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Original Research

The Significant Role of Atopic Skin Diathesis in Prurigo Nodularis

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Abstract

Objectives: Atopic skin plays a significant etiological role in the development of prurigo nodularis (PN). In addition to atopic dermatitis (AD), atopic skin diathesis without eczema can also contribute to the development of PN due to its association with itching. This study aims to evaluate PN in terms of AD/atopic skin diathesis, associated comorbidities, and clinical findings.

Methods: Patients diagnosed with PN based on clinical and histopathological findings between 2014 and 2024 were included in the study. Associated diseases that could contribute to the etiology of pruritus were recorded as comorbidities. The diagnosis of AD was evaluated using the Hanifin-Rajka's diagnostic criteria and atopic skin diathesis using the Erlangen Atopy Score. Patients were classified as atopic and non-atopic groups, and these groups were compared in terms of demographic and clinical findings.

Results: The study included a total of 47 patients, of whom 15 (31.9%) were male and 32 (68.1%) were female. At least one comorbidity was identified in 89.4% (n=42) of the patients, and multiple comorbidities were found in 34% (n=16). Atopic dermatitis and/or atopic skin diathesis were present in 55.3% (n=26) of the patients. Among these, 53.8% (n=14) were diagnosed with AD, while 46.2% (n=12) had only an atopic skin diathesis. Compared to the non-atopic group, the atopic group had a lower median age (p=0.001) and higher serum total IgE levels (p=0.031).

Conclusion: In addition to AD, atopic skin diathesis without eczema also appears to play an important role in the etiology of PN. The lower age and higher IgE levels in patients are factors associated with atopic predisposition.

Keywords: Atopic dermatitis, atopic skin, prurigo nodularis, pruritus, systemic disease, xerosis

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Prurigo nodularis (PN), also known as chronic prurigo, is a chronic inflammatory skin disease characterized by localized or generalized extremely pruritic papular/nodular lesions. The main symptoms include chronic pruritus (lasting more than six weeks), a history and/or signs of recurrent scratching such as excoriations and scars, and multiple pruriginous lesions.[1] Pruriginous lesions are typically excoriated, scaly, and/or crusty papules, nodules, or plaques, often with whitish or pink centers and hyperpigmented borders.[1] The primary pathogenesis involves neuronal sensitivity to itch caused by chronic itching and the development of the itch-scratch cycle.[1,2]

Underlying conditions may include dermatological, systemic, neurological, psychiatric/psychosomatic diseases, or a combination of these.[3,4] However, the etiology remains unknown in a significant portion of patients.[5] Additionally,

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atopic dermatitis (AD) or atopic predisposition has been reported as an underlying cause or contributing factor to pathogenesis in many patients.[3,6,7] AD is characterized by eczematous lesions that appear in age-related locations, such as the cheeks in infants and flexural areas in children and adults, based on the atopic skin diathesis. It is diagnosed according to the diagnostic criteria based on specific clinical findings.[8]

In some cases, there is only an atopic skin diathesis without eczema. Atopic skin diathesis may be an important cause of itching and could be related to the initial symptom of itch-scratch cycle in patients with PN. Identifying individuals with an atopic skin diathesis without AD is therefore crucial. A standardized objective scoring system, known as the Erlangen Atopy Score (EAS), has been developed to evaluate atopic skin diathesis.[9] There is limited data investigating the relationship with atopic dermatitis in PN patients, but there is no data investigating the relationship with atopic skin structure.

The aim of this study is to evaluate patients diagnosed with PN in relation to accompanying AD/atopic skin diathesis and associated comorbidities and to investigate its relationship with clinical factors.

Methods

Patients

This single-center retrospective cross-sectional study included 47 patients diagnosed with PN between 2014 and 2024 in the dermatology outpatient clinic and allergy unit at our tertiary center. All patients diagnosed with PN through clinical and histopathological examination, and whose medical records were accessible, were included in the study. Demographic data, clinical findings including the localization, distribution, and severity of the lesions, and treatments for PN were evaluated in detail. Patients were assessed for factors underlying chronic pruritus through laboratory tests and clinical evaluations. Diseases with the potential to contribute to the etiology of pruritus were recorded as comorbidities. These were classified as dermatologic, systemic, neurological, psychiatric, mixed, and other.[10]

Data Collection Tools

AD diagnosis was evaluated using Hanifin-Rajka's[11] diagnostic criteria in all patients. The Numeric Rating Scale (NRS) was employed to assess the severity of itching. The NRS is an 11-point scale where patients rate the worst itch intensity in the past 24 hours, with 0 indicating "no itching" and 10 indicating "worst itching imaginable".[12]

The Erlangen Atopy Score (EAS) was used to assess atopic skin diathesis.[9] Developed by Diepgen et al.,[9] EAS is a standardized diagnostic method that evaluates atopic skin using 24 variables, including personal and family history of atopy, atopic symptoms and findings, and laboratory investigations. Patients with EAS scores of 10 and above were considered to be at increased risk of atopic skin diathesis.

Xerosis severity was evaluated on a 4-point scale from 0 (absent) to 3 (severe) according to the SCORAD xerosis score.[13] This evaluation was conducted on the anterior part of the lower limbs without the application of moisturizer for two days.

The patients were divided into two groups: those with AD and/or atopic skin diathesis formed the atopic group, while all other patients constituted the non-atopic group. The demographic and clinical findings of the atopic and non-atopic groups were compared.

This study was approved by the local ethics committee of Istanbul University, Istanbul Faculty of Medicine (2024/615), and informed consent was obtained from all patients. This study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were performed using SPSS software version 15 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics included the mean, standard deviation, minimum, and maximum scores for numerical variables, and numbers and percentages for categorical variables. Independent variables in both groups were compared using the Student t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. The alpha significance level was set at $p<0.05$.

Results

A total of 47 patients (15 males, 32 females) comprised the study population. The mean age was 43.0±14.9 years. Lesions were generalized in 93.6% of the patients, and xerosis was detected in 89.4%. AD/atopic skin diathesis was present in 55.3% (n=26). Detailed demographic and clinical data are provided in Table 1. The median age was statistically lower in the atopic group in comparison to the non-atopic-group ($p=0.001$). The mean total IgE level and the incidence of allergic bronchial asthma and allergic rhinitis were significantly higher in the atopic group ($p=0.031$ and $p<0.001$, respectively). Xerosis was found 96.2% in the atopic group and 81.0% in the non-atopic group, the difference was statistically not significant (Table 1).

In 89.4% (n=42) of the patients, at least one dermatologic and/or systemic comorbidity was present, with 34% (n=16) having multiple comorbidities. Dermatologic comorbidi-

Table 1. Demographic features and clinical/laboratory findings of patients. Significant p-values are highlighted in bold.

	Total (n=47)	Atopic group (n=26, 55.3%)	Non-atopic group (n=21, 44.7%)	p#
Demographic features				
Gender				
Female, n (%)	32 (68.1)	19 (73.1)	13 (61.9)	0.53
Male, n (%)	15 (31.9)	7 (26.9)	8 (38.1)	
Age (year), mean (SD)	43.0±14.9	36.7±12.7	50.9±13.9	**0.001***
Median (range)	47 (13-85)	37 (13-57)	52 (23-85)	
Duration of PN (month), mean (SD)	85.3±112.9	92.5±111.9	76.4±116.1	0.31
	36 (3-480)	36 (3-384)	24 (3-480)	
Allergic rhinitis/Asthma bronchiale, n (%)	22 (46.8)	18 (69.2)	4 (19.0)	**<0.001**
Clinical/Laboratory findings				
Localized, n (%)	3 (6.4)	3 (11.5)	0 (0)	0.24
Generalized, n (%)	44 (93.6)	23 (88.5)	21 (100)	
Xerosis, yes, n (%)	42 (89.4)	25 (96.2)	17 (81.0)	0.87
NRS, median (range)	7 (4-10)	7 (4-10)	8 (4-10)	0.70
Total IgE, (IU/ml), median (range)	299 (3-11352)	601 (3-11352)	132 (15-3062)	**0.031**
Treatment				
Antihistamines, n (%)	45 (95.7)	26 (100)	19 (90.5)	0.11
Antidepressants/antipsychotics, n (%)	20 (42.6)	10 (38.5)	10 (47.6)	0.37
Immunosupressants, n (%)	10 (21.3)	7 (26.9)	3 (14.3)	**0.049**
Dupilumab, n (%)	5 (10.6)	5 (19.2)	0 (0)	**0.026**

#Chi-square test, *Mann-Whitney U test; PN: prurigo nodularis; NRS: numeric rating scale; SD: standard deviation.

ties were present in 59.6% (n=28) of patients, while systemic comorbidities were present in 63.8% (n=30) of patients. The most common comorbidities were systemic-metabolic diseases (n=19, 40.4%), followed by psychiatric (n=6, 12.8%) and neurological (n=5, 10.6%) conditions (Table 2). Apart from AD/atopic conditions, two patients were diagnosed with non-atopic dermatologic disorders: one with lichenoid stomatitis and one with bullous pemphigoid. The most common systemic comorbidities were diabetes mellitus (n=12, 25.5%) and Hashimoto's thyroiditis (n=5, 10.6%). The most common psychiatric comorbidities were anxiety disorder (n=3, 6.4%), depression (n=2, 4.3%), and panic attack disorder (n=2, 4.3%).

In the atopic group, 34.6% (n=9) of the patients had mixed comorbidities, whereas 63.4% (n=17) had no accompanying systemic comorbidities. Additionally, 53.8% (n=14) of the patients had at least one systemic comorbidity alongside atopy. In the non-atopic group, 76.2% (n=16) of the patients had at least one comorbidity, and 33.3% (n=7) had more than one comorbidity (Table 2).

Discussion

More than half of the patients (55.3%) with PN had an atopic predisposition in the present study. Among these patients, 53.8% were diagnosed with AD, while 46.2% had only an atopic skin diathesis without eczema. As AD and atopic skin diathesis are both characterized with pruritic skin, the itch-scratch cycle may lead to pruriginous lesions or even PN in both conditions.

The association between prurigo and AD was first noted in the literature in 1980, suggesting that prurigo lesions might form more readily in atopic individuals.[14] The first comprehensive study on this topic was conducted by Tanaka et al. in 1995,[6] which included 31 patients with prurigo, of whom 20 (65%) were diagnosed with AD. This study only considered patients diagnosed with AD based on the Hanifin and Rajka diagnostic criteria, excluding those with atopic skin diathesis only. In a more recent study, Iking et al.[3] evaluated both AD and atopic diathesis, finding that 46.3% of the patients had AD or atopic diathesis. Within this group, 18% had atopic diathesis alone, while 27.5% had a mixed origin.[3] Similar to our study, these results indicated that approximately half of the patients with prurigo exhibited AD/atopic skin characteristics. Besides those diagnosed with AD, atopic predisposition stood out as a significant factor as well. Atopic predisposition, also known as atopic skin diathesis, plays a crucial role in the development of prurigo lesions and should be considered alongside AD when evaluating patients with PN.

Table 2. Comorbidities of patients with prurigo nodularis according to atopy

	Total (n=47) n (%)	Atopic group (n=26) n (%)	Non-atopic group (n=21) n (%)
Comorbidity (at least 1)	42 (89.4)	26 (100)	16 (76.2)
Atopic and/or non-atopic Comorbidity	16 (34.0)	9 (34.6)	7 (33.3)
Only atopic comorbidity	17 (25.5)	17 (63.4)	-
Dermatologic comorbidity	28 (59.6)		
Atopic dermatitis	14 (29.8)	14 (53.8)	-
Atopic skin diathesis	24 (51.1)	24 (92.3)	-
Lichenoid stomatitis	1 (2.1)	-	1 (4.8)
Bullous pemphigoid	1 (2.1)	-	1 (4.8)
Systemic comorbidity (at least 1)	30 (63.8)	14 (53.8)	16 (76.2)
Systemic-metabolic	19 (40.4)	6 (23.1)	13 (61.9)
Diabetes mellitus	12 (25.5)	3 (11.5)	9 (42.9)
Hashimoto thyroiditis	5 (10.6)	2 (7.7)	3 (14.3)
Iron deficiency anemia	2 (4.3)	-	2 (9.5)
Renal transplantation	1 (2.1)	1 (3.8)	-
Cheliac disease	1 (2.1)	-	1 (4.8)
Psychiatric	6 (12.8)	5 (19.2)	
Anxiety disorder	3 (6.4)	3 (11.5)	-
Panic attack disorder	2 (4.3)	1 (3.8)	1 (4.8)
Depression	2 (4.3)	1 (3.8)	1 (4.8)
Neurological	5 (10.6)	3 (11.5)	2 (9.5)
Lumbar hernia	3 (6.4)	1 (3.8)	2 (9.5)
Cerebrovascular disease	1 (2.1)	1 (3.8)	-

In patients with AD, prurigo lesions were described as a morphological variant of AD, known as 'atopic prurigo'.[15] The existing terminology in this area is confusing, with terms like 'atopic prurigo,' 'Besnier's prurigo,' 'atopic PN,' 'PN-like AD,' and 'prurigo type AD' all being used.

The most important component of atopic skin is xerosis and xerosis-related findings such as itch when sweating and wool intolerance. Impaired skin barrier function and associated xerosis are the primary causes of itching in these patients.[16] In our atopic patient group, the rate of xerosis was higher than in the non-atopic group, although this difference was statistically not significant. Other studies have also demonstrated a relationship between xerosis and itching in non-atopic patient groups.[17] In a study evaluating xerosis in PN patients, 60% of the patients were found to have xerosis, with a significant portion reported as non-atopic xerosis.[18] It has been suggested that xerosis in these patients could be related to other systemic comorbidities, such as diabetes, and may play a significant role in the pathogenetic mechanism of the itch-scratch cycle.[18] The presence of xerosis in the non-atopic group could be attributed to existing systemic comorbidities such as diabetes mellitus and Hashimoto thyroiditis in the present series.

The relationship between AD and prurigo may be based on shared pathogenic mechanisms. Itching is the main symptom in both conditions, leading to the itch-scratch cycle. In AD, itching occurs secondary to barrier dysfunction and inflammatory lesions on the skin, while in PN, it can be initiated by sensory neuron dysfunction.[19,20] Both diseases are characterized by Type 2 immune dysregulation. Type 2 inflammation involves the activation of various cytokines, especially IL-4, IL-5, IL-13, and IL-31.[19] These cytokines increase the excitability of peripheral sensory neurons and the neural response to pruritogens.[21]

The lower age of patients in the atopic group was a striking finding. This issue was first highlighted by Tanaka et al.,[6] who classified PN as early-onset atopic and late-onset non-atopic. PN is more common among older individuals, typically appearing in the 6th-7th decade of life.[20] Atopic dermatitis affects patients in the earlier age group. Therefore, AD-related PN may be seen at an earlier age, and the age factor may be a clue for atopic prurigo.

Limited studies in the literature assess the etiological factors in PN. Reported causes include dermatological, systemic-metabolic, neurological, psychiatric diseases, malignancies, and HIV infection.[22,23] However, establishing

definitive cause-and-effect relationships is challenging. Etiological factors vary significantly among populations. In our patient group, we conducted a detailed evaluation of accompanying diseases, which could be related to pruritus. Due to factors like unclear temporal relationships and simultaneous presence of multiple diseases, definitive conclusions on etiological factors were difficult to draw. These accompanying diseases were considered comorbidities, with systemic-metabolic, dermatologic, and psychiatric conditions being most common. Systemic metabolic diseases such as chronic kidney failure, diabetes mellitus, and chronic liver diseases are frequently reported.[24,25] Psychiatric comorbidities, notably anxiety and depression, and frequent use of antidepressants and anxiolytics are prevalent in PN patients.[26] Similarly, psychiatric comorbidities, especially anxiety disorders, were common in our patient group.

It is difficult to identify a single etiological factor in PN patients. A significant portion of patients typically have multiple comorbidities.[3,4] In our patient group, many individuals also had more than one comorbidity. Based on these findings, it has been suggested that prurigo should not be considered a monofactorial disease but rather a symptom resulting from the itch-scratch cycle caused by various underlying conditions that lead to itching.[3]

In this study, notable limitations include the small patient group and the inability to establish a definitive relationship between comorbidities and the etiology of pruritus. However, a significant strength is the comprehensive evaluation of all patients for both AD and atopic skin conditions.

Conclusion

In conclusion, atopic predisposition emerges as a key etiological factor in the PN patient cohort. Besides AD, having an atopic skin diathesis represents a significant risk factor. In PN patients associated with AD/atopic skin diathesis, a lower age is observed, highlighting the importance of considering atopic predisposition, especially in younger patients. Clearer and more detailed definitions on this topic are needed, alongside the establishment of consensus on terminology.

Disclosures

Ethics Committee Approval: The study was approved by the Istanbul University, Istanbul Faculty of Medicine Clinical Research Ethics Committee (date: 05.04.2024, no: 2024/615).

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