Case Report

DOI: 10.4274/tjem.3211
Turk J Endocrinol Metab 2016;20:140-143

Bullous Pemphigoid Induced by Vildagliptin

Vildagliptine Bağlı Büllöz Pemfigoid Olgusu

Bengür Taşkıran, Bahattin Erdoğan*, Canan Solak Şişman**, Güven Barış Cansu

Eskişehir Yunus Emre State Hospital, Clinic of Endocrinology, Eskişehir, Turkey
*Eskişehir Yunus Emre State Hospital, Clinic of Pathology, Eskişehir, Turkey
**Eskişehir Yunus Emre State Hospital, Clinic of Dermatology, Eskişehir, Turkey

Abstract

Bullous pemphigoid (BP) is an uncommon chronic, autoimmune, and subepidermal disease. Tense blisters occur on normal or erythematous skin. It can be induced by medications. There is a number of reports on BP induced by dipeptidyl peptidase 4 (DPP-4) inhibitors (vildagliptin, sitagliptin, saxagliptin). DPP-4 (CD26), present as a cell surface molecule on immune cells, also plays an important costimulatory role in immune activation. BP more commonly affects elderly men. We present a case of BP induced by vildagliptin. A 59-year-old male patient who was diagnosed with type 2 diabetes mellitus had initial hemoglobin A1c level of 12.90%. Initial therapy with premix biphasic aspart insulin bid was switched to metformin and vildagliptin 50/1000 mg combo pill bid after A1c level dropped to 5.7% at 9 months of insulin therapy, Five months after vildagliptin was started, tense vesicles 8-10 in number with an erythematous base developed on the forearms and cruris. Histological examination of the lesions confirmed the diagnosis of BP. Oral antidiabetics were discontinued. He was followed up with diet alone. The lesions regressed spontaneously after cessation of antidiabetics and clobetasol propionate cream bid treatment. A1c was 5.7% 5 months after discontinuation of vildagliptin and metformin. In the literature, it has been reported that onset of BP lesions took 10 days to 2 years. Mostly the patients were on combo therapy with metformin. The lesions improved dramatically after cessation of DPP-4 inhibitors avoiding necessity for systemic treatment for BP. This is the first case of BP induced by DPP-4 inhibitors in Turkey.
Keywords: Bullous pemphigoid, vildagliptin, dipeptidyl peptidase inhibitors

Öz

Büllöz pemfigoid (BP) nadir görülen, kronik, otoimmün ve subepidermal bir deri hastalığıdır. Hem normal hem eritematöz deri üzerinde gergin kabarcıklar oluşur. İlaçlarla ilişkili olabilir. Dipeptidil peptidaz-4 (DPP-4) inhibitörlerinin (vildagliptin, sitagliptin) neden olduğu bir takım bildirimler vardır. İmmün hücreler üzerinde yüzeysel molekül olarak da bulunan DPP-4 (CD26) immün aktivasyonda önemli bir eş zamanlı olarak uyarıcı rol oynar. Vildagliptinin neden olduğu bir BP olgusu sunuyoruz. Tip 2 diabetes mellitus tanısı alan ve ilk hemoglobin A1c değeri %12,90 olan 59 yaşında bir erkek hastaya premiks bifazik aspart tedavisi başlandı. A1c değeri 9 aylık insülin tedavisinin sonunda %5,7'ye düşmesi üzerine tedavi metformin ve vildagliptin 50/1000 mg kombinasyon olarak değiştirildi. Vildagliptin-metformin tedavisi başlandıktan beş ay sonra ön kol ve alt bacak üzerinde eritematöz deri üzerinde 8-10 adet gergin veziküller gelişti. Lezyonların histolojik incelemesi ile büllöz pemfigoid tanısı kondu. Oral antidiabetikler kesildi. Sadece beslenme tedavisi ile izlendi. Oral tedavinin kesilmesi ve topikal klobetasol propiyonat krem tedavisi ile lezyonlar geriledi. Vildagliptin ve metformin kesildikten 5 ay sonra A1c düzeyi %5,7 idi. Literatürde ilaç sonrası BP lezyonlarının oluşması için geçen süre 10 gün ile 2 yıl arası değişmektedir. Hastaların çoğu gliptinle kombine olarak metformin almaktadır. DPP-4 inhibitörlerinin kesilmesinin hemen ardından lezyonlarda dramatik iyileşme görülmesi sistemik tedavi gereksinimini yok edebilir. Yaşlı erkeklerde daha sık görülür. Olgumuz, Türkiye'den bildirilen ilk DPP-4 inhibitor kullanımına bağlı BP bildirimidir.
Anahtar kelimeler: Büllöz pemfigoid, vildagliptin, dipeptidil peptidaz inhibitörleri

Introduction

Bullous pemphigoid (BP) is an uncommon chronic, autoimmune, and subepidermal disease (1). Tense blisters occur on normal or erythematous skin (1). BP may be localized or generalized. It may involve both skin of the extremities and trunk and mucosa. Pruritus may precede bullae formation by weeks or months. It can be induced by drugs, ultraviolet irradiation, and X-ray therapy (1). There is a number of reports of BP induced by dipeptidyl peptidase 4 (DPP-4) inhibitors (vildagliptin, sitagliptin) used for the treatment of type 2 diabetes mellitus (T2DM) (2,3,4,5,6). Although skin lesions were not observed at an increased incidence in clinical trials, there have been post-marketing reports of bullous and exfoliative skin lesions. The enzyme DPP-4 degrades glucagon-like peptide 1 (GLP-1), which is a potent stimulator of insulin production and secretion (7). DPP-4 is expressed by diverse tissues including skin (7). In the skin, many cell types (including keratinocytes) express DPP-4, giving rise to cytokine production, tissue differentiation and collagen metabolism (7). Some factors that are modulated by DPP-4 in vivo, such as proglucagon, GLP-1 and GLP-1 receptor

Address for Correspondence: Bengür Taşkıran MD, Eskişehir Yunus Emre State Hospital, Clinic of Endocrinology, Eskişehir, Turkey
Phone:+90 284 236 09 09 E-mail: bengurtaskiran@yahoo.com.tr **Received:** 27/06/2015 **Accepted:** 13/11/2015

have also been described in cutaneous structures (7). The biological pluripotency of gliptins may lead to a modification of immune response and/or an alteration of antigenic properties of the epidermal basement membrane resulting in BP (8).
DPP-4 (CD26) also presents as a cell surface molecule on immune cells and plays an important costimulatory role in immune activation (9,10). We present a case of BP induced by vildagliptin.

Case Report

A 59-year-old male patient was admitted to the endocrinology outpatient clinic due to new-onset diabetes mellitus (DM) in 2013. He denied any weight loss, abdominal pain, and steroid usage. His past medical history was nonsignificant for pancreatitis, coronary heart disease, cerebrovascular disease, malignancies, and autoimmune diseases. He was a non-smoker. His family history was positive for DM. Initial and follow-up laboratory data are shown in Table 1. He was diagnosed with T2DM. Initial therapy with premix biphasic aspart insulin bid was started due to high level of hemoglobin A1c (HbA_{1c}) (12.9%). At the 3rd month of therapy, rosuvastatin 10 mg/day and ramipril 2.5 mg/day were commenced for ongoing hypercholesterolemia and microalbuminuria. Then, insulin therapy was switched to metformin and vildagliptin 50/1000 mg combo pill bid after HbA_{1c} level dropped to 5.7% at nine months of insulin therapy. Five months after vildagliptin was started, tense vesicles 8-10 in number with an erythematous base developed on the forearms and cruris (Figure 1). He had no fever. He first visited a dermatologist and punch biopsy was done. Histological examination revealed subepidermal bullae formation containing scarce lymphocyte and eosinophils, intraepidermal regeneration foci, perivascular and eosinophilic inflammation in superficial and reticular dermis, minimal acantholysis in epidermis, oedema of papillary dermis, and dermo-epidermal clefting (Figure 2A and 2B). Nikolsky's sign was negative. Oral flantadin and azathioprine and topical clobetasol propionate cream bid were prescribed, but he did not adhere to the therapy. He was readmitted to the endocrinology outpatient clinic to review the therapy. Oral therapy was discontinued. He refused to use other drugs prescribed for BP except topical steroid. He was followed up with diet alone. The lesions regressed spontaneously after cessation of antidiabetics. HbA_{1c} was 5.7% five months after discontinuation of vildagliptin and metformin. The lesions did not recur.

Table 1. Initial and follow-up data of the patient

Laboratory data	Value				
	initial	3rd month	6th month	9th month	1st year
Anti GAD (U/mL)	>0.1 (negative)	-			
Haemoglobin A1c (%)	12.9	7.2	6.7	5.7	6.0
Albumin (g/dL)	4.8	-	-	-	4.6
LDL (mg/dL)	155	137	-	115	-
HDL (mg/dL)	44	43	-	46	-
Triglyceride (mg/dL)	114	88	-	82	-
ALT (U/l)	23	-	18	19	18
Creatinine (mg/dL)	-	-	0.81	-	
Ca (mg/dL)	10.1	-		-	9.4
Spot urinary microalbuminuria (mg/g)	31.4	212.2	7	-	-
TSH (µIU/mL)	-	-	-	1.24	1.61
Vitamin B12 (pg/mL)	-	-	-	205	346
Amylase (U/l)	-	-	-	25	-
WBC (/mm^3)				6430	7560
Eosinophil (/mm^3)	-	-	-	380	350

GAD: Glutamic acid decarboxylase, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, Ca: Calcium, TSH: Thyroid stimulating hormone, WBC: White blood cell, ALT: Alanin aminotransferaz

Discussion

BP is an autoimmune subepidermal blistering disease that typically affects the elderly but may rarely involve children and younger adults (1). BP is the most common immunobullous disease in Western Europe (1). Histological examination of lesions confirms the diagnosis of BP (1). A skin biopsy from a fresh blister stained with haematoxylin and eosin shows subepidermal clefting and an inflammatory infiltrate mainly consisting of eosinophils, however, the diagnosis is confirmed by immunofluorescence studies (IF). The characteristic direct IF picture in BP is a linear deposition of immunoglobulins and/or C3 along the basement membrane zone (BMZ). Mostly, autoantibodies of immunoglobulin G type and less commonly immunoglobulin A, immunoglobulin M and immunoglobulin E that occur against two antigens [BP230 (BPAg1)] and BP180 (BPAg2, collagen XVII) attack components of the adhesion complex of the BMZ and result in subepidermal blistering. (1). Gelatinase activity is important for processing of B180 (3). Seprase, which is highly homologous to gelatinase, has marked gelatinase activity. DPP-4 does not have significant gelatinase activity. Gliptins may modify the activity of allied proteases, such

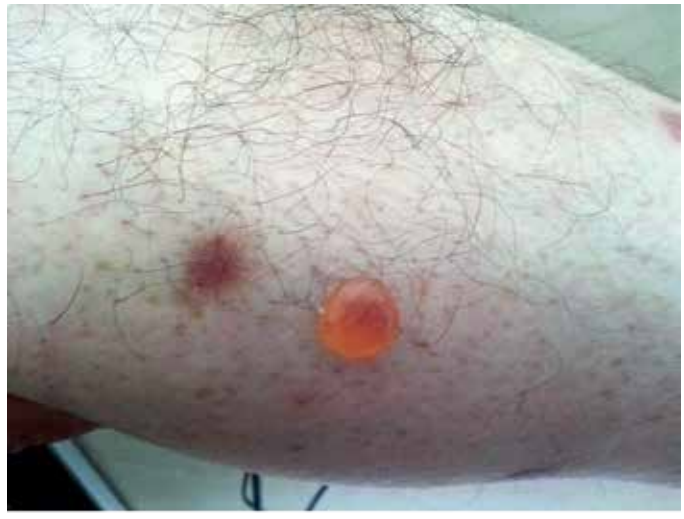

Figure 1. Tense vesicles with an erythematous base developed over lower limb

as separase which in turn affect epidermal basement zone. It has been shown that inhibition of DPP-4 enhances CCL11/eotaxin-mediated recruitment of eosinophils into the dermis and promotes homing of skin targeting lymphocytes (3). Serum levels of antibodies to both BPAg1 and BPAg2 can be measured by commercially available enzyme-linked immunosorbent assay kits. However, false-positive results are possible and it is currently not widely available worldwide. It is a useful additional diagnostic tool in selected cases and in research (1). Our histological evaluation supported the diagnosis of BP, however, neither direct nor indirect IF was available. Topical steroids such as clobetasol propionate are used as first-line treatment for both localized and moderate disease (fewer than 10 new blisters a day) (1). For extensive disease (more than 10 new blisters a day) systemic corticosteroid and immunosuppressive therapy can be used (1). The lesions in our patient remitted immediately after cessation of oral drugs and disappeared with the aid of local clobetasol propionate.

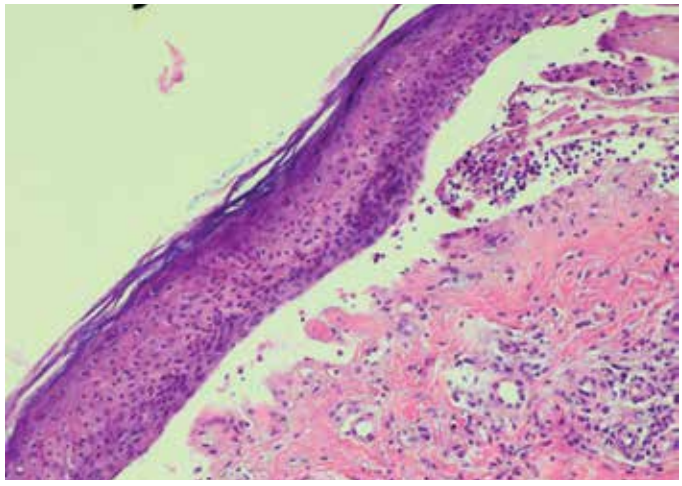

Figure 2A. Subepidermal bullae formation containing scarce lymphocyte and eosinophils, intraepidermal regeneration foci, perivascular and eosinophilic inflammation in superficial and reticular dermis (haematoxylin and eosine x10)

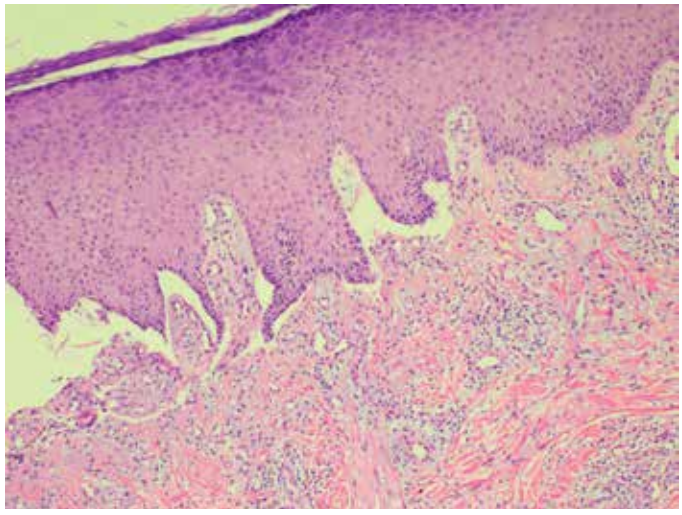

Figure 2B. Minimal acantholysis in epidermis, oedema of papillary dermis, dermo-epidermal clefting, bullae formation, perivascular and eosinophilic inflammation in superficial and reticular dermis (haematoxylin and eosine x20)

To date, there are three epidemiological studies on the association of BP and drug use. A significant relationship of the use of enapril, ampicillin, spironolactone and furosemide with neuroleptics has been described (11,12,13,14,15,16,17). There is no report about ramipril-associated BP in the literature. Only one case of BP induced by rosuvastatin was published from Ireland (18,19). Two weeks after initiation of rosuvastatin, bullous eruptions occurred. In our case, eruptions occurred 11 months after initiation of rosuvastatin. The case was indeed much more related to the recently added vildagliptin and metformin combination. According to the World Health Organization scoring system, vildagliptin-metformin was the probable causative agent in our case. A total of 41 cases of BP associated with vildagliptin (28 cases), sitagliptin (12 cases) and saxagliptin (1 case) use were reported in a French pharmacovigilance report (2). The patients were mostly males (61%) with a mean age of 71.9 years. Delay of occurrence of the BP varied from 10 to 730 days with an average of 261 days. In more than 50% of cases, recovery occurs within one month which strongly suggests the involvement of drug.

Pasmatzi et al. (4) reported two cases (59 year old female and 67 year old man) of BP induced by combination therapy with vildagliptin and metformin combination therapy. Pruritic lesions developed 2 months after the combination therapy. Bene et al. (5) defined 3 cases of BP induced by vildagliptin:

1) A 86-year-old female with T2DM, Alzheimer's disease, and hypertension who developed BP lesions after one-month treatment with vildagliptin and metformin. She was also using simvastatin, irbesartan, hydrochlorothiazide, and nifedipine. Although resolution of lesions was observed with topical clobetasol, BP recurred after 3 months due to ongoing therapy with vildagliptin. Remission could only be sustained after withdrawal of vildagliptin.

2) A 79-year-old male developed BP after 37-month treatment with gliclazide, vildagliptin and metformin. Remission with clobetasol was observed, although remission was sustained only after cessation of vildagliptin.

3) A-77-year-old female patient, who was already on ramipril and atorvastatin therapy, developed BP after 26 months gliclazide and vildagliptin were commenced.

Skandalis et al. (3) reported 5 five cases (2 female, 3 male; aged 67-80 years) of BP induced by gliptins (1 by sitagliptin, 4 by vildagliptin). All were on combination treatment with metformin. The patients were also on angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, statin, diuretics, and Parkinson's disease therapy. Onset of BP took 2-13 months. Attaway et al. (6) reported a 70-year-old male with BP whose lesions developed one year after sitagliptin therapy was commenced. The patient also had a past medical history of hypertension and cerebrovascular accident. He was using lisinopril, simvastatin, and metformin in addition. Remission was sustained after 3 months of systemic steroid therapy. BP during treatment with metformin alone has never been reported. The reported cases are only in combination with gliptins.

In summary, in the literature, onset of BP lesions took 10 days to 2 years. Elder males predominate. Mostly, the patients were on combination therapy with metformin. The lesions improved dramatically after cessation DPP-4 inhibitors avoiding necessity

for systemic treatment for BP. This is the first reported case of BP induced by DPP-4 inhibitors in Turkey.

Although skin lesions were not observed with vildagliptin at an increased incidence in clinical trials, those including blistering and ulceration have been reported in extremities of monkeys in non-clinical toxicology studies. Since there are post-marketing reports of bullous and exfoliative skin lesions associated with vildagliptin use, it must be kept in mind in case of BP.

Ethics

Informed Consent: Informed consent form was obtained from the patient. Anonymity was ensured as possible as can.
Peer-review: Externally and Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Bengür Taşkıran, Canan Solak Şişman, Bahattin Erdoğan, Güven Barış Cansu, Concept: Bengür Taşkıran, Güven Barış Cansu, Design: Bengür Taşkıran, Canan Solak Şişman, Bahattin Erdoğan, Güven Barış Cansu, Data Collection or Processing: Bengür Taşkıran, Canan Solak Şişman, Bahattin Erdoğan, Güven Barış Cansu, Analysis or Interpretation: Bengür Taşkıran, Canan Solak Şişman, Bahattin Erdoğan, Güven Barış Cansu, Literature Search: Bengür Taşkıran, Güven Barış Cansu, Writing: Bengür Taşkıran, Güven Barış Cansu, Canan Solak Şişman, Bahattin Erdoğan.
Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study received no financial support.

References

1. Venning VA, Taghipour K, Mohd Mustapa MF, Highet AS, Kirtschig G. British Association of Dermatologists' guidelines for the management of bullous pemphigoid 2012. Br J Dermatol. 2012;167:1200-1214.
2. Dipeptidyl peptidase-IV inhibitors and bullous pemphigoid in France: Analysis of spontaneous reports from French Regional Pharmacovigilance Centres and manufacturers. 9th Congrès de physiologie, de pharmacologie et de thérapeutique, Isére, France. PM1-091.
3. 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.
4. 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.
5. Bene 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;29:112-114.
6. 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.
7. Kim NH, Yu T, Lee DH. The nonglycemic actions of dipeptidyl peptidase-4 inhibitors. Biomed Res Int. 2014;2014:368703.
8. List JF, He H, Habener JF. Glucagon-like peptide-1 receptor and proglucagon expression in mouse skin. Regul Pept. 2006;134:149-157.
9. Karl T, Hoffmann T, Pabst R, von Horsten S. Extreme reduction of dipeptidyl peptidase IV activity in F344 rat substrains is associated with various behavioral differences. Physiol Behav. 2003;80:123-134.
10. Anz D, Kruger S, Haubner S, Rapp M, Bourquin C, Endres S. The dipeptidylpeptidase-IV inhibitors sitagliptin, vildagliptin and saxagliptin do not impair innate and adaptive immune responses. Diabetes Obes Metab. 2014;16:569-572.
11. Lee JJ, Downham TF, 2nd. Furosemide-induced bullous pemphigoid: case report and review of literature. J Drugs Dermatol. 2006;5:562-564.
12. Mullins PD, Choudhury SL. Enalapril and bullous eruptions. BMJ. 1994;309:1411.
13. Perry A, Sparling JD, Pennington M. Bullous pemphigoid following therapy with an oral beta-blocker. J Drugs Dermatol. 2005;4:746-748.
14. Hodak E, Ben-Shetrit A, Ingber A, Sandbank M. Bullous pemphigoid--an adverse effect of ampicillin. Clin Exp Dermatol. 1990;15:50-52.
15. Bordignon M, Belloni-Fortina A, Pigozzi B, Tarantello M, Alaibac M. Bullous pemphigoid during long-term TNF-alpha blocker therapy. Dermatology. 2009;219:357-358.
16. Bastuji-Garin S, Joly P, Picard-Dahan C, Bernard P, Vaillant L, Pauwels C, Salagnac V, Lok C, Roujeau JC. Drugs associated with bullous pemphigoid. A case-control study. Arch Dermatol. 1996;132:272-276.
17. Lloyd-Lavery A, Chi CC, Wojnarowska F, Taghipour K. The associations between bullous pemphigoid and drug use: a UK case-control study. JAMA Dermatol. 2013;149:58-62.
18. Murad AA, Connolly M, Tobin AM. Rosuvastatin-induced pemphigoid. BMJ Case Rep. 2012;2012.
19. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000;356:1255-1259.