CHAPTER 3

NONBULLOUS PEMPHIGOID: A SYSTEMATIC REVIEW

ANIEK LAMBERTS, JOOST M. MEIJER AND MARCEL F. JONKMAN

Center for Blistering Diseases, Department of Dermatology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Published in Journal of the American Academy of Dermatology, 2018;78(5):989-95.
ABSTRACT

BACKGROUND
Bullous pemphigoid is an autoimmune disease that typically presents with tense bullae and severe pruritus. However, bullae can 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 and/or 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. A minority of patients (9.8%) developed bullae during the reported follow-up.

LIMITATIONS
Results are mainly based on case reports and 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 physicians is needed to avoid delay in diagnosis. (Journal of American Academy of Dermatology https://doi.org/10.1016/j.jaad.2017.10.035.)
The aim of our study was 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.

MATERIALS AND METHODS

SEARCH STRATEGY
The literature search for this review was conducted in the EMBASE and MEDLINE databases on November 4, 2016. Various terms and synonyms for “nonbullous pemphigoid” (Supplementary Appendix; available at http://www.jaad.org) were used. 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 1 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 diagnosti
criteria of pemphigoid: a positive DIF with linear IgG and/or C3c along the basement
membrane zone and/or positive indirect immunofluorescence (IIF), in combina
tion with compatible clinical presentation, histopathologic findings, or other immunoserologic
tests. If the full text was not available online, the text was ordered at the national library. Poster
abstracts were only included if sufficient individual patient data were presented.

DATA COLLECTION
The following variables were gathered: age at diagnosis, sex, duration of symptoms before
diagnosis, clinical presentation, results of diagnostic tests, histopathologic findings, total fol-
low-up time, and blisters 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 I; available at http://www.jaad.org). Fig. 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 individ-
ual patient characteristics concerning age, sex, duration of symptoms, histopathologic findings,
and total duration of follow-up. However, we were able to include the reported clinical presen-
tation and the number of cases that developed blisters during follow-up.

Fig.1 Study selection flow diagram.
Clinical presentation

Table I 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 dermatologic examination are displayed in Table II. Table III presents the location of skin lesions reported in 64 of the 132 cases.

**Table I. Demographics of the reported cases of nonbullous pemphigoid.**

<table>
<thead>
<tr>
<th>Demographic outcome measurements</th>
<th>Total no. reported cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at presentation, years</td>
<td>74.9 (11.8 (39-95))</td>
</tr>
<tr>
<td>Male cases, n (%)</td>
<td>33 (42.3%)</td>
</tr>
<tr>
<td>Cases experiencing pruritus, n (%)</td>
<td>77 (100%)</td>
</tr>
<tr>
<td>Cases with reported mucosal lesions, n (%)</td>
<td>1 (7.1%)</td>
</tr>
<tr>
<td>Mean duration of symptoms before diagnosis, months</td>
<td>22.6 (39.1 (0-240))</td>
</tr>
<tr>
<td>Cases with blister development after diagnosis, n (%)</td>
<td>13 (9.8%)</td>
</tr>
<tr>
<td>Mean duration of symptoms until blisters occurred, months</td>
<td>15.9 (8.4 (7.5-27))</td>
</tr>
<tr>
<td>Mean duration from diagnosis till blisters occurred, months</td>
<td>9.6 (8.6 (1-21))</td>
</tr>
<tr>
<td>Mean total follow-up, months</td>
<td>19.6 (18.6 (0-72))</td>
</tr>
</tbody>
</table>

*SD, Standard deviation.
*Ulceration in the mouth that healed without scarring, other mucosal areas were spared.*

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

<table>
<thead>
<tr>
<th>Skin findings reported</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythematous, urticarial papules and plaques</td>
<td>69 (52.3)</td>
</tr>
<tr>
<td>Papules/nodules</td>
<td>27 (20.5)</td>
</tr>
<tr>
<td>Eczematous lesions</td>
<td>16 (12.1)</td>
</tr>
<tr>
<td>No primary lesions reported*</td>
<td>6 (4.5)</td>
</tr>
<tr>
<td>Dermatitis herpetiformis-like lesions</td>
<td>5 (3.8)</td>
</tr>
<tr>
<td>Ulcerations</td>
<td>3 (2.5)</td>
</tr>
<tr>
<td>Erythroderma</td>
<td>3 (2.5)</td>
</tr>
<tr>
<td>Other</td>
<td>9.6</td>
</tr>
<tr>
<td>Scarring alopecia</td>
<td>19.6</td>
</tr>
<tr>
<td>Vegetations</td>
<td></td>
</tr>
<tr>
<td>Solitary macule</td>
<td></td>
</tr>
<tr>
<td>Excoriations</td>
<td></td>
</tr>
<tr>
<td>Configuration reported</td>
<td></td>
</tr>
<tr>
<td>Annular configuration†</td>
<td></td>
</tr>
<tr>
<td>Figurated configuration</td>
<td></td>
</tr>
<tr>
<td>Gyrated configuration</td>
<td></td>
</tr>
</tbody>
</table>

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

The histopathologic findings were described in 53 individual cases. A perivascular infiltrate was seen most frequently (n=32; 60.4%), which is a nonspecific finding. In addition, nonspecific 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%), and eosinophilic spongiosis was seen in 4 patients (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 patients (15.1%).

**Laboratory Findings**

Table IV shows the reported laboratory findings of patients with nonbullous pemphigoid. In all cases, DIF microscopy was performed. In cases with negative DIF results, the diagnosis was based on positive IIF with additional serologic tests that specified the targeted antigen. IIF was the most commonly performed immunoserologic test (55 cases). The substrate used in IIF was not specified in 15 cases. In the other cases monkey oesophagus (n=27) or human skin (n=13) were used as substrate. The BP230 enzyme-linked immunosorbent assay was the least performed immunoserologic test (n=19). In addition, in 4 cases, immunoprecipitation was used to identify antigens, resulting in a positive reaction to both BP180 and BP230 in 1 case and a positive reaction to only BP230 in 3 cases. Eosinophilia of the peripheral blood was reported in 13 of 15 cases (86.7%).

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

<table>
<thead>
<tr>
<th>Localization</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extremities</td>
<td>43 (67.2)</td>
</tr>
<tr>
<td>Trunk</td>
<td>42 (65.5)</td>
</tr>
<tr>
<td>Generalized</td>
<td>14 (21.9)</td>
</tr>
<tr>
<td>Head and/or neck</td>
<td>7 (10.9)</td>
</tr>
<tr>
<td>Scalp</td>
<td>6 (9.4)</td>
</tr>
<tr>
<td>Hands and/or feet</td>
<td>5 (7.8)</td>
</tr>
</tbody>
</table>

**Table IV.** Laboratory findings in reported cases of nonbullous pemphigoid.

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Cases with positive test results, n (%)</th>
<th>Total no. reported cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIF microscopy, linear IgG and/or C3c depositions</td>
<td>123 (93.2)</td>
<td>132</td>
</tr>
<tr>
<td>IIF, IgG*</td>
<td>42 (76.4)</td>
<td>55</td>
</tr>
<tr>
<td>IIF on salt-split skin, IgG, epidermal binding</td>
<td>46 (90.2)</td>
<td>51</td>
</tr>
<tr>
<td>Nc16a ELISA, IgG</td>
<td>15 (57.7)</td>
<td>26</td>
</tr>
<tr>
<td>BP230 ELISA, IgG</td>
<td>10 (32.4)</td>
<td>19</td>
</tr>
<tr>
<td>Immunoblot BP180, IgG</td>
<td>11 (32.4)</td>
<td>34</td>
</tr>
<tr>
<td>Immunoblot BP230, IgG</td>
<td>20 (55.6)</td>
<td>36</td>
</tr>
</tbody>
</table>

BMZ, Basement membrane zone; BP, bullous pemphigoid; DIF, direct immunofluorescence; ELISA, enzyme linked immunosorbent assay; IIF, indirect immunofluorescence; Nc16a, noncollagen 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 only 13 cases were actually prodromal to bullous pemphigoid. However, for most 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 an older age might 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). Furthermore, in both variants lesions are most frequently located on the trunk and extremities. Most of the skin efflorescences reported in nonbullous pemphigoid cases can also be found in patients with bullous pemphigoid. On the other hand, mucosal involvement was rarely reported in nonbullous pemphigoid and was reported in 10%-30% of patients with bullous pemphigoid.

In 14 cases, the configurations of the skin lesions were reported to be annular, gyrate, figurate, or herpetiform. Two of these patients presented with targetoid lesions. We also found 3 case reports that were possibly drug-induced due to nifedipine, lisinopril, and the combination of allopurinol plus colchicine. Nifedipine and lisinopril were previously associated with bullous pemphigoid; however, it has not been shown that these drugs cause a higher risk to develop bullous pemphigoid. Studies did show that the use of spironolactone and neuroleptics are independent risk factors for the development of bullous pemphigoid.

The reported histopathologic findings in nonbullous pemphigoid differ from bullous pemphigoid in several aspects. Histopathologic findings were commonly nonspecific in nonbullous pemphigoid and resembled eczema or prurigo nodularis. Although 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%. 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 95.2%) followed by IIF on salt-split skin (90.2%). Both DIF microscopy and IIF on salt-split skin have a high specificity (98% and 100%, respectively). Yet, the reported percentage of positive findings in DIF microscopy in nonbullous pemphigoid might be an overestimation, considering this test is regarded as the reference standard for diagnosis of pemphigoid and commonly the only performed immunopathologic test. 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 35.6 months in 15 patients with nonbullous pemphigoid. 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, which were 181 and 24 cases respectively. 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-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. 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. The finding that most 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, nonbullous linear IgA dermatosis, and nonbullous pemphigoid gestationis. Furthermore, we came across reports of pemphigoid patients that first presented with bullae and later experienced a nonbullous flare-up of the disease. 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. How these patients fit the pemphigoid spectrum has not been clarified.

Our systematic review provides insight on reported literature on nonbullous pemphigoid. A limitation of this review is that the results are mainly based on single case reports and small case series. As a consequence, values were missing 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, considering that cases with unusual atypical presentations are more likely to be reported in the literature. Furthermore, the finding that most (90.2%) 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 before blistering. However, it is uncertain whether these symptoms before diagnosis were caused by pemphigoid or 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, the antigens or epitopes targeted by autoantibodies, complement involvement, and eosinophils. 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 diag-
nosis (mean 22.6 months) illustrates that nonbullous pemphigoid can be difficult to recognize for clinicians. Pruritus in elderly patients 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 for elderly patients with unexplained or refractory chronic pruritus and erythematous, urticarial papules and plaques. Further study is needed to evaluate the prevalence of nonbullous pemphigoid.
REFERENCES

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 nodularislike 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").