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CASE REPORT

Efficacy of Upadacitinib in the Treatment of Acquired Reactive Perforating Collagenosis in a Patient with Type 1 Diabetes: A Case Report and A Literature Review

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Abstract: Acquired reactive perforating collagenosis (ARPC) is a rare skin condition characterized by collagen loss through the epidermis. We report the first clinical use of the JAK inhibitor upadacitinib for treating ARPC in a 32-year-old woman with a 17-year history of type 1 diabetes, whose persistent pruritic lesions responded poorly to conventional treatments. The patient started a daily regimen of 15 mg upadacitinib and showed a rapid response within 2 weeks, with significant lesion flattening and no new eruptions. By week 4, her pruritus was fully resolved. By week 16, she transitioned to an every-other-day dosing schedule without adverse effects. This article reviews existing literature on JAK inhibitors in ARPC treatment, indicating favorable outcomes. However, given the characteristics of ARPC, sustained maintenance therapy with JAK inhibitors may be necessary. We also explore the potential role of the JAK-STAT signaling pathway in the pathogenesis of ARPC associated with different types of diabetes, suggesting that JAK inhibitors may offer new therapeutic options for diabetic patients with ARPC. The limitations of this article include a small sample size and a lack of cost-effectiveness analysis. Therefore, larger-scale studies are needed to validate the efficacy and safety of JAK inhibitors in the treatment of ARPC and to further investigate clinical differences among patients with various forms of diabetes complicated by ARPC.

Keywords: upadacitinib, treatment, acquired reactive perforating collagenosis, type 1 diabetes

Introduction

Acquired reactive perforating collagenosis (ARPC) is a perforating dermatosis characterized by the transepidermal elimination of degenerated collagen fibers.[1] The typical clinical presentation of ARPC includes umbilicated keratotic papules or dome-shaped lesions with central depressions (volcano-like),[2] most commonly occurring on the extremities and back, occasionally affecting the face and neck. Pruritus is a common symptom associated with RPC.[3] ARPC is frequently associated with various systemic diseases, with the most common comorbidities including diabetes mellitus, chronic renal failure (with or without dialysis), and hypertension.[4] The pathogenesis of ARPC has not been fully elucidated and likely involves multiple factors. Treatment primarily focuses on controlling systemic symptoms and alleviating pruritus, but current strategies lack standardization. Effective treatments reported include emollients, antihistamines, keratolytics, doxycycline, retinoids, corticosteroids, allopurinol, and ultraviolet B phototherapy,[5] but these have limited efficacy. In recent years, JAK inhibitors have shown significant efficacy in inflammatory skin diseases, offering a new treatment option for refractory ARPC. This article is the first to report the successful experience of upadacitinib treatment in a patient with ARPC associated with type 1 diabetes, and reviews the literature on JAK inhibitors for ARPC treatment, providing new therapeutic approaches and evidence to support clinical practice.

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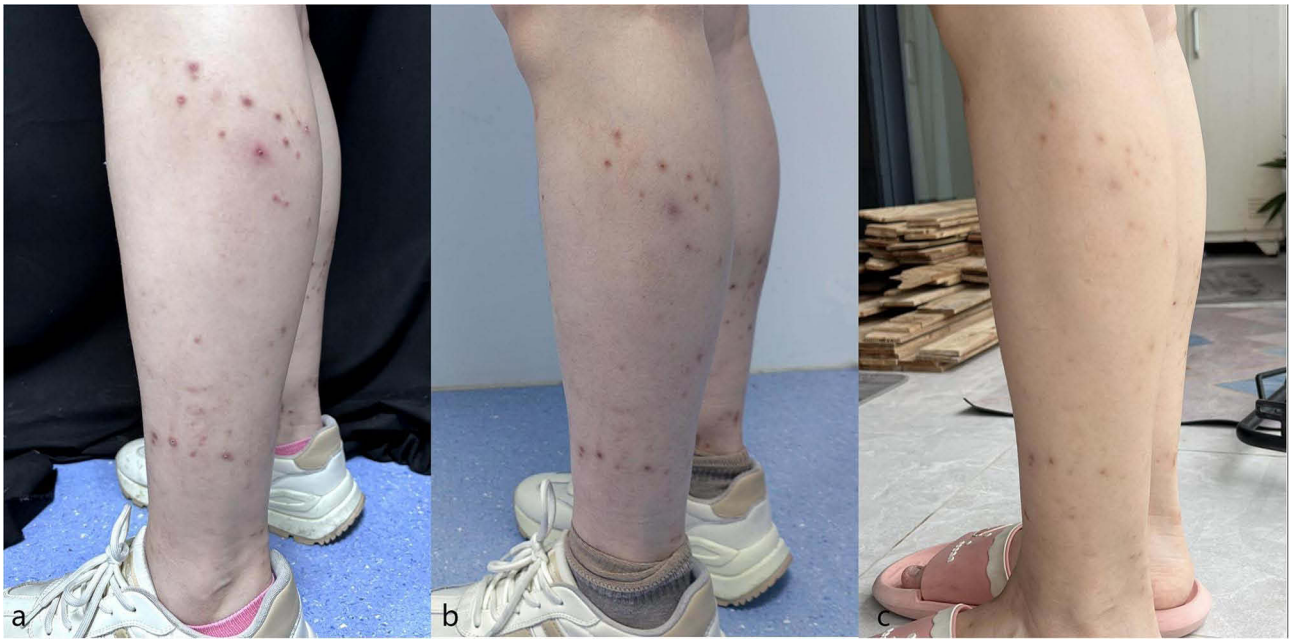

Figure 1 (**a**) Patient Skin Lesions. Before treatment, multiple erythemas, umbilicated papules, and nodules with central keratotic plugs and Koebner phenomenon were observed. (**b**) After 8 weeks of treatment, the rashes flattened, leaving post-inflammatory hyperpigmentation and cicatrices. (**c**) At the 16-week follow-up, the residual hyperpigmentation and scarring showed further improvement compared to the 8-week follow-up.

Case Report

A 32-year-old female presented in March 2024 with multiple pruritic erythematous patches, papules, and nodules on both upper and lower extremities for 2 years. The patient had received systemic anti-inflammatory medications, antihistamines, and topical corticosteroids for 6 months at our hospital with limited effects. Her medical history included a 17-year history of type 1 diabetes, complicated by diabetic peripheral neuropathy. She had no history of atopic dermatitis but had experienced allergic rhinitis since childhood. She was currently using insulin aspart (a rapid-acting insulin analog) to control blood glucose.

Laboratory investigations revealed mildly elevated glycated hemoglobin (6.7%) and elevated random urine microalbumin (30.60 mg/L). Other parameters were within normal limits, including complete blood count, inflammatory markers (high-sensitivity C-reactive protein, procalcitonin), liver function tests, renal function, tuberculosis screening, and hepatitis B and C screening. Physical examination revealed multiple erythematous lesions and umbilicated papules and nodules on the extremities, with central keratotic plugs (Figure 1a). Histopathological examination of a leg lesion revealed a cup-shaped depression in the epidermis containing keratin, necrotic cellular debris, and degenerated collagen, with perivascular lymphocytic infiltration in the dermis (Figure 2a). Van Gieson staining showed transepidermal elimination of degenerated collagen bundles (Figure 2b), confirming the diagnosis of ARPC.

After obtaining informed consent, the patient began treatment with upadacitinib 15mg once daily. After 2 weeks of treatment, most lesions had flattened. There were no new lesions, and pruritus had significantly improved. The Numerical Rating Scale (NRS) score decreased from 10 at baseline to 4 at week 2, and further to 0 at week 4. At the 8-week follow-up, only post-inflammatory hyperpigmentation and scarring remained in the affected areas (Figure 1b). During this visit, the patient reported experiencing pruritus after accidentally stopping the medication for one day, which resolved immediately after resuming treatment. At the 12-week follow-up, she continued treatment at the 15mg dose. At the 16-week follow-up, the residual hyperpigmentation and scarring showed more significant improvement compared to the 8-week follow-up (Figure 1c), prompting us to adjust the dosage to 15 mg every other day. As of the time of writing, the current dose has remained stable, with no new lesions developing and complete resolution of pruritus. Additionally, the patient's complete blood count, liver function, and renal function parameters have remained normal at 1-month and 3-month post-treatment evaluations.

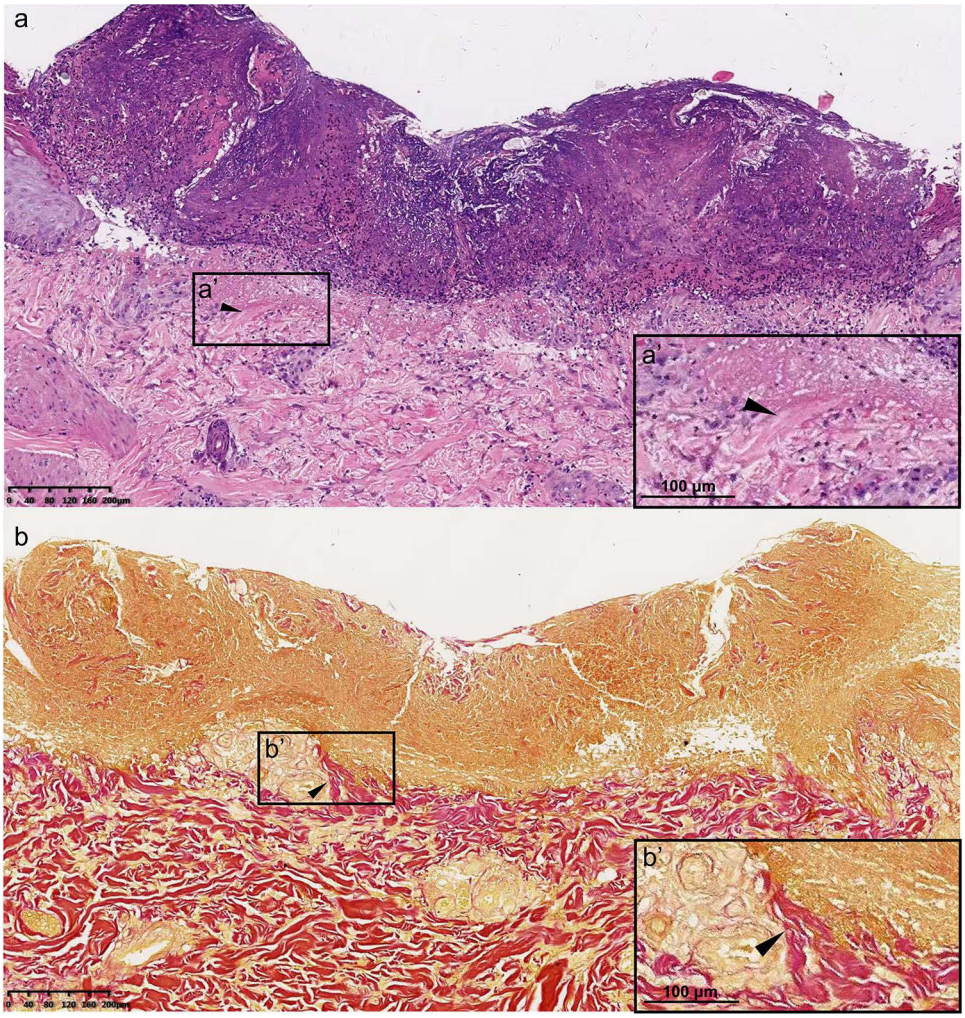

Figure 2 Histopathology. (**a**) Hematoxylin and eosin (H&E) staining demonstrates a cup-shaped epidermal depression containing abundant necrotic material and inflammatory cells, accompanied by necrotic basophilic collagen fibers penetrating the epidermis. Perivascular lymphocytic infiltration is observed in the dermis (×20). (a') Magnified view shows transepidermal elimination of collagen fibers. (**b**) Van Gieson staining reveals transepidermal elimination of red-stained collagen fibers (×20). (b') Magnified view.

Discussion

Previous studies have found that the pathogenesis of ARPC involves multiple factors, primarily mechanical injury (such as scratching), microvascular disease, and metabolic disorders.[1] Recent research indicates increased CD3+ T cell infiltration and upregulation of IL-4 and IL-13 expression in the dermis of ARPC lesions, suggesting that Th2-mediated immune responses are involved in its pathogenesis.[1] JAK inhibitors may alleviate ARPC by blocking the signaling pathways related to these Th2-mediated immune responses.[6]

In recent years, a few studies have reported experiences with JAK inhibitors in treating ARPC. According to Table 1, five patients with acquired reactive perforating collagenosis (ARPC) were treated with three different JAK inhibitors (upadacitinib, baricitinib, and tofacitinib). After the treatment, all cases reported improvements in both pruritus and skin lesions, indicating that JAK inhibitors may have a positive therapeutic effect on ARPC patients. Regarding safety, based on the current studies, JAK inhibitors seemingly demonstrated good tolerance. Only one patient experienced a mild increase in alanine aminotransferase (ALT) levels during treatment, but this returned to normal after 2 weeks. Notably, among the five cases, only one provided detailed information after stopping treatment. This patient experienced a recurrence after discontinuation but obtained symptom relief again upon restarting treatment.[7–10] This situation has also been observed in our patient during follow-up. These observations suggest that long-term maintenance therapy with

Table 1 Case Reports

Drug	Authors	Patient Profile	Treatment Protocol	Clinical Efficacy	Follow-up Outcomes
Upadacitinib	Ding et al[7]	Male, 63y T2DM (poor control) ARPC duration: 3 months	15 mg daily; Maintenance: 15 mg every other day (After 12 weeks);	Pruritus relief: 1 week; VAS score: 10→0 (4 weeks); Lesion resolution: 12 weeks;	Duration: 3 months; Status: no relapse; AE: mild ALT elevation (The 12th week) and returned to normal after 2 weeks;
Baricitinib	Zheng et al[8]	Female, 81y T2DM Coronary disease ARPC duration: 1 year	2 mg daily (8 weeks); 2 mg daily (After relapse);	Eruptions and itching; Complete clearance: 8 weeks; NRS score: 9→0;	Duration: variable; Status: relapsed after stop and relief after taking baricitinib; AE: none reported;
Tofacitinib	Yuan et al[9]	Female, 50y T2DM (15-year history) ARPC duration: 1 year	11 mg daily; 11 mg every other day (After 1 month); Maintenance: 5 mg every other day (After 9 months);	Pruritus relief: 5 days; VAS score: 10→0 (4 months); Lesion size reduction and erythema fading (4 months);	Duration: 9 months; Status: no relapse; AE: none reported;
Tofacitinib	Jiang et al[10]	Case 1: Male, 57y T2DM Dupilumab failure ARPC duration: none reported	5 mg twice daily	Rapid improvement of pruritus and skin lesions	Duration: 6 months; Status: without obvious relapse; AE: well tolerated;
		Case 2: Male, 65y T2DM, steroid failure ARPC duration: 2 year	5 mg twice daily	Significant improvement of pruritus and rash (1 week); Near-complete remission: 3 months;	Duration: 6 months; Status: no relapse; AE: well tolerated;

Abbreviations: T2DM, type 2 diabetes mellitus; VAS, Visual Analog Scale (0–10, higher = worse); NRS, Numeric Rating Scale (0–10); AE, adverse events; ALT, alanine aminotransferase.

JAK inhibitors may be necessary in the treatment of ARPC to reduce relapse risk. This could be closely related to the characteristics of ARPC as a chronic skin condition associated with immune dysregulation and other chronic systemic diseases.[1,4]

In the published literature, the vast majority of reported cases of diabetes mellitus-associated ARPC involve patients with type 2 diabetes, while literature on type 1 diabetes-associated ARPC is limited. Currently, no studies have systematically compared the clinical differences between ARPC associated with these two types of diabetes mellitus. Despite differences in etiology and pathogenesis between type 1 and type 2 diabetes, they may lead to ARPC through common terminal pathways. In a chronic hyperglycemic environment, advanced glycation end-products form and accumulate, then bind to their receptors, triggering multiple downstream signaling pathways, including the JAK-STAT pathway, thereby activating transcription factors such as NF-κB and STAT3. This process not only promotes inflammatory responses and oxidative stress but can also lead to structural changes in collagen proteins through non-enzymatic modification. These changes further contribute to microvascular dysfunction and tissue damage,[11] which may ultimately result in ARPC. Therefore, the JAK-STAT signaling pathway, as a key pathway in Th2 immune responses, may play an important role in the pathogenesis of diabetes-associated ARPC, indicating that therapeutic strategies targeting this pathway may provide new treatment options for patients with diabetes-associated ARPC.

While current literature suggests that the overall safety profile of JAK inhibitors appears favorable, long-term use still requires regular monitoring due to potential risks. Limitations of this article include being a single case report and lack of cost-effectiveness assessment. Future studies with larger sample sizes and exploration of other JAK inhibitors for the treatment of type 1 diabetes-associated ARPC are needed to further validate the effectiveness and safety of this treatment strategy. Additionally, further research could investigate whether there are differences in disease presentation, progression, and treatment response between the two types of diabetes patients with ARPC.

Conclusion

This study systematically reviews the literature on JAK inhibitors for the treatment of ARPC and presents a case of a patient with type 1 diabetes treated with upadacitinib. Although there are differences in the etiology and pathogenesis between type 1 and type 2 diabetes, the response to treatment in this patient was similar to that observed in patients with type 2 diabetes. This finding may support the hypothesis that the JAK-STAT pathway plays an important role in the pathophysiological processes of ARPC, regardless of diabetes type. While the current results are encouraging, further validation in larger cohorts is needed to confirm the efficacy and safety of JAK inhibitors for ARPC complicated by diabetes.

Ethics Statement

Institutional approval was not required for this case report according to our institutional guidelines.

Consent Statement

Written informed consent was obtained from the patient for publication of case details and images.

Disclosure

Authors declare no conflicts of interest in this work.

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