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Patient Journey and the Burden of Systemic Comorbidities and Sequalae in Prurigo Nodularis

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ABSTRACT

Background: Prurigo Nodularis (PN) is a relatively rare chronic inflammatory skin disease characterized by firm pruritic nodules. PN is associated with significantly increased rates of many systemic and non-systemic comorbidities. This results in a higher burden of disease and utilization of specialty care compared to non-PN United States (US) adults. Psychiatric comorbidities associated with PN include depression and anxiety. In this article, we describe the burden of comorbidities. sequelae of disease, inflammatory disease signatures, and the impact of PN in African American and Asian patients. Furthermore, we explore challenges in the recognition and diagnosis of PN and describe methods to increase awareness of PN among dermatologists.

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INTRODUCTION

Patient Journey and the Burden of Systemic Comorbidities and Sequalae in Prurigo Nodularis

Prurigo Nodularis (PN) is a relatively rare condition with prevalence estimates as low as 18 per 100,000 in the US, that disproportionately affects adults in their fifth and sixth decades of life.[1,2] An analysis of the data from the Johns Hopkins Health System found that during the last 5 years, 958 patients were diagnosed with PN with 50% of those patients ranging in age from 45 to 64 years and an additional 17% ranging from 65 to 74 years of age.[3] A nationwide analysis of claims data identified increasing rates of PN with 2658 patients in 2016 and 9,426 patients in 2019.[4] A study using data from All of Us, a National Health Institute database containing health information from US adults similarly found increased prevalence with increasing age, ranging from 0.02% in those under 30 years of age to 0.35% in those over 70 years of age. The same study found that participants with PN had statistically significantly higher rates of comorbidities than US adults without PN, including atopic dermatitis (15.5% vs 1.5%), chronic hepatitis C (6.4% vs 1.4%), chronic kidney disease (29.4% vs 5.7%), congestive heart failure (20.3% vs 3.4%), COPD (23.3% vs 5.2%), depression (54.4% vs 18.0%), HIV (7.4% vs 1.2%), and type 2 diabetes (43.2% vs 12.1%).[5] These comorbidities place a higher systemic burden of disease on patients resulting in higher utilization of specialty care. In a multicenter cohort phase 2 clinical trial, nemolizumab was shown to reduce systemic inflammation, it will be necessary to see in future studies if this lowers comorbidity risk.[6]

A national-representative study looking at private insurance claims data found that patients with PN saw dermatologists more frequently than age-matched controls and patients with atopic dermatitis and psoriasis.[4] This increase in visits when compared to patients with atopic dermatitis and psoriasis provides support for the claims that patients with PN experience a greater disease burden as PN is believed to be the most severe of the pruritic dermatoses.[7]

This chronically severe dermatosis presents a substantial financial burden on patients. An analysis found that the lifetime financial impact was estimated to be $ 323,292 per individual. In addition to the large financial burden, PN also has a large negative impact on the patient's quality of life (QoL). The same analysis found that PN can have greater impairments on QoL than chronic diseases such as strokes and has a comparable impact on chronic kidney disease.[8] Patients with PN are also impacted by many nonsystemic diseases including xerosis cutis (OR 8.02), neurotic excoriations (OR 71.2), atopic dermatitis (OR 9.48), asthma (OR 1.67), and urticaria (OR 2.78).[2]

Impact on Mental Health

Prurigo Nodularis has been associated with psychiatric disorders such as depression and anxiety. Additionally, consumption of anxiolytics and antidepressants is significantly higher among patients with PN.[9] In addition to the psychiatric conditions, other mental health disorders such as schizophrenia, mood disorder, eating disorder, ADHD, substance use, and self-harm also showed increased rates in patients with PN.[2] A study that combined PN and lichen simplex chronicus (LSC) using the National Inpatient Sample Database corroborated this as they found these patients were 2.26 times more likely to have a mental health diagnosis. Furthermore, patients with PN/LSC admitted for any mental health condition were hospitalized 2.18 longer on average and had an increased cost of care of $1,617 compared to those without PN/LSC.[10] There also appears to be gender differences in the prevalence of PN and psychiatric conditions, with women being more commonly affected.[11] This is consistent with the findings of a single institution study of patients seen for pruritus in which females were more likely than males to be diagnosed with comorbid psychiatric conditions.[12]

Inflammatory Disease Signatures in PN

PN is often grouped with atopic dermatitis and psoriasis, however, a recent study found that it has a distinct circulating and cutaneous Th22 immune dysregulation. The source of increased IL-22 secretion was found to be circulating $CD4^+$ and $CD8^+$ T-cells.[13] Plasma assays have demonstrated increases in inflammatory mediators in the systemic response, which likely play a role in the systemic comorbidities seen in patients with PN.[14] A recent proteomic analysis found that among all patients with PN, levels of CDCP1 (a transmembrane protein found in T cells) and MCP-3 (a marker of innate immunity that stimulates monocytes and dendritic cell chemotaxis toward inflammatory skin sites) were elevated. More specifically 2 clusters were identified, providing support for 2 unique endotypes: an inflammatory phenotype, with a predisposition towards atopy, and a neuropathic phenotype, with a predisposition towards myelopathy.[15] Little information is known about PN on a single-cell level, but a recent single-cell transcriptomic profiling (scRNA-seq) provided better insight into this. A unique fibroblast cell population in the skin of patients with PN and the presence of another phenotype in PN fibroblasts characterized by the presence of cancer-associated fibroblasts (CAF) was identified.[16] A multicenter cohort study found that therapy with nemolizumab, a novel IL-31RA inhibitor, was able to reverse circulating blood inflammation.[6] Future registry studies are needed to understand more about the pathogenesis of PN and to evaluate if early treatment may reduce the development of subsequent disease comorbidities.

Patient Spectrum: Skin of Color, Asian, and Caucasian

A study of 909 patients with PN found that African American (AA) patients were 3.4 times more likely to have PN than White patients. Additionally, AA patients with PN were 10.5 times more likely to have HIV than were race-matched controls with atopic dermatitis, and 8 times more likely to have HIV than were African American patients with psoriasis.[17] In a study using TriNetX, a health research network of approximately 64 million patients in 45 large healthcare organizations, all patients with PN were found to have higher all-cause mortality (HR 1.75) than control patients. More specifically subgroup analysis showed that Black patients had the highest mortality (HR 2.07).[14] AA patients with PN favor a Th22/IL-22 profile in both systemic and cutaneous immune response, leading to the possibility that Black patients with PN may experience greater systemic inflammation and this is the cause of their higher mortality.[13,18] It is also important to note that a survey of 6,000 US veterans randomly sampled from the US Veterans Hospital Patient Database found that AA patients had a greater emotional impact and were more likely to visit their primary care providers for pruritis, although they had a similar number of visits to a dermatologist.19 The patient population of this sample rules out the insurance as the main culprit, but still leaves questions about the racial disparities in medical treatment of PN. Single center and national studies have shown PN to be more common overall in women than men, however, a Korean study based on a large dermatology outpatient cohort found PN to be more prevalent in males (56.8%) than females (43.2%). This supports the findings by Boozalis et al in Asian prevalence (58.1% male, 41.9% female).[1,17,20]

Challenges in Recognition and Diagnosis and Increasing Awareness Among Dermatologists

A biopsy of PN may show hyperplastic dermal nerve fibers and decreased density of intraepidermal nerve fibers, but PN remains a clinical diagnosis.[1] Some of the typical features clinicians should look out for include grouped and symmetrically distributed nodules on the extensor surfaces of the extremities and trunk, and the butterfly sign, which is when skin on the upper aspect of the back is spared. In addition to these findings, pruritis is necessary for the diagnosis of PN, but patients may also report a burning or stinging sensation.[1,21,22] Aside from these typical features PN may also have varying presentations and can be recalcitrant to treatment, making it difficult for providers to appropriately manage PN. Dupilumab is currently the only drug approved by the US Food and Drug Administration for the treatment of PN in the US.[23] A survey of 30 providers from 14 European countries highlights the amount of uncertainty around the diagnosis and management of PN, as respondents reported that 90% have prescribed antihistamines despite unanimous agreement that antihistamines are generally ineffective for PN-associated pruritus.[22] In addition to initiating appropriate treatment, in the right clinical context providers should consider screening for psychiatric disorders, HIV, the presence of cognitive impairment, and many of the systemic comorbidities already discussed.[10,11,17]

CONCLUSION

PN has an impact on patients' lives due to the many systemic and nonsystemic comorbidities associated with a higher burden of disease. In addition to these comorbidities, there are also psychiatric comorbidities that are important to understand to improve outcomes. It is worth noting that the burden is augmented in patients with skin of color thus highlighting the importance of addressing racial disparities in the medical treatment of PN. Though diagnosis of PN remains challenging, increasing awareness of common exam and biopsy findings can improve the clinical decision-making process.

DISCLOSURES

Dr Kwatra is an advisory board member/consultant for Abbvie, Amgen, Arcutis Biotherapeutics, Aslan Pharmaceuticals, Bristol Myers Squibb, CaraTherapeutics, Castle Biosciences, Celldex Therapeutics, Dermavant, Galderma, Genzada Pharmaceuticals, Incyte Corporation, Johnson & Johnson, Leo Pharma, Novartis Pharmaceuticals Corporation, Pfizer, Regeneron Pharmaceuticals, and Sanofi and has served as an investigator for Galderma, Incyte, Pfizer, and Sanofi. Dr Chisolm has served as an investigator, scientific advisor, or received research support, from Pfizer, Incyte, Amgen, Galderma, Trevi, Menlo, Abbvie, Janssen, Kiniksa, AstraZeneca, Sanofi, Regeneron, Lilly, and Vifor. Dr Puerta-Durango has no conflicts of interest to declare. Dr Mollanazar has served as an advisory board member for Boehringer Ingelheim, Janssen, Novartis, Regeneron Pharmaceuticals, Inc., Sanofi, Trevi Therapeutics, Menlo Therapeutics Inc, Galderma, Leo Pharma, Abbvie; investigator for Sanofi; and consultant for Novartis, Regeneron, Janssen, and Sanofi.

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