

# Treatment of a perforating dermatosis with apremilast



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**Key words:** apremilast; Down syndrome; elastosis perforans serpiginosa; perforating dermatosis; perforating folliculitis; phosphodiesterase 4 inhibitor.

## INTRODUCTION

Perforating dermatoses (PDs) are characterized by transepidermal elimination of dermal material. The 4 forms of PDs are as follows: acquired PD (includes Kyrle disease), reactive perforating collagenosis, perforating folliculitis (PF), and elastosis perforans serpiginosa (EPS).<sup>1</sup> EPS affects approximately 1% of patients with Down syndrome and manifests as asymptomatic, erythematous, 2- to 5-mm keratotic, umbilicated papules in annular, arcuate, or serpiginous configurations. However, there may be a clinical and histologic overlap among the PD entities. Multiple dermatoses, likely related to immunologic and genetic dysregulation, are associated with Down syndrome and may affect a single patient.<sup>2,3</sup> We present a case of a patient with Down syndrome with psoriasis, hidradenitis suppurativa (HS), and PD, whose PD responded dramatically to apremilast initiated for her psoriasis and HS.

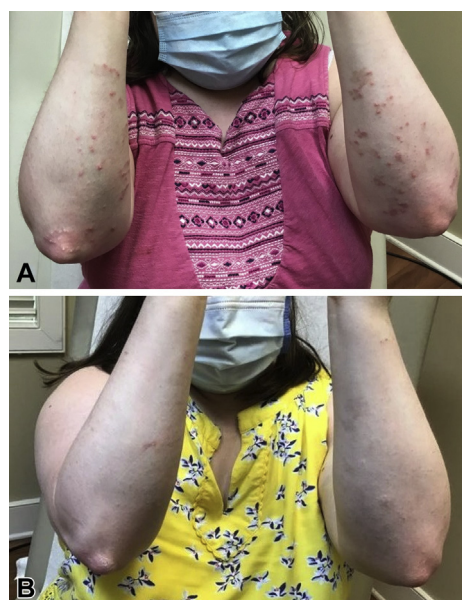
## CASE REPORT

A 29-year-old woman with Down syndrome presented to the dermatology clinic with psoriasis. Clobetasol ointment once daily, prescribed by her primary care physician, had improved plaques on her extremities and trunk. However, lesions on the ventral aspect of the forearms were her main concern and unresponsive to treatment. The ventral aspect of the forearms had numerous asymptomatic erythematous keratotic papules arranged in annular and arcuate patterns (Fig 1). Findings of the potassium hydroxide preparation test of the forearms were negative.

The patient also had erythematous papulonodules, scars, sinus tracts, and double-headed open

### Abbreviations used:

EPS:	elastosis perforans serpiginosa
HS:	hidradenitis suppurativa
PD:	perforating dermatoses
PDE4:	phosphodiesterase 4
PF:	perforating folliculitis



**Fig 1.** A, Perforating dermatosis on the ventral aspect of the forearms before and (B) after treatment with apremilast.

comedones of the axillae and groin, consistent with HS. She was prescribed benzoyl peroxide wash, clindamycin lotion, and oral doxycycline for HS.

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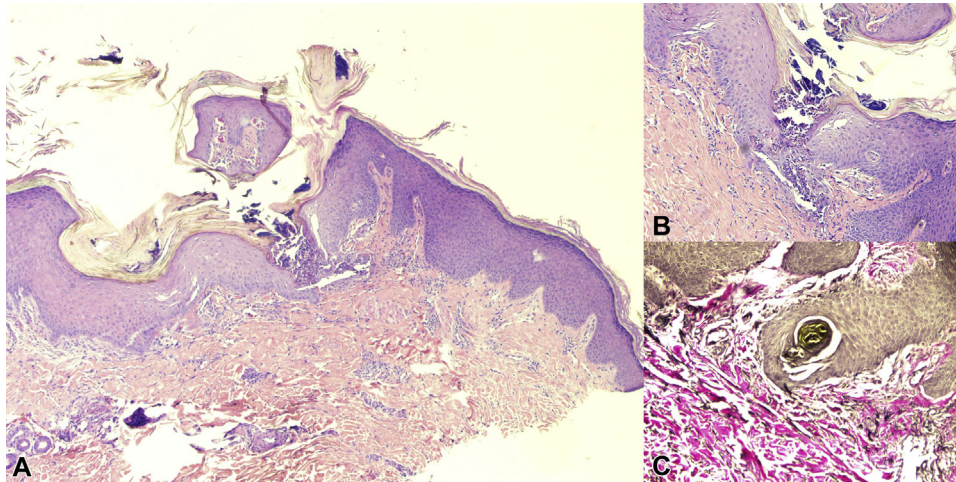
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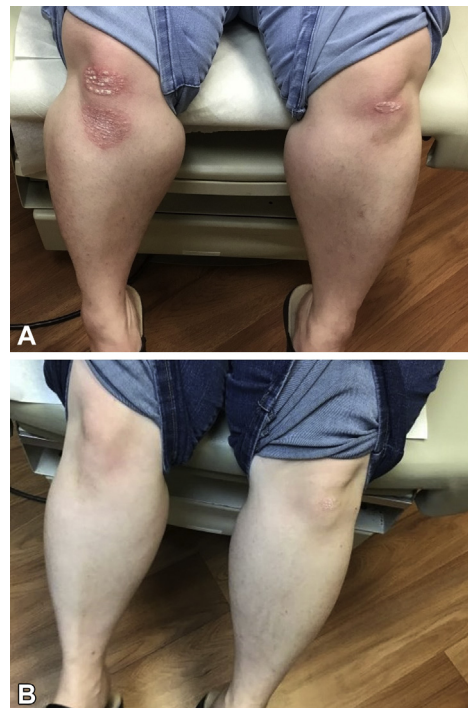
**Fig 2.** Skin biopsy. **A, B,** Dilated and invaginated follicular infundibulum with basophilic debris and a full-thickness epithelial defect. **C,** Histochemical stain for elastic fibers showing transepithelial elimination and accumulation of dermal elastic fibers. (**A and B,** Hematoxylin-eosin stain; original magnifications: **A,**  $\times 400$ ; **B,**  $\times 100$ ; **C,**  $\times 200$ .)

The dosage of clobetasol was increased from once to twice daily for psoriasis and the ventral aspect of the forearms, with the plan to add a keratolytic, if not improved at follow-up. At follow-up, HS and psoriasis were minimally improved, and forearms remained unchanged. Adherence to a topical regimen was challenging.

The clinical differential diagnosis of the forearm lesions included EPS versus partially-treated psoriasis. A 4-mm punch biopsy showed dilation of the follicular infundibulum filled with cornified cells and neutrophils. Occasional collagen fibers were present in the follicular space. Histochemical staining for elastic fibers showed elastotic fibers in the follicular epithelium (Fig 2). The histopathologic findings were interpreted to be consistent with PF. With a clinicopathologic correlation, the patient was diagnosed with PD with features of EPS and PF.

Treatment options for PD were discussed. The patient refused cryotherapy, tape stripping, and tazarotene gel. A laser was not available. She opted for no treatment, hoping for spontaneous resolution.

Given the limited improvement in psoriasis and HS, adalimumab was considered. However, she refused injections. Therefore, apremilast 30 mg twice daily was initiated. At the 3-month follow-up, her psoriasis had nearly cleared and HS was much improved. Surprisingly, PD had resolved (Fig 1). She continued apremilast without adverse effects. At her next 3-month follow-up, her psoriasis had resolved (Fig 3), HS was well-controlled, and PD had not recurred. She had self-discontinued her topical regimen.



**Fig 3.** **A,** Plaque psoriasis on the knees before and **(B)** after treatment with apremilast.

## DISCUSSION

The pathogenesis of PDs is not well elucidated. A dermal chronic inflammatory infiltrate containing lymphocytes, macrophages, and/or multinucleated giant cells has been found at sites of perforation in EPS. The local skin inflammation may induce perifollicular or intraepithelial tunnels through which abnormal elastic fibers are extruded.<sup>4</sup> Relevant to the

case of our patient, case reports on PF in the setting of psoriasis have been published.<sup>5</sup>

Apremilast is a small-molecule phosphodiesterase 4 (PDE4) inhibitor that has been approved by the US Food and Drug Administration for psoriatic arthritis, moderate-to-severe plaque psoriasis, and oral ulcers associated with Behçet disease. However, multiple studies suggest that apremilast may treat other dermatologic disorders. It has been used as an off-label medication for other subtypes of psoriasis, HS, atopic dermatitis, alopecia areata, cutaneous sarcoidosis, and various lichenoid and interface dermatoses.<sup>6</sup> Apremilast is orally administered, has a relatively safe adverse effect profile, and has no requirement for routine laboratory monitoring.

In contrast to biologics, apremilast affects the production of inflammatory mediators at the level of messenger RNA expression. Apremilast inhibits PDE4 specific for cyclic adenosine monophosphate, resulting in increased intracellular cyclic adenosine monophosphate levels and the regulation of numerous inflammatory mediators.<sup>7</sup>

PDE4 is widely expressed in macrophages, lymphocytes, and natural killer cells as well as non-hematopoietic cells such as keratinocytes. PDE4 inhibition inhibits the production of multiple proinflammatory cytokines, including interferon gamma, tumor necrosis factor- $\alpha$ , interleukin 12, interleukin 23, interleukin 12, interleukin 8, and interleukin 2, whereas upregulates the expression of the antiinflammatory cytokine interleukin 10.<sup>8,9</sup>

Apremilast also interferes with the production of leukotriene B<sub>4</sub>, nitric oxide synthase, and matrix metalloproteinase and reduces complex inflammatory processes, including epidermal skin thickening.<sup>9</sup> Leukotriene B<sub>4</sub> and interleukin 8 inhibit neutrophil chemotaxis.<sup>10</sup>

The mechanism of action of apremilast in perforating disorders may be related to its broad immunomodulatory effects leading to decreased local inflammation and perifollicular and/or intraepithelial tunnels through which abnormal elastic fibers could be secreted.

EPS may spontaneously resolve over several years. The spontaneous resolution of our patient's perforating disorder cannot be excluded, although it seems less likely, given the rapid resolution coinciding with the initiation of apremilast. Further study is needed to determine whether apremilast is an effective treatment for PF, EPS, and other perforating disorders.

#### Conflicts of interest

None disclosed.

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