Case Report

Management of Keloid-Associated Pruritus With Topical Crisaborole 2% Ointment: A Case Report

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Abstract

Introduction
The pathophysiology of keloid formation is poorly understood, and current treatments, including intralesional corticosteroids, cryotherapy, and surgery, are often associated with high resistance to treatment and recurrence. The multifactorial pathogenesis of keloid formation suggests that aberrant inflammatory cytokine signaling associated with keratinocyte dysregulation may contribute to keloid-associated pruritus.

Case Presentation
In this paper, we report 2 cases of keloid-associated pruritus that were successfully treated with topical crisaborole 2% ointment, a phosphodiesterase 4 (PDE4) inhibitor. Both patients had previously undergone multiple unsuccessful treatments before being treated with crisaborole 2% ointment. In both cases, the patients experienced complete relief of pruritus with no significant change in keloid size, thickness, or appearance.

Conclusion
We propose that PDE4 inhibitors, such as crisaborole, may be an effective therapy for keloid-associated pruritus.

Keywords
keloid; keloid/physiopathology; keloid/therapy; skin and connective tissue diseases; pathologic processes; fibrosis; pruritus; itching; phosphodiesterase 4 inhibitors; crisaborole

Introduction
Keloids are benign dermal fibroproliferative lesions often occurring at sites of trauma or spontaneously on normal skin. The pathophysiology of keloid formation is poorly understood, and this lack of understanding contributes to the varied treatment methodology in keloid management.[1] The complex abnormal tissue remodeling underlying keloid formation can cause pain, pruritus, and psychological distress. First-line treatment includes intralesional corticosteroids (ILCs), intralesional 5-fluorouracil, and cryotherapy. Surgical excision with adjuvant therapy can be considered for refractory keloids. Adjuvant therapies include radiation therapy, laser-based therapy, silicone gel sheeting, pressure therapy, and topical imiquimod 5% cream. All current interventions yield varying results and are associated with a high degree of resistance to treatment and recurrence.[2] There is a need for alternate approaches to keloid treatment. Herein, we describe 2 cases of keloid-associated pruritus successfully managed with topical crisaborole 2% ointment, a phosphodiesterase 4 (PDE4) inhibitor.

Case Presentation
Case 1
A 41-year-old woman presented with a 22-year history of spontaneous and trauma-induced keloids with associated daily severe pruritus and paresthesia. She complained of sleep-related scratching leading to excoriations, bleeding, and poor-quality sleep. She had no family

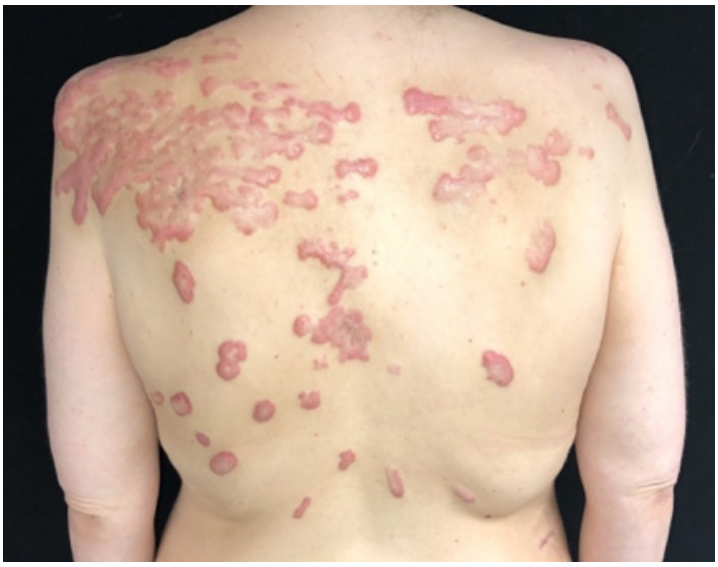

Figure 1. The back and upper left arm showed multiple erythematous smooth, rectangular keloidal nodules and plaques.

history of keloids and a personal history of atopic dermatitis and colon cancer. On exam, classic keloidal scarring was present on her back, chest, left upper extremity, and abdomen (**Figures 1** and **2**). Keloidal scarring was absent at the site of her port scar, which was treated with radiotherapy at insertion and removal. All other keloids recurred or persisted despite treatment by surgical excision, ILCs, and topical corticosteroids.

As all other interventions had been unsuccessful, a trial of crisaborole 2% ointment applied twice daily was initiated for pruritic keloids on her chest. After 1 week, she reported local improvement of pruritus, and treatment was extended to include all symptomatic keloids. At 7 weeks, she reported complete symptomatic relief of pruritus without significant change in keloid size, thickness, or appearance. Symptoms recurred when treatment was interrupted. She has continued to use crisaborole 2% ointment with ongoing control of symptoms.

Case 2

A 62-year-old woman presented with a severely

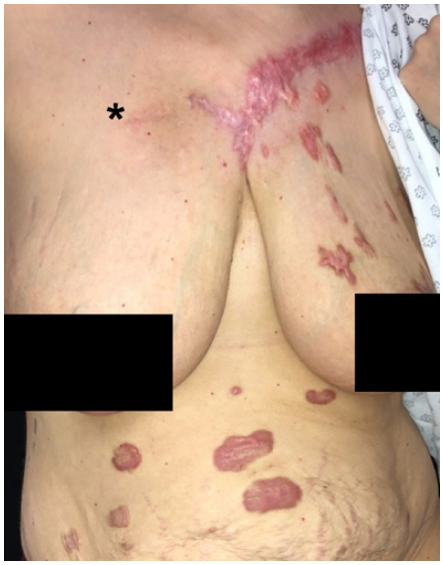

Figure 2. The upper left chest showed a linear keloidal plaque at the site of a prior surgical procedure. On the right upper chest at the site of a port placement is a linear scar without keloid formation (black asterisk). The port site was treated with radiotherapy at insertion and removal.

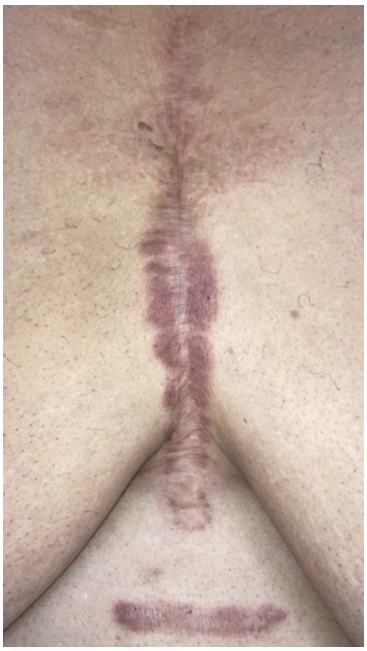

Figure 3. A severely pruritic keloid on the patient's chest secondary to midline sternotomy.

pruritic keloid on her chest, present for 6 years, secondary to midline sternotomy (**Figure 3**). She had no history of atopic dermatitis. Previous therapy with topical steroids and ILCs provided incomplete relief of pruritus, and continued scratching aggravated her symptoms. Based on the response of case 1, crisaborole 2% ointment was prescribed to be applied twice daily. At her follow-up visit 2 weeks later, she noted a complete resolution of pruritus and subjective improvement of erythema, without significant change in keloid thickness. Therapy with ILCs was initiated to address keloid thickness, and topical crisaborole was continued for symptomatic relief. She underwent 3 months of combination treatment with ILCs and crisaborole before she was lost to follow-up. She moved to another state and returned 1 year later, requesting refills. She stated pruritic symptoms returned 6 weeks after running out of crisaborole.

Discussion

Keloid pathogenesis remains poorly understood. While keloidal fibroblasts are presumed to be the primary cell responsible for keloid scar formation, research in keloid pathogenesis has expanded to include a spectrum of cells involved in the wound healing process. Paracrine signaling between epidermal keratinocytes and fibroblasts is an integral component in normal wound healing. Upon injury, inflammatory mediators are expressed by epidermal keratinocytes to promote collagen synthesis and extracellular matrix deposition by dermal fibroblasts. In vitro cultures of keloid keratinocytes with normal fibroblasts show increased expression of cytokines, growth factors for both cell types, and increased extracellular matrix deposition by normal fibroblasts.[3] These findings support keloid pathogenesis as a multifactorial process with other cells, such as keratinocytes or inflammatory cells, having a larger role than previously assumed.

Pruritus is a common symptom of keloid disease. Clinical pruritus can be nerve-related, skin-derived, psychogenic, or of mixed etiology. Mechanisms implicated in pruritus additionally involve communications between the nervous system and immune system.[4] Pruritus can be moderated by localized skin mediators, especially interleukins (ILs) associated with type 2 inflammation, such as IL-2, IL-4, IL-13, and IL-31. Keratinocytes contributed to the initiation of type 2 inflammation via the release of IL-25, IL-33, and thymic stromal lymphopoietin.[5] In keloid disease, aberrant inflammatory cytokine signaling associated with keratinocyte dysregulation may contribute to keloid-associated pruritus in addition to having a role in keloid scar formation. Thus, therapeutic strategies for the treatment of keloidal pruritus include the protection or repair of the skin (eg, silicone-based

therapies), treatment of neuropathic pruritus (eg, gabapentin), or attenuation of immune cell activity (eg, steroids, calcineurin inhibitors, PDE4 inhibitors).[4]

Topical crisaborole, a PDE4 inhibitor, ameliorated severe keloid-associated pruritus in our patients. Pentoxifylline, a nonspecific PDE inhibitor, was noted to have a similar, suspensive effect on pain, itch, and growth in refractory keloids.[6] Pentoxifylline inhibited the proliferation and collagen synthesis of keloid-derived fibroblasts in vitro. In a retrospective study, 6 months of postoperative treatment with ILCs and pentoxifylline significantly reduced keloid recurrence.[7] Although mechanisms for symptomatic relief of keloids using pentoxifylline or crisaborole are not established, elevations in cyclic adenosine monophosphate (cAMP) following PDE4 inhibition are associated with suppression of overactive immune responses—including IL-13.[8] Modulation of G-protein-coupled receptor-Gα, leading to decreased cAMP production in human keratinocytes and mouse skin in vitro, demonstrated epidermal hyperplasia and increased keratinocyte proliferation with reduced differentiation.[9] Thus, expression of cAMP-specific PDE4 in keratinocytes and fibroblasts offers a potential target for the treatment of symptomatic keloid disease. Based on the ability of crisaborole to down-regulate inflammatory markers associated with pruritus and its well-accepted safety profile, we elected to treat our patients' symptoms with crisaborole.[10]

Conclusion

Our cases are interesting as their keloid-associated pruritus had minimal to no response to topical and intralesional steroids; however, they reported clinically important responses to topical crisaborole. This report suggests topical crisaborole, a PDE4 inhibitor with no documented serious adverse effects, can be considered for off-label treatment of symptomatic keloids.[10] Given that current treatment options for keloid disease are limited and have variable efficacy, further studies for the use of crisaborole ointment in keloid disease are warranted.

Conflicts of Interest

The authors declare they have no conflicts of interest.

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