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Lamberts, Aniek; Meijer, Joost M; Jonkman, Marcel F

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Nonbullous cutaneous pemphigoid: a systematic review

Aniek Lamberts, MD, Joost M. Meijer, MD, Marcel F. Jonkman, MD, PhD

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4 Aniek Lamberts, MD¹, Joost M. Meijer, MD¹, Marcel F. Jonkman, MD, PhD¹

5

6 ¹ University of Groningen, University Medical Center Groningen, Department of
7 Dermatology, Center for Blistering Diseases, Groningen, the Netherlands

8

9 **Correspondence address**

10 Marcel F. Jonkman, MD, Ph.D.

11 Department of Dermatology

12 University Medical Center Groningen

13 Hanzeplein 1

14 9700 RB Groningen

15 The Netherlands

16

17 tel: +31-50-3612520

18 fax: +31-503612624

19 email: m.f.jonkman@umcg.nl

20

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38 pemphigoid – clinical presentation – characteristics – systematic review -
39 terminology

40 ABSTRACT

41 Background: Cutaneous pemphigoid (bullous pemphigoid) is an autoimmune bullous
42 disease that typically presents with tense bullae and severe pruritus. However,
43 bullae may be lacking, a subtype termed nonbullous cutaneous pemphigoid.

44 Objective: To summarize the reported characteristics of nonbullous cutaneous
45 pemphigoid.

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

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

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

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

62

63 INTRODUCTION

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

70 The clinical phenotype of cutaneous pemphigoid is polymorphic. The typical
71 presentation consists of tense blisters that arise on erythematous, urticarial plaques, and is
72 accompanied by severe pruritus.^{1,3} Prior to blister formation pruritus can occur as a
73 prodrome, with or without primary skin manifestations.⁷ In contrast to the typical bullous
74 presentation, various atypical variants of cutaneous pemphigoid have been reported with
75 terms such as papular pemphigoid, pemphigoid nodularis, pemphigoid vegetans,
76 erythrodermic pemphigoid, pruritic nonbullous pemphigoid and erythema multiforme-like
77 pemphigoid.⁸⁻¹¹ The nonbullous variant of cutaneous pemphigoid presents with pruritus and
78 various nonbullous findings on the skin, such as erythematous patches, urticarial plaques,
79 papules, nodules, excoriations, eczema, and erythroderma. Moreover, this variant can even
80 present without primary skin lesions, called 'pruritus on primary, non-diseased, non-inflamed
81 skin' according to the International Clinical Classification of Itch.^{11,12} Previous articles have
82 emphasized the need for uniform terminology and discussed the urge for renaming *bullous*
83 *pemphigoid*, since the use of the adjective '*bullous*' is redundant considering that
84 '*pemphigoid*' means 'resembling pemphigus' and pemphigus is Greek for '*blister*'.^{8,13-15}
85 Borradori and Joly proposed the term '*cutaneous pemphigoid*'.¹³ To emphasize the lack of
86 bullae in the nonbullous disease variant, we proposed to add the adjective *nonbullous*.¹⁴
87 Hence, the terminology used in this article.

88 Cohort studies show that at least 20% of all pemphigoid patients do not have blisters
89 at the time of diagnosis.^{3,15} Thus, nonbullous cutaneous pemphigoid is not that uncommon or
90 atypical as may be assumed.¹⁶ The bullous and nonbullous cutaneous pemphigoid
91 phenotypes are immunologically indistinguishable. The diagnosis is usually based on the
92 combination of clinical presentation, histopathological findings, direct immunofluorescence

93 (DIF) microscopy, and immunoserology.¹⁵ One of the main obstacles currently is the lack of
94 consensus on the minimal diagnostic criteria of cutaneous pemphigoid.^{8,13,14,16,17} The
95 absence of blistering in nonbullous cutaneous pemphigoid can make the recognition of this
96 disease difficult for clinicians and may result in a delay of diagnosis.^{18,19}

97 The aim of our study is to characterize and define nonbullous cutaneous pemphigoid
98 by systematic review, which has not been performed before. Our study lists reported clinical
99 presentations, histopathological findings, laboratory findings, and prognosis regarding
100 patients with nonbullous cutaneous pemphigoid.

101 MATERIALS AND METHODS

102 *Search strategy*

103 The literature search for this review was conducted in the EMBASE and MEDLINE
104 databases on the 4th of November 2016. Various terms and synonyms for '*nonbullous*
105 *cutaneous pemphigoid*' were used (supplement 1). There were no limitations on article type.
106 After the selection procedure the references of all included articles were checked for missing
107 articles.

108 *Selection of articles*

109 Language was limited to Dutch, German or English. Independent screening of the titles and
110 abstracts was carried out by AL and JM. Discrepancies between the researchers were
111 resolved through discussion. All articles reporting on one or multiple cases of nonbullous
112 cutaneous pemphigoid were included. Nonbullous cutaneous pemphigoid was defined as all
113 symptomatic cases with a nonbullous phenotype, that lacked a previous history of bullae,
114 and fulfill the following diagnostic criteria of cutaneous pemphigoid: a positive DIF with linear
115 IgG and/or C3c along the BMZ and/or positive indirect immunofluorescence (IIF), in
116 combination with compatible clinical presentation, histopathological findings, or other
117 immunoserological tests. If the full text was not available online it was ordered at the national
118 library. Poster abstracts were only included if sufficient individual patient data was presented.

119 *Data collection*

120 The following variables were gathered: age at diagnosis, gender, duration of symptoms
121 before the diagnosis was made, clinical presentation, results of diagnostic tests,
122 histopathological findings, total follow-up time and whether blisters developed during follow-
123 up. Statistical analyses were done in IBM SPSS statistics 23.

124 RESULTS

125 *Systematic search results*

126 A total of 39 articles presenting a total of 132 cases of nonbullous cutaneous pemphigoid
127 were identified (supplement 2). Figure 1 displays the selection procedure. The first case of
128 nonbullous cutaneous pemphigoid was reported in 1983 by Barker et al.²⁰ The largest case
129 series was from Lamb et al.²¹, who described the clinical presentation of 53 patients
130 diagnosed with 'prodromal bullous pemphigoid'. This large case series did not present
131 individual patient characteristics concerning age, gender, duration of symptoms,
132 histopathological findings and total duration of follow-up. However, we were able to include
133 the reported clinical presentation and the number of cases that developed blisters during
134 follow-up.

135 *Clinical presentation*

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

140 *Histopathology*

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

148 *Laboratory findings*

149 Table 4 shows the reported laboratory findings of patients with nonbullous cutaneous
150 pemphigoid. In all cases DIF microscopy was performed. In cases with a negative DIF result,
151 the diagnosis was based on positive IIF with additional serological tests that specified the

152 targeted antigen. IIF was the most commonly performed immunoserological test (55 cases).
153 The substrate used in IIF was not specified in 15 cases. In the other cases monkey
154 esophagus (n=27) or human skin (n=13) were used as substrate. The BP230 ELISA was the
155 least performed immunoserological test (n=19). Additionally in four cases
156 immunoprecipitation was used to identify antigens, resulting in a positive reaction to both
157 BP180 and BP230 in one case and only a positive reaction to BP230 in three cases.
158 Eosinophilia in peripheral blood was reported in 13 of 15 cases (86.7%).

159 DISCUSSION

160 This systematic review summarizes the reported characteristics of nonbullous cutaneous
 161 pemphigoid. The most frequently reported skin efflorescences were erythematous, urticarial
 162 plaques (52.3%). Pruritus was reported in 100% of the cases. Overall, the duration between
 163 the start of symptoms and the correct diagnosis was very long (mean 22.6 months). Only 13
 164 patients (9.8%) developed bullae during the reported follow-up, thus were actually prodromal
 165 to the bullous phase of cutaneous pemphigoid. However, in the majority of the cases
 166 (90.2%) bullae never occurred. The findings of this review show that although the clinical
 167 presentation of nonbullous cutaneous pemphigoid is various, pruritus at high age may be a
 168 clinical clue.

169 Our study identified several similarities in clinical characteristics of nonbullous and
 170 bullous cutaneous pemphigoid. Both present at older age (mean 74.9 versus 77.2 – 82.6
 171 years).⁴⁻⁶ Furthermore, in both variants lesions are most frequently located on the trunk and
 172 extremities.^{18,22} Most of the skin efflorescences reported in nonbullous cutaneous
 173 pemphigoid cases can also be found in patients with cutaneous pemphigoid with bullae.^{1,15}
 174 On the other hand, mucosal involvement was rarely reported in nonbullous cutaneous
 175 pemphigoid, while reported in 10-30% of patients with cutaneous pemphigoid.^{3,15,22} In 14
 176 cases the configurations of the skin lesions were reported to be annular, gyrate, figurate or
 177 herpetiform.^{21,23-30} Two of these patients presented with targetoid lesions.^{21,25} We also found
 178 three case reports that were possibly drug induced due to nifedipine, lisinopril and the
 179 combination of allopurinol plus colchicine.^{25,31,32} Nifedipine and lisinopril were previously
 180 associated with cutaneous pemphigoid, however it is not shown that these drugs actually
 181 cause a higher risk to develop cutaneous pemphigoid.^{33,34} Studies did show that the use of
 182 spironolactone and neuroleptics are independent risk factors for the development of
 183 cutaneous pemphigoid.^{35,36}

184 The reported histopathological findings in nonbullous cutaneous pemphigoid differ from
 185 cutaneous pemphigoid with typical bullae in several aspects. Histopathological findings were
 186 commonly nonspecific in nonbullous cutaneous pemphigoid and resembled eczema or
 187 prurigo nodularis. While cutaneous pemphigoid with bullae is usually characterized by the
 188 presence of eosinophilic spongiosis (>50%) and a subepidermal split ($\pm$ 80%), in the cases

189 with nonbullous cutaneous pemphigoid histopathological findings only described eosinophilic
190 spongiosis in 7.5% and a subepidermal split in 15.1%.^{1,37} These findings emphasize the
191 need to always perform DIF microscopy and immunoserology in addition to histopathology in
192 patients in which nonbullous cutaneous pemphigoid is suspected. In nonbullous cutaneous
193 pemphigoid DIF microscopy was the most reported positive diagnostic test (positive in
194 93.2%) followed by IIF on salt-split skin (SSS) (90.2%). Both DIF microscopy and IIF on SSS
195 have a high specificity (98% and 100% respectively).³⁸ Yet, the reported percentage of
196 positive findings in DIF microscopy in nonbullous cutaneous pemphigoid might be an
197 overestimation, since this test is regarded as the reference standard for diagnosis of
198 pemphigoid and commonly the only performed immunopathological test.³⁹ Consequently the
199 diagnosis of pemphigoid might be rejected when DIF microscopy is negative and
200 immunoserological analysis might not have been performed.

201 The mean duration of symptoms of nonbullous cutaneous pemphigoid until the correct
202 diagnosis of pemphigoid was 22.6 months. These results seem to be consistent with other
203 research that also found long diagnostic delays in pemphigoid cases that lack bullae.
204 Previously, we reported a mean delay in diagnosis of 33.6 months in 15 patients with
205 nonbullous cutaneous pemphigoid.¹⁴ The studies of Zhang et al. and Sun et al. reported
206 misdiagnosis with eczema, nodular prurigo or other dermatologic diseases in all pemphigoid
207 patients that initially presented without bullae, 181 and 24 patients respectively.^{18,40} In both
208 studies the correct diagnosis was made when bullae appeared, which was after a mean
209 duration of 15.9 months and 20.75 months (range 1 month to 19 years). Although these
210 studies only identified misdiagnosis in prodromal cutaneous pemphigoid patients, they also
211 illustrate the importance of more awareness and better knowledge regarding the
212 characteristics of nonbullous cutaneous pemphigoid. In contrast, Della Torre et al. did not
213 find a significant difference in delay of diagnosis between patients with bullous (n=97) and
214 nonbullous (n=20) cutaneous pemphigoid in their cohort.³ Whether early recognition and
215 immunosuppressive treatment of nonbullous cutaneous pemphigoid can prevent later blister
216 development is unknown.

217 A much debated question is whether patients diagnosed with nonbullous cutaneous
218 pemphigoid are prodromal or have a distinct pemphigoid variant.^{10,21} The finding that the

majority of nonbullous cutaneous pemphigoid patients did not develop blisters during follow-up supports the hypothesis that nonbullous cutaneous 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 cutaneous 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 acquisita⁴¹, nonbullous linear IgA dermatosis⁴² and nonbullous pemphigoid gestationis⁴³. Furthermore we came across reports of cutaneous 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 cutaneous 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 cutaneous 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 cutaneous 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 cutaneous 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 cutaneous pemphigoid

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

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

274 **ABBREVIATION LIST**

275	BP	bullous pemphigoid
276	BP180	180 kDa BP antigen
277	BP230	230 kDa BP antigen
278	BMZ	basement membrane zone
279	DIF	direct immunofluorescence
280	IIF	indirect immunofluorescence
281	SSS	salt-split skin

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480 **LEGENDS TO FIGURES**

481 **Figure 1** Study selection flow diagram

482

483

ACCEPTED MANUSCRIPT

TABLES

485

Table 1

487 **Table 1.** Demographics of the reported cases of nonbullous cutaneous 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

488 SD, standard deviation; * Ulceration in the mouth that healed without scarring, other mucosal areas were spared³²

Table 2

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

Skin findings reported	No. of cases (%)
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%)

491 The clinical presentation was reported in all 132 cases.

492 ¶ all 6 cases presented with secondary lesions in the form of excoriations

493 * two cases presented with erythema multiformis-like lesions

494

Table 3

496 **Table 3.** Reported localization of skin lesions in nonbullous cutaneous pemphigoid

Localization reported	No. of cases (%)
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%)

498 The localization of the lesions was reported in 64 cases

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501

502 **Table 4**

Table 4. Reported laboratory findings

	No. of cases with positive test results (%)	Reported in no. cases
DIF microscopy, linear IgG and/or C3c depositions along the BMZ	123 (93.2%)	132
IIF* IgG	42 (76.4%)	55
IIF on salt split skin, 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

DIF, direct immunofluorescence; IgG, immunoglobulin G; BMZ, basement membrane zone; IIF, indirect immunofluorescence; Nc16a, non-collagen 16a; ELISA, enzyme linked immunosorbent assay.

* different substrates were used by different authors.

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508 **SUPPLEMENTARY MATERIAL**509 **Supplement 1**510 *Keywords used in the systematic search (performed in EMBASE & MEDLINE)*

511 ('non*bullous' AND 'pemphigoid') OR 'non*bullous pemphigoid' OR non*bullous
 512 pemphigoid' OR 'non*bullous BP' OR 'pruritic pemphigoid' OR 'pruritic non*bullous
 513 pemphigoid' OR 'pemphigoid nodularis' OR 'nodular pemphigoid' OR 'prurigo nodularis-like
 514 pemphigoid' OR 'papular pemphigoid' OR 'prodromal BP' OR 'prodromal bullous
 515 pemphigoid' OR 'prodromal pemphigoid' OR 'prodrome of bullous pemphigoid' OR 'non
 516 bullous variant' NEAR/10 'pemphigoid' OR 'nonbullous variant' NEAR/10 'pemphigoid' OR
 517 'bullous pemphigoid mimicking' OR '-like bullous pemphigoid' OR 'erythrodermic bullous
 518 pemphigoid' OR ('bullous pemphigoid' AND 'without blister*') OR ('bullous pemphigoid'/exp
 519 AND 'without blister*') OR ('bullous pemphigoid' AND 'without bullae') OR ('bullous
 520 pemphigoid' AND 'without bullous lesions')

521

522

523 **Supplement 2**524 *List of all included articles presenting cases of nonbullous cutaneous 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

Capsule summary

- What is already known on this topic.
Cutaneous pemphigoid can present without typical bullae and consequently diagnosis can be delayed.
- What this article adds to our knowledge.
The most frequently reported clinical features in these patients are pruritic, erythematous, urticarial papules and plaques.
- How this information impacts clinical practice and/or changes patient care.
Clinicians should consider nonbullous cutaneous pemphigoid in older patients with refractory pruritus.