Nonbullous pemphigoid: Insights in clinical and diagnostic findings, treatment responses, and prognosis

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Background: Nonbullous pemphigoid is an under-recognized phenotype of the autoimmune bullous disease pemphigoid, characterized by the absence of blisters. Several disease aspects have not been studied previously.

Objective: To describe the characteristics of nonbullous pemphigoid.

Methods: A retrospective review study of medical records. The diagnosis of pemphigoid was based on meeting 2 of the following 3 criteria: (1) pruritus, (2) positive direct immunofluorescence microscopy, or (3) positive indirect immunofluorescence microscopy on salt-split skin.

Results: The review included 69 patients. The mean delay in diagnosis was 29 months. Skin examination most often showed pruritic papules/nodules (37%) or pruritus without primary skin lesions (22%). Histopathologic findings were mainly nonspecific. Results of direct and indirect immunofluorescence microscopy were positive in 60% and 69%, respectively. During follow-up, blisters formed in 17%, which was associated with a positive indirect immunofluorescence microscopy (P = .014) and a positive BP180 immunoblot result (P = .032). The Kaplan-Meier estimates of mortality at 1, 2, and 3 years were 14%, 34%, and 46%, respectively, with an 8.6-fold increased all-cause mortality risk.

Limitations: The retrospective study design.

Conclusions: Nonbullous pemphigoid presented with heterogeneous pruritic skin lesions, resulting in delayed diagnosis. Direct and indirect immunofluorescence microscopy are essential to diagnose nonbullous pemphigoid, in contrast to histopathology, mainly showing nonspecific findings. An increased all-cause mortality risk was observed during follow-up. (J Am Acad Dermatol 2019;81:355-63.)

Key words: autoimmune blistering disease; autoimmune bullous disease; case series; clinical characteristics; mortality; nonbullous pemphigoid; pemphigoid; prognosis; treatment.

Pemphigoid is an autoantibody-mediated skin disease mainly affecting elderly patients.[1] Autoantibodies target structural proteins BP180 and BP230 located in the basement membrane zone, inducing an eosinophilic inflammatory response in the skin.[2] Interestingly, the immunologic disease mechanism in pemphigoid can lead to 2 distinct clinical phenotypes, termed bullous and nonbullous pemphigoid.

Bullous pemphigoid (BP) classically presents with severe pruritus and tense blisters on urticarial plaques.[1] There is a high co-occurrence of psychiatric and neurodegenerative diseases, and patients have an increased mortality risk compared with the age-matched general population.[3-6] One in 5 patients

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lack typical blisters, termed nonbullous pemphigoid (NBP).[7] Patients present with pruritus and a wide spectrum of skin manifestations that may resemble other pruritic skin diseases.[8-12] Consequently, patients often have a long diagnostic delay.[13,14] Urticarial plaques and papules/nodules are reported most frequently.[8-12] Blister development during the disease course is reported in 10%.[8]

The diagnosis of NBP is based on the detection of skin-bound IgG or complement C3 in a linear deposition along the basement membrane zone by direct immunofluorescence microscopy (DIF), by circulating antibodies by indirect immunofluorescence microscopy (IIIF) on salt-split skin (SSS), or both.[7] Histopathology is often nonspecific.[8]

To date, little is known about the management and prognosis of NBP. Recommendations for treatment of BP, including whole-body application of superpotent topical corticosteroids as initial therapy, are often followed.[15] This study describes the clinical and diagnostic findings, treatment responses, and follow-up of patients with NBP to support early recognition and improve patient care.

CAPSULE SUMMARY

- Nonbullous pemphigoid is an underrecognized variant of pemphigoid with long diagnostic delays. Patients present with symptoms of pruritus, with or without skin lesions.
- Clinicians should realize that histopathology is not useful for diagnosing nonbullous pemphigoid; direct and indirect immunofluorescence microscopy are required. Patients have an increased all-cause mortality risk.

MATERIALS AND METHODS

Selection of patients and data collection

This retrospective study included patients diagnosed with NBP between 2002 and 2017 at the Dermatology Department of the University Medical Center Groningen, The Netherlands. Inclusion criteria were based on recently established diagnostic criteria by Meijer et al[7] with 2 positive of the following 3 criteria: (1) pruritus, (2) linear IgG, C3 depositions, or both along the basement membrane zone by DIF, or (3) positive staining of IgG on the epidermal side of SSS substrate by IIF.[7] Exclusion criteria were blisters or vesicles before diagnosis or at initial presentation objectified by a physician. Patients were excluded if blisters occurred within 2 months after the onset of pruritus and considered prodromal BP.

Clinical characteristics were assessed by reviewing patient medical records. Data were collected anonymously in electronic case report forms using OpenClinica software (OpenClinica, Waltham, MA). The variables collected were age, date of first symptoms and diagnosis, clinical presentation, skin manifestations, diagnostic findings, treatment response, adverse effects, blister development, and death during follow-up. The study was approved by the University Medical Center Groningen Medical Ethical Committee.

Laboratory tests for pemphigoid

Laboratory techniques DIF, IIF on SSS and monkey esophagus, and immunoblot were performed at our Immuno-dermatology Laboratory, as reported previously.[7] Autoantibodies against the noncollagenous 16A domain of BP180 (NC16A) and BP230 were detected with commercially available enzyme-linked immunosorbent assays (ELISA; cutoff index ≥9 U/mL), according to the manufacturer's protocol (MBL Co, Nagoya, Japan).

Treatment response and safety

Treatment response was assessed by using outcome measurements defined by international consensus, consisting of disease control, partial remission on minimal/off therapy, complete remission on minimal/off therapy, and relapse.[16] We deviated from the consensus definition by allowing a weekly dose of 7.5 mg methotrexate to count for minimal therapy. Reported adverse effects were registered. Uncertainties during retrospective assessment were resolved through discussion with the study team.

Statistical analysis

Correlations between bivariate outcomes were analyzed with the Pearson χ^2 test or Fisher's exact test when appropriate. Comparisons of means for non-normally distributed data were done with the Mann-Whitney *U* test. Estimated cumulative survival after follow-up of 1, 2, and 3 years was assessed by Kaplan-Meier analysis. Univariate Cox regression was performed to investigate the effect of selected variables on 3-year survival. Age-adjusted standardized mortality ratios (SMR) were calculated by comparing the objectified 1-year all-cause mortality rates in NBP with the expected 1-year all-cause mortality rates per age group, using mortality data of the Dutch population during the year 2017, provided by Statistics Netherlands (CBS, www.cbs.nl). The 95% confidence interval for SMR was calculated using Poisson distribution.[17] Statistical significance was defined as a *P* value of

Abbreviations used:

BP: bullous pemphigoid
DIF: direct immunofluorescence microscopy
ELISA: enzyme-linked immunosorbent assay
HR: hazard ratio
IIF: indirect immunofluorescence microscopy
NBP: nonbullous pemphigoid
NC16A: noncollagenous 16A domain of BP180
SMR: standardized mortality ratio
SSS: salt-split skin

<.05. Statistical analyses were performed using IBM SPSS Statistics 23 software (IBM, Armonk, NY).

RESULTS

Patient characteristics and clinical findings

Patients' characteristics are reported in Table I. Patients were relatively old (mean age, 76.1 years) and had several comorbidities, including hypertension (34%), diabetes mellitus (24%), atrial fibrillation (13%), and stroke (12%). Angiotensin-converting enzyme inhibitors were used in 26% and loop diuretics in 20%. Six patients reported a time relation with onset of symptoms and the use of acenocoumarol, simvastatin, candesartan, metoprolol, perindopril, and acitretin.

Observed skin lesions are displayed in Fig 1. There were 15 patients (22%) who presented with pruritus on primary, nondiseased, noninflamed skin, and showed a significantly longer delay in diagnosis compared with patients with primary skin lesions (49.9 vs 22.6 months; $P = .018$).

The average follow-up duration was 22 months, but varied by patient from 0 to 218 months. Factors influencing the follow-up duration include death during follow-up, response to therapy, and transfer of care of elderly patients with physical limitations or long travel distance. Follow-up was longer in patients with systemic treatment.

Diagnostic findings

Diagnostic findings are summarized in Table II. Histopathology most often showed a dermal perivascular infiltrate (98%) with eosinophils (69%) and a subepidermal split in only 1 patient. Pathologists reported nonspecific findings in 21 patients (39%) or findings compatible with cutaneous drug reactions in 18 (33%), eczema in 12 (22%), urticaria in 6 (11%), chronic scratching in 5 (9%), insect bites in 3 (6%), or a psoriasiform dermatitis in 3 (6%).

Table I. Clinical characteristics of patients with nonbullous pemphigoid

General characteristics	Mean (SD) range or No. (%) (N = 69)
Age at diagnosis, y	76.1 (13.5) 39-101
Sex, No.	
Male	29 (42)
Female	40 (58)
Delay in diagnosis, mo	28.9 (53.7) 0-385
Time of follow-up, mo	21.9 (38.2) 0-218
Living in a nursing home	7 (11.5)
Location of symptoms*	
Extremities	58 (92.1)
Back	46 (79.3)
Abdomen	29 (55.8)
Scalp	18 (34.0)
Hands/feet	16 (32.0)
Neck	17 (31.5)
Face	6 (12.0)
Mucosa	0 (0.0)
Findings during skin examination*	
Pruritus†	68 (98.5)
Generalized pruritus	40 (58.0)
Excoriations	52 (76.5)
Localized disease‡	6 (8.7)
Xerosis cutis	8 (11.8)
Papules/nodules	21 (30.9)
Pruritus on primary nondiseased, noninflamed skin	15 (22.1)
Sensu stricto	3
Urticarial papules/plaques	8 (11.8)
With pustules	1
Eczematous lesions	3 (4.4)
Mixed skin findings	
Urticarial papules/plaques + papules/nodules	10 (14.7)
Papules/nodules + eczematous lesions	1 (1.5)
Papules/nodules + erythematous macules	3 (4.4)
Other	7 (10.3)
Erythematous plaques with squamous borders	4
Pityriasis rubra pilaris-like	2
Suberythrodermia	1
Ulcerations	1
Localized livid, erythematous macules	1

SD, Standard deviation.
*Percentages were calculated after exclusion of patients for which data were unknown.
†Data extracted from anamnesis.
‡Defined as the presence of localized lesions involving 1 body site, conforming to the 2015 European consensus on the management of bullous pemphigoid.[15]

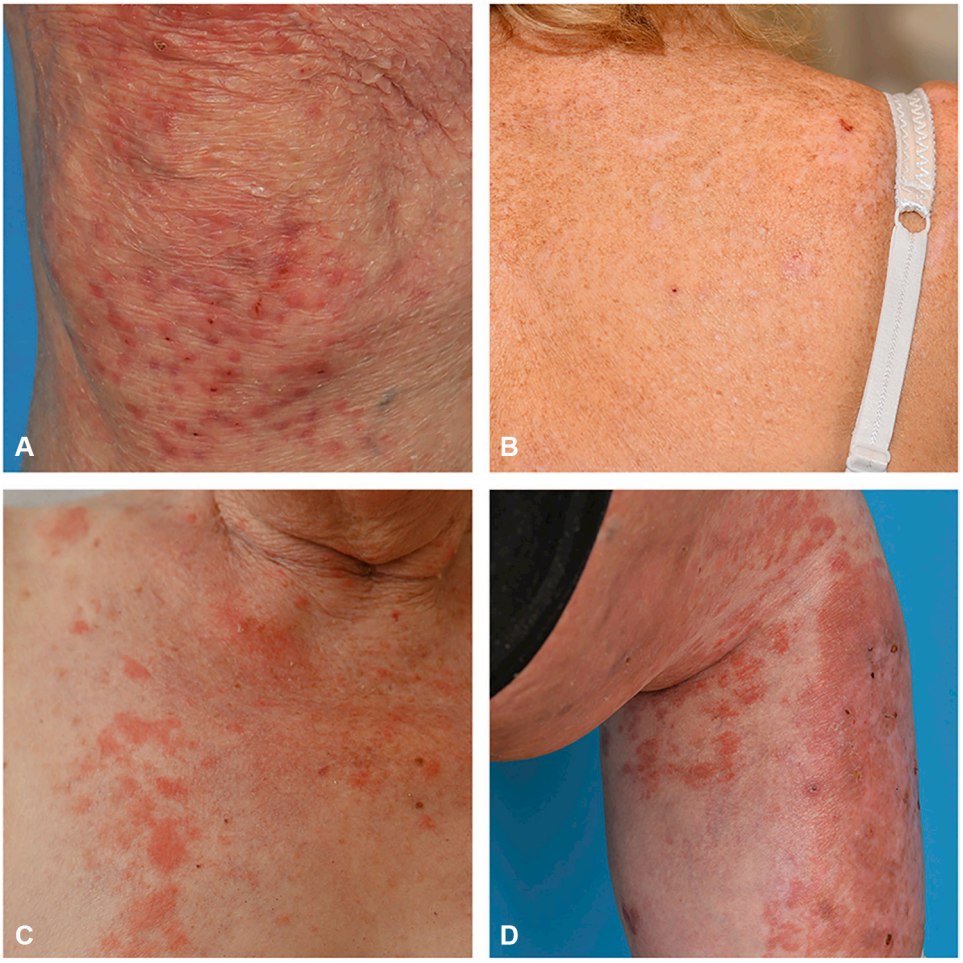

Fig 1. Nonbullous pemphigoid presenting with pruritus and various skin lesions. **A**, Papules and nodules. **B**, Pruritus on primary nondiseased, noninflamed skin with secondary excoriations. **C**, Urticarial papules and plaques. **D**, Eczematous lesions.

DIF results were positive in 41 of 69 patients (60%), of which 20 patients (29%) had a positive IIF on SSS result, and 21 (31%) a negative result. In 10 of these 21 patients, circulating antibodies against BP180 or BP230 were demonstrated by immunoblot or ELISA.

DIF result was negative in 27 of 69 patients (40%), and the diagnosis was based on a positive IIF result on SSS and compatible pruritic symptoms. Additional positive results by IIF on monkey esophagus, ELISA, and immunoblot were found in 26 (96%), 21 (78%), and 17 patients (63%), respectively. DIF was not performed in 1 patient, and the diagnosis based on IIF on SSS positivity.

Immunoblot and ELISA showed that autoantibodies were predominantly directed against BP230. BP230 reactivity correlated with negative DIF (P = .019). Conversely, BP180 reactivity correlated with positive DIF (P = .048). In patients with only BP230 reactivity and no BP180 autoantibodies, a stronger association was seen (P = .001). ELISA titers of IgG against NC16A and BP230 were repeated during follow-up in 16 patients, and changes corresponded to clinical symptoms in 7 patients but did not corresponded in 9.

Treatment response

Treatment strategy varied for individual patients, owing to ineffectiveness of prescribed topical or systemic therapies before diagnosis or to individual patient characteristics and comorbidities. Treatment response to initial and second prescribed therapies are reported in Table III. Topical corticosteroids were often prescribed awaiting diagnostic test results. There were 22 patients who reported adverse effects during the complete follow-up period. Adverse effects were experienced by 47% (n = 32) of the patients treated with methotrexate, and treatment needed to be discontinued in 28%. Azathioprine (n = 10) and dapsone (n = 6) gave adverse effects in 50% of the patients.

Table II. Diagnostic findings in nonbullous pemphigoid

Findings	No. (%) or mean (SD) range
Histopathology*	(n = 54)
Subepidermal split	1 (1.9)
Spongiosis	22 (40.7)
Without inflammatory cells	12 (22.2)
Eosinophilic spongiosis	3 (5.6)
Lymphocytic spongiosis	7 (13.0)
Dermal lymphocytic infiltrate	53 (98.1)
Located perivascular	49 (90.7)
Presence of eosinophils	37 (68.5)
DIF on a skin biopsy specimen*	(n = 68)
Positive DIF result	41 (60.3)
IgG	41 (60.3)
C3c	14 (20.6)
IgA	10 (14.7)
IgM	5 (7.4)
n-serrated pattern	19/41 (46.3)
Indeterminable serration pattern	22/41 (53.7)
Immunoserologic findings	(n = 68)
Positive IIF result	47 (69.1)
IIF on monkey esophagus, IgG	42 (61.8)
IIF on SSS, IgG	45 (66.2)
IIF on SSS, IgA	5 (7.4)
Positive immunoblot results	37 (54.4)
BP180	9 (13.2)
BP230	28 (41.2)
BP230 doubtful	5 (7.4)
Positive ELISA results	41 (60.3)
NC16A	21 (30.9)
Mean titer, U/mL	44.6 (31.4) 11-146
BP230	30 (46.9)
Mean titer, U/mL	39.7 (29.5) 11-122
Eosinophilia in peripheral blood	26/57 (44.8)
Mean titer, $\times 10^9$/L	1.02 (0.61) 0.4-2.4

DIF, Direct immunofluorescence microscopy; *ELISA*, enzyme-linked immunosorbent assay; *IIF*, indirect immunofluorescence microscopy; *NC16A*, noncollagenous 16A domain of BP180; *SD*, standard deviation; *SSS*, salt-split skin.
*Percentages were calculated after exclusion of patients for whom data were unknown.

Disease course

Blisters developed in 12 of 69 patients (17%) during follow-up, after a mean disease duration of 41.4 months (standard deviation [SD], 65.9; range, 5-242 months). At the time blisters formed, 4 patients were in remission off therapy, and 6 were in remission on minimal systemic therapy. Blisters developed in 2 patients during initially prescribed whole-body application of superpotent topical corticosteroids. The mean follow-up time of patients with blister formation was significantly longer (41.4 months [SD, 58.2; range, 2-218]) compared with patients without blister formation (17.7 months [SD, 31.7; range, 0-172], $P = .008$).

Blister development during follow-up was associated with positive IIF on monkey esophagus/SSS ($P = .014$), and positive BP180 immunoblot ($P = .032$). Immunoserology tests and DIF were repeated in 3 of 12 patients with blister formation. Increased autoantibody titers against NC16A and BP230 were detected by ELISA in 2 of 3 patients. DIF was already positive at diagnosis in 2 patients; in the third patient, DIF turned out positive after blisters occurred. Nevertheless, the alteration from negative to positive DIF during follow-up was also observed in 4 patients without blister development.

Mortality rates

During follow-up, 25 patients (36%) died after a mean disease duration of 51.2 months (SD, 40.6; range, 16-153 months). The mean time between diagnosis and death was 24.1 months (SD, 26.3; range, 0-127 months). Causes of death were lung cancer (n = 1), sepsis after a surgical procedure (n = 2), heart failure (n = 2), and most often unknown (n = 20). There were 10 patients lost to follow-up within the 1-year follow-up period and 4 additional patients within the 3-year follow-up period, mainly due to referral to a peripheral hospital after the diagnosis was made. The Kaplan-Meier estimates of 1-, 2-, and 3-year all-cause mortality in NBP were 14%, 34%, and 46%. Univariate Cox regression analysis showed a significant effect of age on the 3-year survival (hazard ratio, 1.04; $P = .028$). No other factors significantly influenced the 3-year mortality risk in our population. The SMR per age group is summarized in Table IV, showing an 8.6-fold increased all-cause mortality risk in the overall NBP population.

DISCUSSION

Patients with NBP endured symptoms for an average duration of 29 months before the correct diagnosis was made. Our study confirmed that histopathologic findings in NBP are nonspecific and that DIF and IIF should be performed to establish the diagnosis of NBP. Methotrexate was most successful in achieving remission, although adverse effects were reported by almost half of the patients. Of importance, an increased all-cause mortality risk was demonstrated, indicating that a lack of blisters is not equivalent to a mild prognosis.

We found a considerable longer diagnostic delay in NBP compared to BP of 29 vs 6 months.[18] Dermatologists should perform DIF and IIF on SSS even in the absence of blisters when considering pemphigoid. The low-hanging fruit of unrecognized

Table III. Treatment response on first and second prescribed therapies in localized and generalized nonbullous pemphigoid*

Therapy	No.	Response unknown No.	No response No. (%)†	DC No. (%)†	Time until DC, wks Mean (SD) range	Remission, PR or CR No. (%)†	PR No. (%)†	Time until PR, wks Mean (SD) range	CR No. (%)†	Time until CR, wks Mean (SD) range	Relapses No. (%)‡	Time until relapse, wks Mean (SD) range
Localized§ nonbullous pemphigoid	6											
First (n = 6) and second (n = 2) therapies												
Lesional clobetasol cream	2	…	2 (100.0)	…	…	…	…	…	…	…	…	…
Doxycyline	2	…	1 (50.0)	…	…	…	…	…	1 off (50.0)	5.0	…	…
Whole-body application of superpotent topical corticosteroids	1	1	…	…	…	…	…	…	…	…	…	…
Triamcinolone lesional	1	…	…	…	…	…	…	…	1 on (100.0)	5.0	…	…
Methotrexate¶	1	…	…	1 (100.0)	11.0	…	…	…	…	…	…	…
Azathioprine‖	1	…	1 (100.0)	…	…	…	…	…	…	…	…	…
Generalized nonbullous pemphigoid	61											
First (n = 61) and second (n = 42) therapies												
Whole-body application of superpotent topical corticosteroids	41	2	11 (28.2)	18 (46.2)	7.4 (8.3) 2-37	10 (25.6)	4 on (10.3); 1 off (2.6)	17.8 (6.9) 9-28	1 on (2.6); 4 off (10.3)	17.0 (11.1) 5-31	12 (42.9)	41.8 (80.3) 2-275
Methotrexate (+ short-term prednisolone in 3)	15	1	3 (21.4)	5 (35.7)	11.8 (11.4) 3-29	6 (42.9)	4 on (28.6); 1 off (7.1)	38.8 (31.5) 8-87	1 on (7.1)	19.0	5 (45.5)	94.6 (100.0) 8-254
Prednisolone	13	1	3 (25.0)	7 (58.3)	4.3 (6.2) 1-18	2 (16.7)	1 on (8.3)	17.0	1 on (8.3)	12.0	9 (100.0)	9.9 (5.3) 1-20
Lesional clobetasol cream	10	1	4 (44.4)	1 (11.1)	7.0	4 (44.4)	2 on (22.2); 1 off (11.1)	8.7 (8.0) 1-17	1 off (11.1)	20.0	1 (20.0)	9.0
Doxycyline (with or without nicotinamide)	5	…	5 (100.0)	…	…	…	…	…	…	…	…	…
Prednisolone + doxycycline	3	…	1 (33.3)	2 (66.7)	1.0 (0.0) 1-1	…	…	…	…	…	1 (50.0)	5.0
Whole-body application of superpotent topical corticosteroids + doxycycline	2	…	1 (50.0)	1 (50.0)	4.0	…	…	…	…	…	1 (100.0)	3.0
Prednisolone + azathioprine	3	…	1 (33.3)	2 (66.7)	3.0 (1.7) 2-5	…	…	…	…	…	1 (50.0)	14.0
Dapsone	3	1	1 (50.0)	1 (50.0)	8.0	…	…	…	…	…	1 (100.0)	1.0
Other therapies	8	…	4 (50.0)	3 (37.5)	3.0 (1.7) 2-5	1 (12.5)	1 off (12.5)	2.0	…	…	…	…
Mometasone	3											
Lesional + tacrolimus	2											
Triamcinolone (lesional)	3											
Terbinafine (systemic)	1											
Tacrolimus (lesional, topical)	1											

CR, Complete remission; *DC*, disease control; *on/off*, on minimal/off therapy, as defined by international consensus[1]; *PR*, partial remission; *SD*, standard deviation.

*Two patients did not receive therapy, 1 patient had minimal complaints and was lost to follow-up, and 1 first stopped suspected related medication and died shortly after.

†Percentages were calculated without taking unknown responses into account.

‡Percentages of patients relapsing were calculated over the number of patients who achieved DC, PR, or CR.

§Localized disease was defined as the presence of localized lesions involving 1 body site, conforming to the 2015 European consensus on the management of bullous pemphigoid.[15]

¶This patient had psoriasis, and methotrexate was chosen as treatment for both skin diseases.

‖This patient used low-dose azathioprine for Crohn's disease, the dose was heightened when pemphigoid was diagnosed.

Table IV. Standardized mortality ratios (SMRs) in nonbullous pemphigoid

Age groups	Total, No.	Mortality, No.	1-year mortality		SMR	95% CI
			Expected*	Observed		
30-59 y	7	0	0.0018	0.0000	0.0	0.0-2.1
60-69 y	10	1	0.0089	0.1000	11.2	9.1-13.7
70-79 y	19	2	0.0243	0.1053	4.3	3.5-5.2
80-89 y	26	5	0.0806	0.1923	2.4	2.1-2.7
≥90 y	7	0	0.2643	0.0000	0.0	0.0-0.1
Total ≥30 y	69	8	0.0134	0.1159	8.6	7.1-10.3

CI, Confidence interval; *SMR*, standardized mortality ratio.
*Expected deaths in the Dutch population are based on population-wide data for the year 2017.

NBP can easily be harvested by the aforementioned tests in elderly patients with refractory chronic pruritus. The diagnostic value of routine histopathology for the diagnosis of pemphigoid is poor.

Eosinophilic spongiosis and a subepidermal split are considered histopathologic hallmarks of BP.[1] In fact, these findings are less typical than implied, as shown in a recent study that could only confirm eosinophilic spongiosis in 50% and a subepidermal split in 54% of patients with BP.[19] We observed that eosinophils infiltrated the epidermis in only in 6% of the patients with NBP. Furthermore, eosinophils were found in a perivascular infiltrate (69%) and in the peripheral blood (45%). Eosinophils are hypothesized to mediate blister formation through secretion of toxic granule proteins.[20,21] In NBP, eosinophils may be activated and attracted toward the skin but may be unable to infiltrate the epidermis and induce blistering.

A notable observation is the predominant reactivity against BP230 in NBP, correlating with a negative DIF result, also described by previous studies.[8,22,23] Hayakawa et al[24] suggested that the intracellular localization of BP230 might hinder binding of autoantibodies in skin, resulting in negative staining by DIF. In contradiction, we found 10 NBP patients with positive DIF and only circulating BP230 autoantibodies.

Meijer et al[7] previously showed that autoantibodies against BP180 NC16A are more often present in BP than in NBP and that serum titers appear higher. The pathogenicity of BP180 autoantibodies was repeatedly confirmed in vitro and in vivo.[7,25] In contrast, BP230 autoantibodies failed to spontaneously induce blisters in several animal studies.[25,26]

Several studies suggest that symptoms and binding capacity of BP230 autoantibodies depend on coinciding intracellular epitope exposure, for instance by ultraviolet irradiation, epithelial injury, or the transient presence of BP180 autoantibodies.[27,28] Recently, BP230 autoantibodies were found to bind in the skin and induce blisters in scurfy mice lacking regulatory T cells.[29] Based on these findings, we suggest that loss of regulatory T-cell function, seen in the aging process, might also influence the pathogenic ability of circulating BP230 antibodies.

Other studies linked epitope recognition to BP phenotype, with less inflammation when antibodies recognized the mid-domain of BP180 or the C-terminal domain of BP230 in patients with BP230 antibodies only.[24,30] Future studies are needed to illuminate the pathophysiology of NBP.

Interestingly, 5 patients with initial negative DIF results turned positive when DIF was repeated. This demonstrates that the minimal diagnostic criteria that were used truly support early diagnosis in pemphigoid.[7] The changed DIF result coincided with blister development in 1 patient, and in general, no trend of altered antigen recognition or relation with biopsy site was observed in these patients.

Our study provides data concerning treatment responses in NBP, with only limited data available on the treatment of localized cases. In generalized cases, the highest effectiveness was seen with methotrexate, followed by lesional clobetasol cream and whole-body application of superpotent topical corticosteroids. Caution is advised for treatment with methotrexate in elderly patients, because many adverse effects were reported. Prednisolone often led to disease control (58%), although all patients relapsed over time, suggesting it is useful for short-term disease control only. Lesional corticosteroids were ineffective in most patients; however, remission was still seen in 28%. Williams et al[31] showed non-inferiority of a treatment strategy starting doxycycline over prednisolone in BP.[32] Our data showed that doxycycline was not effective in 86% of the patients with NBP.

Prognostic data of our study showed that 36% of the study population died after an average disease duration of 51.2 months. Compared with BP, we

found a lower 1-year all-cause mortality rate in NBP, and similar to higher 2- and 3-year all-cause mortality rates.[5,6,33] Moreover, an overall SMR of 8.6 was found in NBP compared with reported SMRs of 3.4, 3.6, and 6.6 in BP.[5,6,33] Our mortality data might be influenced by the low sample size and limited follow-up data of patients who were censored in the Kaplan-Meier analysis. Furthermore, we can hypothesize that the long delay in diagnosis, and therefore prolonged disease exposure without adequate treatment, might influence the prognosis.

A limitation of this study was the retrospective design. Consequently, disease severity measurements, such as the Bullous Pemphigoid Disease Area Index and autoantibody titers during follow-up, were not available. Moreover, we did not know the cause of death in 20 of 25 patients who died.

A selection bias might have affected epidemiology, treatment, and prognostic results, because patients visiting an academic hospital are more likely to have severe complaints. Furthermore, our cohort missed patients residing in nursing homes who are not be able to visit a hospital, which could explain the low co-occurrence of neurodegenerative diseases in our cohort.[3,4]

Another limitation was the significant shorter follow-up in patients without blister formation, not allowing us to draw hard conclusions on the number of patients with late blister development.

CONCLUSIONS

This study brought insight in unrevealed disease aspects of NBP. Most important, pathologists and dermatologists should be aware that NBP cannot be excluded by histopathology and that performance of DIF and IIF are required for diagnosis. Once the diagnosis was established, the best therapeutic effect was seen with methotrexate. The mortality rates in NBP are increased, indicating that a lack of blisters is not equivalent to having a better prognosis.

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