Case Report
Turk J Endocrinol Metab 2018;22:198-203

Two Cases of Bullous Pemphigoid Induced by Vildagliptin

Vildagliptinle İndüklenen İki Tane Büllöz Pemfigoid Vakası

Aslı Doğruk Ünal, Özlem Üstay Tarçın, Gülşen Tükenmez Demirci*, Ebru Demiralay**, Ayşe Tülin Mansur*, Şemsi Yıldız**, Nilgün Güvener Demirağ

Başkent University İstanbul Hospital, Division of Endocrinology and Metabolism Diseases, İstanbul
*Başkent University İstanbul Hospital, Department of Dermatology, İstanbul
**Başkent University İstanbul Hospital, Department of Pathology, İstanbul

Abstract

Purpose: Bullous pemphigoid is an autoimmune blistering disorder that commonly develops in elderly subjects who are prone to an increased risk of mortality and morbidity. Although a few cases of dipeptidyl peptidase-4 inhibitors have been reported earlier, the etiology of bullous pemphigoid is not entirely clear.

Case Report 1: An 81-years-old man presented with bullous pemphigoid after 28 months of treatment with repaglinide, vildagliptin, and metformin. Since his skin lesions were not improving with topical treatment of clobetasol propionate 0.05% ointment, so then he was started on methylprednisolone and azathioprine; however, the skin lesions sustained even then. Remission was achieved only after the withdrawal of vildagliptin.

Case Report 2: A 64-years old man who was on insulin glargine, insulin aspart, and vildagliptin for 12 months, presented with BP of skin and laryngeal mucosa. The skin lesions were resolved after discontinuation of vildagliptin, but the laryngeal involvement continued to exist. Methylprednisolone and azathioprine treatment, for mucosal lesions, were started and continued for six months.

Conclusion: Only a few cases of gliptin induced bullous pemphigoid are present in the literature. One of our cases is the first to demonstrate the latest onset of vildagliptin associated skin reactions while the other case is the first to demonstrate vildagliptin associated mucosal involvement. The exact mechanism of these reactions is unknown, however, it is proposed that it could be caused by modified immune responses. Our cases support the finding that there is a risk of bullous pemphigoid development in patients exposed to vildagliptin. Therefore, it is important to be aware of this risk and stop the vildagliptin treatment in such patients.

Keywords: Diabetes mellitus; bullous pemphigoid; vildagliptin

Özet

Amaç: Büllöz pemfigoid, sıklıkla artmış mortalite ve morbiditeye meyilli yaşlı bireylerde gelişen bir döküntülü otoimmün hastalıktır. Daha once dipeptidil peptidaz-4 inhibitörü ile az vaka bildirilmesine rağmen, büllöz pemfigoidin etiyolojisi tam olarak açık değildir.

Vaka 1: Seksen bir yaşındaki erkek hasta; repaglinid, vildagliptin ve metforminle 28 aylık bir tedavi sonrasında büllöz pemfigoid ile başvurmuştur. Cilt lezyonları topikal %0,05'lik klobetasol propriyonat merhem tedavisi ile geçmediğinden, sonrasında metilprednizolon ve azatioprin başlanmış; fakat, cilt lezyonları hâlâ sebat etmemiştir. Vildagliptinin kesilmesinden sonra remisyon sağlanmıştır.

Vaka 2: On iki aydır insülin glarjin, insülin aspart ve vildagliptin kullanan 64 yaşında erkek hasta; cilt ve larenks mukozada büllöz pemfigoid ile başvurdu. Cilt lezyonları vildagliptinin kesilmesinden sonra söndü, fakat larenks tutulumu devam etti. Mukozal lezyonlar için metilprednizolon ve azatioprin tedavisi başlandı ve altı ay devam edildi.

Tartışma: Literatürde az sayıda gliptinle indüklenen büllöz pemfigoid vakası bulunmaktadır. Hastalarımızdan biri vildagliptinle indüklenen cilt reaksiyonlarının geç başlangıcını gösterirken, diğeri vildagliptinle ilişkili mukozal tutulumun gösterildiği ilk vakadır. Bu reaksiyonların mekanizması tam olarak bilinmemektedir, fakat modifiye immüne yanıtın neden olabileceği ileri sürülmektedir. Çalışmamızda, vildagliptine maruz kalan hastalarda büllöz pemfigoid gelişme riskini desteklemektedir. Bu nedenle, bu riskin farkında olmak ve bu hastalarda vildagliptin tedavisini kesmek önemlidir.

Anahtar kelimeler: Diabetes mellitus; büllöz pemfigoid; vildagliptin

Introduction

Vildagliptin belongs to a class of drugs known as gliptins that are inhibitors of dipeptidyl peptidase-4 (DPP-4). DPP-4 inhibitors increase circulating levels of glucagon-like peptide 1 (GLP-1) and glucose

Address for Correspondence: Aslı Doğruk Ünal, Başkent University İstanbul Hospital, Division of Endocrinology and Metabolism Diseases, İstanbul, Turkey
Phone: 0 532 577 95 58 **E-mail:** aslidogruk@yahoo.com **Received:** 09/06/2016 **Accepted:** 21/07/2016

DOI: 10.25179/tjem.2017-56526

dependent insulinotropic polypeptide regulating glucose-dependent insulin secretion Increased levels of incretins improve insulin sensitivity and reduce inappropriate glucagon production (1). The enzyme DPP-4 is expressed in almost every organ system.Reports indicate that several skin reactions develop not only because of vildagliptin but also sitagliptin (2).

Bullous pemphigoid (BP) is an autoimmune disease identified by deposition of immunoglobulins and complement components in the epidermal basement membrane zone and is associated with autoantibodies against two hemi-desmosomal proteins (3). This chronic disorder is characterized by exacerbations and remissions; the clinical findings in BP are tense, fluid-filled bullae on the skin. Mucosal lesions are found to be present in 10-30% of patients. Since BP causes significant morbidity and excess mortality, so the chronic use of DPP-4 has been associated with increased risk of BP development BP (4, 5).

Here, we report two cases of vildagliptin induced BP, in one, bullae developed after a relatively long period while the other had mucosal involvement.

Case Reports

Case 1: An 81-year-old man presented with pruritic skin lesions with a medical history that included hypertension and type 2 diabetes. He was on irbesartan, vildagliptin, repaglinide, and metformin treatments since the last 28 months. On his physical examination, diffused erythematous plaques with superposed tense bullae, suggestive of BP, were observed (Figure 1), but Nikolsky's sign was found to be absent. His differential blood cell count was non-significant and HbA1c level was 5.2%. Two biopsies were taken for examination by direct immunofluorescence (DIF) method, one from the lesion for routine pathological examination and the other from a non-lesional area. The biopsies were sent to a pathology laboratory with the preliminary diagnosis of BP, prurigo and perforating dermatosis. The biopsy taken from the lesion revealed that the floor of the bulla that was composed of the dermis, showed edema and contained abundant perivascular lymphocytic inflammatory cell infiltrate, histiocytes and eosinophils. In the place of the epidermis, there was a fibrinoid material mixed with scattered amounts of eosinophils and neutrophils on the surface of the biopsy. In the serial sections, there were no morphological findings that were suggestive of any prurigo or perforating dermatosis. The final diagnosis of active chronic inflammation along with ulceration was confirmed after the biopsy. The DIF staining that was performed for immunoglobulin G (IgG), was negative. The patient's condition did not improve using topical treatment because of which treatment with azathioprine and methylprednisolone was started. Vildagliptin was replaced by insulin and metformin due to the presence of high blood glucose levels. After the withdrawal of vildagliptin treatment, the patient's rashes improved significantly and when methylprednisolone and azathioprine were also tapered off there was no recurrence of the lesions for 18 months.

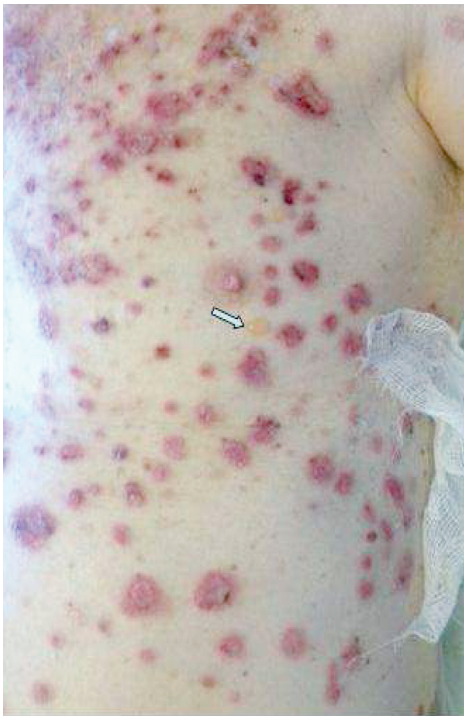

Figure 1: Multiple, diffuse, and scattered erythematous residues of bullae of different sizes all over the trunk. One intact bulla is seen under the left areola (shown by the arrow).

Case 2: A 64-year-old man having type 2 diabetes mellitus and hypertension was treated with insulin glargine, insulin aspart, vildagliptin, telmisartan, allopurinol, doxa-

zosin, and pregabalin for 12 months. He was admitted to the hospital for generalized erythematous vesicular and blistering eruptions and hoarseness. On his general physical examination, erythematous vesiculobullous eruptions were observed on the chest, upper extremities, scalp, and beard (Figure 2a, b). Oral-nose-throat examination of the patient revealed generalized erythema, desquamation and multiple large ulcers of the laryngeal mucosa. His complete blood cell count was normal and the HbA1c level was found to be 5.7%. Two biopsies were taken, one for routine histological examination and the other for DIF, with the incisional biopsy indicating subepidermal cleavage. Scattered erythrocyte and inflammatory cells were present within the blister and there was a mild degree of inflammation composed of lymphocytes and plasma cells, in the dermis. The histological findings from this case were not suggestive of pemphigus vulgaris. The biopsy of the tissue report suggested subepidermal detachment and bulla formation consistent with BP (Figure 3). This diagnosis was supported by DIF result, which showed linear homogeneous deposition of IgG along the basement membrane zone. The patient was commenced on topical steroids while awaiting biopsy reports. The skin lesions seemed to improve after the termination of vildagliptin, but laryngeal involvement still continued. The drugs azathioprine and methylprednisolone were added to his treatment and were continued for six months. It was found that the skin and mucosal lesions did not relapse for nearly 12 months.

Discussion

Following the frequent use of gliptins in the treatment of type 2 diabetes mellitus, a few cases of BP were reported that were found to be associated with vildagliptin and sitagliptin in the literature (6, 7). Up till now, there have been, 14 cases associated with vildagliptin treatment versus four cases with sitagliptin treatment (6, 8-10). Since the FDA did not approve vildagliptin treatment initially due to pre-clinical studies that demonstrated the occurrence of skin lesions, so the skin reactions in humans, most serious of which is Steven Johnson syndrome, were reported only with sitagliptin (2).

DPP-4 is a cell surface glycoprotein expressed throughout the body including the skin and its inhibition may lead to modification of the immune response and alterations in the antigenic properties of the epidermal basement membrane. Increased serum levels of transforming growth factor beta–1 from T-cells have been demonstrated in contrast to the blister fluid (11).

Bullous pemphigoid is an acquired autoimmune disease that occurs mainly in elderly patients and its development is associated

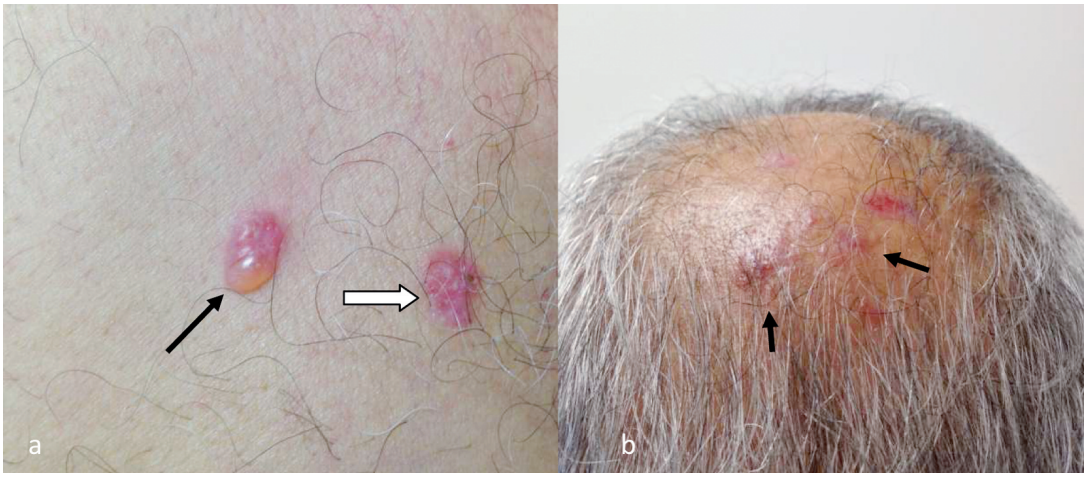

Figure 2: (a) Bullae (shown by the black arrow) and erythematous residue (shown by the white arrow) on the back and **(b)** multiple, diffuse, scattered erythematous residues of bullae in different sizes on the head (shown by the black arrow).

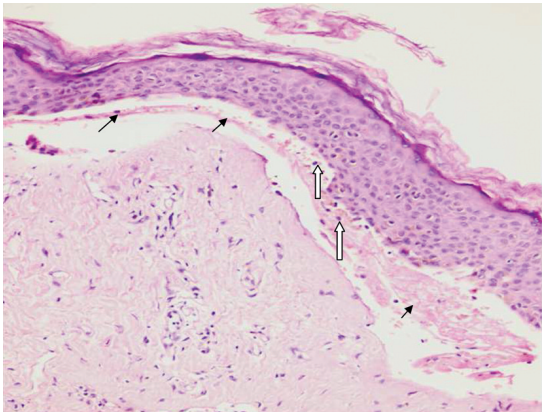

Figure 3: Histopathologic findings of skin showed hyperkeratosis of epidermis at the surface, subepidermal blister with a detached overlying epidermis and dermis (shown by the black arrow), and numerous erythrocytes and inflammatory cells within the blister cavity (shown by the white arrow) (HE, x200).

with the use of various types of drugs (12). Our two cases were based on the use of antihypertensive drugs; however, to the best of our knowledge, there is no case that is reported to be associated with irbesartan and doxazosin in the literature. Thus, we did not cease these drugs either in the course of diagnosis or treatment and besides, skin lesions resolved immediately after discontinuation of vildagliptin.

The cases reported in the previous studies generally developed BP with an onset range of 2-13 months after the treatment with DPP-4 inhibitors (6, 7), but our first case developed BP after a relatively long treatment period of 28 months.

Bullous pemphigoid typically affects the skin whereas the mucous membrane pemphigoid (MMP) especially involves the upper aerodigestive tract (13). Our second case was an example of a BP patient presenting with the mucosal involvement of pharynx. Scarring is the most common consequence of MMP, which distinguishes it from mucosal involvement in BP (14). The relationship between BP and malignancy is not yet clearly known; however, the existence of an increased risk of BP with some cancer types has been reported in the literature. MMP with laminin 332 antibody has been reported to be associated with an increased risk of malignancy (15, 16). In our study, we performed age and gender appropriate cancer screening and followed-up the patients up to 18 months and found that none of the patients developed any type of malignancy.

Direct immunofluorescence is considered to be a gold standard for the diagnosis of BP. A linear IgG and/or linear C3 staining along the basement membrane zone is present in more than 90% of BP cases; however, less intense staining for immunoglobulin M, immunoglobulin A and/or immunoglobulin E may also be present. In early lesions, hematoxylin and eosin staining particularly show eosinophilic spongiosis. Histopathological examination of cutaneous lesions of BP shows subepidermal blister formation and superficial dermal inflammatory cell infiltration of lymphocytes, histiocytes, neutrophils, and eosinophils in variable intensity. In our first case, DIF was negative for IgG and we could not stain the specimen with other Igs and complement. Moreover, on the other hand, it should be kept in mind that there are a few cases of BP with negative DIF reported in the literature (10).

Naranjo et al (17)., defined Adverse Drug Reaction probability rating scale to assess adverse drug reaction by excluding therapeutic failures, intentional and accidental poisoning and drug abuse. Both patients were scored 7 according to Naranjo Scale Questions and weighted scores, which indicated that vildagliptin might be a probable cause of BP (17) (Table 1).

Since patients with BP have a two-fold higher risk of death compared to the general population, so here we emphasize the importance of the relation between DPP-4 inhibitors and BP development. Health professionals, particular diabetologists, should be made aware of this risk. In these BP patients, a prompt diagnosis, the cessation of gliptin and appropriate treatment would provide better prognosis and cause lower mortality.

Source of Finance: During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Table 1. The Naranjo Scale questions and weighted scores.

	Yes	No	Do not know
1 Are there previous conclusive reports on this reaction?	+1	0	0
2 Did the adverse event appear after the suspected drug was administered?	+2	-1	0
3 Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
4 Did the adverse reaction reappear when the drug was readministered?	+2	-1	0
5 Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0
6 Did the reaction reappear when a placebo was given?	-1	+1	0
7 Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
8 Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
9 Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10 Was the adverse event confirmed by any objective evidence?	+1	0	0
The weighted score for both cases		**7**	

Conflict of Interest: No conflicts of interest between the authors and/or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Aslı Doğruk Ünal, Nilgün Güvener Demirağ; Design: Aslı Doğruk Ünal; Data Collection and/or Processing: Aslı Doğruk Ünal, Özlem Tarçın, Gülşen Tükenmez Demirci, Ayşe Tülin Mansur, Ebru Demiralay, Şemsi Yıldız, Nilgün Güvener Demirağ; Analysis and/or Interpretation: Aslı Doğruk Ünal, Özlem Tarçın; Literature Review: Aslı Doğruk Ünal; Writing the Article: Aslı Doğruk Ünal, Özlem tarçın

References

1. Mari A, Sallas WM, He YL, Watson C, Ligueros-Saylan M, Dunning BE, Deacon CF, Holst JJ, Foley JE. Vildagliptin, a dipeptidyl peptidase-IV inhibitor, improves model-assessed beta-cell function in patients with type 2 diabetes. J Clin Endocrinol Metab. 2005;90:4888-4894.
2. Desai S, Brinker A, Swann J, Iyasu S. Sitagliptin-associated drug allergy: review of spontaneous adverse event reports. Arch Intern Med. 2010;170: 1169-1171.
3. Xu L, Robinson N, Miller SD, Chan LS. Characterization of BALB/c mice B lymphocyte autoimmune responses to skin basement membrane component type XVII collagen, the target antigen of autoimmune skin disease bullous pemphigoid. Immunol Lett. 2001;77:105-111.
4. Cigerli O, Parildar H, Unal AD, Tarcin O, Erdal R, Guvener Demirag N. Vitamin D deficiency is a problem for adult out-patients? A university hospital sample in Istanbul, Turkey. Public Health Nutr. 2013;16: 1306-1313.
5. Langan SM, Smeeth L, Hubbard R, Fleming KM, Smith CJ, West J. Bullous pemphigoid and pemphigus vulgaris--incidence and mortality in the UK: population based cohort study. BMJ 2008;337: a180.
6. Aouidad I, Fite C, Marinho E, Deschamps L, Crickx B, Descamps V. A case report of bullous pemphigoid induced by dipeptidyl peptidase-4 inhibitors. JAMA Dermatol. 2013;149:243-245.
7. Pasmatzi E, Monastirli A, Habeos J, Georgiou S, Tsambaos D. Dipeptidyl peptidase-4 inhibitors cause bullous pemphigoid in diabetic patients: report of two cases. Diabetes Care. 2011;34:e133.
8. Skandalis K, Spirova M, Gaitanis G, Tsartsarakis A, Bassukas ID. Drug-induced bullous pemphigoid in diabetes mellitus patients receiving dipeptidyl peptidase-IV inhibitors plus metformin. J Eur Acad Dermatol Venereol. 2012;26:249-253.
9. Béné J, Jacobsoone A, Coupe P, Auffret M, Babai S, Hillaire-Buys D, Jean-Pastor MJ, Vonarx M, Vermersch A, Tronquoy AF, Gautier S. Bullous pemphigoid induced by vildagliptin: a report of three cases. Fundam Clin Pharmacol. 2015;29(1):112-114.
10. Attaway A, Mersfelder TL, Vaishnav S, Baker JK. Bullous pemphigoid associated with dipeptidyl peptidase IV inhibitors. A case report and review of literature. J Dermatol Case Rep. 2014;8:24-28.
11. Giacalone B, D'Auria L, Bonifati C, Ferraro C, Riccardi E, Mussi A, D'Agosto G, Cordiali-Fei P, Ameglio F. Decreased interleukin-7 and transforming growth factor-beta1 levels in blister fluids as compared to the respective serum levels in patients with bullous pemphigoid. Opposite behavior of TNF-alpha, interleukin-4 and interleukin-10. Exp Dermatol. 1998;7:157-161.
12. Stavropoulos PG, Soura E, Antoniou C. Drug-induced pemphigoid: a review of the literature. J Eur Acad Dermatol Venereol. 2014;28:1133-1140.

13. Murono S, Nakanishi Y, Fujimoto M, Yoshizaki T. Hypopharyngeal presentation of cicatricial pemphigoid: videofluorographic and direct laryngoscopic findings. J Laryngol Otol. 2013;127:429-431.
14. Fleming TE, Korman NJ. Cicatricial pemphigoid. J Am Acad Dermatol. 2000;43:571-591.
15. Sadler E, Lazarova Z, Sarasombath P, Yancey KB. A widening perspective regarding the relationship between anti-epiligrin cicatricial pemphigoid and cancer. J Dermatol Sci. 2007;47:1-7.
16. Miyazaki K. Laminin-5 (laminin-332): unique biological activity and role in tumor growth and invasion. Cancer Sci. 2006;97:91-98.
17. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239-245.