Apremilast as an adjuvant therapy for calcinosis cutis

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INTRODUCTION

Calcinosis cutis is a form of dystrophic calcification wherein hydroxyapatite and amorphous calcium phosphate deposits form over damaged subcutaneous tissues despite normal serum Ca^{2+}, $PO4^{3-}$, and parathyroid hormone (PTH) levels.[1,2] When it is widespread, major morbidity from restricted movement and pain are the primary presenting symptoms. Treatments reported include calcium binders (minocycline), calcium channel blockers, surgical excision, lithotripsy, and the calciomimetic sodium thiosulfate in topical, intralesional, or systemic form.[3-5] Cutaneous calcification in these patients occurs due to damaged tissue releasing phosphate-binding proteins that bind serum phosphate, with subsequent precipitation of calcium salts in the tissue.[2] In this study, we review 2 patients with recalcitrant calcinosis cutis who responded to apremilast after not responding to multiple other modalities to help mobilize calcium.

Abbreviations used:

cAMP:	cyclic adenosine monophosphate
CREST:	calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia
IL:	interleukin
PDE-4:	phosphodiesterase 4
PTH:	parathyroid hormone
RA:	rheumatoid arthritis

CASE REPORT 1

A 66-year-old woman with a medical history of morphea, monoclonal gammopathy of undetermined significance, alopecia areata, osteoarthritis, diabetes, and hypertension, presented in 2016 with progressive calcinosis cutis within and beyond areas affected by the morphea of both lower legs (Fig 1). Her current treatments were methotrexate (25 mg/wk for 1 year), calcipotriene, and clobetasol ointments. Physical examination found confluent and nearly plate-like circumferential indurated plaques covering the lower half of both legs. Serum chemistries including Ca^{2+}, $PO4^{3-}$, and PTH were normal. Over the next year, treatments included daily topical sodium thiosulfate 25% w/v (topical in emollient base), pentoxifylline (oral), minocycline (oral), amlodipine (oral), percutaneous ultrasonic lithotripsy (30 treatments), and a series of 10 weekly injections of intralesional sodium thiosulfate (150 mg/mL × 5 mL/wk). There was minimal improvement over this time. She started on apremilast in 2017 and within 2 months began to notice improvement.

Over the next 3 to 6 months, she had had numerous pinpoint erosions with central jagged calcium fragments. Many of these required sharp surgical debridement to remove. Resulting ulcerations required several courses of oral antibiotics due to secondary infection. Apremilast was ultimately decreased to 30 mg once daily, but infections continued to occur. The confluent plaques progressively became more broken up with palpable spaces of normal skin intervening. Despite this clinical improvement, the patient noticed new areas of proximal calf induration. Apremilast was ultimately discontinued because of the recurrent infections within the ulcerated areas of calcification.

CASE REPORT 2

A 59-year-old woman with a medical history of CREST (calcinosis, Raynaud phenomenon,

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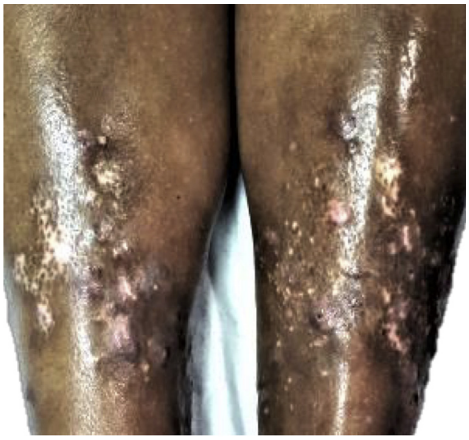

Fig 1. Calcinosis cutis. Patient's presentation of calcinosis cutis on the anterior distal leg at the start of apremilast therapy. Note the hyper- and hypopigmented patches consistent with repigmenting morphea.

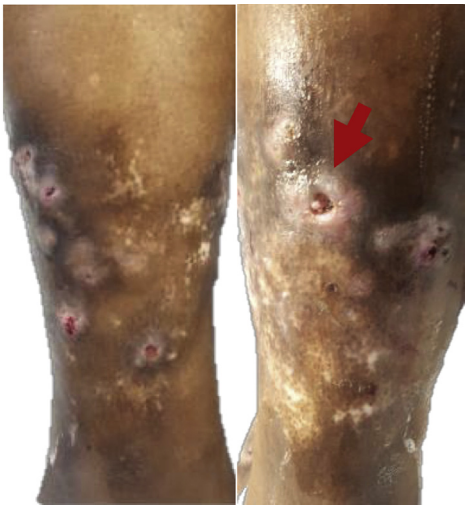

Fig 2. Calcinosis cutis. Patient's presentation after 16 months of apremilast therapy. Note the multiple ulcerations caused by calcium fragment transepidermal elimination.

esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome, rheumatoid arthritis (RA), stasis dermatitis, obesity, and venous ulcers presented in 2016 with generalized pain and diffuse plate-like induration of both lower extremities (Fig 2). She had been treated for 2 years with weekly methotrexate (25 mg subcutaneous) injections for her RA and CREST. Skin biopsy and radiograph confirmed widespread subcutaneous calcification, and there were no serum abnormalities of Ca^{2+}, $PO4^{3-}$, creatinine, or PTH. She was initially treated with sodium thiosulfate 25% w/v (topical in emollient base) and diltiazem (240 mg/d oral). Over the next 3 months, she noted many bumps and a recurrent ulcer on the right posterior calf, but no other change in the condition. Pentoxifylline and minocycline were added, and a series of subcutaneous sodium thiosulfate (150 mg/mL) injections led to some areas of softening and separation within the original confluent plaques of calcification. Apremilast was added for her RA in 2017, and she slowly had softening of the plates of calcifications and numerous pinpoint papules with central jagged calcium fragments being extruded. Sharp surgical debridement was required to facilitate removal of calcium fragments. She remains on apremilast with slow improvement, and calf ulcerations have healed. No infectious complications have been noted.

DISCUSSION

Apremilast is a phosphodiesterase 4 (PDE-4) inhibitor approved for the treatment of rheumatoid arthritis, psoriasis, and psoriatic arthritis.[6] Its mechanism of action involves reducing PDE-4, which acts to breakdown cyclic adenosine monophosphate (cAMP). Increased levels of cAMP downregulate numerous proinflammatory factors including tumor necrosis factor-α, interleukin (IL)-17, and IL-23 and upregulates the anti-inflammatory cytokine IL-10.[7] The mechanism of action of apremilast in patients with calcinosis cutis is unknown, but its ability to downregulate proinflammatory cytokines seems likely to be central. Elevated proinflammatory mediators have been implicated as a main cause of calcinosis cutis, possibly via chronic tissue damage and/or vascular hypoxia. This finding results in tissue fibrosis and increase $PO4^{3-}$ binding, which becomes a scaffold for calcification. Inflammatory cytokines such as tumor necrosis factor, IL-6, and IL-1β contribute to the formation of calcium salts in the tissue and are a driving force to the cutaneous manifestations of calcinosis cutis.[8]

Although these 2 patients represent anecdotal reports, an intriguing hypothetical mechanism is proposed. We look forward to future clinical trials of PDE-4 inhibitors in extensive calcinosis cutis to help elucidate these mechanisms.

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