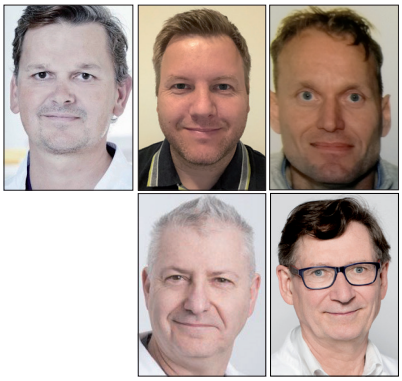
Prurigo Nodularis



Carsten Sauer Mikkelsen[1,2], Kristian Bakke Arvesen[2], Luit Penninga[3], Thomas Ternowitz[4] and Peter Bjerring[2]
[1]Specialist in Dermato-venereology, Private Practice in Dermato-venereology, Brønderslev, Denmark, [2]Specialist in Dermato-venereology, Research lab. Department of Dermato-venereology, Aalborg University Hospital, Denmark, and [3]Specialist in Surgery, Ilulissat Hospital, Avannaa Region, Ilulissat, Greenland, [4]Specialist in Dermato-venerology, Head of Department, Department of Dermato-Venerology, Stavanger University Hospital. Norway.

Case Report

A 72-year-old Danish man, who had lived in Ilulissat in the Avannaa district in the North-western part of Greenland for almost 30 years, consulted the local hospital. He presented with multiple, extremely pruritic, symmetrically distributed, excoriated, lichenified papules on the trunk and especially on the lower extremities (Fig. 1).

A punch biopsy of a lichenified noduli on the lower right leg was sent to Denmark. A pathologist found an acanthotic epidermis with mild spongiosis and dermis, containing a scattered mononuclear infiltrate with slight fibrosis, consistent with lichen simplex chronicus.

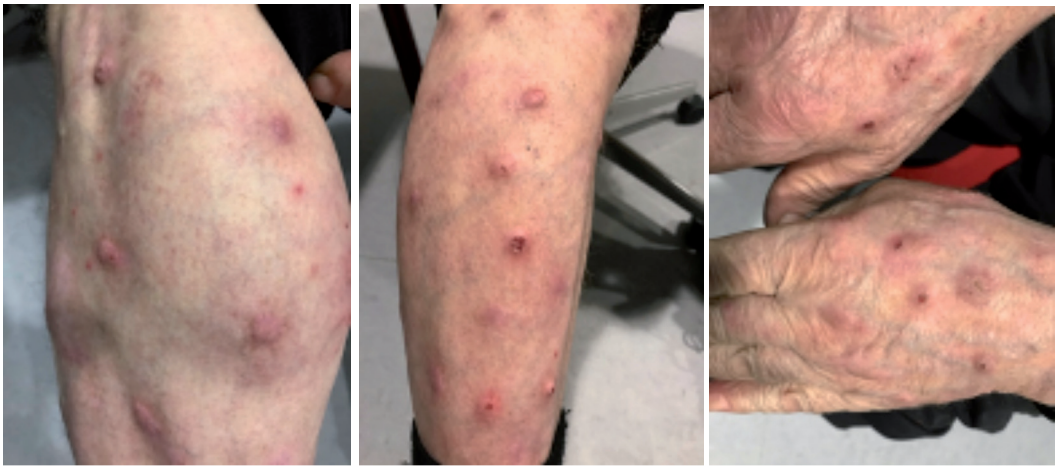
Clinically, our patient's skin lesions were classical prurigo nodularis (PN). The therapeutic course over several years included high-potency topical steroids, intralesional triamcinolone 10 mg/ml, oral antihistamines, and systemic prednisone. The patient achieved no clearance of lesions or any symptomatic relief by any of the above-mentioned treatment modalities.

Since the patient lived in Ilulissat in Greenland broad-banded ultraviolet B phototherapy was not an available treatment option and the patient was not a candidate for either methotrexate or cyclosporine due to his impaired liver and renal function.

Treatment of PN is challenging. Consequently, patients often endure multiple unsuccessful therapeutic trials. Especially in Greenland it can be challenging to treat patients with relatively rare dermatologic diseases because of the limited dermatologic service in the area. Sometimes there are even difficulties in getting a proper diagnosis via the existing teledermatological services.

Discussion

PN is a rare and chronic dermatologic condition featured by multiple intensely itchy, excoriated hyperkeratotic nodules on the extensor surfaces of the arms and legs and on the trunk, with a symmetrical distribution (1).



Prurigo Nodularis Hyde. Photo by Carsten Sauer Mikkelsen.

The disorder can be associated with multiple systemic conditions, including neuropathies, chronic kidney disease, type 2 diabetes, atopic dermatitis and human immunodeficiency virus infection (1, 2). For most patients, multiple underlying causes can be identified. The intense pruritus is often associated with disturbed sleep and reduced quality of life. Anxiety, depression and even suicide in patients with PN have been reported (3, 4).

A large German study examined 108 patients with PN in a predominantly Caucasian population and observed a female predominance (64%) with a median age of onset at 61.5 years (5).

Repetitive itching on the skin may start a cascade of processes in the skin involving the immune system, neurons and epithelial cells, causing an urge to repeated scratching, known as the itch-scratch cycle. Many theories about the pathogenesis of PN have been hypothesized, including growth of the peripheral nerves leading to hypersensitivity of the nerve endings and increased levels of substance P in the small nerve fibres in dermis.

Recent studies on the pathogenetic mechanisms of PN have revealed the importance of pro-inflammatory cytokines, such as IL-31, and neuropeptides in skin lesions that may contribute to altered nerve density and increased inflammation in PN (6–8). Despite the tremendous burden of disease of PN there is surprisingly little known about the aetiology and epidemiology of it.

Recent studies have studied intraepidermal nerve fibre density (IENFD) as an important contributor to chronic pruritus and small fibre neuropathies (9,10). Patients with PN decreased IENFD compared to healthy individuals (9). Furthermore, there is a significant reduction in IENFD in PN skin lesions, which may be due to prolonged scratching, but also in non-lesional PN. Indeed, the resolution of pruritus is associated with the recovery of dermal nerve fibre density (10).

For dermatologists, the management of PN is challenging due to the lack of a fundamental understanding of the disease, combined with limited treatment options.

Treatment

The approach to treating PN is always multifaceted. A strategy of treatment includes both a pharmacological and a non-pharmacological part. Patient education on how to disrupt the itch–scratch cycle is essential. The general advice here is to keep the nails short, wear protective clothes (long sleeves and gloves), and keep the nodules covered with bandages or dressings. Patients are to be encouraged to apply emollients multiple times a day and only use gentle cleansers when showering. To reduce pruritus one can try calamine lotions and lotions containing menthol and camphor. Other recommendations are to stay in a cool comfortable environment and reduce stress.

The pharmacological treatments used to treat PN are multiple but there is only limited data from randomized controlled trials available. The consensus of treating PN is a stepwise treatment approach (11, 12). First step includes the use of potent topical corticosteroids and topical calcineurin inhibitors. The topical corticosteroids are often used under occlusive dressings to increase efficacy. If only a relatively small number of PN elements are present, intralesional injections of corticosteroids or cryotherapy are effective options in the early treatment strategy. UV phototherapy have been widely used but with mixed results, usually as narrowband UVB and bath PUVA (psoralen and UVA).

The next step in topical treatment is the use of a cream containing the chili pepper extract capsaicin. Physicians prescribing this cream must be aware that increased itch is a common side effect. If topical treatments are not effective, systemic treatments are the next step, both on their own and in combination with topical treatments. A number of systemic treatments with different modes of action have been used in treating PN. Gabapentinoids are usually the first steps of systemic treatment. Their modes of action are poorly understood, but seem to reduce the symptoms by inhibiting descending serotonergic facilitation. The use of antidepressants (SSRIs), as next step substantiates that serotonin is part of the pathogenesis of PN. In the treatment strategy of PN the use of immunosuppressants are the next level of pharmaceuticals to prescribe. Amongst immunosuppressants, cyclosporine and methotrexate are most commonly used.

In recent time we have seen more studies showing promising results in treating this burdensome disease. Ständer et al. (13) showed clinically meaningful itch reduction after treating with Serlopitant, a neurokinin-1-inhibitor. Other ongoing trials with promising drugs have been reported to reduce itch in PN. Worth mentioning here are the interleukin-4-receptor A antibody dupilumab and the anti-IL-31 receptor-A antibody nemolizumab. With these targeted drugs we will hopefully get new powerful tools to treat recalcitrant cases of PN.

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