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Dr. Daniel Wong is a board-certified dermatologist. He earned a Bachelor's degree in medical sciences studying clinical biochemistry at Western University. Dr. Wong then went on to obtain his medical doctorate from Western University. He completed his 5-year dermatology residency at the University of Toronto, and currently practices at the DermCare, DerCafe and the Canadian Dermatology Centre in Toronto. His interests include skin cancer, inflammatory skin conditions such as psoriasis, and medical education.

PRURIGO NODULARIS

Introduction

Prurigo nodularis (PN) is a chronic, inflammatory skin disease highlighted by firm hyperkeratotic nodules and severe, unrelenting pruritus. It can affect both men and women of all ages. PN has a significant burden of disease, with a reduction in quality of life, sleep disturbances, anxiety, and depression. PN remains a challenging condition to control for many patients with currently no approved medications in Canada for its treatment. This may change however with some emerging therapeutic agents actively being investigated.[1,2]

Pathophysiology

The etiology and pathogenesis of PN remain unknown but current research postulates that PN is related to both immune and neural dysregulation. The neural dysregulation is supported by increased levels of pan-neuronal marker protein gene product, and nerve growth factor in PN patients. It is also supported by increased levels of known pruritic cytokines of calcitonin-gene related peptide, substance P, and vascular endothelial growth factor (VEGF). In terms of immune dysregulation, PN is thought to be a TH2 response, showing increased infiltrates of eosinophils, T-lymphocytes, and mast cells. These cells contribute to the release of a wide range of pro-inflammatory cytokines including, but not limited to, eosinophil cationic protein (ECP), eosinophil derived neurotoxin (EDN), eosinophil protein X (EPX), major basic protein (MBP), Interleukin (IL)-4, IL-31, and prostaglandins.[3] Understanding the pathophysiology can help explain the rationale for the use of certain treatments in PN. Hopefully, as researchers better understand the pathways involved in PN, more effective and targeted therapies will be developed.

Comorbidities

There are a variety of comorbidities that have been associated with PN. These include many of the same associations that have been linked to chronic pruritus, including atopic dermatitis, anxiety/depression, diabetes, renal disease, Hodgkin's lymphoma, HIV, iron deficiency anemia, COPD, inflammatory bowel disease, and hepatitis. In general, more research and larger studies are required to further explore the associations between these comorbidities and PN to determine if there is a potential casual link.[4]

Clinical Appearance and Differential Diagnosis

PN presents with characteristically firm, hyperkeratotic, excoriated nodules, often clustered together on at least two different extensor surfaces.[5,6] (**Figure 1-3**) The differential diagnosis for PN includes pemphigoid nodularis, actinic prurigo, hypertrophic lichen planus, neurotic excoriations, dermatotillomania, arthropod bites, scabies, multiple keratoacanthomas and atopic dermatitis.[7]

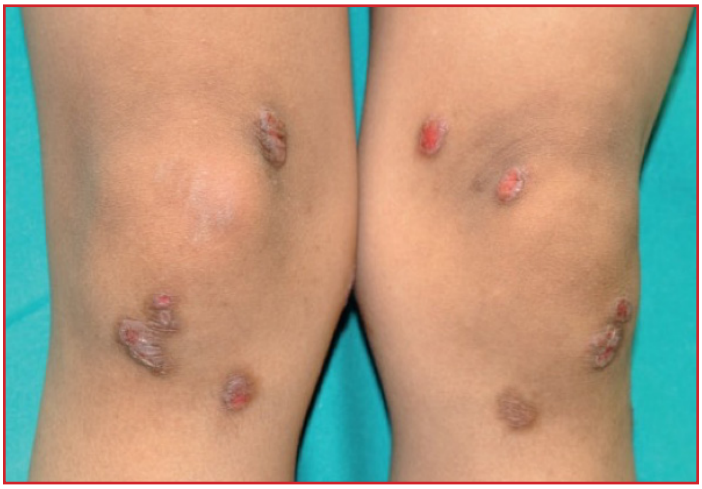

Figure 1. *PN on a patient's knees; Bolognia 4th edition*

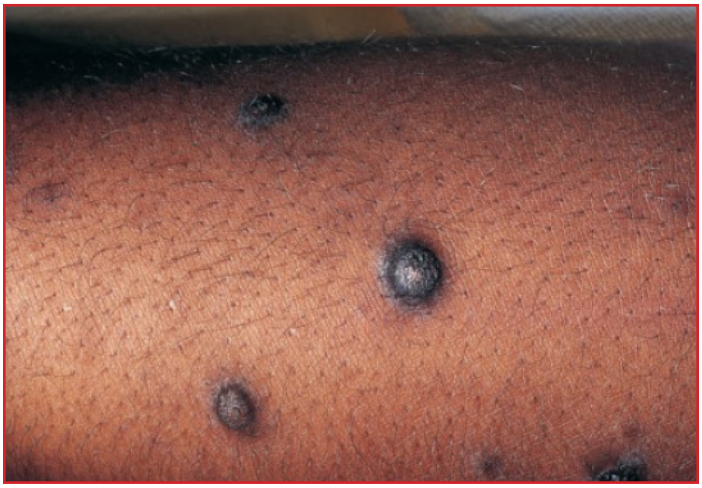

Figure 2. *PN on a patient's leg; Bolognia 4th edition*

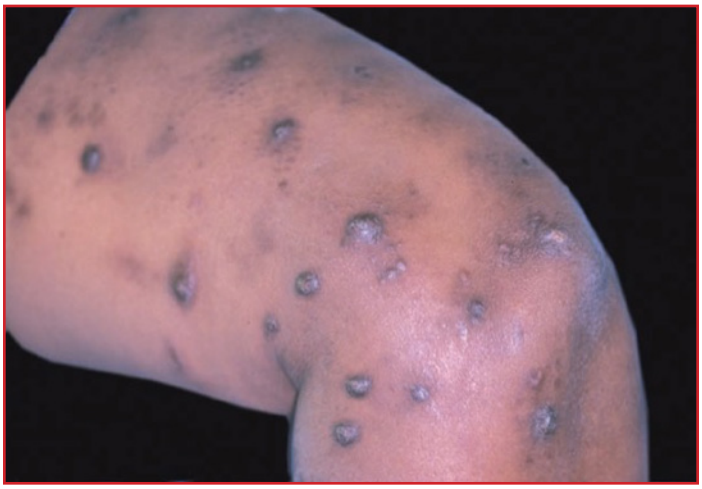

Figure 3. *PN on a patient's arm; Fitzpatrick 8th edition*

Clinical Work up

PN is primarily a clinical diagnosis of intense pruritus lasting 6 weeks or longer with the associated hyperkeratotic nodules. A skin biopsy may not always be necessary, but histology shows orthohyperkeratosis, irregular epidermal hyperplasia, hypergranulosis and an increased number of T-lymphocytes, eosinophils, fibroblasts, and capillaries.[3,7] It is generally recommended that patients suspected of having PN obtain a complete blood count (CBC), a liver function test and a renal function test. Additional consideration for the screening of thyroid function, hemoglobin A1c, human immunodeficiency virus, hepatitis B and C serologies is suggested and may be warranted based on risk factors and a review of systems for the patient. In addition to this, general screenings for an underlying etiology of pruritus can also be investigated if deemed appropriate which include serum protein electrophoresis with serum immunofixation, urinalysis, a chest x-ray, iron studies and stool exam for ova and parasites. Finally, age-appropriate malignancy screening should be up to date, especially if the pruritus has been going on for less than one year.[3]

Management

Treatment of PN remains a challenging task with significant variability in the approach to disease management. All treatments are considered off-label as there are currently no approved targeted therapies for PN. Newer, emerging systemic therapies are currently being investigated in phase 3 clinical trials[7,8] and may soon be available as treatment options. Current treatment modalities tend to work by targeting either the neural or immunological component of PN. In general, treatment can be divided into four categories: topicals, local/procedural, phototherapy, and systemic options.

Topicals

The most used first-line agent for PN is high potency topical steroids. Other treatment options studied including pimecrolimus, calcitriol, topical anesthetics, and capsaicin. **Table 1** provides a summary of these various options and different supporting evidence for them. In the writer's opinion, these topical agents do provide some benefit, but are typically less effective for moderate-to-severe cases.

Local/Procedural

Another commonly used 1st line therapy for PN is intralesional triamcinolone acetonide. This option works locally to reduce the size of nodules and decrease pruritus, but can be quite labour-intensive for severe, widespread disease. Other local and procedural options include cryotherapy and excimer laser.[3,7,8] **Table 1** provides more detailed summary of these options.

Phototherapy

Phototherapy can be an effective treatment option for some patients and is an overall a very safe modality. It can be particularly useful in many of the PN patients that have a more complex medical history where drug interactions and comorbidities can be difficult to work around. Phototherapy access and feasibility limits its use overall, and for some it still may not be sufficient at controlling their pruritus.[3,7] **Table 1** illustrates some further data regarding this option.

Medication	Potential Dosing Regimen	Efficacy	Additional notes
Topicals			
Corticosteroid creams, ointments, lotions	Medium-high potency b.i.d. prn	-Often insufficient as monotherapy -Helpful for mild disease	-Common 1st line agent, sometimes used under occlusion (e.g. with wraps or Unna boot)[3]
Corticosteroid tapes (e.g. betamethasone valerate 0.1% tape, flurandndrenolide tape)	Medium-high potency	-pilot study with 12 patients -Has been shown to reduce pruritus and flatten nodules[9]	-Allows for sparing of non-lesion skin -acts as physical barrier to prevent scratching -expensive
Calcineurin Inhibitors	Tacrolimus or Pimecrolimus b.i.d. prn	-RCT compared to HC 1%, with 30 patients -Has been shown to reduce itch[10]	-Potentially expensive -Good side effect profile
Capsaicin	0.025%-0.3% 4-6x per day	Mixed results. One study has shown potential ability to reduce itching and allow healing in 33 patients[11]	-Works by depleting neuropeptides in small sensory cutaneous nerve fibres -High application frequency -Potential significant skin irritation or burning
Calcipotriol ointment	applied b.i.d.	-RCT with 10 patients -Reduced number and size of nodules compared to betamethasone valerate 0.1%[14]	
Topical Anesthetics (Pramoxine 1%, Lidocaine Spray, Compounded topical anesthetic creams	-Once daily-twice daily application -Compounded topical ketamine (5-10%), amitriptyline (5%) and lidocaine (5%) in lipoderm cream t.i.d.	-Anecdotal evidence -retrospective review of compounded ketamine, amitriptyline, lidocaine showed significant mean improvement in Pruritus Numeric Rating Scale[28]	-theorized to work via modulation of N-methyl-D-aspartate glutamate receptors and sodium channels
Topical Cannabinoid	0.3% cream containing palmitoylethanolamide	-open application study; 14/22 patients demonstrated reduction in itch[32]	-minimal side effects
Local/Procedural Therapies/Phototherapy			
Intralesional Triamcinolone Acetonide (ILTA)	5-10 mg/mL injections directly into nodules q 4,6,8 weeks	Anecdotal evidence. case reports[12,13]	-commonly used treatment modality -difficult for generalized prurigo nodularis
Liquid Nitrogen	Applied directly to lesions q 4,6,8 weeks	-Anecdotal evidence -Case report[13]	-can be used in conjunction with ILTA
Narrowband UVB, PUVA	2-3x per week	-Numerous studies have shown to help reduce itching and improve lesions of PN as monotherapy or in conjunction with other therapies[15,16]	-good options for patients that cannot take oral medications due to underlying comorbidities or potential drug-drug interaction -can be adjunctive therapy -may not be feasible for patient
Excimer Laser, 308nm	Once-weekly	-compared to clobetasol ointment once daily showed significant improvement at week 34[17]	-not readily available -expensive

***Table 1**: topicals, local and phototherapy for treatment of prurigo nodualris. b.i.d.: twice daily; prn: as needed; t.i.d.: three times daily; UVB: ultraviolet B; PUVA: psoralen + ultraviolet A.; courtesy of Daniel Wong, MD, FRCPC*

Systemic Medications

Given the severity of many cases of PN, topicals and local agents are often not sufficient for fully controlling the symptoms of PN. As a result, many different systemic agents have been studied and used historically. These include immunosuppressants such as methotrexate, cyclosporine, and mycophenolic acid; neuromodulators including gabapentinoids, amitriptyline, antidepressants and thalidomide, and newer oral agents including aprepitant and serlopitant.[3,7,8] These medications deliver various levels of efficacy and are also associated with differing side effect profiles. **Table 2** provides a summary of many of these agents. Antihistamines have typically been ineffective and generally are not recommended unless comorbid histamine mediated conditions are suspected.[3,7]

Emerging Therapies

There are several medications currently being investigated for treatment of PN, some of which are showing promising early results. One such agent, nemolizumab[33], has recently gained "breakthrough therapy" designation by the FDA for treating PN. This process is designed to expedite the development and review of drugs that are intended to treat a serious condition where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on clinically significant endpoint(s).[34] Nemolizumab is a monoclonal antibody targeting IL-31, a proinflammatory cytokine upregulated in PN patients. Phase II studies have shown a significant reduction in pruritus scores (numerical rating scale [NRS]) in the nemolizumab treatment arm compared to the placebo group at 12 weeks. This same study also demonstrated improvements in quality of life, and a reduction in number of PN lesions.[31] Currently, nemolizumab is being investigated in phase III clinical trials.

Another newer therapy emerging as a potential effective option for PN is dupilumab. Dupilumab is a monoclonal antibody that works by inhibiting IL-4 and IL-13, which are both proinflammatory cytokines known for contributing to pruritus. Dupilumab is more well known for its treatment of atopic dermatitis but has shown in several case reports and case series to be effective at improving PN.[30] Like nemolizumab, it is also undergoing phase III clinical trials.

Other emerging treatment options being investigated for PN include oncostatin M beta receptor, opioid antagonists, and cannabinoids.[7] [7]. **Table 2** provides additional information about some of these newer therapies.

Conclusion

PN is chronic inflammatory skin disease that is often clinically challenging. Although strides have been made in recent years with understanding this condition and with the development of newer therapeutic agents, further research into the pathophysiology and targeted treatment modalities are still needed to better understand PN.

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Medication	Potential Dosing Regimen	Efficacy	Additional notes
Oral Agents			
Thalidomide	100 mg PO daily	-multiple studies showing efficacy[18,19]	-poor safety profile (especially peripheral neuropathy, teratogenicity, depression, nausea, dizziness, sedation) -not commonly used -thought to work on central neural system, and as immunomodulator
Methotrexate	7.5 mg to 20 mg SC q weekly	-retrospective studies 13-patient study showed >75% reduction in prurigo nodularis area and severity index[20] 39-patient study showed disease response of 91% and 94% at 3 and 6 months respectively[21]	-common side effects of nausea, transaminitis, GI symptoms -mechanism of action for PN unknown
Cyclosporine	3 to 5 mg/kg daily	-case series -19 of 22 patients showed significant improvement with cyclosporine with maximal effect after 2-3 months[22,23]	-theorized to work via inhibition of IL-2 -nephrotoxicity, hypertensive risks with long term use
Pregabalin	75 mg daily	-prospective study -Complete response in 23 of 30 patients at 3 months[24]	-modulates neural gamma-aminobutyric acid signalling -side effects of sedation, headache
Gabapentin	300 mg/day initiated and gradually increased to 900 mg/day	-retrospective study -4 patients had partial or complete response at 3-4 months[25]	-modulates neural gamma-aminobutyric acid signalling -side effects of sedation
Amitriptyline	10 to 60 mg	-beneficial effect in 17 PN patients[26]	-monoamine oxidase inhibitor -inhibits uptake of norepinephrine and serotine -sedative
SSRI inhibitor	Paroxetine 10 to 60 mg daily Fluvoxamine 25 to 150 mg daily	-17 patients showed partial clearing and 14 showed complete lesion healing[27]	-antidepressants -side effects: insomnia, rashes, head aches, sexual dysfunction, GI upset, CNS, cardiovascular
Serlopitant	5 mg daily	-RCT with 127 patients -significant reduction from baseline at 8 weeks in Visual Analog Scale (VAS) compared to placebo at 8 weeks[29]	-neurokinan-1 receptor antagonist -targets substance P -well tolerated, mild-moderate adverse events only -being investigated for chronic pruritus -expensive
Biologics and Emerging Therapies			
Dupilumab	600 mg SC followed by 300 mg SC q 2 weeks	-multiple case series and case reports demonstrating reduction in NRSi (numerical rating scale itch)[30]	-IL4/IL-13 antagonist -excellent safety profile -not FDA approved and expensive -currently in phase 3 clinical trials
Nemolizumab	0.5 mg/kg SC at baseline, week 4, and week 8	-12 week, RCT Phase 2 trial 70-patient study, showing significant reduction in NRS in treatment arm compared to placebo[31]	-works as an IL-31 receptor antagonist, thus lowering IL-31 in PN patients -Currently in phase 3 trials -side effects of GI and MSK symptoms -granted Breakthrough Therapy designation for treatment of pruritus in prurigo nodularis
Oncostatin M (OSM) beta receptor	KPL-716 monoclonal antibody (Vixarelimab) 720 mg SC loading dose followed by 360 mg q weekly.	-data pending -Press release from Kiniska reports statistically significant reduction in WI-NRS at week 8.	-currently in phase II clinical trials -pro-inflammatory signaling molecule similar to IL-6

***Table 2**: Systemic therapies for PN. PO: orally; SC: subcutaneous; SSRI: selective serotonin reuptake inhibitors; GI: gastrointestinal; MSK: musculoskeletal; CNS: central nervous system; RCT: randomized control study; courtesy of Daniel Wong, MD, FRCPC*

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