doi:10.36849/JDD.SF365502

 ORIGINAL ARTICLE Journal of Drugs in Dermatology

Prurigo Nodularis: Current Clinicopathologic Overview and Psychodermatological Perspectives

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ABSTRACT

Prurigo nodularis (PN) is a quintessential neurocutaneous condition characterized by neural sensitization and intractable itch leading to intense scratching. This causes the formation of nodules with epidermal thickening and further release of pro-inflammatory mediators that recruit immune cells and increase dermal nerve proliferation and hypertrophy perpetuating the itch-scratch cycle. Those with PN have a significant quality-of-life (QoL) burden due to itch, anxiety, and sleep disturbance. In addition, PN exhibits psychiatric comorbidities that affect mental wellbeing such as depression, mood disorders, and substance abuse. This paper serves as an overview of the clinicopathologic aspects of PN, the burden of PN on QoL, and the psychodermatological aspects of the disease state.

J Drugs Dermatol. 2023;22:12(Suppl 2):s6-11.

INTRODUCTION

Prurigo nodularis (PN) is a neurocutaneous pruritic disorder that disproportionately affects black individuals.[1] Recent advances in research technologies have allowed for granular elucidation of the pathogenesis of the disease. There exists an interplay between the skin, immune, and nervous systems. Here we discuss the current understanding of the clinicopathologic and epidemiological features of PN, cutaneous and non-cutaneous co-morbidities, as well as the psychodermatologic aspects of the disease.

Definition and Clinicopathologic Features of PN

Also known synonymously as chronic nodular prurigo (CNPG), PN is a subtype of chronic prurigo with an extensive global burden on quality of life (QoL).[2] According to the European Academy of Dermatology and Venereology Task Force for Pruritus, chronic prurigo is defined as "a distinct disease defined by the presence of chronic pruritus (>6 weeks) and multiple localized or generalized pruriginous lesions."[3] It is thought that PN commences with neural sensitization with subsequent development of the itch-scratch cycle.[3] Continued itch results in multiple hyperkeratotic papules and nodules that are typically distributed symmetrically along the extensor surfaces of the extremities.[4-6] Oftentimes lesions can be found on the upper and lower back, sparing the central back due to an inability of the patient to reach those areas to scratch; this finding is known as the "butterfly sign."[7] The PN lesions themselves may also be severely pruritic, leading to the continuation of the itch-scratch cycle. Depending on skin type, PN lesions may appear as red-pink in patients who are White and violaceous papules/nodules in patients with skin of color. On histology, PN lesions demonstrate epidermal hyperplasia, hypergranulosis, spongiosis, compact hyperkeratosis, as well as vertically arranged collagen fibers with an increased number of fibroblasts.[8] Compared to matched healthy skin, lesional PN skin also exhibits greater inflammatory cells including lymphocytes, neutrophils, mast cells, and eosinophils.[9]

Epidemiology of PN

PN is classified as a rare disease by the National Institutes of Health Genetic and Rare Diseases Information Center (GARD)[10] and the National Organization for Rare Diseases (NORD).[11] In the US, the prevalence of PN is estimated to range from 36.7 to 43.9 per 10,000 individuals.[12,13] In Europe, rates of between 0.65 to 11.1 per 10,000 individuals have been cited.[14-16] The estimated prevalence of PN in the United Kingdom is 3.27 per 10,000 individuals, and prevalence increases with age.[17]

The mean age of patients with PN at incident diagnosis is ~60 years, which has been reported in numerous studies.[17-19] African American patients are approximately 3 times more likely to have PN than White patients.[20,21] There is also a gender predilection for PN with females more commonly affected than males.[17,19,22] Estrogen is known to modulate the immune response and has been shown to enhance the production of T helper 2 (Th2) cytokines such as interleukin (IL)-4, IL-5, and IL-13.[23] The immunomodulatory function of estrogen may explain the greater burden of pruritus in females in general.[24]

Most common comorbidities associated with PN include atopic dermatitis (AD) and psychiatric diagnoses such as anxiety and depression.[17,25,26] Other comorbidities include chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, human immunodeficiency virus (HIV), and type 2 diabetes.[27] With respect to chronic kidney disease, circulating plasma angiotensinogen levels were dysregulated only in Black patients with PN.[28] Black patients with PN also had stronger associations with end-stage renal disease and faster progression of their renal disease compared to White patients with PN. Higher all-cause mortality was also observed in Black patients with PN and not in Asian patients with PN.[29] Compared to the general population, patients with PN are more likely to be hospitalized, have longer inpatient stays, and experience a high infectious disease burden, which corresponds to higher healthcare utilization and spending.[30-32] A retrospective study of 15,818 patients with PN showed a disproportionate burden of comorbid tuberculosis infection in patients with PN compared to the general population, which could be attributed to Th2 immune skewing.[33] Lastly, PN may have an association with malignancies of the skin, hematopoietic system, and solid organs.[34]

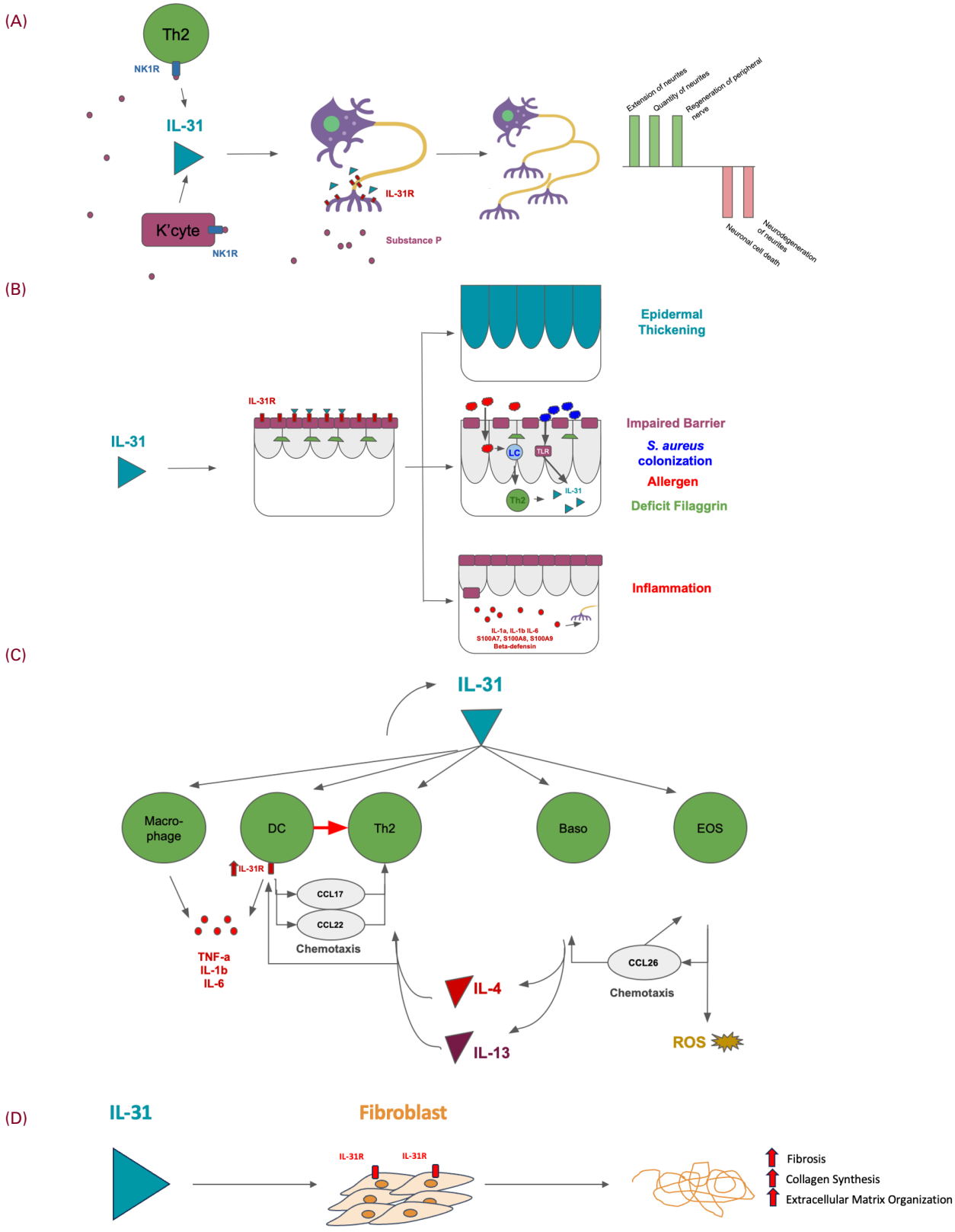
Pathophysiology of PN

Immune and neural dysregulation are central to the pathogenesis of PN.[35,36] The brain and skin are of the same ectodermal embryological origin. The term *brain-skin axis* describes the connection between our nervous/psychiatric and dermatological systems. While it is debated which aspect (immune or neural) occurs first in the initiation of PN, it is clear that both are inextricably intertwined and act in tandem (Figure 1).

Neural sensitization results in intense itching and scratching. The act of scratching causes disruption of the epidermal skin barrier resulting in the release of pro-inflammatory mediators by keratinocytes (eg, IL-1A, S100A), penetrance of allergens that activate epidermal Langerhans cells and T helper 2 (Th2) cells which secrete IL-31, and bacterial colonization with *Staphylococcus aureus* and other microbes that activate keratinocyte toll-like receptors (TLRs) to cause further secretion of IL-31 by keratinocytes.[37,38] IL-31 interacts with IL-31 receptors on numerous cells resulting in pleiotropic effects. On nerve cells, IL-31 stimulates the sensation of itch and proliferation and regeneration of nerve endings, thus causing neural sensitization and release of substance P, which feeds back onto keratinocytes and Th2 cells causing further release of IL-31.[39] IL-31 also acts on numerous immune cells causing a further inflammatory cascade; IL-31 interacts with (1) basophils to stimulate release of Th2-related cytokines IL-4 and IL-13 that then bind to Th2 lymphocytes, (2) eosinophils to release reactive oxygen species (ROS) and CCL26 which causes chemotaxis of basophils, (3) dendritic cells to release CCL17 and CCL 22 to recruit Th2 cells, and (4) macrophages to release TNF-alpha, IL-1b, and IL-6 (Figure 1).[40-43]

Recent gene expression and proteomic data have also identified fibroblasts as key players in PN.[44-49] A single-cell RNA sequencing study comparing individuals with PN to AD and healthy controls found that PN exhibited a unique population of CXCL14-/IL-24+ papillary fibroblasts and upregulation of gene expression signatures corresponding to the activation of cellular pathways involved in fibrosis, extracellular matrix organization and collagen synthesis.[45] While both PN and AD had type 2 immune skewing, PN also exhibited less activation of immune pathways relative to AD.[45] Another single-cell RNA sequencing study also identified 7 unique subclusters of fibroblasts in lesional PN skin compared to non-lesional PN skin with a shift toward a cancer-associated fibroblast (CAF)-like phenotype.[46] This

FIGURE 1. Pathophsyiologic mechanisms of prurigo nodularis. IL-31 is the key orchestrator of disease progression with pleotrophic effects on numerous cell types: (A) neurons, (B) epidermal cells, (C) immune cells, and (D) fibroblasts.



may explain the epidemiological observation that patients with PN have increased risk of CAF-associated malignancies such as squamous cell carcinoma compared to patients with AD.[34] Furthermore, fibroblast-derived secretory proteins WNT5A and periostin were found to interact with several neuronal receptors suggesting a novel fibroblast-neuronal axis. Activation of profibrotic responses and enrichment of fibroblast populations in PN skin relative to AD skin were also confirmed by Ma et al in a third independent single-cell RNA sequencing study.[47] Treatment with nemolizumab, a monoclonal antibody targeting IL-31 receptor α (IL-31RA), reverses the pro-fibrotic transcriptomic and proteomic profiles in both the skin and serum.[39,47,48] These findings strongly suggest a role of fibroblasts and mesenchymal dysregulation in the induction and maintenance of PN as well as their connection with the immune and neural axes, which is unique to PN compared to AD.

Psychodermatological Perspectives of PN

Chronic pruritus, the most defining characteristic of PN, along with unsightly skin lesions, bleeding, pain, sleep loss, and mental health symptoms, is associated with a negative impact on patients' quality of life (QoL).[50-52] Several studies have investigated the impact of PN-associated itch on QoL with the Dermatology Life Quality Index (DLQI) being the most frequently used assessment tool.[51,53,54] A systematic review and meta-analysis also found all studies to have moderate-to-severe pruritus and a very large or extreme effect on QoL.[51]

Pruritus worsens in the evening with the severity of nocturnal pruritus (NP) having a directly correlated impact on the severity of sleep disturbance.[54,55] A recent study of 39 patients with PN found that the majority reported sleep disturbance to a great extent and that it correlated significantly with pruritus timing in the evening.[56] Ständer et al further validated the Sleep Disturbance Numeric Rating Scale (SD NRS) in patients with PN.[57] The SD NRS is a single-item patient-reported outcome (PRO) assessing day-to-day sleep disturbance in patients with pruritic conditions and has been previously validated in AD.[58] Its use as a PRO for assessing PN impact on QoL in the clinic and in clinical trials remains to be determined.

In addition to its impact on QoL, PN also imparts an economic burden. A cohort study of 36 patients with PN by Whang et al found that when compared to controls, patients with PN had worse health performance, which they correlated to an average of 6.5 lifetime quality-adjusted life years (QALYs) lost per patient. This translated to an individual lifetime economic burden of $323,292 and a total societal burden of $38.8 billion.[52]

Psychiatric Conditions in PN

The intense pruritus of PN, as well as the disfiguring skin lesions, can have profound negative effects on the patient's mental health. Likewise, stress and psychological factors can significantly impact the development and severity of PN. While etiology of PN has not been fully elucidated, neuronal sensitization to itch and the development of the itch-scratch cycle has been hypothesized as a simplified origin of the condition. In fact, PN is associated with neural sensitization disorders of pain.[59] Nonetheless, there are significant interplays between dermatology, neurology, and psychiatry in the development and disease process.

Psychocutaneous conditions are those conditions, such as psoriasis, atopic dermatitis, or prurigo, in which psychological stress is a key element in causing exacerbations or flare-ups of the skin conditions.[60] Another classifying term for prurigo is a psychophysiologic disorder, which is a skin condition that is inherently susceptible to psychological stress in disease precipitation or exacerbation.[61]

Patients with PN have higher rates of systemic illnesses (eg, autoimmune conditions) and mental health disease.[62,63] Psychiatric conditions are significantly more prevalent in individuals with PN than in the general population.[64,65] Those found more commonly in patients with PN include eating disorders, self-harm, attention deficit/hyperactivity disorder, schizophrenia, mood disorders, anxiety, and substance use disorders.[13]

Underlying psychiatric conditions can influence the patient's perception of their disease; for example, a patient with comorbid major depressive disorder and pruritic cutaneous conditions might experience an increased sensation of itching.[66] Stress and emotional tensions can contribute to worsening the itching sensation in pruritic conditions such as PN and lichen simplex chronicus.[62]

Effect of PN on Mental Health

Patients with PN have a more than six-fold chance of having body dysmorphic disorder (BDD) symptoms in an observational, cross-sectional multicenter study.[67] BDD is defined in the DSM-5 as preoccupation with one or more perceived defects or flaws in physical appearance that are not observable or appear slight to others. This study also found that BDD symptoms were significantly related to factors including higher psychological stress and feelings of stigmatization.[67] This aptly draws attention to the chicken-or-egg discussion considering the interplay between the dermatological and psychological aspects in PN and demonstrates the close interrelation between the skin condition and mental health.

The increased self-consciousness and feelings of shame and stigmatization experienced in disfiguring skin conditions can easily become preoccupying or debilitating thereby significantly affecting one's daily life. Fear of what others may think of the cutaneous lesions exacerbates the individual's stress and worsens the itching, resulting in further trauma and worsening of the lesions. Patients often report significantly worse itch and scratching when alone and becoming hyper focused on the lesions. Patients often describe avoiding social situations and purposefully altering their dress, for example, wearing long sleeves and pants even in hot climates out of self-consciousness. One study found a direct correlation between severity of PN and increased stigma scores as well as increased likelihood of abstaining from social activities.[68] The study found that in the last 3 months because of their PN, 21.4% missed at least 1 day of work, learning, training, school or university; 72.9% gave up a leisure or sport activity; and 62.9% refused an invitation to a dinner or a party.[68]

PN also exhibits a significant psychological burden and has been linked to anxiety, depression, and suicidal ideation.[69] In a multicenter study from 13 European countries, the investigators reported 19% of total patients with prurigo had suicidal ideations related to their skin condition.[53] A cross-sectional study in 39 patients with PN and healthy controls found patients with PN exhibited higher serum IL-6 and lower serotonin levels, which significantly correlated with the severity of pruritus, but the association of these fluctuations with depression is not yet conclusive.[69]

Mental Health Assessment Tools

A helpful tool, in addition to clinical assessment, to assess the extent to which stress is affecting the patient's function and condition is the use of a patient survey questionnaire initially and possibly on follow-up to quantitatively track psychological measures over time. Examples of these include the Patient Health Questionnaire with 2 (PHQ-2) or 15 (PHQ-15) questions to screen for depression, or the Modified Mini Screen (MMS) for a more global assessment of depression, anxiety, obsessive-compulsive disorder, post-traumatic stress, and psychosis.[70]

Other assessments useful to assess and track psychological aspects of patients affected by PN include DLQI,[71] Patient Unique Stigmatization Holistic tool in Dermatology (PUSH-D),[72] and Epworth sleepiness scale.[73]

CONCLUSION

To conclude, PN has inextricable interplays between psychiatry, immunology, and dermatology. Growing our understanding of the psychodermatology of PN is paramount to improving our treatment of this difficult-to-treat condition and identifying patients at risk for neuropsychiatric comorbidities that may need early intervention.

DISCLOSURES

Naiem Issa is an advisor, consultant, and speaker for Galderma. Mohammad Jafferany and Hannah Riva have no conflicts of interest to declare.

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