

## Prurigo Nodularis: A Benign Dermatosis Derived from a Persistent Pruritus

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**SUMMARY** Prurigo nodularis (PN) is a benign neurodermatitis of unknown etiology characterized by firm, hyperkeratotic pruritic nodules most commonly localized symmetrically on the bilateral extensor lower extremities. PN represents a primary dermatological condition or a dermatological manifestation of repeated traumatic manipulation secondary to chronic pruritus. One must consider underlying causes of pruritus, which may include psychiatric disorders and internal disease. Given its chronicity and relapsing nature, treatment of PN can be challenging. Interruption of the itch-scratch cycle is difficult; long term prognosis remains guarded.

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### INTRODUCTION

Prurigo nodularis (PN), first described by Hardaway in 1880 and named by Hyde and Montgomery (1) in 1909, is a chronic, benign neurodermatitis of unclear etiology characterized by excoriated, intensely pruritic nodules, which are secondary to an intense itch-scratch cycle. It is found mostly on exposed extensor skin surfaces of the lower extremities. After vigorous scratching or rubbing, cutaneous manifestations may include lichenification, neurotic excoriations and ultimately nodulation, PN. Postinflammatory hypopigmentation or hyperpigmentation can also result, often central hypopigmentation highlighted by border hyperpigmentation. Recently, the International Forum for the Study of Itch proposed a classification of the various diseases that present with itch as a means of facilitating diagnosis and improving treatment modalities and outcomes. PN falls under group III, which encompasses chronic secondary scratch lesions (2). There are three types of PN (Table 1).

Recent advances have been made in treatment; however, much remains to be done.

Many conditions may trigger PN, such as arthropod bite reactions, psychiatric illness, and systemic disease, including internal malignancy (Table 2); however, a direct causal link has yet to be found. It has been postulated that nerve growth factor (NGF), substance P, and various other neuropeptides as well as mast cells and eosinophils are involved in the inflammatory and pruritic response of skin in PN (3). The mainstay of treatment for intense pruritus should initially be to detect and subsequently treat any underlying cause. However, this daunting task is usually unaccomplished, and symptomatic relief remains the only option. Unfortunately, chronic pruritus in general and prurigo nodularis specifically are difficult to treat. Topical and intralesional corticosteroids, calcipotriol, capsaicin, narrow-band UVB, thalidomide, and cyclosporine (4) have been used with only limited success.

**Table 1.** Forms of prurigo

- Atopic prurigo nodularis
- HIV-associated prurigo nodularis
- Non-atopic non-HIV linked prurigo nodularis

## EPIDEMIOLOGY

As initially described by Hyde and Montgomery (1), PN most commonly affects the middle-aged and elderly, although it has been seen in young men and children as well (5). Classically, two forms of PN are often delineated: atopic PN and non-atopic PN (6). Atopic PN has an earlier onset and seems to be associated with atopic dermatitis, while simultaneously displaying hypersensitivity to various environmental allergens. Non-atopic PN, in contrast, has an older age of onset and lacks a cutaneous response to allergens. Among our patients, we have distinguished a third form that is associated with human immunodeficiency virus (HIV) disease (Table 1).

PN may be viewed as a hyperplastic form of lichen simplex chronicus (6). There is no racial or sexual predilection for PN, and no increase in mortality other than that associated with the underlying cause (7). Importantly, psychosocial morbidity of chronic, unrelenting, intense pruritus may be significantly damaging to one's quality of life (8).

## HISTOPATHOLOGY

Microscopically, a typical PN nodule may show hypertrophy of cutaneous nerves in the dermis (9,10). It has further been demonstrated that dermal nerves display an inclination towards neuronal hyperplasia (11). Interestingly, PN also shares some features with both psoriasis and ichthyosis as it demonstrates parakeratotic hyperkeratosis accompanied by acanthosis and papillomatosis. Rete ridge elongation with a dense dermal lymphohistiocytic infiltrate may also be evident (7). Epidermal changes are most typical while neuronal changes are neither commonly evident nor required for diagnosis. Using electron microscopy, one can see nerve fibers thickened and dilated with hyperproliferation of Schwann cells and axons along with vacuolization and degeneration of Schwann cells including disruption of internal organelle architecture (10).

## ETIOLOGY AND PATHOGENESIS

PN has generated many theories as to its pathogenesis. Emotional stress may contribute to

**Table 2.** Conditions associated with prurigo nodularis

- Arthropod bite reactions
- Venous stasis
- Folliculitis
- Psychosomatic disorders
- Depression
- Anxiety
- Hyperthyroidism
- Iron deficiency anemia
- Chronic renal failure
- Chronic liver disease (hepatitis B and C,  $\alpha$ -1 antitrypsin deficiency, primary biliary cirrhosis, primary sclerosing cholangitis, other cirrhotic conditions)
- Human immunodeficiency virus
- Manifestation of underlying renal/hepatic/gastrointestinal disease or malignancy
- Mycobacterial infection
- Leukemia
- Lymphoma

PN in some patients, especially those classified as compulsive "pickers" (12). Depression and anxiety maintain a close association (13). In patients with chronic kidney disease, imbalances in levels and accumulation of calcium, phosphorus, magnesium, and aluminum, especially in hemodialysis patients, can be a significant cause of pruritus (3). Viral infection with subsequent immune complex deposition in the skin has also been implicated in PN pathogenesis, most commonly with chronic hepatitis B (14), hepatitis C (15) and HIV (16) infections.

Mast cells, eosinophils, neutrophils, and various component proteins and substances have been studied to ascertain their role in the pathogenesis of PN. Mast cells not only increase in number, but also show changes in morphology, such as an enlarged cell body and a more dendritic shape compared to that in normal skin (17). There is no significant increase in the concentration of mast cell tryptase or neutrophil elastase in the surrounding tissue (10). A key culprit detected in diagnostic skin biopsies of PN is the increased concentration of eosinophil degranulation products, such as eosinophil granule major basic protein, eosinophil cationic protein, and eosinophil-derived neurotoxin, which all have potent ability to damage nerves and exacerbate inflammation (10,17). Interestingly, increased circulating and infiltrating eosinophils in conjunction with their component proteins are also implicated in symptomatic atopic dermatitis (18).

Mast cells have also been implicated in the pathogenesis of PN through a NGF: nerve growth



**Figure 1.** Multiple, excoriated, hyperkeratotic nodules with areas of post-inflammatory hyperpigmentation.

factor receptor (NGFr) mechanism. Mast cells are known to release NGF. With increased mast cells in PN, there is enhanced NGF expression, which may produce neurohyperplasia (19). In normal skin, there is weak immunoreactive epidermal and dermal staining for NGF and p75 NGFr. In contrast, both are overexpressed in Schwann cells and perineurium cells in hyperplastic PN nerves, facilitating the neurohyperplasia seen in this disease (20,21).

Other skin findings thought to be involved in the pathogenesis of PN include an increase in both epidermal Merkel cells (22) and dermal Langerhans cells (23).

### CLINICAL FEATURES AND SIGNIFICANCE

Pruritic processes may be first evident in a manner consistent with either a primary dermatological condition or as a secondary manifestation of an internal disease. Prurigo, from the Latin *prurire* –“to itch”, is a generalized term that describes intensely pruritic cutaneous changes of unknown etiology that are characterized by focal excoriations and distinctive pigmentary alterations when healed. After a perpetual itch-scratch cycle has been established, lichenification of the skin may ensue, resulting in a chronic dermatitis termed lichen simplex chronicus. There are various subtypes of prurigo, of which PN is one.

In a PN patient with chronic pruritus, a comprehensive history and thorough physical exami-



**Figure 2.** Solitary hyperkeratotic nodule (bottom) and hyperkeratotic plaque (top) with adjacent lichenification.

nation are crucial. Underlying causes may include significant internal pathology such as liver or kidney disease, leukemia, lymphoma, or other malignancy (Table 2). Physical examination should carefully assess for jaundice and other signs of liver disease, hyper- or hypothyroidism, lymphadenopathy, infectious etiologies, xerosis, or other abnormalities of the hair, nails, or mucous membranes. Nodular scabies should be considered (24). Neurodermatitis without prurigo nodules may represent dermatitis herpetiformis, pemphigus nodularis, and linear IgA bullous dermatitis.

PN is characterized by several to hundreds of hyperkeratotic, excoriated, pruritic papules or nodules with a tendency for symmetric distribution over the extensor surfaces of extremities. They can vary in size from 2-3 mm to 2 cm in diameter, appearing well demarcated, firm, scaly, and hyperpigmented or purpuric (Fig. 1) (7). In general, PN has been described on all parts of the body. The palms and soles are rarely affected (13). The mid-back may be spared because it may be difficult to reach, a pattern known as the “butterfly sign” (12). The nodular pattern may be follicular or linear while the skin in-between may be lichenified or xerotic (Fig. 2) (13). In contrast, patients with neurodermatitis lack the nodular pattern but still demonstrate significant excoriation, lichenification and xerosis (Fig. 3). In our experience, patients are usually frustrated, often stating that pruritus prevents them from adequately performing their daily activities. Furthermore, the



**Figure 3.** A 33-year-old male schizophrenic with neurotic excoriations and marked lichenification and xerosis of his upper back and neck.

relentless itching with frequently unsuccessful treatment is often experienced by patients as loss of control, associated learned helplessness, and loss of faith in treatment modalities. In one study, psychiatric disorders such as dysthymia, major depressive disorder, or adjustment disorder were significantly associated with intensity as opposed to duration of the itch (8).

In a retrospective analysis of PN patients, a link was identified between PN and psychosocial and metabolic disorders, specifically diabetes mellitus, which was present in 17% of patients (25). Another series of 46 PN patients identified an underlying metabolic disorder in 50% of them (13). Furthermore, 65% to 80% of PN patients may be atopic and have associated xerosis. Interestingly, the possibility of infection with *Helicobacter pylori* has also been recently proposed as a distinct cause of pruritus that may lead to PN (12).

### DIFFERENTIAL DIAGNOSIS

The differential diagnoses are delineated in Table 3. Pemphigus nodularis, hypertrophic lichen planus, mycosis fungoides and nodular scabies are the inflammatory conditions most closely linked.

### Treatment and Follow up

PN represents a therapeutic challenge distinct from the management of prurigo. Patients with PN should be encouraged not to pick, scratch, or rub nodules, as symptoms tend to intensify with repeated manipulation. Patients should use moisturizers to prevent or treat xerosis, which may exacerbate pruritus. When assessing a patient with PN, it is important to search for the underlying

**Table 3.** Differential diagnosis of prurigo nodularis

- Pemphigus nodularis
- Hypertrophic lichen planus
- Nodular scabies
- Keratoacanthomas
- Cutaneous T-cell lymphoma
- Dermatofibroma
- Mastocytosis
- Pilomatrixoma

cause. If one is detected, treatment should be targeted towards the specific disorder with referrals made as deemed medically necessary.

If the underlying cause is not detected, which is most likely the case, treatment remains symptomatic. Initial therapy should consist of a medium to high potency topical steroid applied twice daily for several weeks, often used in conjunction with an occlusive tape to enhance penetration and protect against scratching. Alternatively, intralesional corticosteroids may be administered every four to six weeks. Cordran tape™ does an excellent job for selected nodules in our experience. Topical antipruritics such as 1% menthol or phenol in a cream base, pramoxine with hydrocortisone, or Sarna™ lotion may aid in symptom control (3,26). Sedating antihistamines such as hydroxyzine and promethazine at bedtime may also be important in therapeutic improvement of the patient's quality of life. In our patient population, chlorpheniramine maleate 4 mg, one to two tablets every night at bedtime as needed, shows promise. Selective serotonin reuptake inhibitors and other antidepressants may also be beneficial in relieving the obsessive nature of PN as well as any associated depression. Psychiatric referral may help patients with associated depression or anxiety.

We sometimes use cryosurgery and UV light therapy, both of which have also been successfully employed by others in the treatment of PN. UV light seems to interrupt the itch-scratch cycle, while cryosurgery is thought to ablate peripheral sensory nerves. Two to four 30-second thaw cycles can render patients asymptomatic for a few months (7). Furthermore, the post-treatment inflammation induced by liquid nitrogen cryotherapy is synergistic to intralesional corticosteroid injection (3).

One prospective, randomized, double-blind, right/left comparative study evaluated the efficacy and safety of 50 µg/g calcipotriol ointment applied twice daily with that of 0.1% betamethasone

**Table 4.** Encouraging prurigo nodularis patients

- Daily 500-1,000 scratches cause miserable chronicity, so don't
- Prompt use of emollients and topical immunomodulators
- For acute itch, clench fist for 30 seconds, then pinch
- Itch = healing, if left alone

valerate ointment applied twice daily in the treatment of PN (27). Patients who had multiple, persistent nodules of greater than 5 mm in diameter on bilateral lower extremities were chosen for the study. All had used high potency topical corticosteroids, and most had previously tried intralesional steroids. Treatment consisting of either calcipotriol or betamethasone valerate was randomly assigned to nodules on opposite sides of the leg after a 4-week washout period with an emollient. Results showed a statistically significant reduction in the number of nodules ( $p < 0.5$ ) after 2 weeks with calcipotriol as opposed to 4 weeks with betamethasone valerate. A statistically significant reduction in the size of nodules was accomplished in both calcipotriol treatment arm ( $p < 0.1$ ) and betamethasone valerate arm ( $p < 0.5$ ) after 2 weeks; however, percent change in size favored calcipotriol after 4- and 8-week intervals. It suggested calcipotriol, with its effect on epidermal differentiation and proliferation, is safer and more efficacious than betamethasone valerate ointment in the treatment of PN.

Recently, topical capsaicin has also been shown to reduce the number and symptoms of prurigo nodules (28). Acting *via* a vanilloid receptor on free nerve endings, repeated topical application releases and prevents accumulation of various neuropeptides in C-type and A $\delta$ -type nerves, thereby blocking pain and pruritic sensation while keeping tactile stimulation intact (3). In one study, the application of topical capsaicin (0.025% to 0.3%) four to six times a day for 2 weeks up to 10 months showed complete remission of itching in all 33 patients within 12 days, with doses between 0.05% and 0.1% being most efficacious (28). The downside of capsaicin remains potential non-compliance as a result of the frequency of application necessary for treatment success as well as high rates of relapse upon discontinuation.

As a third line agent, cyclosporine has been shown to be beneficial (4). Two patients with severe nodular prurigo were treated with cyclosporine for periods of 24 and 36 weeks, respectively, using doses of 3-4.5 mg/kg *per* day. In both cases

there was a reduction in the severity of pruritus after 2 weeks of treatment. In one patient there was a considerable, although incomplete, response period. In the other almost complete resolution of the disease was achieved. The improvement was maintained throughout the treatment period. The drug was generally well tolerated, although in one patient there was a rise in serum creatinine, which later returned to normal.

Thalidomide, which has been used since the 1970s in the treatment of PN, remains a potent third line therapy reserved for severe, recalcitrant PN (29). It is thought to act *via* central nervous system suppression and subsequent blockage of peripheral stimulation (3). At a dose of 200 mg daily, significant improvement of pruritus and nodular shrinkage with no significant side effects has been documented (30). At doses below 200 mg/day, PN remissions are generally not achieved (31). Dosing above 200 mg/day is limited by the occurrence of significant adverse effects such as sensory neuropathy, which may be irreversible (32). The critical dosing level may be even lower in patients with HIV. In a prospective study of HIV patients with PN, thalidomide dosed between 33 and 200 mg/day resulted in a 50% reduction in itch and skin involvement. However, 1/3 of patients in the study developed thalidomide peripheral neuropathy, stressing the importance of frequent neurologic assessment (33).

Less common experimental treatments for PN have been documented; however, their long-term efficacy is yet to be determined. Pulsed dye laser treatment once a week for 6 weeks offered successful treatment for one patient (34). Surgical excision may be required in some patients (26).

We attempt to motivate these patients (Table 4) by informing them that 500-1,000 scratches daily cause miserable chronicity. We advocate prompt use of emollients and topical immunomodulators, whether steroids or calcineurin inhibitors. Topical pimecrolimus and tacrolimus have demonstrated considerable success in the treatment of inflammatory skin diseases such as atopic dermatitis, PN and neurodermatitis (prurigo simplex), with significant improvement of pruritic symptoms (35). Their postulated mechanism of action is *via* inhibition of inflammatory cytokines as well as that similar to capsaicin. Furthermore, we advocate the application of crushed ice prepared to the consistency of sherbet for acute intense pruritus. If that does not work, we recommend clenching the fist for 30 seconds, then pinching. We tell our patients that itch equals healing, if left alone.

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