Antidiabetic agents and bullous pemphigoid

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Bullous pemphigoid (BP) is an autoantibody – mediated organ specific autoimmune disorder and is considered as the most common autoimmune bullous disease in the elderly population globally [1, 2]. BP typically presents with pruritic erythematous or urticarial plaques and tense blisters on the trunk and extremities (Figure 1a-b).

There are still gaps in the precise description of blister formation in BP. It is suggested that triggering factors induce loss of immunotolerance against adhesion molecules of the skin, followed by a cascade of events leading to the formation of circulating and tissue bound autoantibodies against target antigens of the basement membrane zone. The target antigens in BP are mainly BP180 (BP80NC16a domain) and BP230, both structural proteins of the hemidesmosomes, located at the dermal - epidermal junction [1]. According to the current knowledge of BP pathogenetic chain, once autoantibodies are bound to the basement membrane zone, there is activation of complement, degranulation of mast cells and release of leukotrienes, TNF- a and other cytokines [1, 2]. The inflammatory cascade continues with the activation of neutrophils and eosinophils, followed by the production of proteolytic enzymes which induce degradation of the dermal epidermal junction and blister formation [1, 2].

There is a growing incidence of bullous pemphigoid worldwide and one of the possible explanations, apart from the increasing life expectancy of the population, is the increasing use of culprit medications [2, 3]. It is possible that certain drugs trigger the breakage of immunotolerance against especially BP180, induce the production of autoantibodies and initiate the blister formation process. Up to now, there are more than 60 drugs associated with BP [3]. Among them, dipeptylpeptidase – 4 inhibitors (DPP-4i or gliptins) carry the highest risk. There is a global concern, as these category of antidiabetic drugs are quite effective and thus widely prescribed [3, 4].

The first case series of a possible association of gliptins with induction of BP were published by Greek centers, one from Patra and one from Ioannina, Greece [5, 6]. In 2016, Garcia et al identified 170 cases of BP in patients taking a DPP-4i in the European Pharmacovigilance database, suggesting that the intake of DPP-4i was more frequently associated with the development of BP when compared with that of other drugs [7]. A disproportionally high number of cases were linked to vildagliptin use [7]. Another report during the same year, from the French Pharmacovigilance database recorded all spontaneous reports of DPP-4i-related BP cases between April 2008 and August 2014 and provided evidence supporting an increased risk of development of BP associated with DPP-4i exposure, especially with vildagliptin exposure [8]. The increased risk of developing BP among diabetic patients under treatment with DPP-4 was clearly shown in one of the largest retrospective, nationwide, population-based, case-control studies from Korea. The authors suggest that the use of DPP-4 inhibitors is associated with the development of BP in patients with diabetes and particularly the use of vildagliptin in male patients [9].

The pathogenesis of DPP-4i-associated BP remains largely unclear. Dipeptylpeptidase IV (also known as CD26) is an aminopeptidase expressed in various types of cells. It acts also as a cell surface antigen present on T lymphocytes (CD26) and thus, it may be reasonable to consider that the inhibition of CD26 expression on

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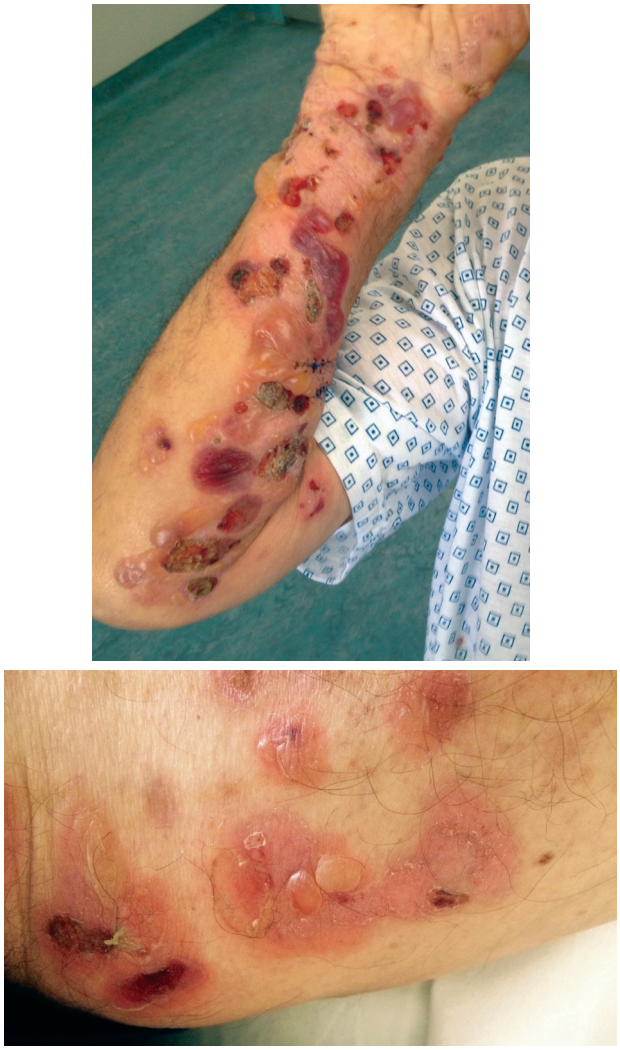

Figure 1(a-b). Erythematous plaques and tense blisters on the extremities.

T-cells may provoke an immune response [10]. Another element under consideration is that DPP-4 is a cell-surface plasminogen receptor that converts plasminogen to plasmin. Plasmin is a major serine protease which may cleave BP180 into its 120 and 97 kD ectodomains and therefore, suppression of DPP-4 may be associated with the development of novel epitopes for DPP-4i-BP autoantibodies [3, 11]. Additionally, inhibition of DPP-4 induces the infiltration of eosinophils into the skin, a key - cell population in BP pathogenesis [12]. It is also interesting that selective BP180 immunotolerance breakage by DPP-4i exposure is reported in HLA-DQB1_03:01 Japanese carriers [13].

In the current literature there is a controversy regarding clinical and immunological features of the so-called "gliptin induced pemphigoid". In studies from Japan there is evidence that this is a distinct, recently described form of BP with a less inflammatory phenotype, fewer infiltrating eosinophils in lesional skin, a different pathogenic epitope - the extracellular non-NC16A region of BP180 outside the NC16A domain - and predilection for certain HLAs [14, 15].

On the other hand, according to European studies, gliptins just trigger the development of bullous pemphigoid and there is no need to describe a separate clinical form of the disease. In a multicenter retrospective case - control study from France and Switzerland, it was shown that there were no apparent differences in clinical presentation and initial management between patients with diabetes and BP who had been treated with DPP-4i and patients with diabetes and BP who had not been treated with DPP-4i [16]. In our center in Thessaloniki, we performed a retrospective study in a sample of 143 BP patients and we found no differences in the clinical and immunological features, apart from a higher number of relapses in patients with classic BP [17].

One of the critical questions regarding the induction of a certain eruption by any drug is the time of exposure. According to Tan et al (2017) in order for a drug to be a trigger for BP it should be (i) started within 1 year preceding the diagnosis of BP, (ii) taken for more than 2 weeks and (iii) not stopped for more than 1 month prior to diagnosis [18]. Relevant literature shows that there is a long latency period between the initiation of gliptin treatment and development of BP in the majority of cases, leading to the assumption that gliptins aggravate and not really induce BP [3].

Quite recently, an analysis based on pharmacovigilance databases provided clear evidence of a BP-DPP-4i association [19]. Nevertheless, elderly patients take various medications and have other concomitant diseases. A rather reasonable question to be answered is whether DPP-4i alone are sufficient to induce BP or other factors are also required to induce breakdown of immunotolerance to BP180.

In conclusion, there is sufficient evidence nowadays regarding the association of DPP-4 inhibitors and BP in elderly diabetic patients. Although there are still gaps in the interpretation of gliptin associated BP, in the detailed description of phenotype, immunological profile and overall course, it is necessary to replace this pharmacological class with other antidiabetic medication in diabetic patients with bullous pemphigoid.

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