistamine drugs were prescribed, resulting in the regression of skin lesions after 2 weeks.

These cases underscore the potential connection between DPP4i and BP, particularly in elderly patients with diabetes. Discontinuation of the DPP4i and appropriate treatment can lead to successful BP remission.

DISCUSSION

The cell surface protein CD26, also known as DPP4, serves as both a T-cell lymphocyte surface glycoprotein and a host of DPP4 enzymatic activity. This CD26/DPP4 antigen is expressed across various cell types in the body, including skin cell membranes and immune cells[2,3]. This dual presence raises the possibility that DPP4i may exert effects on both immune and skin cells.

DPP4i, a class of antidiabetic drugs frequently combined with metformin, operate through the incretin system[2]. They elicit several effects, such as the reduction of Th1 activity and the augmentation of TGF beta 1 production via the Th3 regulatory system[4]. Additionally, DPP4i can induce eosinophil activation in the skin through CCL11/exotoxin signaling[5]. These mechanisms link DPP4i actions with immune responses involved in the pathogenesis of BP[6].

Recent investigations have illuminated an elevated risk of BP associated with DPP4i drug treatment, with a reported increase of nearly two to three times[7]. Several cases related to DPP4i have been reported. Among the DPP4i implicated, ligandliptin, vildagliptin, and Anagliptin are prominent in the induction of BP[8]. Notably, although the less selective DPP4i, vildagliptin, is a common culprit, sitagliptin does not seem to be linked to DPP4i-induced BP[7,9]. The duration of treatment leading to DPP4i-induced BP varies in the literature, ranging from 8 days to 4 years[10-12]. This can cause a delay in diagnosis and treatment. Key risk factors include older age and male gender, with most cases affecting individuals aged 80 years [7,13]. In the presented cases, the age also tended to be older, with a mean age of 75 years; two patients were men and two were women. Consistent with the existing literature, vildagliptin and linagliptin emerged as the DPP4i drugs responsible for drug-induced BP in the presented cases[10,11,13]. Two types of DPP4i drugs (linagliptin and vildagliptin) were also implicated in our cohort of patients.

DPP4i-induced BP typically exhibits lower levels of inflammation and erythema than classical BP[1,9]. However, we did not observe this in our cohort. The diagnosis relies on skin biopsies from the lesions and direct immunofluorescence staining. Skin biopsy and direct immunofluorescence on perilesional skin remains the gold standard for diagnosis even in DPP4i-induced BP. While classic BP involves autoantibodies targeting the NC16A domain, patients with DPP4i-induced BP exhibit autoantibodies against the mid-portion of the BP180 antigen (collagen XVII)[1,9]. A retrospective study suggests that linagliptin-induced BP may be more challenging to treat than vildagliptin-induced BP. The complex and unclear pathological mechanisms underpinning DPP4i-induced BP confer a risk of mortality[14]. The diagnostic process may be complicated by the varying durations of treatment leading to disease onset. Replacing one DPP4i with another is not recommended[12,15]. Persistent cutaneous symptoms despite steroid administration were observed in all presented cases. After cessation of DPP4i, improvement was observed within 2 weeks. Consequently, an early diagnosis and prompt discontinuation of DPP4i drugs are crucial measures. Treatment options include systemic or topical glucocorticoids[8,9]. These findings strongly suggest a causal role for DPP4i in this disease. However, this study has limitations such as the lack of a control group, the observational nature of case reports, and the need for randomized controlled trials to establish causality.

Diagnosing DPP4i drug-induced BP can prove challenging because of the varying durations of treatment precipitating the condition. Clinicians must be alert to this potential complication, particularly in elderly diabetic patients. Swift diagnosis and immediate discontinuation of the offending drug often result in effective treatment and healing of skin lesions.

Ethics

Informed Consent: Patients' consent form was obtained.

Author Contributions

Design: B.C., Data Collection and/or Processing: K.G., Literature Search: N.U., B.C., Writing: N.U.

Conflict of Interest: The authors have no conflict of interest to declare.

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