

ONLINE FIRST

Bullous Pemphigoid as Pruritus in the Elderly

A Common Presentation

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Importance: In the literature, patients with bullous pemphigoid have been reported to have itch without blisters. Clinical observations in these patients have varied from eczematous or urticarial to papular or nodular skin lesions. Here we investigated the spectrum of clinical variants.

Observations: Fifteen patients with itch without blisters had immunopathologic findings of bullous pemphigoid. Mean age at diagnosis was 81.7 years. No blistering occurred during the mean 2.2 years of follow-up. Mean delay of diagnosis was 2.8 years. Clinical symptoms were heterogeneous: pruritus sine materia (no primary skin lesions), eczematous, urticarial, papular, and/or nodular skin lesions were seen. Treatment with potent topical

corticosteroids or methotrexate sodium led to remission in 11 patients.

Conclusions and Relevance: Itch without skin lesions can be the only symptom of bullous pemphigoid. Therefore, it is important to include serologic and direct immunofluorescence in the diagnostic algorithm of itch. We propose the unifying term *pruritic nonbullous pemphigoid* for all patients with immunopathologic findings of bullous pemphigoid, itch, and no blisters.

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BULLOUS PEMPHIGOID (BP), THE most common subepidermal autoimmune blistering disease, is characterized by autoantibodies targeting the 180-kD BP antigen (BP180, BPAG2, or type XVII collagen) and/or the 230-kD BP antigen (BP230 or BPAG1).¹ The elderly are more frequently affected, and the associated morbidity is significant. In a recent study, pruritus, urticaria, and tense blisters were reported as the 3 main clinical pillars of BP.² Diagnosis of BP is commonly based

In this study, we describe a series of patients with immunopathologic findings of BP who had pruritus sine materia or pruriginous skin lesions without blisters.

Patients meeting the criteria were selected from the biobank database of the Center for Skin Blistering Diseases in Groningen, the Netherlands, from 2002 through 2012. The inclusion criteria were no blisters, with either depositions of IgG and/or C3c along the basement membrane zone (BMZ) in the n-serrated or indefinable pattern or a positive salt-split skin (SSS) analysis with binding to the epidermal side of the blister, in combination with a positive NC16A or BP230 enzyme-linked immunosorbent assay (ELISA).

We included 1 patient with SSS-epidermal binding without any other confirming positive test for BP. This patient was included because of clinical features correlating with pruritic non-BP and after exclusion of other pruritic disorders (eg, eczema and drug reactions).

Lesional, perilesional, and/or nonlesional skin biopsy specimens were studied by DIF for BMZ depositions of IgG, IgA, IgM, and C3c, as described previously.⁴ Sera of patients were tested by IIF on monkey esophagus and human SSS substrate.⁴

See Practice Gaps

on the combination of clinical presentation, histopathologic features, direct immunofluorescence (DIF), and the serologic detection of autoantibodies by indirect immunofluorescence (IIF) and/or the identification of the involved autoantigens.¹⁻⁴ Previous studies have described patients with pruritus and immunopathologic findings of BP but no blister development.⁵⁻⁹ As a result, pruritus alone or nonbullous skin lesions are frequently misdiagnosed as xerosis, a drug reaction, dermatitis, renal impairment, liver impairment, or scabies in elderly patients.

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Table 1. Clinical Characteristics and Therapy of 15 Patients With Pruritic Nonbullous Pemphigoid

Patient No./Sex/Age, y	Clinical Symptoms	Therapy
1/M/87	Pruritus sine materia	Prednisolone (10 mg/d) + MTX (10 mg/wk)
2/M/88	Pruritus sine materia	MTX (10 mg/wk)
3/F/64	Pruritus sine materia	Clobetasol propionate cream, 0.05%
4/F/82	Eczematous lesions	Clobetasol propionate cream, 0.05%
5/M/94	Eczematous lesions	Clobetasol propionate cream, 0.05%
6/M/95	Eczematous lesions	Prednisolone (7.5 mg/d) + azathioprine (100 mg/d)
7/F/88	Eczematous lesions	Clobetasol propionate cream, 0.05%
8/F/39	Eczematous lesions and erythematous papules	MTX (7.5 mg/wk)
9/F/87	Erythematous papules	Clobetasol propionate cream, 0.05%
10/F/79	Erythematous papules	Clobetasol propionate cream, 0.05%
11/M/94	Erythematous papules	Nonresponse (intolerance to MTX, nonresponse to prednisolone (20 mg/d) + mycophenolate-mofetil (500 mg/d))
12/F/92	Erythematous papules	Clobetasol propionate cream, 0.05% + MTX (5 mg/wk)
13/M/71	Erythematous papules and nodules	MTX (15 mg/wk)
14/M/87	Erythematous papules and nodules	Mometasone furoate cream, 0.1% + prednisolone (7.5 mg/d)
15/M/80	Urticarial plaques	Prednisolone (5 mg/d)

Abbreviation: MTX, methotrexate sodium.

Immunoblot analysis was performed with an extract of cultured human keratinocytes as described previously.³ The anti-NC16A and anti-BP230 ELISA (both from Medical and Biological Laboratories, Co, Ltd) were performed according to the protocols of the company. Index values less than 9 U/mL were considered negative.

REPORT OF CASES

Of the 15 patients who met our inclusion criteria, all reported severe itch and comprised 11.5% of all patients diagnosed with BP in our biobank (N=130). Mean age at onset of symptoms was 78.9 years (range, 44-93 years). Except for 2 patients (aged 39 and 64 years), all were older than 70 years. Mean age at diagnosis was 81.7 years (range, 39-95 years). Mean delay of diagnosis was 2.8 years (range, 6 months to 11 years). In 1 case, the patient had pruritic symptoms lasting 11 years that were considered eczema prior to the correct diagnosis. The mean follow-up time was 2.2 years (range, 3 months to 8 years).

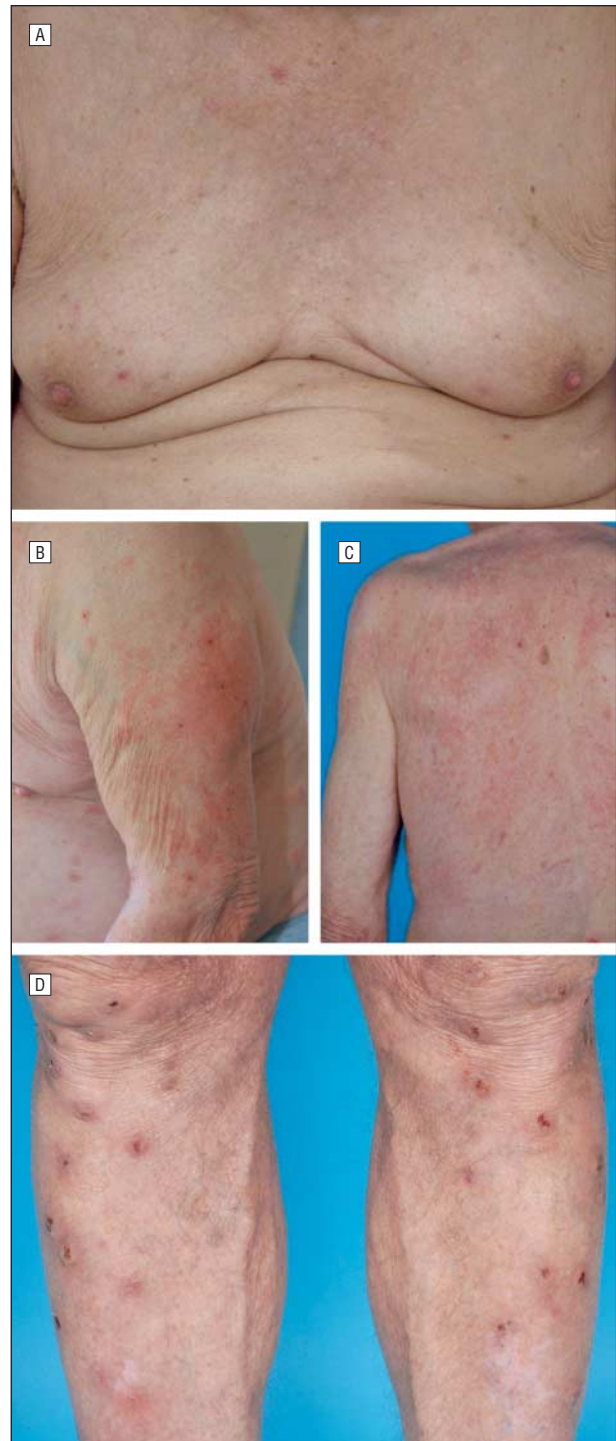


Figure. The heterogeneous clinical presentation of pruritic nonbullous pemphigoid. Clinical presentations of pruritic nonbullous pemphigoid by pruritus sine materia (patient 2) (A), urticarial plaques (patient 15) (B), eczematous lesions (patient 6) (C), and excoriated nodules (patient 13) (D).

Twelve patients had pruritus and excoriations with pruriginous skin lesions comprising eczematous lesions, urticarial plaques, erythematous papules, or nodules (**Table 1**). The distribution included the extremities (n=7), trunk (n=2), and generalized locations (n=3). In 3 patients who had only pruritus sine materia, linear excoriations were the only visible manifestation of disease (**Figure**).

Table 2. Immunodermatologic Findings Suggestive of a Form of Pemphigoid in 15 Patients With Pruritic Nonbullous Pemphigoid

Patient No.	Direct Immunofluorescence	Location of Biopsy	Indirect Immunofluorescence		IIF SSS, Epidermal Binding	Immunoblot BP180	Immunoblot BP230	NC16A ELISA, U/mL	BP230 ELISA, U/mL
			Monkey	Esophagus, BMZ					
1	IgG+	H	IgG+		IgG3+	—	—	—	23
2	IgG+	H		—	—	—	—	—	59
3	—	H	IgG+		IgG2+	—	+/-	29	30
4	—	P, H, L	IgG+		IgG+	—	+/-	—	25
5	IgA3+, IgG2+, and C3 2+	H		—	IgA+	—	—	—	—
6	IgG+/2+	L		—	—	—	—	17	—
7	IgG2+ and C3 2+	L	IgG+		IgG+	+	+	27	71
8	IgM and IgG+	L	IgG+		IgG+	—	—	—	—
9	IgA+, IgG+, and C3 2+	L	IgG+		—	—	—	—	—
10	—	P, H	IgG+		IgG+	—	—	23	19
11	—	P, H	IgG+		IgG2+	—	—	—	—
12	IgG+	L	IgG+		IgG2+	—	+	—	34
13	C3c 2+	L	IgG+		IgG2+	—	+/-	13	38
14	IgG+	P		—	—	—	—	—	—
15	IgG+ and C3c+	P	IgG+		IgG3+	—	—	—	16

Abbreviations: BMZ, basement membrane zone; ELISA, enzyme-linked immunosorbent assay; H, healthy skin; IIF, indirect immunofluorescence; L, lesional skin; P, perilesional skin; SSS, salt-split skin analysis; +, positive; —, negative.

Eleven patients had at least 1 biopsy specimen with a positive DIF that had IgG and/or C3c BMZ deposition. Seven patients had an n-serrated pattern (patients 1, 2, 5, 7, 12, 14, and 15), while 4 patients had an indefinable (patients 6, 8, 9, and 13) pattern. Direct immunofluorescence was performed on lesional skin (6 of 7 positive), perilesional skin (3 of 5 positive), or healthy skin (2 of 7 positive) (**Table 2**). In 1 patient, DIF from perilesional skin was negative but positive from lesional skin. Four patients had a negative DIF but a positive IIF showing IgG circulating autoantibodies on monkey esophagus and SSS (epidermal binding). Immunoblot on BP180 was negative in all but 1 patient; immunoblot on BP230 was positive in 5 patients. NC16A ELISA was positive in 5 patients (range of index, 13-29 U/mL) and BP230 ELISA in 9 patients (range of index, 16-71 U/mL) (Table 2). Routine histology performed for 12 patients was nonspecific or showed spongiotic dermatitis with eosinophils. In all patients, treatment was started with a potent topical corticosteroid application over the entire body: clobetasol propionate cream, 0.05%, or mometasone furoate cream, 0.1%. The dosage of the potent topical corticosteroid was 20 g/d in the first month, 20 g every other day in the second month, 20 g twice a week in the third month, and 20 g once a week in the fourth month. Six of 15 patients reached clinical remission while receiving this treatment. Methotrexate at a dose of 5 to 15 mg/wk in combination with a 5-mg dose of folic acid 2 days after intake was given in 6 of 9 patients who did not respond to topical corticosteroid treatment (Table 1). Five patients reached clinical remission while receiving this treatment. The sixth patient did not tolerate methotrexate due to facial edema. Additional treatment with 20 mg/d prednisolone in combination with mycophenolate-mofetil, 500 mg/d, also appeared insufficient. One patient (patient 11) died of cardiac failure that was not related to the disease or treatment. Three patients who did not respond to topical corticosteroid treatment reached clinical remission on

low-dose oral prednisolone (5-7.5 mg/d). One received additional azathioprine (100 mg/d).

DISCUSSION

Bullous pemphigoid may start with pruritus in the prodromal stage, while blisters develop weeks or months later.^{2,10-14} In a Swiss study population, 20% of 160 patients diagnosed with BP did not have blisters.¹⁵ In the literature, patients have been reported with itch combined with immunopathologic findings compatible with BP but without the formation of blisters, when followed up for several months or even years.^{5-9,11,14,16-19} In previous studies, most of these patients were older than 70 years, with a follow-up of 4 months to 6 years. In the present study, the mean age was 81.7 years. According to the definitions from an international expert panel, pruritus is considered a sufficient symptom for the diagnosis of BP if the immunologic criteria are met.²

Pruritus is also a component of the subjective Bullous Pemphigoid Disease Area Index.² Among all patients with pemphigoid in our Center for Skin Blistering Diseases, approximately 1 (13%) in 8 did not develop blisters, while all experienced itch. The skin symptoms consisted of erythematous, excoriated papules or nodules and urticarial or eczematous plaques. Three (20.0%) of 15 patients had only pruritus without primary skin lesions (pruritus sine materia). This implies that a dermatologist who sees an elderly patient with unexplained itch, even without evident skin manifestations, should consider BP. In such cases, IIF and DIF should be performed.

Diagnosis was reached by a positive DIF with IgG and/or C3c along the epidermal BMZ or SSS-epidermal binding in combination with a positive ELISA (NC16A or BP230). Earlier studies reported individual cases suggestive of BP in the absence of a positive DIF.^{5,20} Additional findings included a positive IIF on monkey esopha-

gus or detection of BP180 or BP230 autoantibodies by immunoblot. Our ELISA results concord with those of Feliciani et al,²⁰ who found that BP230 ELISA is more often positive than NC16A ELISA. In our study, more positive DIF results came from biopsy specimens of lesional skin than those of perilesional or healthy skin. In 1 patient, perilesional DIF from healthy skin was negative, while lesional DIF from a papule was positive. Future studies should point out if a lesional DIF biopsy for this group of patients is indicated, instead of a perilesional biopsy, which is recommended for BP.²¹ Histopathologic analysis is nonspecific or shows spongiotic dermatitis with eosinophils, which can be suggestive of BP.^{5-7,17}

In the literature, there is no unanimity on how to name this subset of patients. The coined terms include *pruritic pemphigoid*, *pemphigoid nodularis*, *papular pemphigoid*, *prurigo nodularis-like pemphigoid*, *nonbullous BP*, *prodromal BP*, and *BP incipiens*.^{5-7,9,20,22,23} In our opinion, the latter 2 terms can be used only retrospectively when blisters have appeared. Furthermore, lesions that may accompany the pruritus are heterogeneous. The term *nonbullous BP* seems adequate but lacks the most important clinical characteristic: pruritus. We therefore propose the unifying term *pruritic nonbullous pemphigoid*, to trigger the dermatologist to think of pemphigoid when confronted with an elderly individual who has itch.

Treatment of this intense pruritic condition is essential. In line with previous authors, we suggest a therapeutic ladder starting with whole-body application of potent topical corticosteroids such as clobetasol propionate cream.^{6,20,24} If the patient does not respond, our preferred treatment is methotrexate in a low-dose prescription (5-15 mg/wk) corresponding with treatment of BP.²⁵⁻²⁷ When insufficient, a wide range of other therapeutic options have proven successful.^{5-9,17,18,20}

Progression of pruritic non-BP to BP rarely occurs.^{6,28} The most intriguing question is why these patients do not develop blisters. When antigens were identified, they were mostly BP230.^{29,30} Rabbit and mouse model studies showed that BP230 autoantibodies induce skin fragility but do not lead to the development of blisters. Another explanation might be that IgE autoantibodies against BP180³¹ induce pruritus, while IgG along the BMZ is insufficient to induce blisters.³²

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