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CHAPTER 3
Nonbullous pemphigoid: a systematic review

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Abstract

Background
Bullous pemphigoid is an autoimmune disease that typically presents with tense bullae and severe pruritus. However, bullae may be lacking, a subtype termed nonbullous pemphigoid.

Objective
To summarize the reported characteristics of nonbullous pemphigoid.

Methods
The EMBASE and MEDLINE databases were searched using 'nonbullous pemphigoid' and various synonyms. Case reports and series describing nonbullous pemphigoid were included.

Results
The search identified 133 articles. After selection 39 articles were included, presenting 132 cases. Erythematous, urticarial plaques (52.3%) and papules/nodules (20.5%) were the most reported clinical features. The mean age at presentation was 74.9 years. Histopathology was commonly nonspecific. Linear depositions of IgG/C3 along the basement membrane zone were found by direct immunofluorescence microscopy in 93.2%. Indirect immunofluorescence on salt-split skin was positive in 90.2%. The mean diagnostic delay was 22.6 months. The minority of patients (9.8%) developed bullae during the reported follow-up.

Limitations
Results are mainly based on case reports/small case series.

Conclusion
Nonbullous pemphigoid is an underdiagnosed variant of pemphigoid that most often does not evolve to bullous lesions, and mimics other pruritic skin diseases. Greater awareness among doctors is needed to avoid delay in diagnosis.

Introduction

Bullous pemphigoid (BP) is the most common autoimmune bullous disease affecting the skin and mucous membranes, with autoantibodies directed against the 180-kDa BP antigen (BP180) and the 230-kDa BP antigen (BP230) located in the basement membrane zone.[1] The disease commonly affects older patients and is associated with an increased risk of mortality, as well as a significant decline in quality of life and psychological well-being.[2-6]

The clinical phenotype of pemphigoid is polymorphic. The typical presentation consists of tense blisters that arise on erythematous, urticarial plaques, and is accompanied by severe pruritus.[1,3] Prior to blister formation, pruritus can occur as a prodrome, with or without primary skin manifestations.[7] In contrast to the typical bullous presentation, various atypical variants have been reported with terms such as papular pemphigoid, pemphigoid nodularis, pemphigoid vegetans, erythrodermic pemphigoid, pruritic nonbullous pemphigoid and erythema multiforme-like pemphigoid.[8-11] The nonbullous variant of pemphigoid presents with pruritus and various nonbullous findings on the skin, such as erythematous patches, urticarial plaques, papules, nodules, excoriations, eczema, and erythroderma. Moreover, this variant can even present without primary skin lesions, called 'pruritus on primary, non-diseased, non-inflamed skin' according to the International Clinical Classification of Itch.[11,12]

Cohort studies show that at least 20% of all pemphigoid patients do not have blisters at the time of diagnosis.[3,13] Thus, nonbullous pemphigoid is not that uncommon or atypical as may be assumed.[14] Bullous and nonbullous pemphigoid are immunologically indistinguishable. The diagnosis is usually based on the combination of clinical presentation, histopathological findings, direct immunofluorescence (DIF) microscopy, and immunoserology.[13] One of the main obstacles currently is the lack of consensus on the minimal diagnostic criteria of pemphigoid.[8,14-17] The absence of blistering in nonbullous pemphigoid can make the recognition of this disease difficult for clinicians and might result in a delay of diagnosis.[18,19]

The aim of our study is to characterize and define nonbullous pemphigoid by systematic review, which has not been performed previously. Our study lists reported clinical presentations, histopathologic findings, laboratory findings, and prognosis regarding patients with nonbullous pemphigoid.

Methods

Search strategy

The literature search for this review was conducted in the EMBASE and MEDLINE databases on the 4th of November 2016. Various terms and synonyms for *'nonbullous pemphigoid'* were used (supplementary appendix). There were no limitations on article type. After the selection procedure the references of all included articles were checked for missing articles.

Selection of articles

Language was limited to Dutch, German or English. Independent screening of the titles and abstracts was carried out by Drs Lamberts and Meijer. Discrepancies between the researchers were resolved through discussion. All articles reporting on one or multiple cases of nonbullous pemphigoid were included. Nonbullous pemphigoid was defined as all symptomatic cases with a nonbullous phenotype, that lacked a previous history of bullae, and fulfilled the following diagnostic criteria of pemphigoid: a positive DIF with linear IgG and/or C3c along the basement membrane zone and/or positive indirect immunofluorescence (IIF), in combination with compatible clinical presentation, histopathologic findings, or other immunoserologic tests. If the full text was not available online it was ordered at the national library. Poster abstracts were only included if sufficient individual patient data was presented.

Data collection

The following variables were gathered: age at diagnosis, gender, duration of symptoms before diagnosis, clinical presentation, results of diagnostic tests, histopathologic findings, total follow-up time, and blister development during follow-up. Statistical analyses were done in IBM SPSS statistics 23.

Results

Systematic search results

A total of 39 articles presenting a total of 132 cases of nonbullous pemphigoid were identified (supplemental table 1). Figure 1 displays the selection procedure. The first case of nonbullous pemphigoid was reported in 1983 by Barker et al.[20] The largest case series was from Lamb et al.[21], who described the clinical presentation of 53 patients diagnosed with 'prodromal bullous pemphigoid'. This large case

series did not present individual patient characteristics concerning age, gender, duration of symptoms, histopathological findings and total duration of follow-up. However, we were able to include the reported clinical presentation and the number of cases that developed blisters during follow-up.

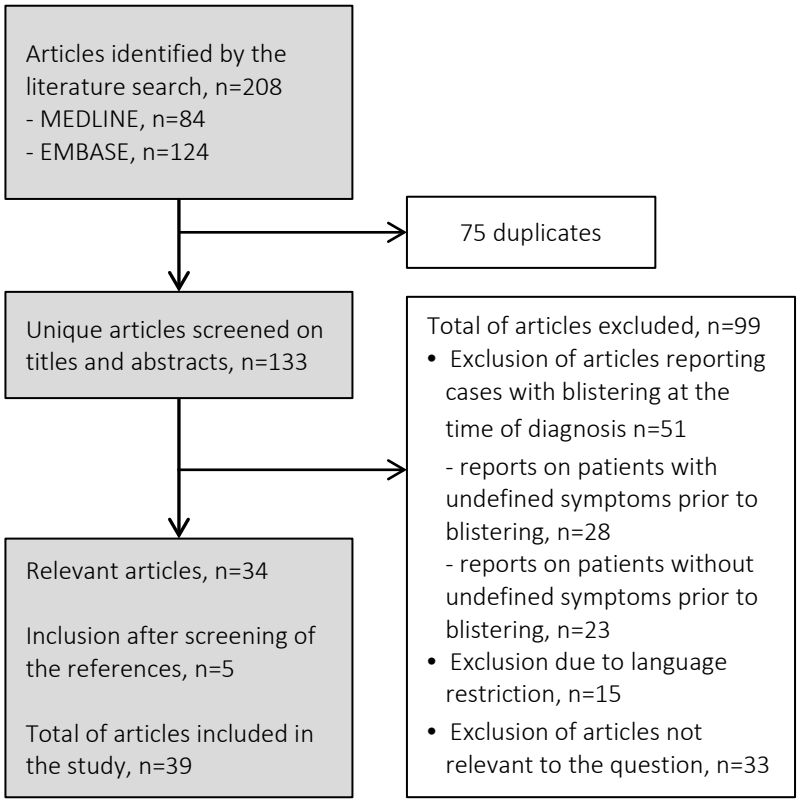

Figure 1. Study selection flow diagram

Clinical presentation

Table 1 shows the demographics of the reported patients with nonbullous pemphigoid. The mean age at presentation was 74.9 years. The reported efflorescences and configurations of skin lesions seen at dermatological examination are displayed in table 2. Table 3 presents the location of skin lesions, reported in 64 of the 132 cases.

Table 1 Demographics of the reported cases of nonbullous pemphigoid

Demographic outcome measurements		Reported in no. of cases
Mean age at presentation, in years	74.9 (SD 11.8; range 39-95)	78
Male cases, proportion	33 (42.3%)	78
Cases experiencing pruritus, proportion	77 (100%)	77
Cases with reported mucosal lesions, proportion	1* (7.1%)	14
Mean duration of symptoms before diagnosis, in months	22.6 (SD 39.1; range 0-240)	50
Cases with blister development after diagnosis, proportion	13 (9.8%)	132
- Mean duration of symptoms until blisters occurred, in months	15.9 (SD 8.4; range 7.5-27)	5
- Mean duration from diagnosis till blisters occurred, in months	9.6 (SD 8.6; range 1-21)	7
Mean total follow-up, in months	19.6 (SD 18.6; range 0-72)	46

*SD, standard deviation; * Ulceration in the mouth that healed without scarring, other mucosal areas were spared.*[32]

Histopathology

The histopathological findings were described in 53 individual cases. A perivascular infiltrate was seen most frequently (n=32; 60.4%), which is a non-specific finding. Additionally, non-specific findings not further specified were reported in 14 cases (26.4%). Eosinophils were present in the biopsies of 25 cases (47.2%) and neutrophils in 7 cases (13.2%). Spongiosis without eosinophils was reported in 10 cases (18.9%), while eosinophilic spongiosis was seen in 4 (7.5%). The presence of dermal edema was reported in 8 cases (15.1%). The presence of a microscopic subepidermal split was reported in 8 cases (15.1%).

Laboratory findings

Table 4 shows the reported laboratory findings of patients with nonbullous pemphigoid. In all cases DIF microscopy was performed. In cases with a negative DIF result, the diagnosis was based on positive IIF with additional serological tests that specified the targeted antigen. IIF was the most commonly performed immunoserologic test (55 cases).

Table 2. Skin findings and configurations reported in 132 cases of nonbullous pemphigoid

Skin findings reported	n (%)
Erythematous, urticarial papules and plaques	69 (52.3)
Papules/nodules	27 (20.5)
Eczematous lesions	16 (12.1)
No primary lesions reported*	6 (4.5)
Dermatitis herpetiformis-like lesions	5 (3.8)
Ulcerations	3 (2.3)
Erythroderma	3 (2.3)
Other:	
Scarring alopecia	1 (0.8)
Vegetations	1 (0.8)
Solitary macule	1 (0.8)
Excoriations	30 (22.7)
Configuration reported	
Annular configuration**	8 (6.1)
Figurated configuration	2 (1.5)
Gyrated configuration	1 (0.8)

** All 6 cases presented with secondary lesions in the form of excoriations. ** Two cases presented with erythema multiformis-like lesions*

Table 3. Localization of skin lesions reported in 64 cases of nonbullous pemphigoid

Localization	n (%)
Extremities	43 (67.2)
Trunk	42 (65.6)
Generalized	14 (21.9)
Head and/or neck	7 (10.9)
Scalp	6 (9.4)
Hands and/or feet	5 (7.8)

The substrate used in IIF was not specified in 15 cases. In the other cases monkey esophagus (n=27) or human skin (n=13) were used as substrate. The BP230 ELISA was the least performed immunoserologic test (n=19). Additionally in four cases

immunoprecipitation was used to identify antigens, resulting in a positive reaction to both BP180 and BP230 in one case and only a positive reaction to BP230 in three cases. Eosinophilia in peripheral blood was reported in 13 of 15 cases (86.7%).

Table 4. Laboratory findings in reported cases of nonbullous pemphigoid

Diagnostic test	Cases with positive test results, n (%)	Total no. reported cases
DIF microscopy, linear IgG and/or C3c depositions along the BMZ	123 (93.2)	132
IIF, IgG*	42 (76.4)	55
IIF on SSS, IgG, epidermal binding	46 (90.2)	51
Nc16a ELISA, IgG	15 (57.7)	26
BP230 ELISA, IgG	10 (52.6)	19
Immunoblot BP180, IgG	11 (32.4)	34
Immunoblot BP230, IgG	20 (55.6)	36

*BMZ, basement membrane zone; BP, bullous pemphigoid; DIF, direct immunofluorescence; ELISA, enzyme-linked immunosorbent assay; IIF, indirect immunofluorescence; SSS, salt-split skin; Nc16a, non-collagen 16a. * different substrates were used by different authors.*

Discussion

This systematic review summarizes the reported characteristics of nonbullous pemphigoid. The most frequently reported skin efflorescences were erythematous, urticarial plaques (52.3%). Pruritus was reported in 100% of the cases. Overall, the duration between the start of symptoms and the correct diagnosis was very long (mean 22.6 months). Only 13 patients (9.8%) developed bullae during the reported follow-up, thus were actually prodromal to bullous pemphigoid. However, in the majority of the cases (90.2%) bullae never occurred. The findings of this review show that although the clinical presentation of nonbullous pemphigoid is various, pruritus at high age may be a clinical clue.

Our study identified several similarities in clinical characteristics of nonbullous and bullous pemphigoid. Both present at older age (mean 74.9 years in nonbullous pemphigoid versus 77.2 – 82.6 years in bullous pemphigoid).[4-6] Furthermore, in both variants lesions are most frequently located on the trunk and extremities.[18,22] Most of the skin efflorescences reported in nonbullous pemphigoid

cases can also be found in patients with bullous pemphigoid.[1,13] On the other hand, mucosal involvement was rarely reported in nonbullous pemphigoid, while reported in 10-30% of patients with bullous pemphigoid.[3,13,22] In 14 cases the configurations of the skin lesions were reported to be annular, gyrate, figurate or herpetiform.[21,23-30] Two of these patients presented with targetoid lesions.[21,25] We also found three case reports that were possibly drug induced due to nifedipine, lisinopril and the combination of allopurinol plus colchicine.[25,31,32] Nifedipine and lisinopril were previously associated with bullous pemphigoid, however it is not shown that these drugs actually cause a higher risk to develop bullous pemphigoid.[33,34] Studies did show that the use of spironolactone and neuroleptics are independent risk factors for the development of bullous pemphigoid.[35,36]

The reported histopathologic findings in nonbullous pemphigoid differ from bullous pemphigoid with typical bullae in several aspects. Histopathologic findings were commonly nonspecific in nonbullous pemphigoid and resembled eczema or prurigo nodularis. While bullous pemphigoid is usually characterized by the presence of eosinophilic spongiosis (>50%) and a subepidermal split (± 80%), in the cases with nonbullous pemphigoid histopathologic findings only described eosinophilic spongiosis in 7.5% and a subepidermal split in 15.1%.[1,37] These findings emphasize the need to always perform DIF microscopy and immunoserology in addition to histopathology in patients in which nonbullous pemphigoid is suspected. In nonbullous pemphigoid DIF microscopy was the most reported positive diagnostic test (positive in 93.2%) followed by IIF on salt-split skin (SSS) (90.2%). Both DIF microscopy and IIF on SSS have a high specificity (98% and 100% respectively).[38] Yet, the reported percentage of positive findings in DIF microscopy in nonbullous pemphigoid might be an overestimation, since this test is regarded as the reference standard for diagnosis of pemphigoid and commonly the only performed immunopathologic test.[39] Consequently the diagnosis of pemphigoid might be rejected when DIF microscopy is negative and immunoserologic analysis might not have been performed.

The mean duration of symptoms of nonbullous pemphigoid until the correct diagnosis of pemphigoid was 22.6 months. These results seem to be consistent with other research that also found long diagnostic delays in pemphigoid cases that lack bullae. Previously, we reported a mean delay in diagnosis of 33.6 months in 15 patients with nonbullous pemphigoid.[16] The studies of Zhang et al. and Sun et al. reported misdiagnosis with eczema, nodular prurigo

or other dermatologic diseases in all pemphigoid patients that initially presented without bullae, 181 and 24 patients respectively.[18,40] In both studies the correct diagnosis was made when bullae appeared, which was after a mean duration of 15.9 months and 20.75 months (range 1 month to 19 years). Although these studies only identified misdiagnosis in prodromal bullous pemphigoid patients, they also illustrate the importance of more awareness and better knowledge regarding the characteristics of nonbullous pemphigoid. In contrast, Della Torre et al. did not find a significant difference in delay of diagnosis between patients with bullous (n=97) and nonbullous (n=20) pemphigoid in their cohort.[3] Whether early recognition and immunosuppressive treatment of nonbullous pemphigoid can prevent later blister development is unknown.

A much debated question is whether patients diagnosed with nonbullous pemphigoid are prodromal or have a distinct pemphigoid variant.[10,21] The finding that the majority of nonbullous pemphigoid patients did not develop blisters during follow-up supports the hypothesis that nonbullous pemphigoid is not a prodromal stage but merely a variant within the clinical spectrum of pemphigoid diseases. We can conclude that 'prodromal pemphigoid' is an incorrect term and that there is a need for consensus regarding the terminology to describe this disease variant. We strongly argue for insertion of the term nonbullous pemphigoid in the EMTREE.

During our literature search we identified a number of other subepidermal autoimmune blistering diseases with nonbullous clinical presentations: nonbullous epidermolysis bullosa acquisita[41], nonbullous linear IgA dermatosis[42] and nonbullous pemphigoid gestationis[43]. Furthermore we came across reports of pemphigoid patients that first presented with bullae and later experienced a nonbullous flare-up of the disease.[44-49] These cases strengthen the idea that nonbullous pemphigoid should be seen as a disease variant within the spectrum of pemphigoid diseases. Previous publications reported a higher prevalence of BP-specific autoantibodies in older dermatology patients (>75 years) without blisters, healthy blood donors, and elderly individuals with pruritus.[50-52] How these patients fit the pemphigoid spectrum has not been clarified.

Our systematic review provides insight on reported literature on nonbullous pemphigoid so far. A limitation of this review is that the results are mainly based on single case reports and small case series. Consequently missing values were present in the summarized data. Moreover, in some publications the

clinical picture was described very briefly. A second limitation of this review is the risk of reporting bias, since cases with unusual atypical presentations are more likely to be reported in the literature. Furthermore, the finding that the majority (90.2%) of nonbullous pemphigoid patients did not develop blisters during the reported follow-up (mean 19.8 months;range 0-72) might be slightly biased by selection, since we excluded cases of pemphigoid that were diagnosed after bullae appeared, even though authors retrospectively described pruritic symptoms prior to blistering. However, it is uncertain whether these symptoms prior to diagnosis were caused by pemphigoid, or by other pruritic dermatoses, such as prurigo nodularis or eczema. This study therefore highlights the importance of larger observational studies with longer follow-up for a better representation of nonbullous pemphigoid

Another interesting focus for future research is why patients with nonbullous pemphigoid do not develop bullae. Several factors have been suggested to influence blister formation, such as autoantibody titers,[53] the antigens or epitopes targeted by autoantibodies,[22,54] complement involvement,[55,56] and eosinophils.[57] More knowledge of the underlying pathophysiology of this subtype of pemphigoid might lead to more awareness and less delay in diagnosis of nonbullous pemphigoid.

In conclusion, our review showed that the reported clinical presentation of nonbullous pemphigoid can be heterogeneous. The reported long duration of symptoms until correct diagnosis (mean 22.6 months) illustrates that nonbullous pemphigoid can be difficult to recognize for clinicians. Pruritus in elderly is a common denominator in patients with nonbullous pemphigoid and in our opinion the most important clue for recognition. Clinicians should therefore perform DIF on a skin biopsy and immunoserologic analysis on a blood sample in elderly with unexplained or refractory chronic pruritus and erythematous, urticarial papules and plaques. Further study is needed to evaluate the prevalence of nonbullous pemphigoid.

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Supplementary appendix

Keywords used in the systematic search (performed in EMBASE & MEDLINE):

('non*bullous' AND 'pemphigoid') OR 'non*bullous pemphigoid' OR non*bullous bullous pemphigoid' OR 'non*bullous BP' OR 'pruritic pemphigoid' OR 'pruritic non*bullous pemphigoid' OR 'pemphigoid nodularis' OR 'nodular pemphigoid' OR 'prurigo nodularis-like pemphigoid' OR 'papular pemphigoid' OR 'prodromal BP' OR 'prodromal bullous pemphigoid' OR 'prodromal pemphigoid' OR 'prodrome of bullous pemphigoid' OR 'non bullous variant' NEAR/10 'pemphigoid' OR 'nonbullous variant' NEAR/10 'pemphigoid' OR 'bullous pemphigoid mimicking' OR '-like bullous pemphigoid' OR 'erythrodermic bullous pemphigoid' OR ('bullous pemphigoid' AND 'without blister*') OR ('bullous pemphigoid'/exp AND 'without blister*') OR ('bullous pemphigoid' AND 'without bullae') OR ('bullous pemphigoid' AND 'without bullous lesions')

Supplemental table

Supplemental table 1. All included articles presenting cases of nonbullous pemphigoid

First author	Publication year
Barker et al.[20]	1983
Bingham et al.[58]	1984
Amato et al.[24]	1988
Borradori et al.[59]	1990
Wolf et al.[60]	1992
Ross et al.[49]	1992
Strohal et al.[10]	1993
Bourke et al.[45]	1994
Wever et al.[61]	1995
Jeong et al.[62]	1995
Cliff et al.[63]	1996
Kawahara et al.[53]	1997
Alonso-Llamazares et al.[64]	1998
Alonso-Llamazares et al.[65]	1998
Scrivener et al.[66]	1999
Ameen et al.[32]	2000
Schmidt et al.[67]	2002
Powell et al.[68]	2002
Goel et al.[69]	2003
Mechtel et al.[70]	2003
Tashiro et al.[30]	2005
von Felbert et al.[71]	2005
Lamb et al.[21]	2006
Yesudian et al.[72]	2009
Matsudate et al.[73]	2009
Axelrod et al.[25]	2010
Safa et al.[74]	2010
McCourt et al.[75]	2010
Geiss Steiner et al.[76]	2010
Lehman et al.[77]	2011
Patel et al.[29]	2012
Bakker et al.[11]	2013
Balakirski et al.[78]	2014
Liu et al.[31]	2014
Kabuto et al.[27]	2015
Altman et al.[23]	2015
Park et al.[28]	2015
Huet et al.[79]	2016
Ise et al.[26]	2016