Nonbullous pemphigoid: A systematic review

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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. (J Am Acad Dermatol 2018;78:989-95.)

Key words: autoimmune blistering disease; autoimmune bullous disease; bullous pemphigoid; characteristics; clinical presentation; nonbullous pemphigoid; terminology; systematic review.

Bullous pemphigoid (BP) is the most common autoimmune bullous disease affecting the skin and mucosal 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 for mortality, as well as a significant decline in quality of life and psychologic well-being.[2-6]

Abbreviations used:

BP:	bullous pemphigoid
BP180:	180-kDa BP antigen
BP230:	230-kDa BP antigen
DIF:	direct immunofluorescence
IIF:	indirect immunofluorescence

The clinical phenotype of pemphigoid is polymorphic. The typical presentation consists of tense blisters that arise on erythematous, urticarial

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plaques and is accompanied by severe pruritus.[1,3] Before 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 of pemphigoid 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, in which case it is called pruritus on primary, nondiseased, noninflamed 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 might be assumed.[14] Bullous and nonbullous pemphigoid are immunologically indistinguishable. The diagnosis is usually based on the combination of clinical presentation, histopathologic 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 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 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, the text 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, sex, duration of symptoms before diagnosis, clinical presentation, results of diagnostic tests, histopathologic findings, total follow-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).[10,11,22-56] 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 individual 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 presentation and the number of cases that developed blisters during follow-up.

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.