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Thalidomide for the treatment of chronic refractory prurigo nodularis

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Abstract

Prurigo nodularis (PN) is a highly pruritic skin condition that is caused by chronic scratching. It occurs in patients with chronic itch and is characterized by multiple hyperkeratotic papules and nodules. The pathogenesis of PN is unclear, but involves a complex interplay of numerous pathways including neurogenic and inflammatory factors. As such, PN is very difficult to treat and patients are often refractory to multiple medications before finding a treatment that is effective. We present a woman with a 20-year history of exuberant prurigo nodularis who failed multiple therapies, including dapsone, azathioprine, mycophenolic acid, prednisone, topical steroids, and phototherapy. She only obtained significant relief of chronic pruritus and lesion flattening with thalidomide 100mg daily. Thalidomide is an antipruritic and anti-inflammatory agent that has shown to be very effective in treating a variety of dermatologic conditions. However, its use today is limited by concerns for its teratogenic and neuropathic side effects. With strict adherence to medication protocols, these adverse effects can be minimized. As such, thalidomide should be considered for patients with refractory dermatologic conditions.

Keywords: thalidomide, itch, pruritus, prurigo nodularis

Introduction

Prurigo nodularis (PN) is a chronic, highly pruritic skin condition that significantly impairs patients' quality of life. It is characterized by multiple (often up to hundreds) hyperkeratotic, pruritic papules and nodules that are distributed symmetrically on the shoulders, back, buttocks, and limbs [1]. The PN lesions form as a reaction to chronic scratching. Thus, the goal of treatment for PN is to break the cycle of repeated itching and scratching to allow time for the skin to heal [2].

The pathogenesis of PN is not yet completely understood, but recent findings suggest that the interaction between cutaneous nerve fibers and immune cells plays an important role in its development. There is evidence of reduced intraepidermal unmyelinated C-fiber density in affected PN skin [1-3]. It has also been observed that gabapentin and pregabalin, two therapies commonly used to treat neuropathic pain, are often successful at treating PN [1-3]. Together, this suggests that a small fiber neuropathy of the intraepidermal nerve fibers contributes to the formation of PN [1-3].

Furthermore, several neuropeptides, such as substance P (SP) and calcitonin gene-related peptide (CGRP), have an increased expression in PN [4, 5]. SP induces neurogenic inflammation, mast cell degranulation, and induction of nerve growth factor (NGF) keratinocyte expression [2]. NGF leads to activation, sensitization, and sprouting of skin nerves, and may directly induce pruritus by binding to cutaneous nerve fibers [2, 7]. NGF also leads to proliferation and differentiation of keratinocytes, which may explain the epidermal hyperplasia associated with PN [2, 8]. Finally, inflammation

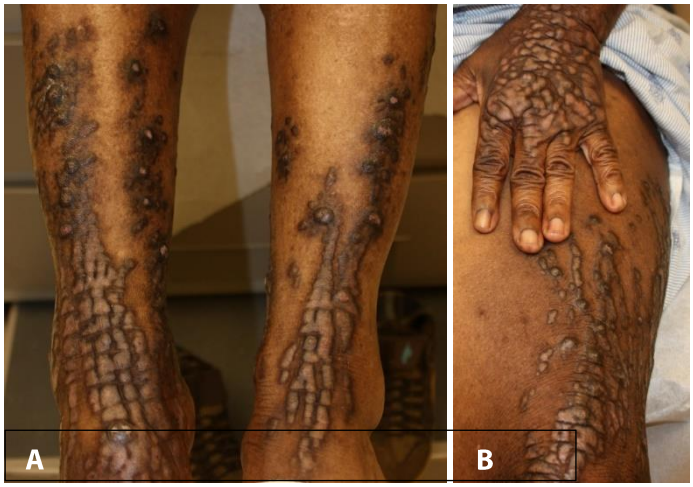

Figure 1. ***A)*** *Thick lichenified nodules on the patient's bilateral dorsal legs.* ***B)*** *Thick lichenified nodules on the patient's left dorsal hand and left lateral thigh.*

caused by T-lymphocytes, eosinophils, and mast cells contributes to the development of PN [9].

Because there are numerous pathways involved in PN development, treatment remains a frustrating challenge. There is no standard therapy for PN and treatment response is often limited and unsatisfactory for patients. Common therapies used for PN include topical medications such as calcipotriol ointment, systemic treatments such as gabapentin, pregabalin, aprepitant, naltrexone, dapsone, azathioprine, mycophenolic acid, prednisone, and thalidomide, and physical therapies such as phototherapy [1]. However, it is difficult to predict which patients will respond to which treatments.

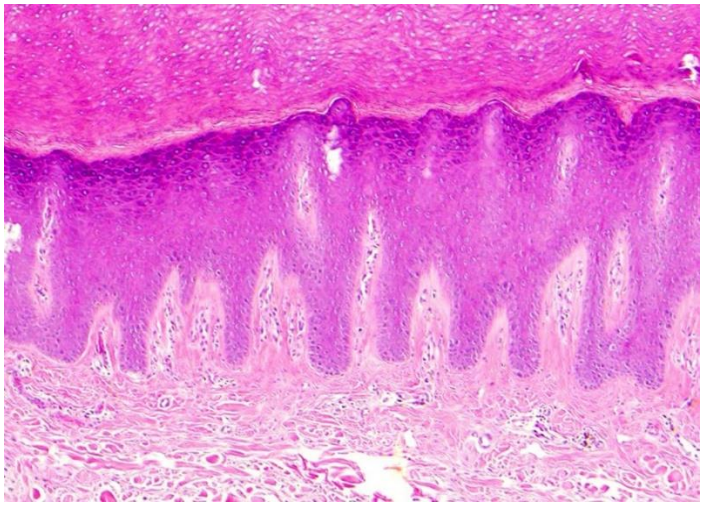

Figure 2. *Biopsy of a nodule on the thigh confirmed lichen simplex chronicus/prurigo nodularis. H&E, 20×.*

We report a patient with severe PN, refractory to numerous systemic and physical therapies, who finally experienced significant relief with thalidomide. Although dermatologists often avoid this drug owing to its known teratogenic and neuropathic side effects, thalidomide is useful in many dermatological conditions and should be considered when patients remain refractory to multiple other treatments.

Case Synopsis

A 69-year-old woman initially presented to the outpatient dermatology clinic in 1997 with exuberant prurigo nodules affecting the extremities. She reported significant pruritus associated with the prurigo nodules. She had no history of atopy or xerosis.

Detailed exam revealed thick lichenified papules coalescing into plaques on the patient's bilateral dorsal feet and legs (**Figure 1**A), dorsal hands, anterior thighs (**Figure 1**B), and forearms. The head, neck, chest, and back were spared. Many of the plaques were linear on examination.

Extensive laboratory workup to identify an underlying cause for pruritus was negative, including her complete blood count, comprehensive metabolic panel, thyroid function tests, hepatitis panel, HIV, and SPEP. The patient's medications included cholecalciferol (vitamin D3), fexofenadine for seasonal allergies, and sterile lubricant eye drops for dry eyes. A recent biopsy performed in 2012 showed hyperkeratosis and hypergranulosis of the epidermis with classic elongation of the rete ridges, histological features consistent with lichen simplex chronicus (LSC), (**Figure 2**). These biopsy results confirmed that the patient's clinical presentation was consistent with prurigo nodularis with features of LSC.

In 2012, fifteen years after her initial presentation, the patient was started on thalidomide after failing multiple other treatments, including methotrexate, phototherapy, dapsone, azathioprine, mycophenolic acid, prednisone, doxepin, and several other topical treatments.

The patient was initially started on a low dose of 50mg daily to monitor for side effects. She tolerated the dose well. Side effects were limited to constipation, which she was able to control with prune juice and intermittent stool softeners. She denied excessive daytime somnolence, dizziness, numbness, tingling, or pain in her hands or feet concerning for neuropathy. She reported significantly reduced pruritus associated with the PN lesions and improvement in lesion flattening after just a few weeks of treatment. A complete blood count (CBC) and comprehensive metabolic panel (CMP) were performed to assess for pancytopenia and renal failure, which were all within normal limits.

The patient's thalidomide dose was increased to 100mg daily after two months of symptom improvement and limited side effects. After four months, the patient estimated an approximately 50% improvement in her PN.

Throughout the next three years, the patient continued to follow-up in the dermatology outpatient clinic every 3-6 months to assess for symptom improvement, to monitor for side effects, and to check a CBC and CMP. She continued to report significant improvement in pruritus and lesion regression with minimal side effects (limited to constipation). After three years of thalidomide 100mg daily, the patient experienced near resolution of her PN lesions (**Figure 3**). The patient's visual analogue score (VAS) for itch improved from 10/10 intensity before thalidomide to 1/10 intensity after treatment. As such, the patient was advised to slowly taper off the medication. The patient began the taper with alternating doses of 100mg and 50mg daily for 6 months, which she tolerated well without increasing pruritus. She was recently tapered down to 50mg daily for one month and subsequently plans to trial a month completely off thalidomide.

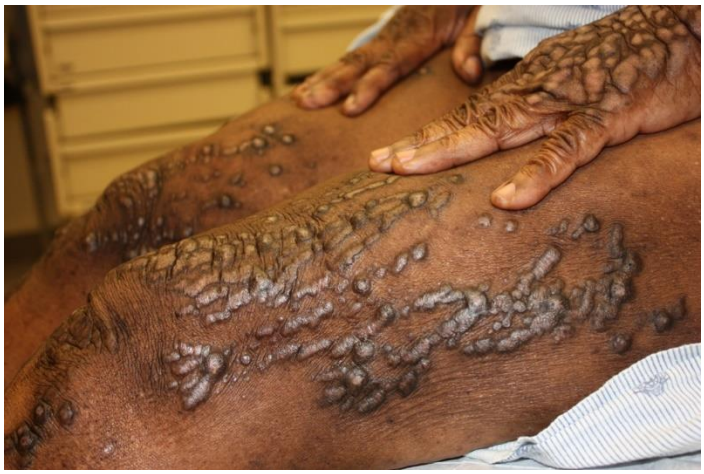

Figure 3. *Before A) and after B) treatment with thalidomide 100mg daily for 3 years.*

Case Discussion

Thalidomide was first introduced in 1956 and quickly gained widespread popularity around Europe as a sleeping aide owing to its hypnosedative effects [10-12]. The medication was never approved in the United States for that indication because of its side effects of sensory nerve deficits [10-12]. By 1961, thalidomide was completely withdrawn from the global market due to its association with phocomelia, a birth defect characterized by severe limb defects [10-12]. However, in 1965, thalidomide regained popularity owing to its unparalleled effect at treating erythema nodosum leprosum [10-12]. The Food and Drug Administration (FDA) finally approved thalidomide for treating that condition in 1998 [10-12].

Since then, thalidomide has been successful in treating numerous dermatological conditions refractory to other medications. Thalidomide has recently been discussed as an alternative therapy for various causes of chronic refractory pruritus, including uremic pruritus, prurigo nodularis, primary biliary cirrhosis, actinic prurigo, and paraneoplastic pruritus [10]. Thalidomide has been shown to be effective for erythema nodosum leprosum, discoid lupus erythematosus, Behçet syndrome, cutaneous graft versus host disease, sarcoidosis, pydoerma gangrenosum, Langerhans cell histiocytosis, and recurrent aphthous stomatitis [10-13].

Thalidomide works via numerous pathways as a central depressant, anti-inflammatory agent, immunomodulator, and neuromodulator [10]. It inhibits TNFα production and the NFκB cascade, and is involved in interleukin-8, -10, -12, cyclooxygenase-2, and IFNγ regulation [10]. It also upregulates keratinocyte proliferation and migration, increases

TGFβ production, and stimulates re-epithelialization, which contributes to wound healing [10].

Furthermore, as a neuromodulator, thalidomide may affect the type C unmyelinated fibers involved in the neural pathways of itch by dysregulating Wallerian degeneration [10]. This neuromodulatory function may explain thalidomide's efficacy in treating PN, although the exact pathomechanism is still unclear. There are numerous case reports, case series, single-arm trials, and a randomized controlled trial documenting the dramatic effect of thalidomide in treating PN, with success rates nearing 100% [10]. Daily dosing in the literature ranges from 15-300mg daily, with 50-100mg daily being most common [10-13].

Still, the use of thalidomide today is limited by its teratogenic and neuropathic side effects [10]. The most notorious side effects are its teratogenic effects, namely phocomelia; thalidomide must be avoided in women of childbearing ages. Risk of phocomelia is highest when thalidomide is taken in the first trimester and a single dose of 100mg has been associated with birth defects [11, 12]. In the United States, patients receiving thalidomide, as well as practitioners prescribing the medication, must be registered in the S.T.E.P.S. database (System for Thalidomide Registration and Prescribing Safety) to prevent fetal exposure. Women of childbearing age must agree to regular pregnancy testing while on the medication [14]. Other common side effects of thalidomide include constipation, fatigue, somnolence, dizziness, neuropathy, and change in mood [10-13]. These side effects may be dose dependent and risk of peripheral neuropathy has been shown to increase after a cumulative dosage of 50g or more, but there is some evidence that up to 50% of patient may see reversal of side effects once the medication is discontinued [11].

Conclusion

Thalidomide has shown great efficacy in treating itch and inflammation associated with multiple dermatologic conditions. As such, thalidomide should be considered as an antipruritic and anti-inflammatory agent for patients with certain refractory conditions, including PN. Thalidomide's adverse effects can be minimized with strict adherence to protocol, close monitoring via FDA-approved programs, and cessation of therapy as soon as abnormalities are observed [10]. It is important to consider thalidomide therapy for patients with PN who truly cannot obtain relief from conventional treatment.

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