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Review

Atypical presentations of bullous pemphigoid: Clinical and immunopathological aspects

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ABSTRACT

Bullous pemphigoid may occur in extremely variegated manners, misleading even experienced dermatologists. Indeed the type and/or distribution of lesions may be unusual. Furthermore, there may be an atypical demographic profile of patients, a different clinical course and a different responsiveness to therapy. Up to 20% of the cases the onset is characterized by a non-bullous phase, lasting weeks, months or in particular cases remaining the only manifestation of the disease. During this early phase lesions are generally pruritic erythematous, eczematous or urticarial; however, lesions may also resemble polycyclic, targetoid, nodular or lichenoid lesions. These atypical lesions may also coexist with typical bullae. Other atypical presentations include a vesicular eruption and an erythroderma. Manifestations in children differ from adult forms, presenting an exclusive genital involvement in 50% of cases or a preponderant involvement of the face, the palms and the soles. Rarely bullous pemphigoid is confined to certain body areas, due to particular triggering factors or to a lower disease activity. Therefore, the need to formulate universally recognized diagnostic criteria is increasingly evident, especially for atypical bullous pemphigoid. Direct immunofluorescence of perilesional skin and detection of circulating autoantibodies are mandatory in the diagnosis, especially when the clinical presentation is doubtful.

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1. Introduction

Bullous pemphigoid (BP) is a rare autoimmune blistering disease, with an annual incidence ranging from 6 to 13 new cases per 1 million population per year [1–3]. BP typically affects elderly people (65–75 years of age) and males are slightly more affected than females [1,4].

Classically, BP is clinically characterized by large (1–3 cm), tense, serous or hemorrhagic bullae, which appear on erythematous, urticarial or eczematous lesions or apparently normal skin. Blisters evolve into eroded and crusted areas and then heal with no scarring. Sometimes post-inflammatory changes in pigmentation or *milia* might be visible [5]. The bullae generally appear in clusters and quickly become widespread. The sites of predilection include the lower abdomen, proximal extremities (especially the inner thighs), flexor surfaces of the forearms, groin

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and axillae. The face and the neck are usually not affected. The involvement of the oral cavity is rare, limited to 10–30% of patients [1]. This is the typical clinical picture of BP; however, BP may occur in an extremely variegated and deceiving manner.

In the past, especially in the nineties, the predominant tendency was to label encyclopedically all of the unusual presentations of BP as actual variants of BP. However some of these hypothetical variants have been reported only once or twice in the literature and have never been reconfirmed by more recent studies.

Examples of such supposed variants are pigmented pemphigoid, seborrheic pemphigoid and polymorphic pemphigoid. The term polymorphic pemphigoid was used many years ago in the literature [6,7] to define patients with an atypical subepidermal bullous disease with mixed clinical and histological features of both BP and of other blistering diseases such as dermatitis herpetiformis and linear IgA dermatosis [8]. Yet, this term is not precise, since patients who actually were affected by linear IgA dermatosis or vesicular BP or mixed subepidermal diseases were reported under this terminology; therefore, such variant should be considered obsolete [8]. Furthermore, probably both pigmented pemphigoid and seborrheic pemphigoid actually represent an unusual expression of BP correlated to peculiar characteristics of the affected patient. To the best of our knowledge, only one case of pigmented BP has been described and the authors themselves consider it an atypical presentation ascribable to the patient's phototype IV [9]. Whereas, the supposed variant of seborrheic pemphigoid is most likely, explained by an excessive secretion of sebum or a concomitant seborrheic dermatitis, that may have been the triggering factors for BP, a sort of Koebner phenomenon. Only two cases of seborrheic pemphigoid have been reported [7,10] and in the past twenty years this term has been no longer used.

Therefore, trying to categorize all variations in the presentation of BP as atypical variants is probably of little significance, because BP is by its very nature, a polymorphic disease. In this review we intend to give a quick overview only of the well-documented atypical presentations BP, which could mislead even experienced dermatologists (Table 1). The clinical presentation can be atypical because of the unusual type of lesions and/or the atypical distribution of the lesions.

2. Atypical presentations of bullous pemphigoid

The onset of classical BP is often characterized by a non-bullous phase of variable duration; from weeks to several months and in a few cases it may be the only manifestation of BP. Some authors report that such condition in up to 20% of the patients [1]. Lesions are itchy erythematous or eczematous patches and urticarial plaques [11]. A correct diagnosis during this phase might be difficult, since the early lesions are non-specific and might resemble a broad spectrum of conditions, such as chronic prurigo, eczema, urticaria and toxic drug reactions. Therefore, in elderly patients with a long lasting highly pruritic eczema-like or urticarial erythema, after excluding more common etiologies, BP should be taken into consideration in the differential diagnosis [12,13].

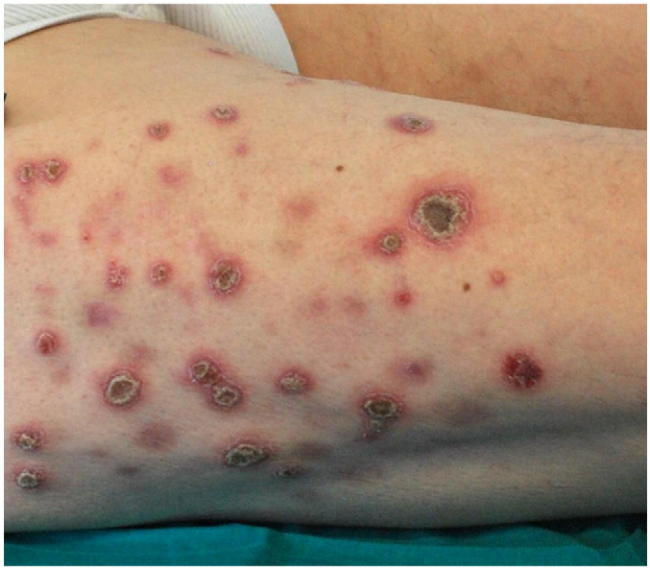

Fig. 1. Pemphigoid nodularis: polymorphic lesions representing the progressive stages of the disease: erythematous papules and nodules, nodules topped by blisters and finally sero-hemorrhagic crusts resulting from the rupture of bullae.

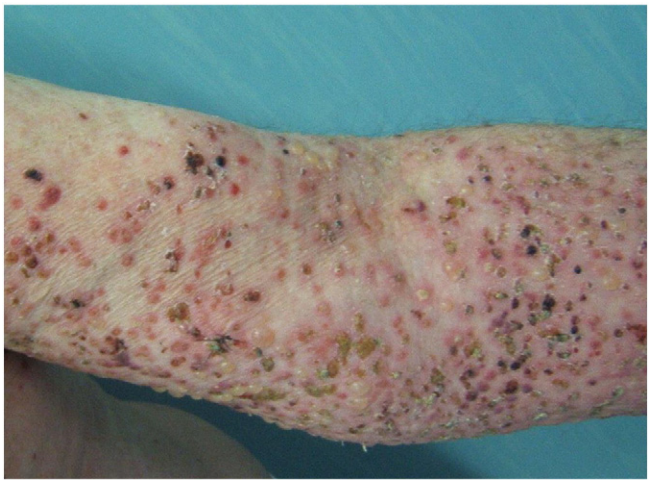

Fig. 2. Vescicular bullous pemphigoid: serous and hemorrhagic vesicles on erythematous skin, with sero-hemorrhagic crusts.

Very rarely the manifestations are even more atypical at this stage, resembling polycyclic or targetoid, nodular, lichenoid or vesicular lesions, making the diagnosis even more difficult. Such initial lesions may be the only sink sign throughout the entire disease or evolve later on into blisters.

Indeed, BP might present with lesions resembling figurate erythema, annular erythema or erythema giratum repens, with polycyclic and annular aspects [14,15]. In patients with these types of lesions underlying malignancies have been reported [16–20]. Therefore, it should be noted that further investigation to rule out such an eventuality is necessary.

The clinical diagnosis of BP can be challenging in the setting of erythema multiforme (EM)-like lesions. Till now, only four case reports describe EM-like BP [21–24]. In all reported cases, patients presented clinical features of both EM and BP, with wide-spread bullous lesions and multiple target lesions; Alcalay et al. described in three patients also severe erosions in almost all the mucous membranes, configuring EM major-like lesions [23]. Out of these four case reports, in three drug-induced EM-like BP was suggested; the suspected drugs were penicillins [23], furosemide [21] and in the third case the patient was receiving multiple medications (citalopram, thioridazine, and flupenthixol) [24]. Only Hayakawa et al. report an idiopathic form of EM-like BP [22].

Hyperkeratotic, excoriated, and pruritic nodules on the extremities can be the first sign of the disease, anticipating by weeks, or months the blisters. However, sometimes blisters cannot be observed throughout the whole course of the disease, making diagnosis substantially difficult. Many authors have defined this particular form of BP pemphigoid nodularis (PN) [25–34] Fig. 1. Patients, mostly elderly women, show mixed clinical features of both prurigo nodularis and BP. From a pathogenetic perspective, it is interesting to notice that the antibody titre is often low in such patients, perhaps not sufficient to induce blister formation, but subclinical pemphigoid with pruritus, excoriations, and nodules [35]. This form of BP is especially difficult to treat, since it is quite often unresponsive to conventional therapy with potent topical steroids, often requiring systemic steroids and different immunosuppressive agents used alone or in combination [36,37] and lesions persist for years and may easily relapse.

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