

Review Article

Bullous Pemphigoid Challenge: Analysis of Clinical Presentation and Diagnostic Approach

Eleni Papakonstantinou* and Ulrike Raap

Department of Dermatology and Allergy, Hannover Medical School, Germany

*Corresponding author

Eleni Papakonstantinou, Department of Dermatology and Allergy, Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany, Tel: 49-17615329833; Fax: 49-511-532-18543; Email: Papakonstantinou.Eleni@mh-hannover.de

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Abstract

Bullous pemphigoid (BP) is the most common autoimmune blistering disease characterized by autoantibodies directed against the 180 kD antigen (BP180) and the 230 kD antigen (BP230). It occurs most frequently in elderly patients and has a rising incidence. The typical clinical features of BP are large, tense bullae preceded by urticarial plaques and severe pruritus. However, the clinical manifestations of BP can vary greatly among the patients which often make the diagnosis of the disease difficult. The diagnosis of BP is based on a combination of clinical, histopathological and immunological criteria related to the stadium and the severity of the disease. Due to the variable clinical manifestations and the disadvantages of each diagnostic method alone there is a need for a stepwise diagnostic approach in order to establish the BP diagnosis.

This article is an updated review of the scientific literature on the variable clinical presentations and diagnosis of BP. Our review aims to explain the diverse atypical forms of the disease and to show a stepwise workup in order to establish the diagnosis and start with the appropriate treatment, which is helpful for clinicians.

Keywords

- Bullous pemphigoid
- Review
- Atypical clinical presentations
- Diagnostic approach

ABBREVIATIONS

BP: Bullous Pemphigoid; DIF: Direct Immunofluorescence; IIF: Indirect Immunofluorescence; ELISA: Enzyme-linked Immuno Sorbent Assay

INTRODUCTION

Bullous pemphigoid (BP) is the most common autoimmune blistering disease caused by the production of autoantibodies (BP180, BP230) against hemidesmosomal BP autoantigens BPAG1 and BPAG2 in the basement membrane [1]. It is characterized by large, tense bullae in the skin preceded by urticarial plaques and severe pruritus although the clinical manifestation of the disease can vary among the patients. BP shows an increasing tendency in the later years with an overall estimated incidence of 21.7 cases per million inhabitants per year in Europe which is about 3-fold higher in comparison to the estimated incidence of 15 years ago [2,3]. BP commonly affects patients older than 70 years of age and has an incidence of 12.1 to 66 new cases per million inhabitants per year in epidemiological studies in Europe [3,4]. Interestingly, patients with BP show a higher mortality rate in comparison with the normal population [5].

Among BP patients, higher mortality rates are shown in older patients, patients with a low Karnofsky-Index, concomitant diseases, low serum albumin level and patients who undergo an immunosuppressive therapy [6,7]. Neurologic disorders have

also been reported in association with bullous pemphigoid. It is supposed that about one third of BP patients had at least one neurological disease [8]. Concomitant diseases such as cardiovascular, pulmonary disorders, diabetes mellitus and diverse drug reactions have also been reported to correlate with BP [9-11]. Also physical agents such as UV radiation [12,13] or x-rays [14] have been reported as trigger factors of BP. Other dermatological diseases such as psoriasis and lichen planus have been described in association with BP [15]. A correlation between malignancy and bullous pemphigoid has also been reported but remains rather controversial as both the incidence of BP and malignancies rise with increasing age [16,17].

CLINICAL MANIFESTATION OF BULLOUS PEMPHIGOID

The clinical manifestation of BP can individually vary in type and/or distribution among the patients. The typical clinical features of BP are large (1-3 cm), tense, serous or hemorrhagic bullae usually based on erythematous or urticarial lesions or often on normal skin (Figure 1). The bullae are located subepidermally and are more stable compared to those in pemphigus diseases. Blistering is followed by the development of erosions and/or crusted plaques but usually heals without scarring. In some cases post inflammatory pigmentation changes remain after healing [18]. Predilection sites are proximal extremities (flexures of thighs and forearms), intertriginous areas, palmoplantar skin



Figure 1 Typical manifestation of bullous pemphigoid with tense, serous bullae based on erythematous and urticarial lesions.

or lower abdomen. Face and neck are usually unaffected but there are always exceptions with atypical localization between BP patients. In 10-30% of BP patients there is an involvement of the mucous membranes commonly with the manifestation of painful erosions [9]. The most common manifestation is in the oral mucosa; however genital mucosa and rarely conjunctivae can also be affected [9]. In contrast to mucosal pemphigoid, the nasopharyngeal mucosal membranes remain by BP patients almost always unaffected [18,19].

The onset of BP is often characterized by a premonitory, non-blistering phase which can last from weeks to several months and is reported in up to 20% of the BP patients [9]. This condition which is known as pruriginous or pre-bullous form of BP includes the presence of erythematous, eczematous or urticarial lesions accompanied by severe pruritus. The lesions are non-specific and the diagnosis at this early stage remains rather difficult. Thus, BP remains often misdiagnosed as the lesions resembling prurigo simplex subacuta, chronic prurigo, eczema or urticaria. In some cases this condition is the only manifestation of BP but it may also coexist with typical blisters. Therefore, by elderly patients with long-lasting itchy prurigo-like, urticarial or erythematous skin lesions bullous pemphigoid should be taken into consideration when it comes to the differential diagnoses.

Besides the pre-bullous form of BP there are more variants of the disease with different clinical manifestations (Table 1).

The localized bullous pemphigoid is a special variant of the disease characterized by chronic intermittent lesions localized on a restricted area of the body. Most commonly it occurs on the extremities or neck of the patients. Localized bullous reaction may also be induced by ictus reaction and bullosis diabeticorum. Sometimes the lesions remain localized but usually spread to different body areas within a few weeks or months. The pathophysiology of the elective localization of BP remains unknown but it is assumed that lower disease activity or localized triggering factors are the causative factors of this BP form [20,21]. A low disease activity may explain the rare form of umbilical bullous pemphigoid which manifests with bullae and

Table 1: Different clinical manifestations of BP and differential diagnoses.

Clinical forms of BP	Clinical manifestation	Differential diagnosis
Pre-bullous or premonitory bullous pemphigoid	Erythematous, eczematous or urticarial plaques, severe pruritus	Prurigo simplex subacuta Chronic prurigo Eczema Urticaria
Localized bullous pemphigoid (umbilical, pretibial, peristomal, physical agents-induced, unilateral)	Bullae localized on a restrict body area	Bullous ictus reaction Bullosis diabeticorum
Pemphigoid nodularis	Polymorphic skin lesions, commonly pruritic papules and nodules, or nodules covered by blisters and hemorrhagic crusts	Prurigo nodularis
Vesicular bullous Pemphigoid	Small vesicles on urticarial or erythematous base symmetrically located on trunk and extremities	Dermatitis herpetiformis Linear IgA-Dermatose
Lichen planus pemphigoid	Polygonal lichenoid pruritic papules and plaques, or blisters on pre-existing lesions or normal skin	Lichen planus
Dyshidrosiform bullous pemphigoid	Vesicles or bullae commonly located on the palmoplantar areas	Dyshidrosiform hand- and foot eczema Tinea pedum
Bullous pemphigoid vegetans	Erythematous, erosive and vegetating plaques on intertriginous areas	Pemphigus vegetans
Seborrheic pemphigoid	Ruptured bullae and erosions covered with crusts on the seborrheic areas	Pemphigus erythematosus
Erythrodermic bullous pemphigoid Variants: lichenoid erythroderma exfoliative erythroderma	Erythroderma along with blistering formation which pre-exists or follows the erythroderma, usually UV-induced	Cutaneous T-Cell lymphoma Dermatitis solaris Burning/Scalding
Annular erythema-like bullous pemphigoid	Annular erythematous papules plaques with or without blistering formation	Sjögren's syndrome Subacute cutaneous lupus erythematosus Lupus erythematosus profundus Pemphigus foliaceus
Figurate erythema-like bullous pemphigoid	Polycyclic erythematous plaques with peripheral spread	Wells' syndrome Eosinophilic dermatoses
Erythema gyratum repens- like bullous pemphigoid	Gyrate erythematous plaques commonly lined by trailing edge of scale	Paraneoplastic syndrome (adenocarcinomas of the gastrointestinal tract, lung or breast cancer)
Erythema multiforme (EM)- like bullous pemphigoid	Targetoid lesions and wide-spread bullae	Erythema multiforme Viral exanthema
Juvenile bullous pemphigoid	Bullae on palmoplantar areas, rarely mucous membrane involvement, healing with post inflammatory hyperpigmentation	Scabies Bullous impetigo

erosions localized on the umbilical area [21]. Another variant of this group is the pretibial bullous pemphigoid presenting with bullae and erosions localized on the pretibial area of the legs [22,23].

Physical agents such as radiation therapy, ultraviolet radiation [14], photodynamic therapy [12,13], electrical or chemical burns [24,25] traumas, surgical procedures or skin grafts [20,26,27] have been reported as localized trigger factors of BP [28]. Furthermore, topically applied medication (such as antipsoriatic treatment with tar, anthralin or psoralens) [29] and vaccinations (anti-influenza vaccine, tetanus toxoid booster, tetracoc vaccine) [30-32] have also been reported in the literature in association with localized BP [33]. Another rare entity of localized BP is the BP around stomas presenting with rash and bullae around stomas [34,35] and has often to be distinguished from contact dermatitis. Long et al. reported two cases of unilateral BP in hemiplegic patients with bullae localized on the hemiplegic side of the patients [36].

The exact pathomechanism for the development of BP is not clear and several hypotheses have been proposed. The most reliable one suggests that BP patients already have low non-pathogenic titers of anti-basement membrane autoantibodies which are able to induce blistering [37]. Physical agents such as the above mentioned ones can cause tissue damage and induce inflammatory processes leading to activation of granulocytes. The activated granulocytes can then release proteolytic enzymes and thus cause dermal-epidermal split and blistering [38].

Another BP variant is the pemphigoid nodularis presenting with polymorphic skin lesions from papules and nodules to nodules covered by blisters which rupture and leave hemorrhagic crusts [39,40]. Pruritic nodules and scratch excoriations are mostly found on the extremities and it is often difficult to distinguish them from these of a prurigo nodularis. In some cases blisters do not appear at all which makes the diagnosis even more difficult. Some patients however show clinical features of both prurigo nodularis and BP. Interestingly, these patients are more commonly women and have lower antibody titer, probably not adequate enough to induce blistering [41].

Another variant is the vesicular bullous pemphigoid presenting with small vesicles on urticarial or erythematous base which are symmetrically localized on trunk and extremities [42,43]. Clinically it resembles dermatitis herpetiformis and linear IgA - dermatosis.

BP can also manifest with polygonal lichenoid pruritic papules on normal skin resembling clinically and histologically lichen planus. This form of BP is known as lichen planus pemphigoides and commonly affects the palmoplantar areas [44,45]. The same localization but a different clinical manifestation has the dyshidrosiform pemphigoid presenting with vesicles and blisters localized on the palms and soles of the patients. This form resembles dyshidrosiform dermatitis and often has to be distinguished from tinea as well [46,47].

The BP vegetans is a rather rare variant of the disease which manifests with purulent, verrucous and crusted lesions localized on intertriginous areas or rarely on face or neck [48,49]. This form of BP has to be differentiated from pemphigus vegetans.

Seborrheic pemphigoid represents an atypical form of BP presenting with ruptured bullae and erosions covered with crusts on the seborrheic areas. This is also a rather rare form and only a few cases have been reported so far. It should be distinguished from pemphigus erythematosus [50,51].

Another unusual manifestation of BP is the erythrodermic BP which is characterized by blistering formation which present prior or follow the onset of erythroderma and is usually UV-induced [52]. Cases with other variants such as lichenoid erythroderma [53] and exfoliative erythroderma [54] but also cases without blistering at all have also been reported [55,56].

BP rarely presents with lesions resembling other dermatological conditions such as annular erythema [55], figurate erythema [56,57] or erythema gyratum repens [58]. In these patients a correlation with underlying malignancies such as adenocarcinomas of the gastrointestinal tract, lung or breast cancer has been reported and should be taken into consideration [59-61]. BP can also present in an erythema multiforme (EM)-like form with targetoid lesions and wide-spread bullae mimicking both EM and BP [62]. Such cases have been reported in association with drug intake and there is only one idiopathic case reported in the literature [62]. Drugs associated with EM-like BP are amlodipine [63], furosemide [64] or various penicillins [65]. Mehravaran et al. reported a case of a drug induced EM-like BP due to citalopram, thioridazine, and flupenthixol [66].

BP in children, known as juvenile bullous pemphigoid, is rare. This form of BP presents in infants with bullae on palmoplantar areas and the head whereas the genital area can also be affected in older children and teenagers. One case reports a newborn baby with severe BP [67]. This form should be distinguished from scabies or bullous impetigo. The differences regarding the localization of the lesions in adults and children are not yet completely understood but it is supposed that BP-specific antigens are differently expressed between these age-groups [68].

DIAGNOSTIC APPROACH OF BULLOUS PEMPHIGOID

The variable clinical manifestation of BP including the atypical forms of the disease makes the diagnosis of bullous pemphigoid difficult. The diagnosis of BP is based on a combination of clinical, histopathological and immunological criteria [9]. A diagnostic algorithm can help the clinicians to perform the essential examinations in order to establish the diagnosis (Figure 2).

Patients' history

The diagnostic approach begins with a thorough medical history. The clinician should initially obtain important information regarding the time point and type of onset of the disease. Furthermore it is essential to evaluate the clinical symptoms of the disease and the effect on patients' quality of life.

Information regarding previous drug intake (over a 1 to 6 month period), infections, malignancies and neurological diseases in the medical history may help the clinician to detect potential trigger factors [69].

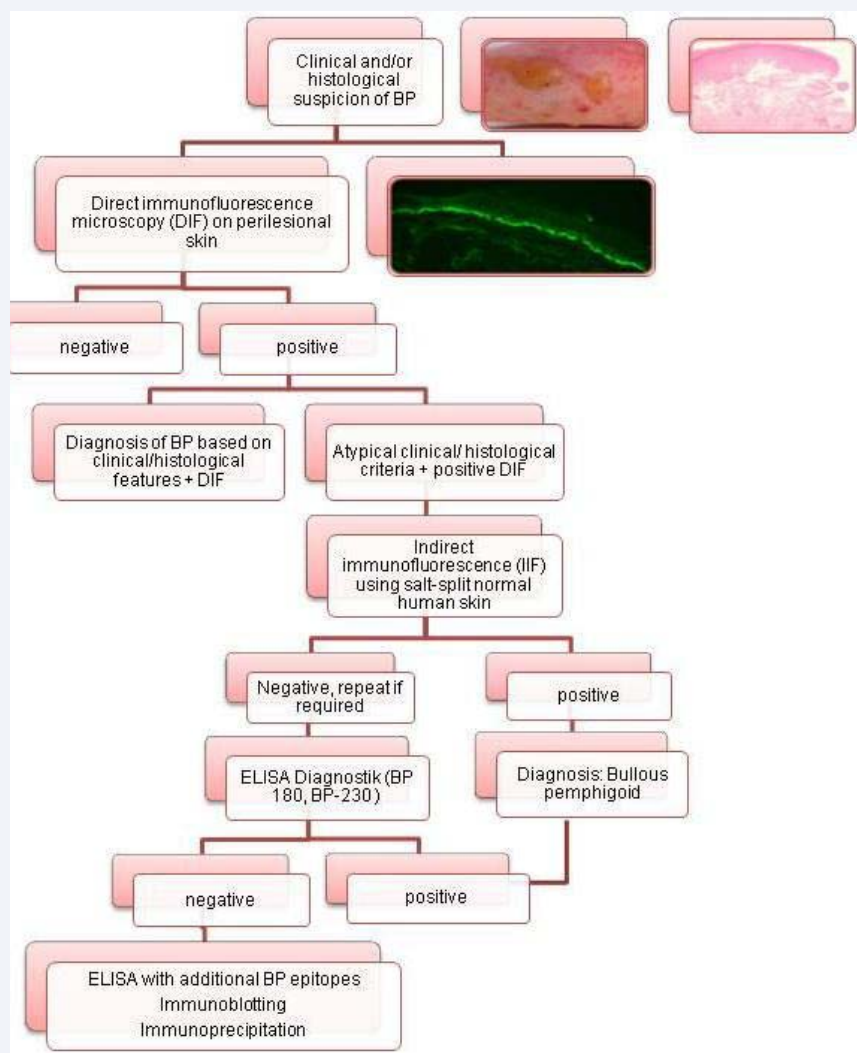


Figure 2 Stepwise diagnostic workup for the diagnosis of BP.

Clinical manifestation

The clinical presentation and symptoms of the patient gives the clinician the first evidence to initiate the diagnostic workup. In case of classical BP with subepidermal blistering, urticarial lesions and pruritus the diagnosis can be easily made. Severe long lasting pruritus is characteristic for the disease. In case of atypical manifestation of BP the diagnosis remains challenging and requires further diagnostics.

In an attempt to define predictors for the diagnosis of bullous pemphigoid four clinical criteria have been demonstrated. Therefore, lack of scarring, absence of head and neck involvement, absence of mucosal involvement and age greater than 70 years old are predictive of BP. The presence of 3 of these 4 clinical criteria allowed the diagnosis of BP with a sensitivity of 90% and a specificity of 83 %, respectively [70]. Further studies confirmed these criteria but indeed underlined the need for combined diagnostic criteria in means of laboratory testing and histopathology [71,72]. These tests are of a great importance as the wide clinical spectrum of the disease often does not allow a diagnosis based on clinical findings only. It is remarkable

however, that even the atypical forms of BP have the same immunopathological patterns with the classic form enabling the right diagnosis.

Histological examination

The first step in the diagnostic approach in order to confirm a clinical suspicion is the histopathology. Biopsy specimens should be obtained from the edge of an active lesion and include some adjacent normal unaffected skin so that the level of the blister can be accurately identified. The histological findings of classical BP include subepidermal blistering, dermal infiltrate of eosinophils and neutrophils such as absence of acanthosis [73]. Histologic sections of the nonspecific lesions present in the non-bullous phase of bullous pemphigoid are characterized by infiltrates of eosinophils in the dermal-epidermal junction, eosinophilic spongiosis (epidermal spongiosis with eosinophils within the epidermis) and subepidermal clefts. It should be taken into consideration that histological findings can lead to a diagnosis in only around 50% of cases [74]. Therefore, a histology examination is not helpful in a further differentiation between

bullous autoimmune dermatoses. Furthermore, factors such as biopsy technique, transport material and keeping conditions can affect the quality of the biopsy material and thus the histological result. Additionally, any previous therapies with systemic or topical corticosteroids or other immunosuppressant drugs may affect the histological findings.

Immunopathological tests

Immunofluorescence microscopy plays a key role in the diagnostic analysis of bullous autoimmune diseases including BP [75]. Direct immunofluorescence (DIF) is performed on perilesional skin and can detect tissue-bound autoantibodies [76]. The direct immunofluorescence (DIF) is the gold standard in the diagnosis of BP which has a great sensitivity in the range of 82–91 % [77,78] and specificity of 98 % [78]. DIF in BP demonstrates a deposition of IgG (70-90% of patients) and C3 (90-100% of patients) or both of them along the basement membrane zone of the patient [77]. However DIF alone cannot reliably distinguish BP from other subepidermal bullous disorders such as cicatricial pemphigoid, epidermolysis bullosa acquisita, pemphigoid gestationis or linear IgA dermatosis. A salt-split skin technique is a useful diagnostical tool and helps differentiate BP from these conditions. In this technique DIF on the patient's autologous skin is incubated with 1 mol/L NaCl at 4°C for 24 h and reveals IgG on the epidermal side of the blister (roof type) by patients with BP. This technique can differentiate BP from other subepidermal blistering disorders with IgG localized on the dermal side of the blister (floor type).

An analysis of the n-serrated pattern of DIF can also be helpful to distinguish BP from epidermolysis bullosa acquisita especially when combined with IIF [79]. Furthermore immunohistochemistry can be useful for the diagnosis of BP by detecting linear deposits of C3d and C4d along the epidermal basement membrane. However this technique has to be further validated [80].

DIF alone however is often not able to verify the diagnosis of BP. Thus other methods such as indirect immunofluorescence (IIF), enzyme-linked immunosorbent assay (ELISA) or immunoprecipitation may be useful.

The characterization of circulating autoantibodies has an important diagnostic power and can be made by performing IIF or ELISA.

The indirect immunofluorescence (IIF) is the most commonly used method in the diagnostic of blistering diseases. By using monkey esophagus one can reveal the presence of circulating IgG autoantibodies that typically bind to the epidermal side of salt-split human skin [9]. In up to 90% of cases with BP IgG autoantibodies can be found with this method while in 5-10% of cases IgA autoantibodies can also be detected [9].

ELISA on the other hand, is a more delicate and widely used method of autoantibody characterization using a recombinant protein of BP180 NC16 (the extracellular domain harboring immunodominant epitopes of BP autoantibodies) [81]. In contrast to IIF, ELISA can be easily reproduced, can test more samples and provides a quantitative analysis [82]. BP180 ELISAs are commercially available and have a high specificity while

the sensitivity ranges from 72 to 98% [83,84]. The latter one increases using NC16A domain and other extracellular portions of BP180 or when combined with BP230 [81,83].

Interestingly, serum levels of anti-BP180 IgG detected with ELISA correlate well with the phenotype and the disease severity of BP [85]. Some BP patients however show no IgG reactivity against the BP180-NC16a and thus are negative using the BP180 ELISA [86]. It is supposed that few patients react with an additional antigenic site which is located outside the NC16a domain [87,88]. On the other hand autoantibodies to BP180 and/or BP230 may be detectable in patients with no bullous diseases but other irrelevant diseases or even healthy ones [89]. Desai et al. however have shown that circulating autoantibodies found on healthy subjects do not bind the NC16A domain [90]. However, although high in specificity, it has been recently shown by the group of Jonkman et al. that BP circulating autoantibodies assessed with ELISA are higher in elderly patients with neither pruritus nor BP [91]. All these underlie the need for a combined diagnostic approach. Immunoprecipitation and immunoblot are other valid techniques but not easily available for the routine testing and they have been mostly replaced by ELISA [72].

A recently developed new IIF method called BIOCHIP IF mosaic provides a parallel determination of anti-BP180 and anti-BP230 based on recombinant antigenic substrates [92]. Previous studies have shown that this method for BP180-testing has a good sensitivity ranging from 77–100% and an even better specificity of 84–100% [92-94]. When it comes to BP230, although the specificity is similarly good, the sensitivity is significantly lower, ranging from 39–94% [92-94]. Therefore it is suggested that the BIOCHIP IIF mosaic system can be compared to ELISA but only in detecting BP180 autoantibodies. It is a suitable alternative test to IIF and ELISA providing thus a quicker, cheaper and easy to use screening tool for patients with suspected BP. Thus the BIOCHIP IF is suggested as an initial screening test to identify patients with BP before performing ELISA.

Previous studies have compared the above mentioned methods in order to find the most appropriate ones for the diagnosis of BP. Sardy et al. [78] showed that the combined sensitivity of the ELISA assays (88.8%) can approach that of DIF (90.8%). Yew et al. [95] recently showed IIF has the highest sensitivity, followed by the BP180 ELISA assay when it comes to the initial diagnosis of BP. Interestingly it could be shown that BP180 ELISA assay additionally to IIF provides no significant increase in diagnostic sensitivity [95].

Therefore, we consider that DIF and IIF should be the first immunological tests performed in the initial diagnosis of BP followed by ELISA assays when the latter one has been negative or in order to exclude other bullous autoimmune diseases with roof-pattern in IIF such as mucous membrane pemphigoid. ELISA assays and especially anti-BP180 diagnostic tests are helpful in monitoring of BP as they correlate with disease severity and relapse in some BP cases [96-97].

CONCLUSION

BP is a polymorphic disease with various clinical manifestation and symptoms. Blistering cannot be considered as a criterion for

the diagnosis as it can be missing not only initially but also during the whole disease. The atypical clinical forms of the disease make the establishment of the diagnosis more difficult and the need for widely accepted diagnostic criteria crucial.

The clinician should be aware of the diverse atypical forms of the disease. The clinical presentation should give the suspicion of the disease but should be considered as a rather minor criterion given that about 20% of BP cases have atypical manifestations. However, it is important to know that even BP cases with atypical manifestation reveal the same immunopathological features with the classic form which enables the diagnosis of BP.

Regarding the diagnostic approach of the disease we are convinced that DIF of perilesional skin showing IgG or C3 deposits and the detection of circulating antibodies against the two main BP antigens are the two more important and helpful methods. As circulating antibodies can be detected in non-BP patients and healthy subjects ELISA alone cannot be a valuable diagnostic tool.

In particular we suggest that DIF should be the first step in the immunological diagnostic of BP followed by IIF and ELISA assays (Figure 2). ELISA assays and especially anti-BP180 are the most appropriate tests for the monitoring of the disease.

Taken all this into consideration we conclude that a combination of clinical, histopathological and immunological tests in a right diagnostic order is required in order to establish an early and precise diagnosis which may have important therapeutical outcomes as well.

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