Prurigo Nodularis and Its Management

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KEYWORDS

• Prurigo nodularis • Chronic pruritus • Itch • Pruritus • Scratch lesions • Therapy

KEY POINTS

- Prurigo nodularis occurs along with single or multiple distributed hyperkeratotic intensively itchy nodules.
- Prurigo nodularis is difficult to treat and causes a high disease burden.
- New treatments that target the neural system offer significant hope for this intractable itch.

INTRODUCTION

Many patients with chronic pruritus suffer from prurigo nodularis (PN), an intensely pruritic, chronic disease that occurs as a result the so-called vicious itch–scratch cycle.[1] PN is a subtype of chronic prurigo CPG that was recently defined as being its own disease entity.[2]

It is thought that 50% of patients with PN suffer from an atopic disposition.[3] Besides dermatoses, several systemic diseases, infections, and psychiatric and neurologic disorders are known to trigger PN and the frequently treatment-refractory itch–scratch cycle.[4] PN is regarded as having the highest itch intensity among the many diverse types of chronic pruritus.[4,5] It can not only cause sleep disturbances and psychiatric comorbidities, but also a diminished quality of life.[6]

EPIDEMIOLOGY

There is a severe lack of epidemiologic data detailing the prevalence and incidence of PN. Findings based on case series indicate that all age groups, including children,[7] can be affected by PN; however, the elderly were found to be the most frequently affected patient group.[4] Increased numbers of PN lesions are also associated with African Americans suffering from atopic eczema more than any other racial group.[8] Conclusions have not been made regarding gender differences owing to a lack of consistent reporting.[4]

PATHOPHYSIOLOGY

Although the detailed pathogenesis remains nearly unclear, cutaneous inflammation and neuronal plasticity seem to play a crucial role in PN.[9] The neural dermal hyperplasia (Pautrier's neuroma) associated with PN was already observed by Pautrier in 1934.[10] Histopathologic studies have established that changes occur in nearly all types of skin cells, including collagen fibers, epidermal keratinocytes, mast cells, dendritic cells, endothelial cells, eosinophils, and the epidermal and dermal nerve fibers.[11,12] An increased quantity of fibroblasts and capillaries, a papillary dermal fibrosis, and dense dermal interstitial and perivascular infiltrate with elevated numbers of T cells, mast cells, and eosinophil granulocytes has been observed

Disclosure Statement: The authors have nothing to disclose.

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Dermatol Clin ■ (2018) ■–■

https://doi.org/10.1016/j.det.2018.02.003

in the dermis of PN lesions. In the epidermis, an irregular epidermal hyperplasia or pseudoepitheliomatous hyperplasia, a thick compact orthohyperkeratosis, focal parakeratosis, and hypergranulosis can be observed. However, the altered nerve fibers structure seems to be of the greatest importance.[12]

Skin cells can trigger inflammation and pruritus via releasing the substances interleukin (IL)-31, tryptase, eosinophil cationic protein, histamine, prostaglandins, and various neuropeptides such as nerve growth factor, substance P (SP), and calcitonin gene-related peptide.[13–16] From a comparison of skin biopsies from patients with PN and healthy skin, it was found that a 50-fold upregulation of IL-31 messenger RNA occurred in the PN biopsies.[17] Recent studies have determined that the T-cell–derived cytokine IL-31 produces severe pruritus in mouse models via binding to a heterodimeric IL-31 receptor A and oncostatin M receptor, which is expressed on epithelial cells, including keratinocytes and on IL-31RA(+)/TRPV1(+)/TRPA1(+) neurons and eosinophils.[18–20]

SP is produced and secreted by neurons, binding to the neurokinin-1 receptor expressed in the skin and central nervous system.[21] After binding in the skin, neurogenic inflammation, brief vasodilation, plasma extravasation, and mast cell degranulation develop.[21] An increased expression of this neuropeptide in PN has previously been observed by researchers,[22] possibly indicating the discovery of a causal proinflammatory signal important to the development of PN. The SP antagonist (an neurokinin-1 antagonist) aprepitant has demonstrated positive effects on pruritus in patients with PN.[23] These findings underline the importance of SP for PN. Calcitonin gene-related peptide is also overexpressed in PN.[24] This neuropeptide has a similar mechanism resulting in neurogenic inflammation via the regulation of inflammatory cells such as eosinophils and mast cells.[24] In addition to neuropeptides, increased numbers of neutrophins are also found in the nerve fibers of those with PN.[15]

When compared with findings in the dermis, the epidermis of skin affected by PN, as well as its interlesional skin, revealed hypoplasia of the sensory nerves.[13,24] Furthermore, biopsies of healed nodules displayed a recovering epidermal nerve fiber density.[25] A functional small fiber neuropathy was, however, undetectable in patients with PN.[26] It is, therefore, likely that the reduced epidermal nerve fiber density is a consequence of recurrent scratching rather than the result of a small fiber neuropathy.[26]

CLINICAL PRESENTATION

Crusted or excoriated, hyperkeratotic, light to bright red papules, nodules, or plaques with hyperpigmented margins are distinguishing characteristics of PN. Skin lesions can range from either a few millimeters to 2 to 3 cm in size and in number from just a few to hundreds of lesions. Patients can be graded into mild (≤20 lesions), moderate (20–100 lesions) to severe (>100 lesions) forms of PN (unpublished data, Jasmin Pölkin, 2018). On top of the lesions, independent of their number, excoriations and crusts can be present, pointing to ongoing scratching. In most cases, the lesions have a generalized, symmetric distribution on the extensor surfaces of the trunk and extremities. Localized PN exists, for example, in local dermatologic (leg venous insufficiency) and neuropathic (eg, brachioradial pruritus at the arms) diseases. The central back is difficult for patients to reach with their hands, leaving them unable to scratch it. This untouched area of the skin usually resembles a butterfly shape and is thus aptly named the "butterfly sign"[1,9,27] (**Fig. 1**). PN is an intensely pruritic condition. Most of the affected patients report a combination of sensations rather than just only pruritus, ranging from warmth and cold to stinging, burning, and tingling. These sensations occur independent of the etiology.[4]

In addition to the sensorial and visually evident symptoms, PN is known to have a significant, negative influence on patients' quality of life owing to sleep disturbances, behavioral and adjustment disorders, social isolation, and psychological hardship.[28,29]

ETIOLOGIC FACTORS

Dermatoses

Several inflammatory dermatoses have been linked to PN, of which atopic eczema has been

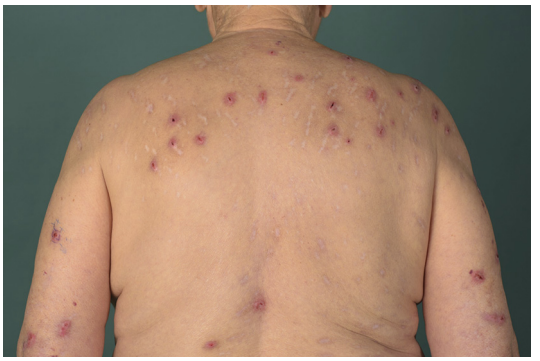

Fig. 1. A 77-year-old woman with prurigo nodularis owing to atopic predisposition with typical distribution of lesions, including the "butterfly sign" (no lesions on the center of the back).