Successful management of a severe case of chronic giant acquired reactive perforating collagenosis with allopurinol

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INTRODUCTION

Reactive perforating collagenosis is one of 4 perforating dermatoses in which biochemically altered collagen is extruded from the dermis. Lesions are often induced by superficial trauma and are present with underlying systemic disease, most commonly chronic kidney disease and type 2 diabetes mellitus (T2DM).[1] Clinically, it is a chronic condition distinguished by severely pruritic annular hyperkeratotic or ulcerated lesions, often located on the extremities. Here, we report successful treatment with allopurinol of a chronic and unusual presentation of the "giant" variant of acquired reactive perforating collagenosis (ARPC).

Abbreviations used:

AGE:	advanced glycation end
ARPC:	acquired reactive perforating collagenosis
GARPC:	giant acquired reactive perforating collagenosis
T2DM:	type 2 diabetes mellitus

CASE REPORT

A 77-year-old woman presented to the emergency room with a 5-month history of severe erosions of the gluteal cleft, crusting, and punched-out ulcerations of the buttocks, torso, and groin with sparse keratotic papules. She reported intense pruritus, burning, and oozing as the rash migrated from her buttocks to the proximal lower extremity and torso. She was confined to her bed due to extreme pain. The patient had not seen a primary care physician for several years.

Physical exam revealed erythematous and full thickness annular crateriform lesions 0.5-5.4 cm in diameter with purulent and sanguineous discharge (Fig 1, *A*). No bullae or vesiculation was observed. Koebnerization was evident by the coalescing lesions creating curvilinear patterns up to 9.5 cm in length along the buttocks and upper posterior extremities.

Histologic interpretation revealed an ulcerated specimen with a significant neutrophilic crust (Fig 2, *A*). Mixed dermal inflammatory infiltrate and dermal fibrosis were observed, however there was no evidence of vessel wall thickening. The vertical extrusion of degenerated basophilic collagen fibers through the reticular dermis and dense neutrophilic crust visualized by Van Gieson stain were consistent with a diagnosis of reactive perforating collagenosis (Fig 2, *B*).

Culture analysis reported the presence of *Cladosporium*, *Klebsiella pneumoniae*, and *Proteus*

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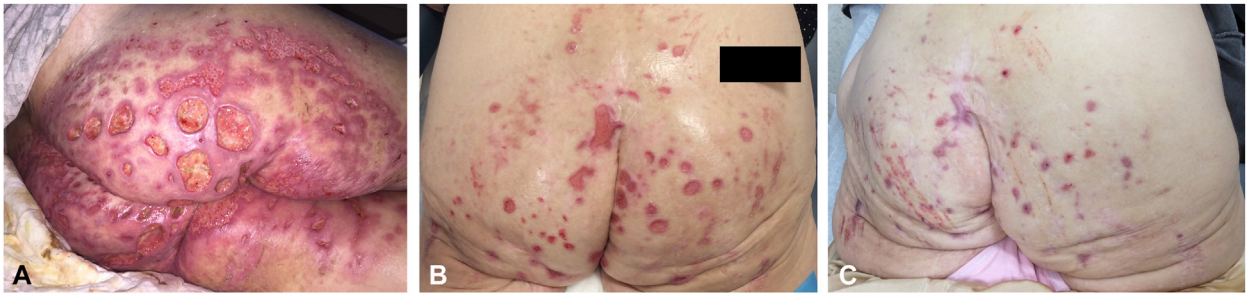

Fig 1. A, Giant acquired reactive perforating collagenosis: Large, erythematous ulcerations with purulent discharge in the gluteal region, gluteal cleft, and the posteromedial region of the thigh. **B,** Giant acquired reactive perforating collagenosis: Relapse of ulcers 3 years after initial presentation. **C,** Giant acquired reactive perforating collagenosis: Relapse, post 2 months with 100 mg daily allopurinol.

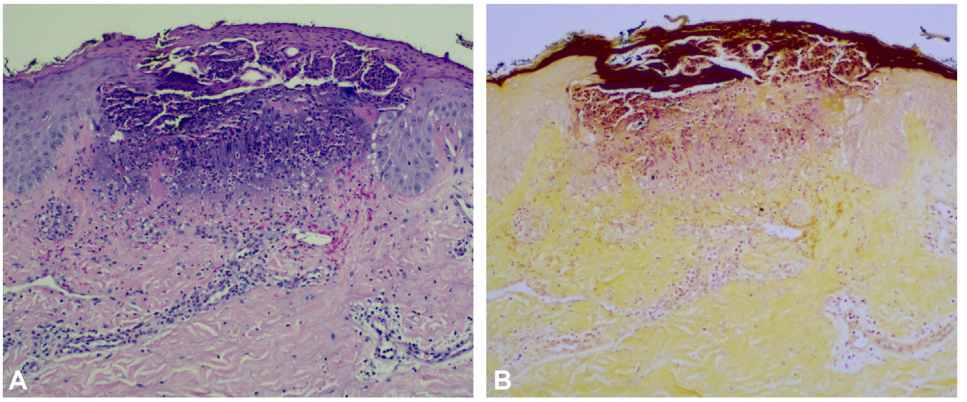

Fig 2. A, Histopathologic section of punch biopsy (H&E stain): Ulcer with neutrophilic crust, mixed superficial dermal inflammatory infiltrate, and dermal fibrosis. **B,** Histopathologic section of punch biopsy (Van Gieson's stain): Trans-epidermal elimination of altered collagen fibers into neutrophilic crust.

penneri species. Due to signs of symptomatic infection, we prescribed cephalexin 500 mg thrice daily for 3 weeks and hydroxyzine 25 mg twice daily for severe pruritus. Acitretin was started at 10 mg daily at week 1 and gradually increased to 40 mg daily by the 10th month. Topical treatment included mupirocin, gentamicin, and lidocaine ointment 5% to control infection and pruritus, respectively. We later prescribed 30 mg of oxycontin for severe pain.

Laboratory testing found elevated white blood cell of 12,600 per microliter, HbA1c of 7.2%, and a fasting glucose level of 114 mg/dL. Additionally, labs showed elevated cholesterol levels (237 mg/dL), elevated thyroid stimulating hormone (12.29 MCIU), and normal free thyroxine (0.96 ng/dL). No macro or microvascular complications of diabetes were observed. We referred the patient to primary care for management of uncontrolled T2DM and subclinical hypothyroidism, consequently beginning treatment with metformin 500 mg daily and levothyroxine 88 mcg daily.

Treatment of concomitant DM and hypothyroidism facilitated the accelerated closure of wounds, which began a year after starting treatment. After closure, the patient was prescribed a prophylactic low dose 20 mg acitretin daily. Though initial lesions significantly improved with oral retinoids, residual pruritus and resultant scratching prompted new, chronic lesions 3 years later (Fig 1, *B*). Acitretin was discontinued, and allopurinol 100 mg daily was started. After 2 months, the patient reported a significant reduction in pruritus, and no new lesions were observed (Fig 1, *C*).

DISCUSSION

Mehregan et al initially classified ARPC as a childhood perforating disorder in which structurally altered collagen is vertically extruded due to epidermal trauma.[2] Later recategorized as an adult-onset disease, early diagnostic criteria of the condition suggested 3 parameters: (1) transepidermal elimination of necrotic collagen tissue, (2) central

keratotic plug, and (3) disease onset after 18 years of age.[3] Giant acquired reactive perforating collagenosis (GARPC) is a larger variant within the class of transepithelial elimination disorders with unknown etiology. First identified by Hoque et al, GARPC is characterized by cup-shaped epidermal depressions or ulcers ranging from 1-3 cm in length.[4]

ARPC is most frequently documented with concomitant T2DM and chronic kidney disease, as well as other systemic pathologies including malignancies, hypothyroidism, liver disorders, neurodermatitis, AIDs, and malignant hypertension.[1,3,4]

The giant variant typically presents as large (>1 cm) crateriform lesions. Central adherent keratotic plugs, severe pruritus, and erythematous halos are characteristics of this condition. Our patient exhibited an atypical presentation of the "giant" variant of this disease, forming lesions without the presence of crusted plaques and central keratin plugs. Koebnerization due to intense pruritus may prompt neighboring crateriform lesions to coalesce into larger ulcers. Lesions often develop on the trunk or limbs, areas easily accessible by hand.[4]

The etiology of GARPC is unknown, however many theories have been posited for ARPC, tying superficial trauma of the skin to the elimination of biochemically altered type IV collagen fibers from the basement membrane. An early proposed mechanism for ARPC hypothesized that micro crystal-like deposits in the dermis biochemically altered collagen fibers. Scratching then causes microtrauma leading to the degradation of the basement membrane and transepidermal elimination of collagen fibers.[5]

Altered collagen may be induced by hypoxic states due to vessel wall thickening associated with diabetic microvasculopathy.[6] Furthermore, advanced glycation end (AGE) collagens, promoted by hyperglycemia and oxidative states, may promote the elimination of collagen. Keratinocytes cultured on AGE collagens displayed higher levels of differentiation markers.[7] This may promote the transepidermal elimination of attached collagen fibers by differentiating keratinocytes.

The effectiveness of allopurinol is proposed to stem from 2 potential mechanisms that reduce the synthesis of modified collagen. Allopurinol, a xanthine oxidase inhibitor, may decrease elevated uric acid levels correlated with T2DM, reducing crystal deposits within the dermis. Additionally, allopurinol reduces the production of free radicals, which may reduce the production of AGE collagens.[4] Allopurinol may act as a protective agent, preventing alteration and extrusion of dermal collagen.

Extracellular matrix components may alter tissue repair pathways in ARPC by promoting early keratinocyte differentiation, proliferation, and epithelial perforation. TGF-beta3 expression and fibronectin levels have been found to be elevated in dermal ARPC lesions, and may serve as markers of epithelial repair.[8,9]

While there is no agreed-upon standard of treatment for GARPC, the treatment of underlying systemic diseases has shown to be effective for treating RPC.[10] Oral and topical retinoid, narrow band ultraviolet B phototherapy, and allopurinol have been used with promising results for treating GARPC.[4,11,12] Treatment with allopurinol has shown to relieve pruritis, resolve current lesions, and prevent the development of new lesions within 2-4 months.[4] No side effects have been reported in the treatment of GARPC with allopurinol, and the rate of recurrence postallopurinol treatment is unknown. Topical steroids and oral antihistamines have been used with limited efficacy.[11] Behavior modification may limit scratching and the development of new lesions.

We present a rare and severe case of chronic GARPC in the presence of T2DM and hypothyroidism. Patients being treated with acitretin should be monitored for safety with long-term usage. Although the exact mechanism is unknown, allopurinol may provide patients with greater symptomatic relief and help them to achieve long-term remission. Symptomatic management and choice of treatment are integral to reducing pruritus, pain, inflammation, and consequent scratching behavior, all of which contribute to the chronic nature of this condition. The causes of GARPC remain unclear and warrant further research into its pathogenesis.

Conflicts of interest

None disclosed.

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