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Review article

Prurigo Nodularis: Literature Review

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Abstract

Multiple, hard, flesh-to-pink papules, plaques, and nodules, often seen on the extensor surfaces of the limbs, are characteristic of prurigo nodularis, a persistent skin condition. The itchy lesions may strike people of any age. It often occurs in tandem with another condition that causes constant itching, such atopic dermatitis or another dermatosis. The clinical symptoms are the primary indicators. However, there may be numerous instances when lichen simplex chronic us and hypertrophic lichen planus are indistinguishable from a clinical standpoint. Therefore, it is crucial to confirm the diagnosis by dermoscopy and histology. Many other therapy strategies are being used, including those using powerful antipruritics, immunomodulators, and neuromodulators. After a diagnosis has been made, treatment might take a long time, thus patient education and counseling are crucial to ensuring they stick with the plan. A subset of chronic prurigo, prurigo nodularis (PN) manifests as hyperkeratotic, very itchy papules and nodules that are often seen in a symmetrical pattern. PN develops with persistent pruritus in the setting of a wide variety of dermatological, systemic, neurological, or mental disorders. Although the specific pathophysiology of PN is not well understood, chronic scratching may be a primary cause. Topical steroids, capsaicin, calcineurin inhibitors, ultraviolet (UV) treatment, systemic injection of gabapentinoids, -opioid receptor antagonists, antidepressants, and immunosuppressants are the current gold standard in treating PN. Clinical trials are being conducted on cutting-edge therapeutic modalities such blockers of neurokinin-1, opioid, and interleukin-31 receptors.

Introduction

Multiple hard nodules of flesh to pink hue often appear on the extensor surfaces of the extremities, and this is the characteristic presentation of prurigo nodularis (PN), a persistent skin condition. The condition can affect people of any age, and the lesions are extremely itchy. It often occurs in tandem with another cutaneous hypersensitivity illness, such as atopic dermatitis or persistent itching due to a variety of sources. The diagnosis is primarily clinical, though it may be necessary to differentiate from certain conditions that mimic it clinically. The illness is generally resistant to therapy and is linked with substantial physical and psychological morbidity. A patient with advanced PN may need a wide variety of general measures, pharmaceutical methods, and psychosocial therapy [1-4].

When combined with the stress and discomfort of living with a chronic illness, skin problems may have a significant impact on a person's mental and emotional health [1,2]. Clinical experience has demonstrated that the detrimental effect of skin disease might be especially relevant when lesions and symptoms such as itch are present [3,4]. Prurigo nodularis (PN), also known as chronic nodular prurigo, is a chronic inflammatory skin disease characterized by persistent itching, the development of firm pruritic nodular lesions, and the presence of signs of and a history of repeated scratching, including excoriation and lichenification [1,2]. As stated in greater detail below, PN may have a diverse clinical presentation, especially across various ethnic groups, and can manifest in popular, nodular, plaque, or umbilicated subtypes [2-5]. Most patients with PN say that their symptoms are present either all or most of the time, and the degree of itch may have a significant impact on patients' psychological well-being [6-8]. In addition, psychological stress may induce and/or worsen the illness [6-8].

Regulatory organizations have not yet authorized any therapies for PN [7,9]. Off-label use of medicines such as topical corticosteroids, intralesional corticosteroids, neuroleptics, antidepressants, thalidomide, biologics, phototherapy, and systemic immunosuppressants has been common in the lack of authorized drugs [7]. On the downside, the effectiveness and safety of various medicines have varied depending on their intended patients and treatment plans [7]. Major therapeutic aims in PN include alleviation of pruritus and improvement of lesions to a clinically significant degree. Increased knowledge of neuroimmune-inflammatory pathways in the skin has led to important discoveries in the pathogenesis of PN, as it has for other skin disorders in recent years, most notably psoriasis and atopic dermatitis. There is currently optimism that the development of more tailored medicines that engage with particular pathways in the immune system may soon lead to improved management techniques for PN.

Etiology

It is still unclear what causes prurigo nodularis. While the importance of an undisturbed itch-scratch cycle is without dispute, the precise chain of events that culminates in the clinical picture is still up for debate. Patients with persistent prurigo due to dermatological, systemic, viral, or neuropsychiatric causes may develop prurigo nodularis as a result of their constant itching [5-6].

Anecdotal evidence shows that infectious organisms such hepatitis C, Helicobacter pylori, Strongyloides stercoral is, mycobacteria, and HIV have a causal role in PN, or at least are associated with it [7,8].

When dealing with PN lesions, you'll notice an increase in the number of epidermal (merkel cells) and dermal (papillary dermal nerves) sensory structures [9]. Unlike with lichen simplex chronic us or neurodermatitis, this neurological change is exclusive to PN.

In PN, there is an increase in mast cell and neutrophil density, but there is no evidence of an increase in degranulation products. In contrast, eosinophils themselves stay at stable levels,

but their by-products, including major basic protein and eosinophil-derived neurotoxic, are elevated.

Pruritus in PN seems to be caused by cutaneous neurogenic inflammation mediated by several neuropeptides, including substance P, calcitonin gene-related peptide (CGRP) [10], and vanilloid receptor subtype 1. (VR-1). The latter may be used as a topical medicinal agent since it binds to capsaicin. Interleukin 31(IL-31), a T-cell-derived highly pruritogenic cytokine, is similarly overexpressed in people with PN [11].

Epidemiology

There is a dearth of epidemiological data on the prevalence and incidence of PN. Case-series data shows that PN may affect persons of any age, including children as young as nine, albeit the elderly are the most often afflicted group [5]. As an added note, there seems to be a higher prevalence of PN lesions in African American patients with atopic eczema compared to patients of other races [10]. Due to inconsistent reporting, we are unable to make any firm conclusions on sex differences [5].

Incidence rates of PN are estimated to be between between 1% and 2%. Patients with PN typically present between the ages of 51 and 65, though some cases have been reported outside of this age range [5,12]. Although the condition affects both men and women, it seems to be more common and severe in women [13]. Studies have revealed that those who are genetically predisposed to developing allergies do so at a younger age [5,14,15]. Since African-Americans are 3. four times more likely to have prurigo nodularis than white patients [12], it appears that ethnicity and genetic predisposition play a role. Prurigo nodularis has been linked to psychiatric disorders, renal failure, and internal malignancy. It has been reported that PN in HIV-positive patients is a good indicator of severe immunosuppression [16].

Pathophysiology

There is some debate on what causes PN. Epidermal hyperplasia, leading to skin thickening, was triggered by chronic and/or repeated mechanical stress or severe frictional assault on the skin. The mechanical rubbing/scratching causes dyschromic changes, usually hyperpigmentation, in addition to the formation of plaques and nodules, often with lichenification. Hyperpigmented noduloplaques with excoriations, crusting, and sometimes secondary bacterial infection develop from the sporadic, severe, and uncontrollable itching that characterizes PN.

Based on immunohistochemical findings, it seems that the quantity of dermal nerve fibers is elevated in the papillary dermis. Thin, unmyelinated epidermal nerves have been hypothesized to convey the intense prurigo. Lesions in the PN are characterized by an increased expression of the growth factors nerve growth factor (NGF) and tyrosine receptor kinase A (TrkA). It's possible that they're linked to the increased production and storage of neuropeptides such substance P and calcitonin gene-related peptide [17]. Intraepidermal (but not dermal) nerve fiber density is significantly reduced in skin biopsies taken from PN lesions. This discovery first led researchers to question whether or not subclinical small nerve fibre neuropathy had a role in the pathogenesis, but more recent research suggests that this decrease may be due to continuous scratching. This was shown by the fact that the density of nerve fibers inside the epidermis returned to normal after the lesions had healed. [18].

Signal transducers and activators of transcription (STAT) 1, 3, and 6 have all been used to examine the function of helper T cytokines, T helper 1 and T helper 2, in the development of prurigo nodularis. Except for three cases, anti-pSTAT 6, a marker for the Th2 cytokines interleukin (IL)-4, IL-5, and IL-13, stained the entire epidermis of all skin samples. These results point to a crucial role for Th2 cytokines in the pathophysiology of prurigo nodularis [19].

The precise pathophysiology of PN is unknown, however cutaneous inflammation and neural plasticity seem to play a role (11).

Histopathological examinations demonstrated an increase in dermal nerve fiber density as well as alterations in a wide variety of skin cell types, including mast cells, collagen fibers, Merkel cells, epidermal keratinocytes, dendritic cells, and endothelial cells [14-16]. Tryptase, IL-31, prostaglandins, eosinophil cationic protein, histamine, and neuropeptides such substance P, calcitonin gene-related peptide (CGRP), and nerve growth factor (NGF) are all released by the aforementioned cells, causing inflammation and pruritus (16–19). IL-31 mRNA is upregulated 50-fold in PN skin biopsies compared to healthy skin biopsies [20]. The T-cell-derived cytokine IL-31 has been shown in mouse models to cause severe pruritus and inflammation [21] by binding to a heterodimeric IL-31 receptor (IL-31 receptor A and oncostatin M receptor subunits) on C fibers, keratinocytes, macrophages, and eosinophils that express transient receptor potential cation channel subfamily V or A member 1 (TRPV1+/TR In contrast, the absence of improvement after taking antihistamines suggests that histamine is not a primary mediator of PN [23]. Substance P may have a role in neuronal and dermal hyperplasia [25], as shown by the increased expression of NGF (24). Overexpressing CGRP also causes neurogenic inflammation by controlling the production of inflammatory cells such eosinophils and mast cells [26].

Sensory nerve hypoplasia has been found in the epidermis of PN skin, including intersessional skin, as compared to healthy skin [16,27]. This is in contrast to findings in the dermis. In addition, biopsies taken from the nodules after they had healed showed a return to normal in the number of epidermal nerve fibers [27]. Patients with PN did not exhibit symptoms of small-fiber neuropathy in a functional assessment [28]. Repetitive scratching, rather than tiny fiber neuropathy, is thus the most probable cause of the decreased density of epidermal nerve fibers [27].

Histopathology

Histopathology of prurigo nodularis lesions may reveal epidermal hyperplasia, pseudoepitheliomatous hyperplasia, and thick, ortho hyperkeratosis. Lesions from prurigo nodularis may show focal parakeratosis with irregular acanthosis, as well as a generic dermal infiltration involving lymphocytes, macrophages, eosinophils, and neutrophils. Differentiating prurigo nodularis from lichen simplex and hypertrophic lichen planus sometimes requires histological analysis. However, the lack of pseudoepitheliomatous hyperplasia and nerve fiber thickening in lichen simplex lesions does not exclude a histological diagnosis of PN. To accurately identify PN from LS [20], it is required to link clinical and histological results together. As with PN, HLP is characterized by epidermal hyperplasia, hyper granulosis, and compact hyperkeratosis. Increased numbers of fibroblasts and capillaries, as well as a more vertical arrangement of collagen fibers, may be seen in the dermis of patients with both diseases. In HLP, basal cell degeneration is confined to the apexes of rete ridges, and there is no evidence of band-like inflammation, in contrast to PN [21].

History and Examination

Firm, dome-shaped, pruritic nodules ranging in size from millimeters to centimeters are a signature finding in patients diagnosed with prurigo nodularis. Nodules may appear in a variety of shades, including flesh, erythema, pink, and brown/black. Lesions might present initially as regions of normal skin or xerosis. Itching, or pruritus, causes patients to scratch at the lesions until a dome-shaped nodule develops. The extensor surfaces of the patient's arms and legs are often affected [22]. Lesions may also be observed in the occipital area of the scalp. It is also possible for the sacrum, abdomen, and upper back to be affected. Hard-to-reach spots, such

the upper mid-back, are often ignored. The term "butterfly sign" is often used to refer to this discovery. In general, the hands, feet, face, and flexor regions are left alone. There is connected with intense pruritus that may be extremely upsetting for the people with prurigo nodularis. It may be intermittent or constant, and it often becomes worse in hot weather or when the skin is irritated by clothes. Prickling, stinging, and temperature changes at the site of inflammation are all symptoms of pruritus [5]. It has been observed that in certain instances, atopic dermatitis and xerosis are present in association with prurigo nodularis and may be the beginning cause. Lesions might frequently seem excoriated owing to the pruritus related with PN. Excoriated lesions are at higher risk of subsequent infection and might seem crusty, erythematous or unpleasant if infected. Prurigo nodularis may also be localized in the context of an underlying local dermatosis such as venous stasis, postherpetic neuralgia, or brachioradial pruritus [23].

Evaluation

The clinical diagnosis is prurigo nodularis. Patients with prurigo nodularis often report a history of persistent, severe itching accompanied by excoriations and pink, nodular lesions on the extensor surfaces. Diagnosing PN vs. HLP may be aided by dermoscopy. A dermoscopy investigation of HLP showed pearly white patches with peripheral striations, gray-blue globules with comedo-like apertures, red spots and globules, brownish-black globules, and yellow structures. Under dermoscopy, PN was characterized by the presence of red spots and globules, as well as pearly white patches with peripheral striations [24]. Lesions that are bleeding, have created ulcers, or are resistant to first-line treatments may need a skin biopsy. The causes of persistent pruritus should be investigated in individuals with prurigo nodularis and severe pruritus for whom a specific trigger cannot be identified. Diseases of the kidneys, liver, or thyroid, HIV infection, cancer, or parasite infection may all cause significant pruritus [25]. A chest x-ray, urinalysis, stool exam, HIV antibodies, and complete blood cell count (CBC) are all useful in determining the potential causes of these symptoms. Patients with atopic dermatitis and PN often have high serum IgE levels [26].

Treatment

Prurigo nodularis treatment should include many methods. Patients should be given information on how to minimize the need to scratch sores, reassurance that their pruritus has a legitimate medical reason, and guidance in identifying and addressing any underlying mental health issues that may be contributing to their compulsive skin picking behavior. Both local and systemic treatments aim to break the cycle of itching and scratching.

General care

- To prevent the nodules from becoming infected, patients should keep their nails short, wear protective clothing like long sleeves and gloves, and keep the nodules bandaged.
- It's recommended that people use mild soaps when washing their skin and use emollients multiple times daily to prevent dryness.
- Lotions containing calamine, as well as menthol and camphor, may help alleviate the itching.
- Rest easy in a nice, cool place.
- Getting rid of stress is essential.

Specific care

- Class one topical corticosteroids, intralesional corticosteroids, topical calcineurin inhibitors, topical capsaicin, and topical vitamin D analogs are all potential topical therapies for prurigo nodularis, although none have been studied in randomized trials.
- Applying a topical corticosteroid, such clobetasol dipropionate 0.05% ointment, once nightly while the affected area is occluded with plastic wrap is recommended as initial treatment for at least two to four weeks.
- Intralesional injections of triamcinolone acetonide at 10 mg/mL to 20 mg/mL have been found to reduce lesion size and itching [27-31].
- Long-term use of pimecrolimus 1% is equally effective as that of hydrocortisone [32].
- When compared to betamethasone valerate 0.1% ointment, calcipotriol ointment is more effective [33].
- Because it increases the threshold for pruritic stimuli, menthol at low concentrations (less than 5%) reduces pruritus [34].

Oral immunosuppressive

- No randomized studies evaluating the use of these systemic medications have been documented, thus the advantages of the medicines must be weighed against the dangers before initiating therapy [13].
- Patients with severe, intractable prurigo nodularis may benefit from oral immunosuppressive treatment.
- Cyclosporine, at a mean dosage of 3.1 mg/kg, improved clinical outcomes and reduced pruritus in a single-institution retrospective analysis [38].
- Complete or partial remission was seen after 2.4 months of treatment with methotrexate at a dosage of 5-20mg/kg weekly. The median time to response for these individuals was 19 months [39].
- Reports of success with azathioprine and cyclophosphamide treatment [40,41] are also present.
- A patient with prurigo nodularis who had been treated with cyclosporine reported a significant decrease in pruritus after starting oral tacrolimus medication [42].
- Atopic dermatitis with prurigo nodularis responded well to three rounds of intravenous immunoglobulin, followed by methotrexate and topical steroid [43].

Novel treatment

- Both thalidomide and lonidomide were banned in the 1980s. Thalidomide is an immunomodulatory drug that suppresses tumor necrosis factor-alpha [43]. It also works as a central and peripheral depressive. The neurotoxic effects are assumed to be responsible for the therapeutic action against prurigo nodularis [44]. Prurigo nodularis may be treated with lenalidomide, a stronger molecular version of thalidomide, with fewer cases of peripheral neuropathy [45].
- Chronic pruritus may also be treated with tricyclic antidepressants or selective serotonin reuptake inhibitors. Together with medical doctors, it is essential that patients be examined by mental health experts.
- To reduce itching, naloxone and naltrexone block the Mu-opioid receptors on nociceptive neurons and interneurons [46].
- Substance P-mediated signalling in the development of prurigo nodularis may be blocked by the NK1r antagonists aprepitant and serlopitant [47]. Prurigo nodularis patients treated with aprepitant alone reported a significant decrease in itching.
- In individuals with moderate to severe atopic dermatitis, the IL 31 receptor antibody Nemolizumab significantly

reduced pruritus ratings. Its function in prurigo nodularis is, however, not well understood.

Prognosis and Complications

A positive prognosis is expected for patients with prurigo nodularis. It is a persistent disorder, generally preceded by an underlying source of pruritus. However, prurigo nodularis is a different entity from these underlying causes and may remain after the resolution of the predisposing illness [48].

It's possible for prurigo nodularis lesions to develop a secondary infection if they're scratched. Clinical signs of infection include redness, pain, warmth, and fever, so keeping an eye out for these is crucial. Antibiotics, either topically or systemically, should be administered to cover skin flora if secondary infection is suspected [49].

Conclusion

The chronicity of prurigo nodularis, the length of the therapy, and the possible side effects of the medicine are all factors that discourage patients from seeking treatment. There are potential benefits and drawbacks to the treatment that should be discussed with the patient, as well as the usage of any off-label drugs. Adherence to therapy may be improved by patient education. As prurigo nodularis is difficult to cure and the patient may grow disappointed by the lack of progress, it is important to address the likely duration of treatment. The skin condition known as prurigo nodularis is persistent and has the potential to seriously diminish the patient's standard of living. In order to break the cycle of itching and scratching, patients should be urged to keep up with their treatment. If necessary, behavioral treatment may be used. Patients should be warned that prurigo nodularis lesions may be long-lasting and challenging to entirely clear up.

When dealing with prurigo nodularis, it's best to assemble a multidisciplinary team that includes your general care physician, a nurse practitioner, a dermatologist, and a mental health nurse. Patients should be given information on how to minimize the need to scratch sores, reassurance that their pruritus has a legitimate medical reason, and guidance in identifying and addressing any underlying mental health issues that may be contributing to their compulsive skin picking behavior. Both local and systemic treatments aim to break the cycle of itching and scratching. To prevent the nodules from becoming infected, patients should keep their nails short, wear protective clothes such long sleeves and gloves, and keep the nodules bandaged. It's recommended that people use mild soaps while washing their skin and use emollients numerous times daily to prevent dryness. Sarna and other lotions containing menthol and camphor, in addition to calamine, help alleviate the itch. Night-time administration of a sedating antihistamine, such as hydroxyzine, may be effective in reducing pruritus that occurs during sleep. Chronic pruritus may also be treated with tricyclic antidepressants or selective serotonin reuptake inhibitors.

Declarations

Ethics approval and consent to participate

Not applicable

List of abbreviations

PN: Prurigo Nodularis
HIV: Human Immunodeficiency Virus
NGF: Nerve Growth Factor
TrK: Tyrosine Receptor Kinase
STAT: Signal Transducers and Activators of Transcription
IL: Interleukin
HLP: Hyperkeratosis Lenticularis Perstans

Conflicts of Interest

Author declare no conflict of interest.

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