



# A patient with concurrent prurigo nodularis and squamous cell carcinomas of keratoacanthoma type: The role of aprepitant in diagnostic clarity

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## INTRODUCTION

Prurigo nodularis (PN) is a chronic pruritic disorder characterized by a neuronal itch-scratch cycle, with subsequent development of hyperkeratotic, excoriated, or crusted nodules.<sup>1</sup> The lesions of PN may clinically resemble squamous cell carcinomas (SCC), especially keratoacanthoma (KA) type, which presents a challenge for oncologic surveillance particularly in patients at high risk for nonmelanoma skin cancer (NMSC) development. While multiple therapies, such as antihistamines, corticosteroids, phototherapy, and thalidomide have been reported, there are currently no effective treatments approved by the US Food and Drug Administration for PN.<sup>1</sup>

PN originates in part due to a chronic itch-scratch cycle, which causes chronic skin irritation and damage. Although no one causative chemical mediator of itch has been identified, substance P is thought to be a major contributor to the neurocutaneous transmission of pruritus.<sup>2</sup> By acting through the neurokinin-1 (NK1) receptor on epidermal dendritic cells, dermal fibroblasts, mast cells, and keratinocytes, substance P plays a role in neurogenic inflammation, pain, and pruritus.<sup>2</sup> In addition to its action at NK1 receptors, recent mouse studies suggest that substance P may also act via Mas-related G-protein-coupled receptors (Mrgprs) on mast cells and dorsal root ganglia neurons to mediate neurogenic itch.<sup>3,4</sup> The NK1 receptor antagonists inhibit substance P-mediated neurogenic inflammation by

### Abbreviations used:

KA:	keratoacanthoma
Mrgprs:	Mas-related G-protein-coupled receptors
NMSC:	non-melanoma skin cancer
NK1:	neurokinin 1
PN:	prurigo nodularis
SCC:	squamous cell carcinoma

blocking both NK1 receptors and Mrgprs and have demonstrated variable efficacy in the treatment of pruritus and PN.<sup>2,3,5</sup>

Here we present a case of an immunocompromised patient with multiple prior NMSCs and multiple treatment-refractory PN successfully treated with the NK1 receptor antagonist aprepitant.

## CASE REPORT

A man in his 70s with well-controlled HIV presented with a 1-year history of generalized pruritus and diffuse hyperkeratotic, hyperpigmented excoriated papulonodules with crusting over the bilateral upper/lower extremities, trunk, and neck. Initial biopsy findings from different discrete lesions on the lower extremities were consistent with PN, lichen simplex chronicus, and eruptive KAs. Review of medications and laboratory workup, including IgE, for potential causes of pruritus were unremarkable.

The patient's pruritus persisted during subsequent follow-up, and he continued to develop new

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**Fig 1.** Right lower extremity before aprepitant treatment with biopsy site indicated by black arrow. This site was biopsied for concern of squamous cell carcinoma but was interpreted as prurigo nodularis on histology.

papulonodules. Several of these lesions represented biopsy-proven KA-type SCC, which were challenging to distinguish from innumerable prurigo nodules, despite dermoscopic assessment and longitudinal monitoring (Fig 1). He did not respond to common first-line treatments for PN including topical corticosteroids (due to lack of efficacy), acitretin (due to refractory hypertriglyceridemia), and thalidomide (due to lower extremity edema and gastrointestinal symptoms). Gabapentin provided only modest improvement in pruritus.

As his PN continued to complicate oncologic surveillance, the patient was treated with a single 4-day course of aprepitant, 80 mg daily, with the aim of improving his pruritus and PN. The patient's pruritus significantly improved; however, he experienced a gradual increase in pruritus over 2 months necessitating a second 4-day course of aprepitant, 80 mg daily. At the 4-month follow-up examination, a durable reduction in pruritus and near-complete resolution of PN was noted (Fig 2). The patient has had a continued durable response to aprepitant, 80 mg  $\times$  4 days every 3 months at 10 months without need for further biopsy to date for oncologic surveillance of NMSCs.

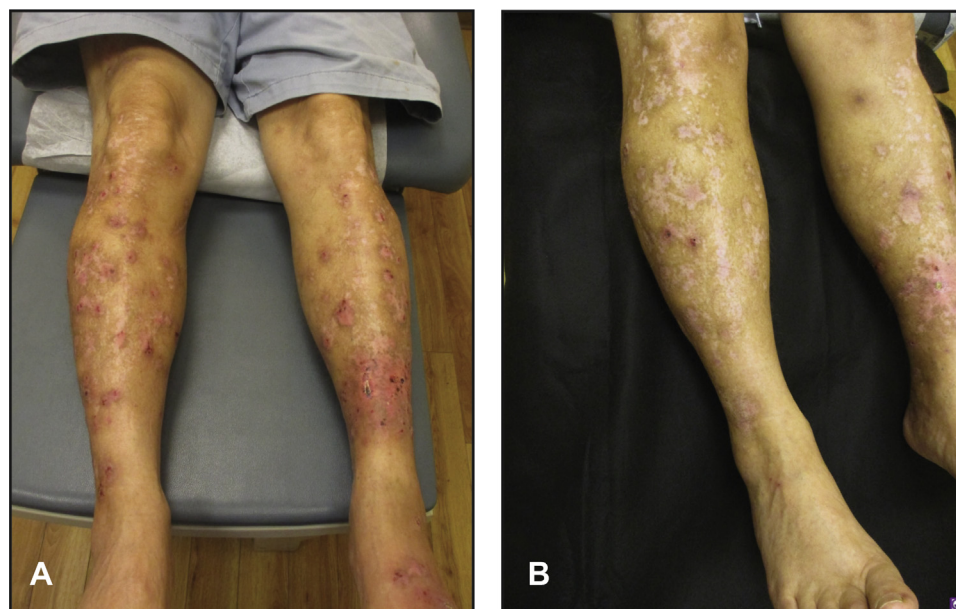
## DISCUSSION

PN is a challenging disorder to treat, and management primarily relies on multiple off-label

treatments including topical corticosteroids, phototherapy, gabapentinoids, thalidomide, and naltrexone.<sup>1</sup> Because our patient did not respond to multiple first- and second-line therapies, the NK1 receptor antagonist, aprepitant, was trialed, as evidence suggested an improvement in pruritus severity in patients with PN and pruritus secondary to cutaneous T-cell lymphoma, solid tumors, anti-tumoral immunotherapies.<sup>1,2,6</sup> Recently, dupilumab, a monoclonal antibody directed against the interleukin receptor, was found to improve generalized PN; however, cost and administrative burdens may limit the accessibility of dupilumab in PN.<sup>7</sup> Although aprepitant was used off label for pruritus in this case, the low overall dose (80 mg  $\times$  4 days) and infrequent dosing (every 3 months) made this an affordable option in this patient with refractory pruritus and PN.

Initial studies of aprepitant for chronic pruritus found a significant antipruritic effect in patients with PN; however, more recent phase II trials failed to replicate this antipruritic effect in PN.<sup>5,6</sup> Animal studies, case series, and case reports of aprepitant for the use of chronic pruritus displayed promising results, suggesting that select patients may experience clinical responses, as in our case.<sup>2,5,6</sup> Although the phase II data conflict with the significant clinical outcome of our case, exclusion criteria included infectious and chronic diseases, which may explain the difference in benefit in our patient compared with the study population.<sup>5</sup> The discrepancy of clinical response between human and animal studies may occur, because aprepitant acts as an antagonist of mouse but not human Mrgprs isoforms.<sup>3,4</sup> Future research may be directed at investigating NK1 antagonists with increased affinity for human Mrgprs. In contrast to aprepitant, the novel NK1 receptor antagonist serlopitant improved chronic pruritus in a recent phase II trial, indicating that other agents of the same drug class may be equally or more efficacious.<sup>8</sup>

Differentiation between PN and cutaneous neoplasms is imperative to reduce unnecessary morbidity while maximizing early detection of low-risk and potentially aggressive NMSC. However, this delineation may be clinically challenging, as SCCs were previously found to arise in fields of prurigo nodules and can have an overlapping phenotypic appearance. One case series found that KA-type SCC co-occurred within a field of prurigo nodules in 7 elderly patients with diffuse actinic skin damage, which raised concern for the clinical differentiation of these lesions.<sup>9</sup> Furthermore, chronic prurigo may increase risk for SCC, as one case series reported SCC



**Fig 2.** A, Lower extremities at 1-month follow-up after 1 course of 80 mg aprepitant for 4 days. B, Lower extremities at 2-month follow-up after aprepitant treatment with significantly decreased excoriations and prurigo nodules.

occurring within 2 long-standing biopsy-proven prurigo nodules.<sup>10</sup> Although case series suggest that PN may contribute to the development KA-type SCC, future studies are needed to determine if adequate resolution of PN nodules reduces subsequent risk of KA-type SCC at the site of prior PN.

Aprepitant is a relatively inexpensive, accessible, and potentially effective treatment for refractory PN and may be particularly useful in select patients in whom diagnostic certainty for cutaneous malignancy is required. Our case demonstrates a dramatic, durable improvement in both pruritus and PN lesions after two 4-day courses of aprepitant, allowing for improved cutaneous oncologic surveillance and decreased need for additional invasive diagnostic procedures and biopsies.

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