

Pemphigoid nodularis - rare presentation of bullous pemphigoid: A case report and literature review

CORINA VORNICESCU¹, SIMONA CORINA ȘENILĂ¹, RODICA COSGAREA¹,
ELISABETA CANDREA¹, ALEXANDRA DANA POP² and LOREDANA UNGUREANU¹

Departments of ¹Dermatology and ²Physiology, 'Iuliu Hațieganu' University
of Medicine and Pharmacy, 400006 Cluj-Napoca, Romania

Received August 13, 2018; Accepted September 25, 2018

DOI: 10.3892/etm.2018.7057

Abstract. Pemphigoid nodularis (PN) is a rare clinical variant of bullous pemphigoid characterized by the presence of nodular prurigo-like lesions and pemphigoid blisters. The diagnosis is confirmed by direct immunofluorescence (DIF)/indirect immunofluorescence (IIF) and immunoserology tests. For some patients, with long mean duration of symptoms, the correct diagnosis of PN is delayed because the disease is not recognized. We present a case and summarize the reported characteristics of PN. The search in MEDLINE database, after selection, resulted in 36 articles presenting 47 cases of PN. Between published cases a female predominance was noted (female to male ratio of 1.8:1), almost half of the reported patients were non-Caucasian, and the mean age at presentation was 66.2 years. The mean duration until the diagnosis was almost 2 years. Sixteen patients also had other autoimmune diseases. Twenty-two patients developed vesicles/bullae/urticarial plaques before or after the diagnosis. Peripheral eosinophilia and high levels of serum total IgE were reported in 10.6 and 27.2% of patients, respectively. ELISA for either BP180, BP230 or both were positive in all tested cases. DIF and IIF microscopy were positive overall in 100 and 92.3% of cases, respectively. Corticosteroids, either topical or systemic, were the most efficient therapeutic option,

although many others were used. PN remains a diagnostic and therapeutic challenge in elderly patients with unexplained refractory chronic pruritus associated with papulo-nodular lesions.

Introduction

Bullous pemphigoid (BP) is the most common autoimmune bullous disease affecting the skin and mucosal membranes, with antibodies directed against the 180-kDa BP antigen (BP180) and the 230-kDa BP antigen (BP230) located in the basement membrane zone (1). BP commonly affects older patients and females are slightly more affected than males (2).

Up to 20% of the patients with classical BP may have at the onset of the disease a non-bullous phase of variable duration with non-specific itchy lesions (eczematous patches, urticarial plaques, polycyclic, targetoid, nodular, lichenoid or vesicular lesions) (3).

Pemphigoid nodularis (PN) is a rare variant of BP having clinical features of prurigo nodularis with an autoantibody profile of BP (4). Hyperkeratotic, excoriated and pruritic nodules on the extremities can be the first sign of PN anticipating the blisters by weeks or months. In some cases the blisters cannot be observed through-out the whole course of the disease making diagnosis substantially difficult (3). The pathogenesis of PN is not well understood. Skin physical trauma like persistent scratching exposes hidden antigens of the basal membrane to the immune system, leading to the production of autoantibodies in predisposed individuals (5).

The aim of the study is to present a case of PN and a systematic review of the published PN cases regarding clinical aspects, histopathological features, laboratory findings and treatment options.

Case report

Caucasian, 81-year female, with a history of ischemic heart disease, chronic obstructive pulmonary disease and bilateral gonarthrosis was admitted in to the hospital in July 2016 for a nodular-excoriated eruption on her trunk and extremities with abrupt onset, ~2 months before admission. Clinical examination revealed violaceous, highly pruritic nodular lesions, some with excoriations, other with a pale and atrophic center (Fig. 1).

Correspondence to: Dr Simona Corina Șenilă, Department of Dermatology, 'Iuliu Hațieganu' University of Medicine and Pharmacy, 3-5 Clinicilor Street, 400006 Cluj-Napoca, Romania
E-mail: corina.senila@umfcluj.ro

Abbreviations: BP, bullous pemphigoid; BP180, 180 kDa BP antigen; BP230, 230 kDa BP antigen; DIF, direct immunofluorescence; ELISA, enzyme-linked immunosorbent assay; Ig, immunoglobulin; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; IIF, indirect immunofluorescence; NSAID, non-steroidal anti-inflammatory drugs; PN, pemphigoid nodularis; Pts, patients; SD, standard deviation; TNF- α , tumor necrosis factor- α

Key words: pemphigoid nodularis, pruritic excoriated nodules, serum total IgE, direct immunofluorescence, ELISA, bullous pemphigoid

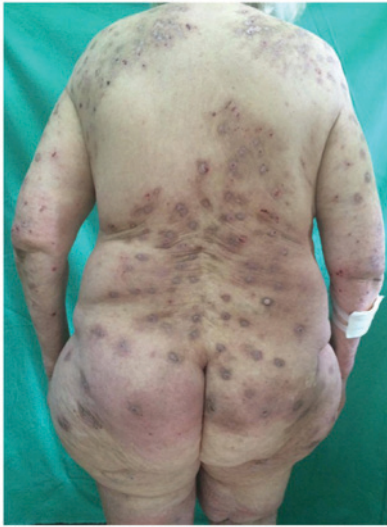


Figure 1. Primary lesions - multiple hyperkeratotic nodules, postinflammatory hyper/hypopigmentation, multiple excoriations.



Figure 3. Secondary lesions - urticarial plaques with postbullous erosions on the surface and excoriations on the forearm.

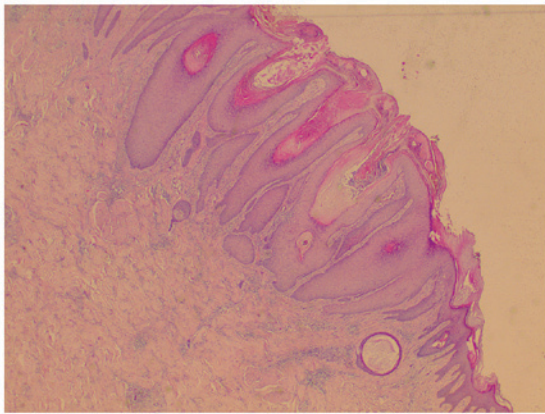


Figure 2. Histopathological exam showing marked hyperkeratosis, focal parakeratosis, and mild spongiosis, mixed inflammatory infiltrate (lymphocytes, plasmacytes, neutrophils, eosinophils) with a diffuse and perivascular pattern in the dermis; magnification, x10; haematoxylin and eosin staining.

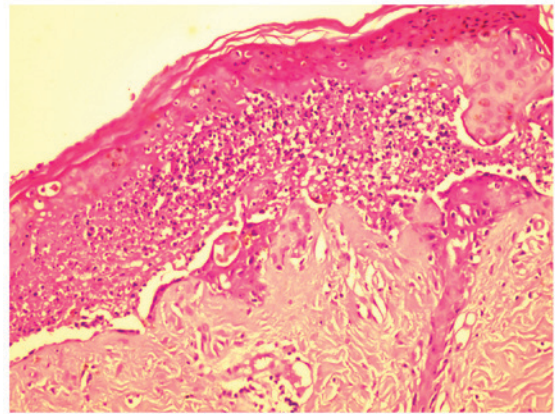


Figure 4. Histopathological exam showing hyperkeratosis, focal parakeratosis, spongiosis, subepidermal bulla and a lymphoplasmacytic and neutrophilic infiltrate with diffuse and perivascular pattern; magnification, x10; haematoxylin and eosin staining.

Most lesions presented a hyperpigmented, bluish halo. The lesions were located on the trunk and limbs, with sparing of the face and interscapular region. All the skin was dry and scaly. The emotional and psychosocial background was stable. Complete blood count, liver and kidney function were normal. Thyroid function was normal, but levels of thyroid peroxidase and antithyroglobulin antibodies were increased. IgE level in the blood was elevated (2002.9 UI/ml; normal <100.0 UI/ml). The first skin biopsy showed marked hyperkeratosis, focal parakeratosis, and mild spongiosis; the dermis had marked mixed inflammatory infiltrate (lymphocytes, plasmacytes, neutrophils, eosinophils) with a diffuse and perivascular pattern. PAS stain showed no mycotic colonies (Fig. 2). Direct immunofluorescence (DIF) performed from the margin of the same lesion was negative; ELISA for BP180 and BP230 were also negative. Screening for an underlying malignancy was negative.

At this point, she was diagnosed with prurigo nodularis, atopy, autoimmune thyroiditis and xerosis cutis. In order

to interrupt the cycle of itching-scratching a treatment with topical corticosteroids and calcipotriol for 6 weeks was started, with no improvement.

After 2 months urticarial plaques appeared with no evidence of blister formation (Fig. 3). A new skin biopsy was performed from these new lesions showing hyperkeratosis, focal parakeratosis, spongiosis, subepidermal bulla and a lymphoplasmacytic and neutrophilic infiltrate with diffuse and perivascular pattern (Fig. 4).

DIF revealed linear C3 deposits along the basal membrane (Fig. 5). ELISA from serum was positive for BP230 antibody (79.0 U/ml, normal <20.0 U/ml) and was negative for BP180. The clinical and histologic aspect, together with C3 linear distribution at the basal membrane and positivity of BP230 antibodies were consistent with the rare diagnosis of pemphigoid nodularis. She started a treatment with prednisone (0.5 mg/kg/day) for 2 weeks which was gradually tapered by 5 mg/week in the following 6 weeks. Topical therapy consisted in one application of clobetasol propionate 0.05% in

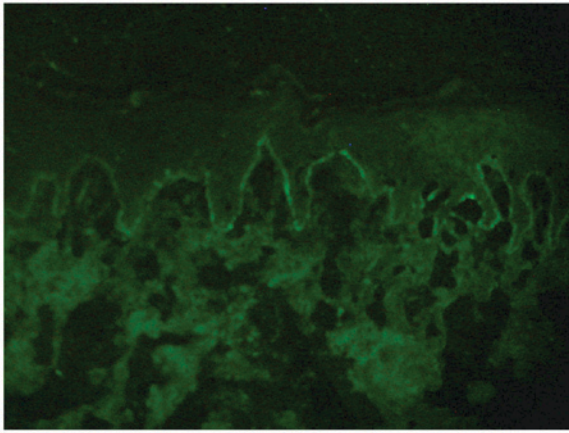


Figure 5. DIF microscopy - linear deposit of C3 along the basement membrane zone.

the evening. The pruritus, nodules and urticaria-like eruption remitted under corticotherapy. In order to minimize the risk of adverse reactions and thus to discontinue the treatment with systemic corticosteroids, we introduced fexofenadine hydrochloride (240 mg/day), montelukast sodium (10 mg/day) and continued topical applications of clobetasol propionate. After 3 months, the nodular lesions were improved, without any sign of recurrence.

Unfortunately, 2 weeks after the last visit the patient died due to a hemorrhagic stroke, which, in our opinion, was unrelated to the autoimmune bullous disease.

Materials and methods

We conducted a literature search in English and French of the MEDLINE database on 18th May 2018 using the following terms: 'nodular pemphigoid', 'pemphigoid nodularis', 'pemphigoid' and 'nodularis', without limitations on article type and restricted the papers to those published in English or French. We collected data on: age at diagnosis, sex, origin, associated diseases, duration of symptoms before diagnosis, clinical presentation, results of diagnostic tests, treatment options and outcome.

The study was approved by the Ethics Committee of the Emergency County Hospital (Cluj-Napoca, Romania), and written informed consent was provided by the patient for this study.

We defined PN patients as patients who presented with a pruritic papulo-nodular eruption followed by a positive analysis of either DIF, indirect immunofluorescence (IIF) or immunoserology. Statistical analysis was performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA) software. Data were presented as mean \pm SD.

A total of 51 articles were found. We excluded from our review: three articles because of language limitations, 6 articles due to incomplete data and 6 articles were not relevant to the question.

A total of 36 articles included in the study presented 47 cases of PN between 1981 and 2018 (Table I). All the characteristics of the cases reported are summarized in Tables II-V.

The female to male ratio was 1.8:1. The mean age of onset was 66.2 years, SD \pm 12.3, median age 70 (for patients aged

Table I. All included articles and cases reported.

Author (refs.)	No. of cases reported	Publication year
36 articles	47 cases	1981-2018
Yoneda <i>et al</i> (22)	1	2018
Zhang <i>et al</i> (23)	1	2017
Amber <i>et al</i> (4)	1	2017
Yoshimoto <i>et al</i> (24)	1	2017
Dangel <i>et al</i> (25)	1	2016
Asahina <i>et al</i> (15)	1	2015
Kwong and Lim (26)	1	2015
Al-Salhi and Alharithy (27)	1	2015
Das and Bandyopadhyay (28)	1	2014
Mochizuki <i>et al</i> (9)	1	2013
Matsudate <i>et al</i> (29)	2	2009
Koga <i>et al</i> (30)	1	2009
Aboumaria <i>et al</i> (31)	1	2008
Teraki and Fukuda (32)	1	2008
McGinnes <i>et al</i> (16)	1	2006
Gach <i>et al</i> (33)	2	2005
Tashiro <i>et al</i> (34)	2	2005
Sakuma-Oyama <i>et al</i> (35)	1	2003
Powell <i>et al</i> (5)	5	2002
Schachter <i>et al</i> (6)	1	2001
Gao <i>et al</i> (36)	1	2001
Ameen <i>et al</i> (37)	1	2000
Cliff and Golden (38)	3	1997
Kossard (39)	1	1996
Tamada <i>et al</i> (40)	1	1995
Bourke <i>et al</i> (41)	1	1994
Ratnavel <i>et al</i> (42)	1	1994
Gallo <i>et al</i> (43)	1	1993
Borradori <i>et al</i> (44)	1	1992
Ross <i>et al</i> (45)	3	1992
Borradori <i>et al</i> (46)	1	1990
Tani <i>et al</i> (47)	1	1989
Shimizu <i>et al</i> (48)	1	1988
Roenigk and Dahl (49)	1	1986
Massa and Connolly (50)	1	1982
Yung <i>et al</i> (51)	1	1981

41-91 years) and 13.3 years, SD \pm 2.1, median age 14 (for patients aged 11-15 years). Most of the patients were non-Caucasian [49.0%, 23 patients (pts)], 12 pts were Caucasian (25.5%) while for 12 pts the origin was not mentioned. As comorbidities, we found autoimmune diseases (rheumatoid arthritis, ulcerative colitis, autoimmune thyroiditis, IPEX, bullous pemphigoid, dermatitis herpetiformis, idiopathic chronic eosinophilic pneumonia) in 16 pts (34.0%), inflammatory diseases (psoriasis) in 1 pts (2.1%), allergic diseases (asthma and atopic diathesis) in 2 pts (4.2%) and diabetes mellitus in 3 pts (6.4%) (Table II).

For all patients the primary lesions were considered as pruritic, hyperkeratotic or excoriated papules and/or nodules, on the extremities and trunk, and 46.8% (22 pts) developed secondary lesions (blisters, vesicles, urticarial plaques) before or after the diagnosis of PN has been established. One case

Table II. Demographic and personal history characteristics.

Data	% (no. of pts)
Sex	
Male	36.2 (17)
Female	63.8
Female:Male ratio	1.8:1 (30)
Age (years; mean \pm SD)	
11-15 (3 pts)	13.3 \pm 2.1; 14 years
41-91 (44 pts)	66.2 \pm 12.3; 70 years
Origin	
Caucasian	25.5 (12)
Non-Caucasian	49.0 (23)
Not mentioned	25.5 (12)
Associated diseases	
Autoimmune	34.0 (16)
Allergic	4.2 (2)
Inflammatory	2.1 (1)
Diabetes mellitus	6.4 (3)

No. of pts, number of reported patients.

had oral mucosa involvement. Data concerning the duration of the disease (after onset of initial lesions) was found in 35 out of 47 pts (for 7 pts data was not recorded, and 5 pts had prior blistering autoimmune disease). Mean duration was 23.6 months, SD \pm 31.9, with the median value of 9 months. Histopathological examination from a hyperkeratotic nodule was performed in 37 pts (78.7%); spongiosis and/or subepidermal cleft was noted in 13 pts (35.1%), which are not suggestive for prurigo nodularis, and dermal eosinophils in 23 pts (62.2%), while one patient presented non-specific features. High serum total IgE levels were found in 13 pts (27.7%) and eosinophilia in 5 pts (10.6%) (Table III).

Diagnosis was confirmed by immunofluorescence analysis (DIF: linear deposits of IgG and/or C3 along the basement membrane zone, IIF on monkey esophagus or 1M salt-split normal human skin: linear deposit of IgG with epidermal binding $>1:80$) and circulating autoantibody tests. Of 47 cases, DIF from pruritic papule and/or nodule was carried out in 30 pts and was positive in 26 pts (86.7%). All 21 pts that developed secondary lesions presented positive perilesional DIF (100%).

IIF was performed in 39 pts and was positive in 36 (92.3%). Immunoblot (western blotting) analysis was performed for 19 pts; it was positive in all cases: 4 pts for 180 kDa (21.1%), 11 pts (57.9%) for 230 kDa (220 kDa) and 4 pts (21.1%) for both. Nineteen patients were analyzed by ELISA and positive tests were found in all patients; for BP180 in 12 pts (63.1%), for BP230 in 1 pts (5.3%) and for both (BP180+BP230) in 6 pts (31.6%) (Table IV).

Post-therapeutic clinical outcome of reported cases was evaluated as 'good' (significant improvement of pruritus, gradual resolution of skin lesions), 'partial' (persistence of some skin lesions) and 'no response'. We summarized available data as the name of drugs, dosage (minimal and maximal), and

Table III. Clinical, histopathological and blood tests findings.

Data	% (no. of pts)
Clinical aspect	
Primary lesions ^a and/or secondary lesions ^b	100 (47) 46.8 (22)
Duration of symptoms before diagnosis (months)	
Mean \pm SD, 23.6 \pm 31.9 (range 1-132)	74.5 (35)
Median 9	
Histopathology, from a nodular lesion	78.7% (37)
Spongiosis and/or cleft	35.1 (13)
Eosinophilic infiltrate	62.2 (23)
Blood tests	
Eosinophilia	10.6 (5)
High value of total IgE	27.7 (13)

^aPrimary lesions: pruritic papules and/or nodules; ^bsecondary lesions: urticarial plaques, vesicles, tense bullae. No. of pts, number of reported patients.

duration of administration in Table V. We found that the best therapeutic options were systemic and topical corticosteroids.

Discussion

Our systematic review summarized the reported characteristics of PN, a rare variant of BP having clinical features of prurigo nodularis with an autoantibody profile of BP. The features of the present case report are similar to the ones reported in the literature, highlighting the elderly patient group, presenting initial papulo-nodular pruritic lesions and secondary vesicular/ bullous lesions or urticarial plaques. This atypical onset of PN partially explains the diagnosis delay, especially in the absence of obvious clinical signs of BP. We consider that clinicians should take into consideration DIF microscopy in elderly patients with pruritic papulo-nodular eruption.

As for the pediatric patients, autoimmune blistering diseases are rare and their prevalence unclear. Interestingly, in the few cases of PN reported in children, most of them had previous long-standing BP, suggesting a hyperproliferative integrin profile (6).

Mucosal involvement was reported in 10-30% of patients with BP (7). Our review shows a lower incidence of 2.1%, suggesting that oral mucosa involvement is less frequent in PN.

Drug-induced disease due to various medication (antibiotics, NSAID, diuretics, anti-TNF- α , antidiabetics, antiarrhythmics and antihypertensives) was reported in some cases of BP (8). We found only one patient who was treated for rheumatoid arthritis with etanercept (anti-TNF- α drug) before the onset of PN, which imposed a discontinuation of the drug with favorable effect (9).

Histopathologic findings in PN show features of prurigo nodularis (orthohyperkeratosis, focal parakeratosis and irregular epidermal hyperplasia) (10) and bullous pemphigoid

Table IV. Characteristics of immunofluorescence microscopy and immunoserologic tests.

Immunologic tests	Positive (%)	Negative (%)	No. of pts
DIF, pruritic papule and/or nodule	26/30 (86.7)	4/30 (13.3)	46
DIF, once the secondary lesions appeared ^a	21/21 (100)	0	
IIF (monkey esophagus/salt-split skin)	36/39 (92.3)	3/39 (7.9)	39
Immunoblot 180 kDa	4/19 (21.1)	-	19
Immunoblot 230 kDa	11/19 (57.9)	-	
Immunoblot 180 kDa and 230 kDa	4/19 (21.1)	-	
ELISA BP180	12/19 (63.1)	-	19
ELISA BP230	1/19 (5.3)	-	
ELISA BP180 and BP230	6/19 (31.6)	-	

^aPerilesional; no. pts, number of reported cases; DIF, direct immunofluorescence; IIF, indirect immunofluorescence.

Table V. Treatment of reported cases.

Therapy	Max dose	Min dose	Duration	Clinical outcome (no. of pts)		
				Good	Partial	No response
Topical corticosteroids	-	-	18 weeks	4	1	4
Prednisone	1 mg/kg/day	0.5 mg/kg/day	6-10 months	9	1	0
Prednisolone	1 mg/kg/day	0.1 mg/kg/day	3 months	7	9	1
Betamethasone	20 mg/day	0.5 mg/day	NM	2	0	0
Methylprednisolone	0.4 mg/kg	0.2 mg/kg	>6 months	1	0	0
Azathioprine	50 mg tid	50 mg/day	12 months	7	1	0
Dapsone	100 mg/day	50 mg/day	NM	3	1	0
IVIg	2 g/kg/day, 5 days	-	10 months	2	1	0
Minocycline	100 mg bid	100 mg/day	NM	2	1	2
Mycophenolate mofetil	2 g/day	1.5 g/day	NM	1	1	0
Sulfamethoxy-pyridazine	500 mg tid	500 mg/day	2-4 years	1	1	0
Fexofenadine + Montelukast	240 mg bid +10 mg	-	4 weeks	1	1	1
Niacinamide	500 mg tid	-	6 months	1	0	2
Suplataste tosilate	300 mg/day	-	NM	1	0	0
Rituximab	375 mg/mp	-	NM	1	0	0
Triamcinolone i.m.	60 mg	-	NM	0	1	0
Cyclosporine	NM	NM	NM	0	1	0
Methotrexate	15 mg/week	NM	3 months	0	0	1
Cyclophosphamide	NM	NM	NM	0	0	1
Oral Antihistamines	NM	NM	NM	0	0	6

NM, not mentioned; good, significant improvement of pruritus, gradual resolution of the skin lesions; partial, persistence of some skin lesions.

(eosinophilic spongiosis more than 50% and a subepidermal cleft 80%) (11). Skin nodule biopsies revealed spongiosis and/or subepidermal split in some cases but, more frequently, dermal eosinophilic infiltrate, indicating the necessity of performing DIF microscopy and immunoserology assays in addition to the histopathological examination.

DIF and IIF on salt-split skin microscopy have high specificity, 98 and 100%, respectively (12) in BP and they are the most reported positive diagnostic tests in nonbullous pemphigoid, 93.2 and 90.2%, respectively (1). In the PN cases

that were reported, DIF microscopy performed from nodular lesions was positive in most cases, while it was positive in all patients when secondary lesions were clinically obvious. IIF was positive similar to the previously reported data. As a result, a negative DIF does not exclude PN.

The diagnosis must be completed with immunoserology testing as ELISA or Immunoblot (western blotting). Since 2002 most reported cases of PN were confirmed by ELISA and we found that all were positive, either for BP180, BP230 or both. Moreover, ELISA testing can be useful in follow-up,

the levels of BP antibodies decreasing as the clinical aspect improves under treatment.

A recent study indicated that BP patients can have pathologic peripheral eosinophilia (50.2%) (13). This finding was significantly correlated with the age of patients (older patients) and the severity of the palmoplantar involvement. Moreover, peripheral eosinophil count is significantly correlated with levels of both anti-BP180 IgG and IgE (14). The association between serum eosinophilia and BP or PN is still unclear as Kridin found no correlation between atypical clinical variants of BP (prurigo-like type) and serum eosinophilia (13), while our data revealed serum eosinophilia in some patients, who also had high levels of serum total IgE and anti-BP180 IgG antibody. Eosinophils play an important role in the pathogenic cascade of BP and PN as well as in other autoimmune diseases (15,16).

Elevated IgE levels were reported in 70% of patients with BP in 1974 (17). It was also shown that IgE abnormalities and impaired B lymphocyte function is correlated with serum levels of soluble CD23 (18). Although in the review of Saniklidou *et al* on bullous pemphigoid no correlations were found between IgE levels and the nodular form of the disease (19), our data showed high levels serum total IgE in 13 patients (27.7%). Ten out of the later thirteen patients had positive DIF performed from nodular lesions, positive IIF and tissue eosinophilia.

Although literature data did not find an increased risk for autoimmune disorders in patients with BP (20), we found one third of patients having this association. These findings could be explained by a genetic susceptibility to develop autoimmune diseases.

Treatment in PN remains difficult and challenging as the condition is chronic, severely pruritic, occurring in elderly patients with multiple comorbidities. Due to adverse effects of immunosuppressive medication there is a need to find therapeutic alternatives. Reported data regarding treatment are incomplete, lacking details such as dosage, duration of administration.

The best therapeutic results were obtained using systemic corticosteroids, azathioprine, dapsone, intravenous Ig, minocycline. However, topical and systemic corticosteroids continue to remain the gold standard in PN. Our review shows that the therapeutic response is directly correlated with the dose and the treatment duration.

In our case, after a significant improvement of the pruritus and the aspect of the nodules under corticosteroid treatment, we chose to continue due to comorbidities, with a combination of montelukast sodium (leukotriene receptor inhibitor) and fexofenadine hydrochloride (second generation antihistamine antagonist) (21). Unfortunately, we could not evaluate the therapeutic outcome on the long-term, due to the death of the patient, which we believe was unrelated to PN.

Our review has a few limitations. The first is that the results are based on case reports and small case series. Moreover, data regarding the treatment is inconsistent in most of the published articles. As strength, our review offers a clear overview concerning the most important aspects of PN in cases reported so far.

In conclusion, PN should be recognized as a rare form of bullous pemphigoid and must be taken into consideration as

a differential diagnosis of pruritic papulo-nodular eruption in the elderly. Refractory, chronic and unexplained pruritus in those patients should lead to skin biopsy and DIF/IIF microscopy as well as immunoserology analysis to detect PN.

Acknowledgements

Not applicable.

Funding

The publication of the manuscript was partially supported by the Transylvanian Association of Dermatologists (ADT).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

CV, SCS, LU were responsible for the conception of manuscript and the interpretation of data. ADP and RC contributed to the interpretation and analysis of data. EC contributed to drafting the manuscript and revising it critically for important intellectual content. All authors contributed to the literature search, read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Emergency County Hospital (Cluj-Napoca, Romania). The patient provided written informed consent for the present study.

Patient consent for publication

The patient gave written consent for the investigations that were performed (blood tests and biopsy) and for the publication of medical data for scientific purposes.

Competing interests

The authors declare that they have no competing interests.

References

1. Lamberts A, Meijer JM and Jonkman MF: Nonbullous pemphigoid: A systematic review. *J Am Acad Dermatol* 78: 989-995, 2018.
2. Alpsoy E, Akman-Karakas A and Uzun S: Geographic variations in epidemiology of two autoimmune bullous diseases: Pemphigus and bullous pemphigoid. *Arch Dermatol Res* 307: 291-298, 2015.
3. Cozzani E, Gasparini G, Burlando M, Drago F and Parodi A: Atypical presentations of bullous pemphigoid: Clinical and immunopathological aspects. *Autoimmun Rev* 14: 438-445, 2015.
4. Amber KT, Korta DZ, de Feraudy S and Grando SA: Vesiculobullous eruption in a patient receiving psoralen ultraviolet A (PUVA) treatment for prurigo nodules: A case of PUVA-aggravated pemphigoid nodularis. *Clin Exp Dermatol* 42: 833-835, 2017.
5. Powell AM, Albert S, Gratian MJ, Bittencourt R, Bhogal BS and Black MM: Pemphigoid nodularis (non-bullous): A clinicopathological study of five cases. *Br J Dermatol* 147: 343-349, 2002.

6. Schachter M, Brieva JC, Jones JC, Zillikens D, Skropek C and Chan LS: Pemphigoid nodularis associated with autoantibodies to the NC16A domain of BP180 and a hyperproliferative integrin profile. *J Am Acad Dermatol* 45: 747-754, 2001.
7. Di Zenzo G, Della Torre R, Zambruno G and Borradori L: Bullous pemphigoid: From the clinic to the bench. *Clin Dermatol* 30: 3-16, 2012.
8. Stavropoulos PG, Soura E and Antoniou C: Drug-induced pemphigoid: A review of the literature. *J Eur Acad Dermatol Venereol* 28: 1133-1140, 2014.
9. Mochizuki M, Fujine E, Tawada C, Kanoh H and Seishima M: Pemphigoid nodularis possibly induced by etanercept. *J Dermatol* 40: 578-579, 2013.
10. Zeidler C, Yosipovitch G and Ständer S: Prurigo nodularis and its management. *Dermatol Clin* 36: 189-197, 2018.
11. Schmidt E and Zillikens D: Pemphigoid diseases. *Lancet* 381: 320-332, 2013.
12. Sárdy M, Kostaki D, Varga R, Peris K and Ruzicka T: Comparative study of direct and indirect immunofluorescence and of bullous pemphigoid 180 and 230 enzyme-linked immunosorbent assays for diagnosis of bullous pemphigoid. *J Am Acad Dermatol* 69: 748-753, 2013.
13. Kridin K: Peripheral eosinophilia in bullous pemphigoid: Prevalence and influence on the clinical manifestation. *Br J Dermatol*: Apr 16, 2018 (Epub ahead of print).
14. Messingham KN, Holahan HM, Frydman AS, Fullenkamp C, Srikantha R and Fairley JA: Human eosinophils express the high affinity IgE receptor, FcεRI, in bullous pemphigoid. *PLoS One* 9: e107725, 2014.
15. Asahina A, Niizuma A, Ohzono A, Ishii N, Koga H and Hashimoto T: Pemphigoid nodularis with diverse IgG, IgA and IgE antibodies showing neutrophilic papillary microabscesses. *Acta Derm Venereol* 95: 239-240, 2015.
16. McGinness JL, Bivens MM, Greer KE, Patterson JW and Saulsbury FT: Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) associated with pemphigoid nodularis: A case report and review of the literature. *J Am Acad Dermatol* 55: 143-148, 2006.
17. Arbesman CE, Wypych JJ, Reisman RE and Beutner EH: IgE levels in sera of patients with pemphigus or bullous pemphigoid. *Arch Dermatol* 110: 378-381, 1974.
18. Schmidt E, Bröcker EB and Zillikens D: High levels of soluble CD23 in blister fluid of patients with bullous pemphigoid. *Arch Dermatol* 131: 966-967, 1995.
19. Saniklidou AH, Tighe PJ, Fairclough LC and Todd I: IgE autoantibodies and their association with the disease activity and phenotype in bullous pemphigoid: A systematic review. *Arch Dermatol Res* 310: 11-28, 2018.
20. Taylor G, Venning V, Wojnarowska F and Welch K: Bullous pemphigoid and autoimmunity. *J Am Acad Dermatol* 29: 181-184, 1993.
21. Shintani T, Ohata C, Koga H, Ohyama B, Hamada T, Nakama T, Furumura M, Tsuruta D, Ishii N and Hashimoto T: Combination therapy of fexofenadine and montelukast is effective in prurigo nodularis and pemphigoid nodularis. *Dermatol Ther (Heidelb)* 27: 135-139, 2014.
22. Yoneda K, Ishii N, Nakai K, Kubota Y and Hashimoto T: Localized nodular pemphigoid. *Int J Dermatol* 57: 587-589, 2018.
23. Zhang W, Liu Y and Li C: Generalised nodules in pemphigoid nodularis. *Lancet* 389: 1930, 2017.
24. Yoshimoto N, Ujiie H, Hirata Y, Izumi K, Nishie W and Shimizu H: Bullous pemphigoid developed in a patient with prurigo nodularis. *J Eur Acad Dermatol Venereol* 31: e187-e189, 2017.
25. Dangel B, Kofler L and Metzler G: Nodular subtype of bullous pemphigoid. *J Cutan Med Surg* 20: 570-572, 2016.
26. Kwong HL and Lim SP: Pemphigoid nodularis mimicking nodular prurigo in an immune-suppressed patient with rheumatoid arthritis. *Acta Derm Venereol* 95: 237-238, 2015.
27. Al-Salhi W and Alharithy R: Pemphigoid nodularis. *J Cutan Med Surg* 19: 153-155, 2015.
28. Das D and Bandyopadhyay D: Juvenile pemphigoid nodularis: Report of a rare case. *Indian Dermatol Online J* 5: 189-192, 2014.
29. Matsudate Y, Ansai SI, Hirose K, Kubo Y and Arase S: Pemphigoid nodularis: The importance of ELISA for diagnosis. *Eur J Dermatol* 19: 83-84, 2009.
30. Koga H, Hamada T, Ohyama B, Nakama T, Yasumoto S and Hashimoto T: An association of idiopathic chronic eosinophilic pneumonia with pemphigoid nodularis: A rare variant of bullous pemphigoid. *Arch Dermatol* 145: 1339-1340, 2009.
31. Aboumaria A, Pelletier F, Aubin F, Algros MP, Afifi Y and Humbert P: Pemphigoid nodularis. *Ann Dermatol Venereol* 135: 251-252, 2008 (In French).
32. Teraki Y and Fukuda T: Pemphigoid nodularis associated with psoriatic erythroderma: Successful treatment with suplatast tosilate. *Br J Dermatol* 158: 424-426, 2008.
33. Gach JE, Wilson NJ, Wojnarowska F and Ilchysyn A: Sulfamethoxypyridazine-responsive pemphigoid nodularis: A report of two cases. *J Am Acad Dermatol* 53 (Suppl 1): S101-S104, 2005.
34. Tashiro H, Arai H, Hashimoto T, Takezaki S and Kawana S: Pemphigoid nodularis: two case studies and analysis of autoantibodies before and after the development of generalized blistering. *J Nippon Med Sch* 72: 60-65, 2005.
35. Sakuma-Oyama Y, Powell AM, Albert S, Oyama N, Bhogal BS and Black MM: Lichen planus pemphigoides evolving into pemphigoid nodularis. *Clin Exp Dermatol* 28: 613-616, 2003.
36. Gao XH, Lin J, Yang C, Ma L, Wang G, Wang Y and Chen HD: A case of Kaposi's sarcoma associated with pemphigoid nodularis. *J Dermatol* 28: 388-392, 2001.
37. Ameen M, Harman KE and Black MM: Pemphigoid nodularis associated with nifedipine. *Br J Dermatol* 142: 575-577, 2000.
38. Cliff S and Holden CA: Pemphigoid nodularis: A report of three cases and review of the literature. *Br J Dermatol* 136: 398-401, 1997.
39. Kossard S: Prurigo papules with blisters. *Australas J Dermatol* 37: 104-105, 1996.
40. Tamada Y, Yokochi K, Oshitani Y, Nitta Y, Ikeya T, Hara K and Owaribe K: Pemphigoid nodularis: A case with 230 kDa hemidesmosomes antigen associated with bullous pemphigoid antigen. *J Dermatol* 22: 201-204, 1995.
41. Bourke JF, Berth-Jones J, Gawkrödger DJ and Burns DA: Pemphigoid nodularis: A report of two cases. *Clin Exp Dermatol* 19: 496-499, 1994.
42. Ratnavel RC, Shanks AJ, Grant JW and Norris PG: Juvenile pemphigoid nodularis. *Br J Dermatol* 130: 125-126, 1994.
43. Gallo R, Parodi A and Rebora A: Pemphigoid nodularis. *Br J Dermatol* 129: 744-745, 1993.
44. Borradori L, Prost C, Wolkenstein P, Bernard P, Baccard M and Morel P: Localized pretibial pemphigoid and pemphigoid nodularis. *J Am Acad Dermatol* 27: 863-867, 1992.
45. Ross JS, McKee PH, Smith NP, Shimizu H, Griffiths WA, Bhogal BS and Black MM: Unusual variants of pemphigoid: From pruritus to pemphigoid nodularis. *J Cutan Pathol* 19: 212-216, 1992.
46. Borradori L, Rybojad M, Verola O, Flageul B, Puissant A and Morel P: Pemphigoid nodularis. *Arch Dermatol* 126: 1522-1523, 1990.
47. Tani M, Murata Y and Masaki H: Pemphigoid nodularis. *J Am Acad Dermatol* 21: 1099-1104, 1989.
48. Shimizu H, Hayakawa K and Nishikawa T: A comparative immunoelectron microscopic study of typical and atypical cases of pemphigoid. *Br J Dermatol* 119: 717-722, 1988.
49. Roenigk RK and Dahl MV: Bullous pemphigoid and prurigo nodularis. *J Am Acad Dermatol* 14: 944-947, 1986.
50. Massa MC and Connolly SM: Bullous pemphigoid with features of prurigo nodularis. *Arch Dermatol* 118: 937-939, 1982.
51. Yung CW, Soltani K and Lorincz AL: Pemphigoid nodularis. *J Am Acad Dermatol* 5: 54-60, 1981.



This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.