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OPEN ACCESS JOURNALS

Archives of Clinical & Experimental Dermatology

Research | Vol 4 Iss 1

Clinical, Biological and Histological Phenotype of Induced Bullous Pemphigoid

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Received: April 15, 2022; **Accepted:** April 27, 2022; **Published:** May 04, 2022

Abstract

Background: Bullous pemphigoid (BP) is an autoimmune disease characterized by subepidermal blistering. The pathogenesis of the disease is unidentified in most cases. Drugs can trigger BP. We report a series of drug-induced BP.

Methods: A prospective study of all patients diagnosed with BP at the dermatology departments of Ibn Rochd university hospital in Casablanca during the period 2018–2021.

Results: Eight patients with a mean age of 49 years, were admitted for management of extensive bullous lesions that appeared after various medications. Skin biopsy, direct and indirect immunofluorescence confirmed the diagnosis of BP. The pharmacovigilance investigation showed an I5B4 causality assessment score for all the drugs, interpreted as highly probable. The diagnosis of vaccine-induced BP was made, and the inducing drugs have been discontinued. All the patients had a favorable outcome.

Discussion and Conclusion: Precipitating factors, such as vaccines and drugs, could induce or exacerbate BP disease in the context of several predisposing factors. Therefore, unusual characters of BP must search the medication regimen. The differential diagnosis between classic BP and DIBP can prove to be quite difficult because there is no clear clinical criteria and no definite proof for this diagnosis.

1. Introduction

Bullous pemphigoid (BP) is an autoimmune disease characterized by subepidermal blistering. The pathogenesis of the disease is unidentified in most cases, but sometimes certain medications have been implicated. This drug-induced variant of BP usually shares common clinical, histopathological, and immunofluorescence findings with conventional BP [1], it is therefore difficult to differentiate them. The objective of our series is to study the clinical, biological and histological phenotype of this entity for a rapid diagnosis and a better management.

Citation: Hali F, Araqi Houssaini L, Marnissi F, et al. Clinical, Biological and Histological Phenotype of Induced Bullous Pemphigoid. 2022;4(1):131.

2. Methods

A prospective study of all patients diagnosed with BP at the dermatology departments of Ibn Rochd university hospital in Casablanca during the period 2018-2021 was carried out. Those patients diagnosed with BP probably induced according to the World Health Organization causality assessment system [2], were included in the study. A diagnosis of BP was established on the basis of characteristic clinical, histopathological, and immunological features, according to the Guidelines of the European Dermatology Forum [3].

3. Results

Eight patients (5 females and 3 males), with a mean age of 49 years, were included (TABLE 1). At the time of their BP diagnosis, one patient was being treated with angiotensin-converting enzyme, one with beta-blockers, one with statins, one with levodopa, one with gliclazide and three had received AstraZeneca COVID-19 vaccines. Based on the Bullous Pemphigoid Disease Area Index, all patients were classified as extensive BP [3]. All these patients had severe pruritus, large bullae, a positive Nikolsky's sign (FIG. 1), the presence of pseudonocardia and the predominance of lesions in the extremities. Oral mucosal involvement was present in six cases, four with mild involvement and two with extensive lesions along the palate and along the oral mucosa and pharynx, respectively (FIG. 2). Histopathological and direct immunofluorescence findings were identical to those observed in idiopathic BP for five patients, while the other three had additional signs of toxidermia (keratinocyte necrosis and apoptotic bodies). Indirect immunofluorescence revealed the presence of IgG against the epidermal side of the blister in the seven patients. According to the French method of imputability, the pharmacovigilance investigation showed an I5B4 causality assessment score for the above-mentioned drugs, interpreted as highly probable [4]. Indeed, all the molecules had a chronological score C3 (likely) and a semiological score S2 (plausible); whose association concluded to an intrinsic imputability I5 (very likely); with an extrinsic imputability B4 (expected adverse effect). The blood count showed a very high count of eosinophils (average of 2280/mm^3). The diagnosis of drug-induced BP was made, and the inducing drugs were stopped. Three patients progressed well on dermocorticoids alone, while the four others required oral corticosteroid therapy (0.5 mg/kg/day).

TABLE 1. **Patient's characteristics.**

Patients	**Age/Sex**	**Incriminated drug/vaccine**	**Duration between drug and eruption**	**BPDAI***	**Mucosal involvement**	**Eosinophils count/mm^3**	**Histopathological findings**	**DIF**	**Treatment**
Patient 1	62/F	Angiotensin-converting enzyme	15 days	86	Yes	3090	Signs of toxidermia	Negative	Corticosteroids therapy

Patient 2	50/F	B-blockers	8 months	83	No	2050	Classic one	Positive	Dermocorticoids
Patient 3		Statins	6 months	99	Yes	1980	Classic one	Positive	Corticosteroids therapy
Patient 4	60/M	Levodopa	1 year	75	No	899	Signs of toxidermia	Positive	Dermocorticoids
Patient 5	51 /M	AstraZeneca COVID-19	7 days	82	Yes	2045	Classic one	Positive	Corticosteroids therapy
Patient 6	54/F	Second dose of AstraZeneca COVID-19	1 month	100	Yes	1000	Classic one	Positive	Dermocorticoids
Patient 7	68/M	Second dose of AstraZeneca COVID-19	10 days	98	Yes	2600	Classic one	Negative	Corticosteroids therapy
Patient 8	51/F	Gliclazide	2 months	75	Yes	4600	Signs of toxidermia	Positive	Corticosteroids therapy

*BPDAI: Bullous Pemphigoid Disease Area Index

TABLE 2. **Phenotypic differences between classical and induced bullous pemphigoid.**

	Classic BP	**Induced BP**
Clinical features	- Old age -Negative Nikolsky sign -No mucosal involvement -Lesions on urticarial skin	-Younger age of onset -Positive Nikolsky sign -Mucosal involvement -Lesions on normal skin -Pseudocardial lesions
Histological features	-Moderate eosinophilic infiltrate - Sub-epidermal detachment -Positive IFD	-Marked eosinophilic infiltrate -Intra-epidermal vesicles -Necrotic keratinocytes -Thrombus formation -Positive or negative IFD
Biological features	Moderate blood hypereosinophilia	Very marked blood hypereosinophilia

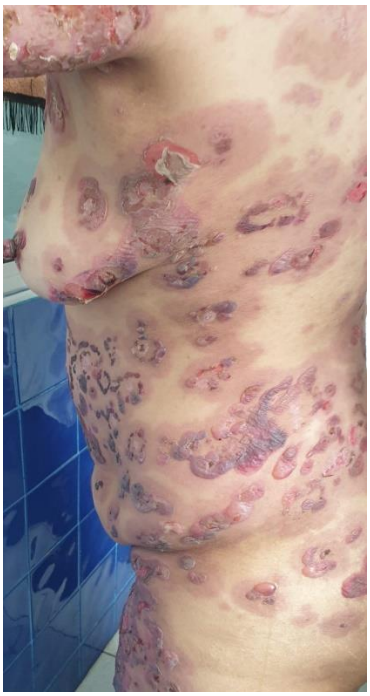

FIG. 1. **Large tense bullae with positive Nikolsky sign.**

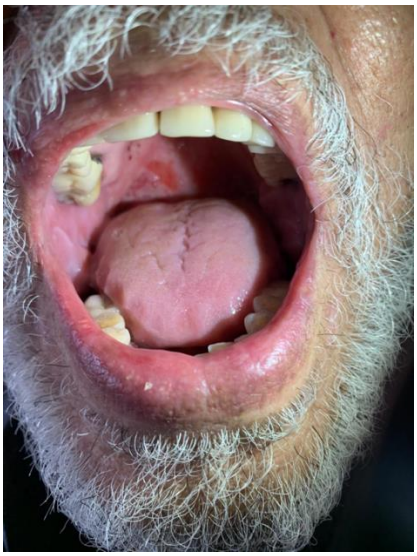

FIG. 2. **Large erosions along the palate.**

4. Discussion

Drug-induced bullous pemphigoid was described in 1970 and 1980 following Sulfasalazine, and ACE inhibitors respectively [5,6]. Later on, more than 50 different drugs have been associated with the appearance of BP and as new therapies emerge, this number is very likely to increase [7]. In our series, many of the drugs identified as being causative of BP were similar to those that have been reported previously, except for the COVID 19 vaccine [8]. The diagnosis of drug induced BP should be considered case of non-improvement or exacerbation under standard treatment, or if new drug intake. As for clinical characteristics, drug-induced bullous pemphigoid appears on a younger age compared to the classic one, with severe pruritus. Lesions usually appear as tense bullae on normally appearing skin. They may be accompanied by erythema multiforme type of

lesions on extremities. Nikolsky sign can be positive in some cases [9]. Mucosal involvement can also be present [10]. The biological phenotype of this entity is characterized by a very high eosinophil count, but there is no specific antigen for it [11]. The histology can be similar to the classic BP but sometimes we can find toxidermia signs as intraepidermal vesicles, necrotic keratinocytes, marked eosinophilic infiltrate and thrombus formation. In fact, the literature described two types of drug-induced BP. The proper one, which is directly caused by the medication, and which heals after stopping it; and the drug-triggered BP, which is declenched by the medication and maintained by immunological and genetic factors. It has been hypothesized that the pathogenesis of DIBP is linked to the combination and interaction of various mechanisms and not to a single one. The drug could induce anti-basal membrane antibody formation by T-lymphocytes dysregulation. Another possible theory considers that drugs act as antigens, involving endogenous proteins in covalent binding. In this way, they could modify their antigenic properties exposing hidden antigenic sites or generating new antigens [12]. Moreover, drugs containing Sulphur could disrupt the dermo-epidermal junction by interacting with the sulfhydryl groups in desmosomes [13]. As for vaccine-induced BP, it could be possible that the inflammation caused by vaccination may lead to disruption of the basement membrane, followed by subsequent production of anti-basement membrane specific antibodies in predisposed individuals. Over the years, an association of drug-induced BP with various vaccines has been suggested. Vaccines for influenza, swine flu, tetanus toxoid and HZV have all been implicated [14]. Regarding the treatment of drug-induced BP, the most important thing is to stop the imputable drug [15]. Then, according to the clinical severity, we can use topical corticosteroids, oral ones but also immunosuppressants.

5. Conclusion

Precipitating factors, such as drugs and vaccines, refer to a specific event or trigger that could induce or exacerbate BP disease in the context of several predisposing factors. As BP mostly affects elderly people, usually assuming several drugs, it is arduous to establish the triggering role of a specific medication. Therefore, unusual characters of BP (TABLE 2) must search the medication regimen. The differential diagnosis between classic BP and DIBP can prove to be quite difficult, because there is no clear clinical criteria and no definite proof for this diagnosis.

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