VILDAGLIPTIN– INDUCED BULLOUS PEMPHIGOID

ANDREEA-ROXANA FURTUNESCU*,**, OANA-LAURA TORKASHVAN**, RĂZVAN CORNIA**, VASILE BENEA**, SIMONA-ROXANA GEORGESCU*,**

Summary

Bullous pemphigoid (BP) is the most commonly occurring autoimmune blistering disorder affecting the elderly. It is a multifactorial polygenic disease and the exact pathogeny is yet to be elucidated.

BP incidence and prevalence have increased in recent years, probably because of population ageing, the increased prevalence of diseases associated with BP, especially neurological, the more frequent use of certain medications that may induce BP, as well as to more accurate diagnosis.

Many drugs have been implicated in the induction of BP, most frequently gliptins, PD-1/PD-L1 inhibitors, loop diuretics and other cardiovascular medication, penicillin and derivatives.

We hereby report the case of a 68-year-old patient who presented to our dermatology clinic for a highly pruritic generalized cutaneous eruption with erythematous plaques, tense bullae and erosions. The patient's history was significant for type II diabetes mellitus and he was started on a combination of metformin and vildagliptin 5 months before.

The patient was diagnosed with DPP-4 inhibitor-induced BP and was started on systemic and topical corticosteroids, as well as doxycycline. Vildagliptin treatment was withdrawn. The patient has a good initial evolution under treatment, but was later lost to follow-up.

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Introduction

Bullous pemphigoid (BP) is the most commonly occurring autoimmune blistering disorder affecting the elderly, with a prevalence of 189.5 cases per million people, and an incidence of 12.1 per million per year. Females are affected slightly more than men, with a female to male ratio of 1.44. The average age of onset of the disease is of 75 years old and the prevalence increases with older age [1, 2]. The most affected regions are North America and Europe [3].

To the best of our knowledge, a single study has been published so far about the incidence and prevalence of autoimmune blistering diseases in Romania, only analysing data available for the Northwestern region of the country. Surprisingly, in this study, PV was more prevalent than BP, representing 47.4% of the total cases of blistering diseases, while BP only 34.5%. The authors attributed this finding to the specificities of the genetic profile of the population, stating that other factors, such as lifestyle, diet, smoking and a lower life expectancy compared to Western Europe may also be involved. The calculated incidence for BP was of 2.5 per million and the prevalence of 14.6 per million. Women were more affected, with a female to male ratio of 1.5. The age of onset ranged from 45 to 87 years old, with a mean of 73 ± 1.77 years [4].

BP is associated with significant morbidity and mortality and the burden of the disease

* "Carol Davila" University of Medicine and Pharmacy, Bucharest
** "Dr. Victor Babeș" Clinical Hospital of Infectious and Tropical Diseases, Bucharest

seems to be increasing, with many countries reporting significantly higher incidence rates of BP in the recent years. In France the estimated incidence of BP in 2005 was three times higher than the one recorded 15 years prior [5], while in the UK the incidence was estimated to increase by 17% each year [6]. The increase in BP incidence has been attributed to population ageing, the increased prevalence of diseases associated with BP, especially neurological (dementia, multiple sclerosis, Parkinson), the more frequent use of certain medications that may induce BP (diuretics, dipeptidyl dipeptidase, checkpoint inhibitors, etc.), as well as to more accurate diagnosis, due to the better recognition of non-bullous forms of the disease and to the improvement of laboratory tests [2, 7, 8].

Being diagnosed with BP seems to increase the risk of death up to three-fold in the first 2 years following the diagnosis [6, 7, 9].

BP is a multifactorial polygenic disease and the exact pathogeny is yet to be elucidated. Autoantibody formation against the BP180 and BP230 hemidesmosomal proteins leads to a loss of adhesion at the level of the dermo-epidermal junction, with the formation of tense, sub-epidermal bullae. The bullae often arise on erythematous areas or on urticarial plaques. Lesions are highly pruritic and, in some patients a pre-bullous stage of the disease exists, in which intense pruritus and non-specific eczematous or papular lesions occur before the apparition of the characteristic blisters. Unlike pemphigus vulgaris (PV), the mucous membranes are usually spared in BP.

Many triggers that can induce or exacerbate BP lesions have been reported, such as infection, local trauma, surgery, ultraviolet radiation, radiotherapy, certain medications, etc. [10].

Case presentation

We hereby report the case of a 68-year-old patient who presented to our dermatology clinic for a generalized cutaneous eruption that first appeared 2 weeks prior and extended rapidly. The patient presented with erythematous plaques, tense bullae and erosions. The lesions were highly pruritic. He also had large bullae on his feet, that broke and evolved into intensely painful erosions. The mucous membranes were spared and the patient was apyretic.

The patient's history was significant for type II diabetes mellitus, hypertension, chronic kidney disease and hip joint replacement in 2018. He was under chronic treatment with indapamide, metoprolol, enalapril and a combination of metformin and vildagliptin that had been introduced 5 months before.

Upon admission, the laboratory findings showed leucocytosis of 14 000 cells/mL with marked eosinophilia of 5 100 cells/mL, a slight inflammatory syndrome with C-reactive protein levels of 0.43 mg/dL, elevated creatinine with a glomerular filtration rate of 54 mL/min and slight hyperglycaemia of 128 mg/dL.

A diagnosis of DPP-4 inhibitor-induced BP was formulated based on the clinical manifestations, the patient's history and the laboratory findings.

A skin biopsy was taken. The results came back a two weeks later, showing a subepidermal blister, filled with a serous liquid and numerous neutrophils and eosinophils. A dense perivascular and diffuse eosinophil infiltrate was seen in the underlying dermis. These findings were consistent with the diagnosis of BP.

The treatment was started on 200 mg of intravenous hydrocortisone per day, 100 mg doxycycline every 12 hours and topical betamethasone. The diabetes medication was changed to metformin 1000 mg twice daily, with good glycaemic control during the hospitalisation. The eruption was significantly improved and after 2 weeks no more new lesions appeared. The leucocyte and eosinophil count and C-reactive protein levels were normal on the 2-week follow-up. The patient was discharged from hospital on a dose of 40 mg of prednisone/day, that was later slowly tapered, doxycycline and topical betamethasone. His evolution was favourable at the follow-up visit 2 weeks later, but, unfortunately, he did not present to his next appointments.

Discussions

Several medications have been implicated in the onset of BP. The first case of drug-associated bullous pemphigoid (DABP) was published in 1970, in an 11-year-old boy who was under sulfa-

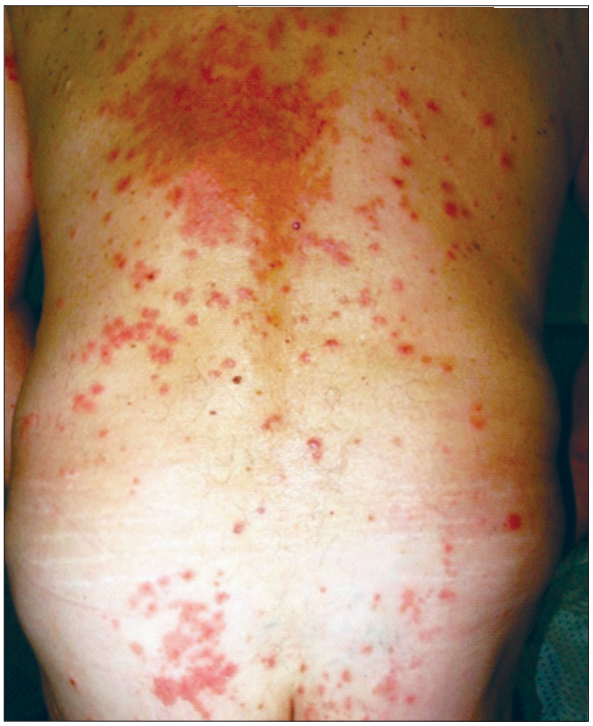

Figure 1. Erythematous plaques with tense blisters and erosions on their surface.

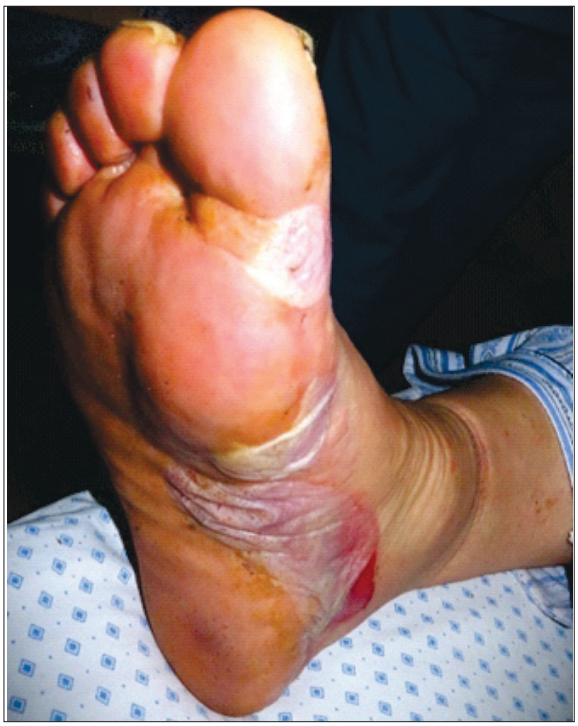

Figure 2. Large-size bullae on the feet.

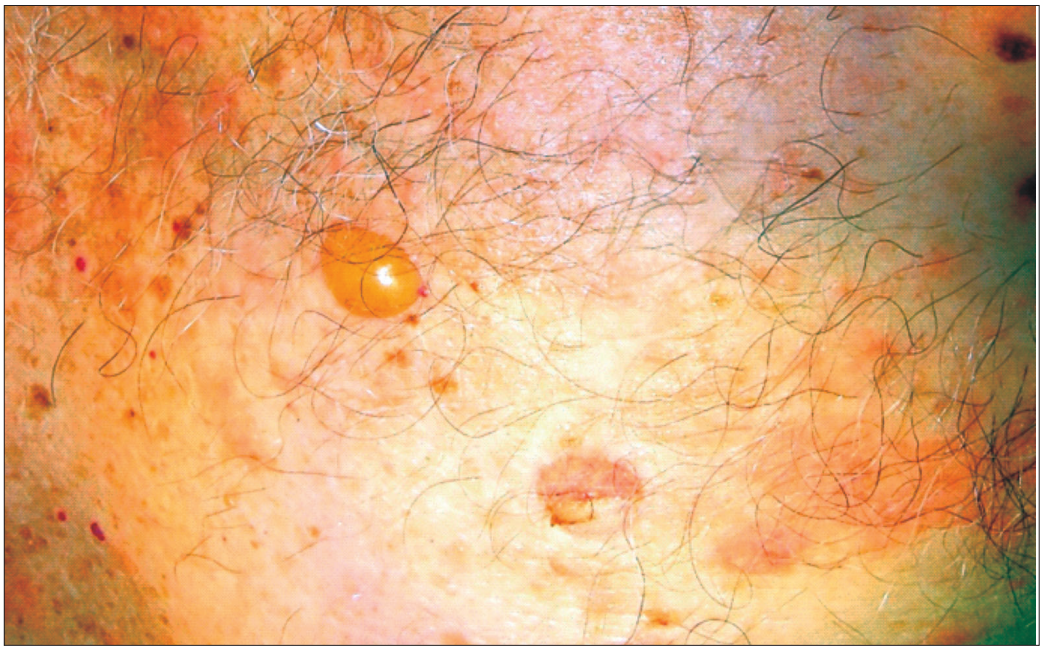

Figure 3. Tense epidermal blister and erythematous plaques.

salazine treatment for ulcerative colitis [10]. Since then, many drugs have been potentially incriminated for the induction of BP. However, in many cases, a definite causal relationship remains difficult to prove.

DABP usually responds to treatment with topical or systemic corticosteroids. It can present as an acute disease that remits after the withdrawal of the offending drug, or in a chronic form, in which the disease remains active even after the withdrawal of the implicated drug and prolonged treatment is needed [11,12].

There are different pathogenic mechanisms that have been postulated for the induction of drug-associated BP. In individuals with a genetic predisposition, certain medications can either boost the immune response or modify the antigenic properties of the basal membrane zone. Drugs can bind to molecules of the *lamina lucida* and induce the formation of antibodies, acting as haptens. They can also stimulate the immune response by inducing structural changes in certain molecules and uncovering of previously hidden epitopes. Also, a "two-step" theory has been proposed, in which two separate drugs may induce the disease. It has also been suggested that certain drugs inhibit CD8 suppressor lymphocytes, which leads to increased antibody production. [11,12]

The predisposing genetic factors for BP have not yet been assessed by many studies. However, the disease seems to be associated with the HLA DQB1*0301 in European populations. Other alleles have been identified that may be responsible for BP, and different alleles seem to be implicated in the population of Japan. HLA DQB1*0301 has been reported to be implicated in drug-induced BP. These HLA alleles facilitate antigen presentation of basement zone antigens to T cells, initiating autoimmunity [1,12].

The drugs most frequently implicated in the induction of pemphigoid are gliptins, PD-1/PD-L1 inhibitors, loop diuretics and other cardiovascular medication, penicillin and derivatives (Table I) [13].

Gliptins, or dipeptidyl peptidase 4 (DPP-4) inhibitors, are oral hypoglycemic agents that have been used for the treatment of diabetes mellitus type 2 since 2006. They can be administered in monotherapy or in combinations, most often

Table I. Medications associated with BP

Systemic	
Diuretics	Bumetanide Furosemide Spironolactone
Antihypertensive drugs	Amlodipine Captopril Enalapril Nifedipine
DPP-4 inhibitors	Linagliptin Vildagliptin
Checkpoint inhibitors	Durvalumab Ipilimumab Nivolumab Pembrolizumab
Antibiotics	Ampicillin Cephalexin Ciprofloxacin Metronidazol Penicillin Sulfapyridine*
NSAIDs	Aspirin Ibuprofen
Salicylates	Sulphasalazine
Chelating agents	Penicillamine
Antidepressants	Benzodiazepines Doxepin Escitalopram Fluoxetine Sertraline
Antipsychotics	Haloperidol Melperone Periciazine Phenothiazine Quetiapine Risperidone
Anticonvulsants	Carbamazepine
Biologics	Adalimumab Etanercept Ustekinmab
Anti-Parkinsonians	Biperiden Levodopa
Dementia medication	Memantine
Topical	5-fluorouracil Anthraline Benzyl benzoate Diclofenac

with metformin. They have been found to increase the risk of developing BP, independent on metformin use. Many mechanisms have been proposed for the development of gliptin-associated BP, although none have been formally proven. In the Japanese, an association with HLA-QB1*03:01 has been reported. [12]

DPP-4 is a plasminogen receptor expressed on the cell surface. It is implicated in the activation of plasminogen to plasmin. Plasmin normally cleaves BP-180 in the immunodominant NC-16A domain. The lower rate of plasmin formation with DPP-4 inhibitor use may lead to altered BP-180 cleavage and induce antibody formation. DPP-4 is also expressed on the surface of keratinocytes. Its inhibition may lead to increased eosinophil chemotaxis and activation, leading to blister formation. [13-16]

The risk of developing BP is 2-3 times higher for patients under gliptin treatment. Gliptin use induces BP independent of metformin use. The interval from treatment introduction to the appearance of skin lesions varies among studies, with a median latency of 6-26.4 months. Thus, the possibility of drug induced BP should not be overlooked even if patients have been taking DPP-4 inhibitors for a long time. BP cases have been reported as early as 8 days after the introduction of DPP-4 inhibitors as well [13,17,18].

As for the clinical manifestations, DPP-4-induced BP seems to more frequently exhibit mucous involvement, to have less inflammatory lesions and to be associated with lower peripheral blood and lesional eosinophil levels. However, the severity of the disease seems to be similar to that of idiopathic BP. The treatment outcomes are better in patients in which gliptin treatment is discontinued. There have been reports of BP relapse upon rechallenge with the incriminated DPP-4 inhibitor [13,17,19,20].

Conclusions

The presentation of our patient is typical for a case of drug-associated bullous pemphigoid. Among DPP-4 inhibitors, vildagliptin showed the highest risk of BP development, which was almost 10 times higher than in patients that were not taking gliptins, followed by linagliptin. The association was by far stronger in men (odds ratio 21.38 for men and 4.12 for women) [13,17,18]. It is important to conduct a good interview of the patient in order to establish the temporal relationship between the disease onset of the administration of medications. This can be difficult, especially considering that many of the elderly patients take many different medications at the same time. Rechallenge tests are often not performed for patient safety concerns. Previous reports from the literature can help support the causal hypothesis.

Other studies from the literature reported less inflammatory lesions and lower eosinophil counts in DPP-4 inhibitor-induced BP, as well as mucous membrane involvement. Our patient, however, had a classical presentation with erythematous plaques underlying the bullous lesions, marked eosinophilia and strictly cutaneous involvement. The resolution of skin manifestations occurred relatively rapidly after corticosteroid initiation and vildagliptin withdrawal. Unfortunately, the patient was lost to follow-up.

DABP can occur a few days after the introduction of a certain medicine, but most often there is a latency period of a few months before the apparition of the cutaneous manifestations. In the case of our patient, the BP manifestations occurred 5 months after the introduction of vildagliptin. Clinicians should be aware of the possibility that certain commonly used medications may induce BP and conduct a thorough medical history in order to identify the potential culprits, since withdrawal of the responsible drug is part of DABP management.

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Conflict of interest
NONE DECLARED

Correspondance address: Vasile Benea
"Dr. Victor Babeș" Clinical Hospital of Infectious and Tropical Diseases, Bucharest
e-mail: beneav@yahoo.com