REVIEW

Prurigo Nodularis and the Pain Cascade: Understanding the Pathogenesis and Approach to Management

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OBJECTIVE: Prurigo nodularis (PN) is a chronic inflammatory dermatologic condition characterized by symmetrically distributed, intensely pruritic, hyperkeratotic nodules. This review aims to explore the role of the central and peripheral nervous systems in PN, focusing on the pain cascade pathway and its implications for novel therapeutic approaches. **METHODS:** A review of the literature on PN and the pathophysiology of the pain cascade was performed. Original and review articles published before April 1, 2025, were evaluated for relevance. **RESULTS:** The pathophysiology of PN involves repetitive scratching that leads to skin thickening and an exaggerated immune response, with key roles played by eosinophils, helper T (Th) cell 2 cytokines (interleukin [IL]-4, IL-13, IL-31), and neuroimmune interactions that perpetuate the itch-scratch cycle and the pain cascade. Management requires a multimodal approach including behavioral strategies, topical corticosteroids, intralesional therapies, and phototherapy. Systemic treatments, ranging from immunosuppressants and neuromodulators to targeted biologics, are often necessary due to the refractory nature of PN. Monoclonal antibodies such as dupilumab and nemolizumab, which target specific cytokine pathways, have significantly advanced treatment options. Ongoing trials with emerging agents emphasize the importance of immunomodulation in transforming PN care and guiding future therapies. **CONCLUSION:** PN is a chronic dermatologic condition that severely impacts quality of life. Emerging research into its pathophysiology indicates immune and neuronal dysregulation. Recent therapeutics have changed the standard of care for patients with PN. Continued future research into pathophysiology and the pain cascade can inform development of additional novel therapeutics.
KEYWORDS: Prurigo nodularis, neuropathic pain

Prurigo nodularis (PN) is a chronic inflammatory dermatologic condition characterized by symmetrically distributed, intensely pruritic, hyperkeratotic nodules.[1–4] The most common symptom of PN is intense pruritus. PN is known to cause a significant burden on quality of life, often contributing to sleep disturbances, emotional distress, and psychological comorbidities such as anxiety and depression.[1,2,5–11]

PN has long been recognized as a condition with multifactorial etiology involving dermatologic, neurologic, and immunologic pathways, yet its exact pathophysiology remains incompletely understood.[1–3] While traditionally considered a disorder of cutaneous inflammation and dysregulated itch-scratch cycles, emerging research suggests a complex interplay between the peripheral and central nervous systems in the pathophysiology of PN.[2,4] The neurologic pain cascade, which involves nociceptive sensitization, neuropeptide release, and central modulation, may play a critical role in perpetuating chronic pruritus and dysesthetic symptoms in PN.[12–15] Recent studies have highlighted the involvement of key neural pathways, including dysregulation of small-fiber nerve endings, increased expression of pruritogenic mediators such as substance P, and central sensitization mechanisms analogous to those observed in chronic pain syndromes.[13] In addition, the complex interplay between cutaneous nerve fibers, immune cells, and cytokine signaling forms the foundation of the neuroinflammatory loop driving the disease.[3,4,13] In particular, the sensitization of pruriceptive neurons and the upregulation of cytokines such as interleukin (IL)-31 contribute to heightened itch perception and neuropathic features of PN.[4,16] Understanding this neural component is crucial for the development of effective therapies.

This review aims to explore the role of the central and peripheral nervous systems in PN, focusing on the pain cascade pathway and its implications for novel therapeutic approaches. Understanding chronic pruritus and neuropathic pain may pave the way for innovative, mechanism-based treatments that improve outcomes for patients with PN.

CLINICAL PRESENTATION AND EPIDEMIOLOGY

PN presents clinically as multiple, firm, flesh-to-pink colored papules, plaques, and nodules.[1–4,17] They are symmetrically distributed, intensely pruritic, hyperkeratotic nodules. Lesions are typically on the extensor surfaces of the extremities and trunk and can range in number from

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several to more than 100.[1] PN may coexist with other cutaneous hypersensitivity disorders, including atopic dermatitis or chronic pruritus.[17] Therefore, its diagnosis is primarily clinical and requires differentiation from similar conditions such as lichen simplex chronicus or hypertrophic lichen planus.[17] PN affects a variety of individuals and the prevalence is estimated at 2.88 per 100,000 patient-years from 2008-2018 and 14.1 per 100,000 people in 2021.[10,11] PN impacts both genders but predominantly affects women.[11,18] Studies have also demonstrated that ethnicity and genetic predisposition may have an important role since African American patients are 3 to 4 times more likely to have PN compared to White patients.[19–23]

PATHOPHYSIOLOGY AND THE PAIN CASCADE

The pathophysiology of PN continues to undergo investigation. Current understanding is that recurrent mechanical trauma to the skin induces epidermal hyperplasia, resulting in thickening of the skin.[17] The itching in PN is typically severe and episodic, and it often occurs at discrete points in the body, such as extensor surfaces.[1,4,13,17] The repetitive mechanical trauma of the skin causes plaque and nodule formation, often with lichenification, excoriations, and hyperpigmentation.[17]

Immunohistochemical studies have shown that there are increased dermal, interstitial, and perivascular infiltrates in the dermis of PN lesions.[2] These infiltrates primarily consist of increased levels of T lymphocytes, mast cells, and eosinophilic granulocytes.[2,4,17,24] Mediators such as IL-31, tryptase, eosinophil cationic protein, histamine, prostaglandins, and neuropeptides have been postulated to be involved in the robust inflammatory response and contribute to the intense itching phenomenon.[2,4,17,24] More specifically, eosinophils have been shown to play a crucial role in cutaneous inflammation and pruritus.[4,24] Inflammatory agents released by eosinophils include neuropeptides, eosinophil cationic protein, eosinophil-derived neurotoxin, eosinophil protein X, and major basic protein.[2,25] Eosinophil cationic protein and eosinophil-derived neurotoxin are particularly noteworthy due to their neurotoxic properties and their marked elevation in the skin of patients with PN.[2–4,25]

Additionally, helper T (Th) 2 cytokines, particularly IL-4, IL-13, and IL-31, have a key role in the pathogenesis of chronic pruritus and neuronal sensitization in PN.[2–4,16,17,27] Messenger RNA for IL-31 has been found to be more abundant in PN lesional skin compared to healthy skin.[2,16] IL-31 has been postulated to propagate itch and the pain cascade by binding to the heterodimeric IL-31 receptor α and oncostatin M receptor.[2] Further, IL-4 and IL-13 activate sensory neurons, and activated neuronal IL-4 receptor α (IL-4Rα) mediates pruritus by sensitizing sensory neurons.[4,27] IL-4 stimulation also upregulates IL-31Rα expression in a dose-dependent manner and is the central driver of Th0 to Th2 polarization.[4,27] The expression of inflammatory cytokine receptors on neurons serves as a bridge between immune and neuronal dysregulation as well as the interaction between neuropeptides and immune cells.[4] Th2 cytokines can directly activate sensory neurons, which relay the pruritic signals from the dorsal root ganglion, through the spinothalamic tract, to the somatosensory and anterior cingulate cortices.[4,28]

IL-4 and IL-13 also induce the production of periostin, an extracellular matrix protein, that has a pathogenic role in chronic inflammation and skin fibrosis, furthering the pain cascade.[4,29] Studies have demonstrated that dermal periostin is increased in the dermis and decreased in the epidermis in patients with PN compared to healthy skin.[4,30] Dermal periostin has been correlated with intensity of pruritus.[30] Periostin has also been found to be active in PN lesions and elevated in the blood of patients with PN.[31]

The distribution of nerve fibers in the lesional and nonlesional dermis of patients with PN has been investigated. There has been shown to be increased dermal nerve fibers in the papillary dermis of patients with PN.[17] Thin, unmyelinated epidermal nerves are thought to be the transmitters of PN.[17] Nerve growth factor (NGF) and tyrosine receptor kinase A are overexpressed in PN lesions.[17] Stimulation of sensory neurons through scratching can lead to the release of these neuropeptides, ie, substance P, nerve growth factor, and calcitonin gene-related peptide, which may activate immune cells and contribute to neurogenic inflammation propagating the pain cascade.[2,17]

Histopathologic analyses have demonstrated that the dermis of patients with PN exhibits a significantly increased density of NGF receptor and protein gene product 9.5 (PGP 9.5) compared to healthy controls.[17,25] Conversely, the epidermis in PN is notably depleted of NGF receptor-positive fibers and contains markedly fewer PGP 9.5–positive fibers.[25] Despite this apparent reduction in intraepidermal nerve fiber density, no definitive evidence of functional small fiber neuropathy has been established in these patients.[32] This observation challenges the notion of a primary neurodegenerative process and instead suggests that the loss of epidermal fibers may be secondary to mechanical denervation from chronic excoriation. Nonetheless, the increased dermal innervation and its potential association with peripheral neuropathic mechanisms[15] underscore the need for further investigation of the pain cascade.

MANAGEMENT

Management of PN requires a multifaceted and individualized approach aimed at breaking the itch-scratch cycle and promoting nodule healing. Patients should be educated on strategies to reduce scratching, while any underlying causes of pruritus or psychological comorbidities, such as anxiety or compulsive skin picking, should be identified and treated. Prior to 2022, there were no United States Food and Drug Administration (FDA)-approved therapies specifically for PN, leading to reliance on off-label treatments with significant variability in clinical practice.[3] With the introduction of monoclonal antibodies, dupilumab and nemolizumab, PN treatment has taken a more targeted approach. Yet, effective management of PN targets both the neural and immunologic components of the disease and is achieved through a multimodal regimen incorporating both topical and systemic therapies, tailored to the patient's age, comorbidities, disease severity, and treatment tolerance.

Topical and intralesional therapy. The first-line topical therapy for PN is high-potency topical corticosteroids. Betamethasone valerate 0.1% tape has been shown to reduce pruritus and flattened nodules in patients with PN compared with moisturizing itch relief cream alone.[33] Flurandrenolide tape has also shown efficacy.[13] Clobetasol dipropionate 0.05% ointment is another high-potency corticosteroid that can treat PN.[17] Application of a physical barrier to deter scratching of the skin is important to prevent propagation of lesions.

For thicker lesions, intralesional corticosteroid injections can be effective in decreasing pruritus and flattening PN lesions. Intralesional injections of triamcinolone acetonide have demonstrated clinical improvement in PN.[2,17,34,35] However, it is recommended to limit the use of intralesional corticosteroids to patients with fewer than 10 lesions to reduce the risk of adverse effects.[20]

Topical anesthetics are an additional therapeutic option for chronic pruritus. Pramoxine 1% lotion, lidocaine spray, and compounded topical anesthetic creams can provide modest itch relief for mild PN.[2,36] Additional nonsteroidal therapies that can treat PN include pimecrolimus, calcipotriol, menthol, and capsaicin.[17] Pimecrolimus has been reported to be as effective as hydrocortisone and can potentially be implemented in a long-term regimen for PN.[37] One study revealed that calcipotriol, a vitamin D derivative, had greater efficacy than betamethasone valerate 0.1%.[38] Low concentrations (<5%) of menthol have alleviated pruritus by increasing the threshold for pruritic stimuli.[39] Capsaicin can also decrease pruritus and pain by disrupting small sensory cutaneous nerve fibers.[40]

Phototherapy. Ultraviolet phototherapy is increasingly used to decrease pruritus in a variety of dermatologic conditions. Phototherapy with psoralen–ultraviolet-A (PUVA), including bath and topical PUVA, long-wavelength UVA, narrowband ultraviolet B light therapy (NB-UVB), and monochromatic excimer light of 308nm, result in a significant improvement of PN nodules.[17,41,42] A recent study reported that NB-UVB phototherapy resulted in a complete response in 80% of patients, demonstrating the efficacy of treatment.[42] Phototherapy for patients with PN is an adjunct treatment and should be considered in the context of their clinical disease course.

Systemic treatments. Patients with PN often require systemic therapies due to the refractory nature of the disease course. Systemic treatment options include immunosuppressants, gabapentinoids, μ-opioid receptor antagonists, antidepressants, neurokinin-1 receptor (NK1r) antagonists, and monoclonal antibodies.

Given the role of immune dysregulation in the pathophysiology of PN, oral immunosuppressive therapy is a treatment option. Methotrexate and cyclosporine have demonstrated a decrease in pruritus and greater healing of lesions in several studies.[43–45] However, these agents should be considered for patients with severe, recalcitrant PN due to their systemic adverse effect profiles. Limited evidence suggests that treatment with azathioprine and cyclophosphamide have also been successful.[6,47] Oral tacrolimus is another therapy that showed a reduction in pruritus.[48] While not routinely used, intravenous immunoglobulin has also shown benefit in case reports.[49]

Gabapentinoids, including gabapentin and pregabalin, target the sensory neurons disrupted in the pathogenesis of PN itch. Gabapentinoids reduce symptoms through the inhibition of calcium signaling of nociceptive neurons in the peripheral and central nervous systems.[50–52] These agents often require higher doses to achieve meaningful itch reduction, which frequently leads to sedation, a common side effect of gabapentinoids.

Additionally, μ-opioid receptor antagonists can be considered for treatment of pruritus in PN. Studies have shown that mixed κ-opioid agonist/μ-opioid antagonists nalbuphine and intranasal butorphanol show efficacy to decrease pruritus, but there is limited evidence specifically for PN.[53–55] Some studies describe that antidepressants can treat mild to moderate pruritus.[52,53] Paroxetine, fluvoxamine, duloxetine, and amitriptyline have all been shown to have benefits for neuropathic pain and pruritus.[56,57]

NK1r antagonists, such as aprepitant, also have efficacy in reducing pruritus. NK1r may prevent substance P–mediated signaling in the pathogenesis of PN.[58] Aprepitant, FDA approved for chemotherapy-associated nausea and vomiting, has been studied as an off-label treatment for chronic refractory pruritus.[59] Initial data suggested that aprepitant may be effective in reducing PN-associated pruritus, but a Phase II trial failed to show efficacy in reducing itch severity.[60] Furthermore, thalidomide, an immunomodulatory agent that acts as a central and peripheral depressant and inhibits tumor necrosis factor α (TNF-α), has demonstrated some efficacy in treating PN.[61] It can be used for patients with PN refractory to treatment due to its side effect profile, which includes neurotoxic and teratogenic effects and an increased risk of peripheral neuropathy as well as birth defects in pregnant patients.[62]

As the understanding of the immunologic pathways underlying PN has advanced, monoclonal antibodies have emerged as promising targeted therapies. These agents offer a novel approach by specifically modulating key cytokines and immune mediators involved in the chronic itch and inflammation associated with PN.

Dupilumab was the first FDA-approved monoclonal antibody treatment for PN in 2022.[63,64] It is an IL-4Rα monoclonal antibody that simultaneously blocks IL-4 and IL-13 signaling.[65] As research into the pathogenesis of PN has evolved to show the impact of IL-4 and IL-31 for chronic pruritus and neuronal sensitization, blockage of these cytokines was a natural target for therapeutic effect. Numerous trials have demonstrated that dupilumab has high efficacy in treating both pruritus and PN lesions.[65–68] In a Phase III trial, dupilumab achieved clinical and statistically significant improvement in itch (≥4-point reduction in Worst Itch Numerical Rating Scale [WI-NRS]: 58.8% dupilumab vs. 19% placebo), clear or almost clear skin (Investigator's Global Assessment [IGA] for Prurigo Nodularis Stage: 46.4% dupilumab vs. 17.1% placebo), and both (35.5% vs. 8.9%) after 24 weeks.[65] Dupilumab was recently evaluated in moderate-to-severe PN and found to effectively improve pruritus, nodular lesions, and quality of life.[69] Additionally, a recent study examined the role of dupilumab in systemic inflammation.[70] Results demonstrated that dupilumab decreased systemic cytokines, including Th1 (interferon [IFN]-γ, TNF-α), Th2 (IL-4, IL-13), and Th17/Th22 (IL-6, IL-22) signaling as well as cytokines of innate immunity (IL-19, toll-like receptor 1, nitric oxide synthase 2), immune cell migration (CCL20, CD177), and fibrosis (IL-11, IL-22).[70] Plasma cytokine levels of IL-11, nitric oxide synthase 2, IL-13, IL-4, and IFN-γ showed the strongest correlations with pruritus severity.[70] Additionally, analysis from two Phase III trials showed that 49.7% of patients treated with dupilumab achieved a clinically meaningful improvement (≥4-point drop) in Skin Pain-NRS vs. 20.9% receiving placebo, demonstrating significant reduction in pain.[71]

Nemolizumab is the only other FDA-approved monoclonal antibody treatment for PN, approved in 2024. Nemolizumab is an IL-31Rα antagonist that blocks IL-31 signaling.[72] In a large Phase III trial, nemolizumab achieved clinical and statistically significant improvement in itch compared to placebo (≥4 points on the Peak Pruritus NRS: 56.3% nemolizumab vs. 20.9% placebo) and a greater percentage had an IGA 0 or 1 (37.7% vs. 11.0%) at Week 16.[73] Additional analyses have continued to demonstrate efficacy for nemolizumab for PN.[74,75] In a Japanese trial,

nemolizumab also resulted in a greater reduction in pruritus, severity, and sleep disruption compared to placebo.[75] Nemolizumab was well tolerated with concurrent use of topical corticosteroids.[75]

Vixarelimab is another monoclonal antibody under investigation for the treatment of PN. Vixarelimab binds to the β subunit of the oncostatin M receptor and inhibits signaling of IL-31 and oncostatin M.[76] Vixarelimab was studied in a small Phase II trial and demonstrated a statistically significant decrease in WI-NRS (50.6% vs. 29.4%) and IGA, as well as increased sleep by 8 weeks of treatment compared to placebo.[77]

Additional drugs are currently under investigation as potential therapeutics. Barzolvolimab is a monoclonal antibody targeting the KIT receptor, a tyrosine kinase receptor found on mast cells.[14] The KIT receptor is activated by stem cell factor to regulate differentiation, migration, and activation of mast cells. A small Phase IB trial demonstrated the safety and tolerability of barzolvolimab and assessed its optimal dose.[78] Results showed a reduction in itch among 57% of patients with PN treated with the highest dose.[78]

Ruxolitinib is another novel treatment currently in trials.[14,79] Ruxolitinib is a Janus kinase (JAK) (eg, JAK1 and JAK2) inhibitor that blocks activation of the JAK-signal transducer and activator of transcription (STAT) pathway by inflammatory cytokines.[14] This pathway leads to an exaggerated inflammatory response, activation of eosinophils, and suppression of regulatory T cells; inhibiting the pathway is suspected to diminish the pathogenesis of PN.[80] Ruxolitinib cream is approved for atopic dermatitis and currently undergoing a Phase III trial for PN.[79] Preliminary results indicate a reduction in itch and a greater decrease in IGA compared to placebo.[79] Abrocitinib is an oral JAK1 inhibitor that also blocks activation of the JAK-STAT pathway.[14] It is currently in a Phase II trial to evaluate the efficacy in patients with PN and those with chronic pruritus of unknown origin.[81] Additionally, povorcitinib is an oral JAK1 currently in a Phase II trial for PN.[82]

Given the positive results of dupilumab, nemolizumab, and additional therapies in trials, immunomodulatory therapies have become part of the standard of care for patients with PN. These results underscore the potential of targeted immunotherapy to transform the management of PN and continue to explore how the pathogenesis can guide future treatment.

CONCLUSION

PN is a chronic dermatologic condition that severely impacts quality of life. Emerging research into the pathophysiology indicates that immune and neuronal dysregulation, including Type 2 inflammation, play an important role in pruritus, skin lesions, fibrosis, and the pain cascade. A range of cytokines, including those central to the Type 2 response, has been implicated in PN pathophysiology. Given discoveries into the role of IL-4, IL-13, and IL-31, novel therapeutics have been developed, including dupilumab and nemolizumab, that have changed the standard of care for patients with PN. Continued research into the pathophysiology and pain cascade can further enhance the improvement of novel therapeutics.

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