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CASE REPORT | INFLAMMATORY BOWEL DISEASE

Successful Treatment of Severe Pyoderma Gangrenosum and Ulcerative Colitis With Upadacitinib

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ABSTRACT

Pyoderma gangrenosum (PG) is a rare inflammatory and ulcerative skin disorder that is often associated with an underlying systemic disease, including inflammatory bowel disease. Many treatments used to treat inflammatory bowel disease are also used for the treatment of PG, including systemic therapies, immunomodulators, and tumor necrosis factor-α inhibitors; however, their efficacy in PG is limited. Novel treatments of PG are needed. We report the case of a 62-year-old woman with steroid-refractory PG and concomitant ulcerative colitis successfully treated for both conditions with upadacitinib, a selective Janus kinase inhibitor.

KEYWORDS: pyoderma gangrenosum; ulcerative colitis; upadacitinib

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the bowel, which includes Crohn's disease and ulcerative colitis (UC). IBD requires close monitoring of disease activity through clinical symptoms, biochemical markers such as C-reactive protein (CRP) and fecal calprotectin, imaging (such as intestinal ultrasound [IUS]), and endoscopy.[1] Treatment of IBD includes corticosteroids, immunomodulators, and an expanding array of advanced therapies that include biologics and synthetic small molecules, such as Janus kinase (JAK) inhibitors.[2]

IBD is frequently accompanied by extraintestinal manifestations thought to be driven by overlapping inflammatory pathways or environmental triggers. Pyoderma gangrenosum (PG) manifests as extremely painful inflammatory and ulcerative skin lesions resulting from increased inflammatory cytokines and neutrophil migration.[3] Concomitant IBD is seen in approximately 50% of patients with PG, whereas 0.4%–2.6% of patients with IBD may develop PG.[4] Given the low incidence and complex diagnosis of PG, evidence-based treatment is currently limited. However, a recent Delphi consensus proposed specific diagnostic criteria (Table 1).[5]

Steroids, cyclosporine, and infliximab (IFX)—which are also used in UC—are the only treatments that have been shown to be efficacious for PG in randomized controlled trials.[6,7] Although topical steroids are often attempted, high-dose oral corticosteroids are currently recommended as first-line.[3] If no improvement is seen, then immunosuppressants and biologics are commonly used as adjunct therapy.[3] Other IBD medications that have also been used in PG include azathioprine, mycophenolate mofetil, adalimumab, and ustekinumab.[8-11] Case reports have suggested the efficacy of JAK inhibitors to treat PG in the setting of UC or axial spondyloarthropathy, but we report the first case demonstrating the speed of onset and efficacy of monotherapy of upadacitinib (UPA) in the treatment of both steroid-refractory PG and UC.[12,13]

CASE REPORT

We present the case of a 62-year-old nonsmoking woman with UC who presented with severely active colitis and pain caused by lower limb multifocal PG. She had been diagnosed with PG 1 year prior, with skin biopsy findings of epidermal hyperplasia with underlying dense neutrophilic inflammation. She was previously treated with systemic glucocorticoids, oral cyclosporine 4 mg/kg, and topical triamcinolone 0.1% with initial partial improvement, but further treatment was limited by acute kidney injury. Owing to

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Table 1. Meeting 1 major criterion and 4 of 8 minor criteria has a high sensitivity and specificity for a diagnosis of PG[5]

Diagnostic criteria for PG	
Major criterion (1)	**Minor criteria (8)**
Tissue biopsy shows neutrophilic infiltrate	Exclusion of infection Pathergy History of IBD or inflammatory arthritis History of a sentinel lesion within 4 d of the ulcer's appearance Peripheral erythema and tenderness at the ulcer Multiple ulcerations and ≥1 on the anterior lower leg "Wrinkled paper" scars at healed ulcer sites Decreased ulcer size within 1 mo of starting immunosuppression

IBD, inflammatory bowel disease; PG, pyoderma gangrenosum.

recurrent pain, glucocorticoids were restarted, along with IFX 5 mg/kg every 8 weeks. Although she had improvement of her leg ulcer, she developed new nodules on her right ankle confirmed to be additional PG lesions. Treatment was complicated by worsening congestive heart failure, and IFX was discontinued. The patient subsequently experienced worsening pain and ulcer drainage, requiring inpatient admission.

She had been diagnosed with left-sided UC 5 years prior, previously treated with mesalamine. She was not on any advanced IBD-directed therapy. A colonoscopy completed 1 month prior showed Mayo endoscopic score 2 disease to the descending colon (Figure 2). At the time of her admission, she had a high frequency of bloody diarrhea, bowel urgency, and multiple nocturnal awakenings.

Her initial CRP was 36 mg/L (normal <5 mg/L), and she had extensive involvement of her right lower extremity from her PG (Figure 1). IUS showed mild inflammation in the sigmoid and descending colon, characterized by an increase in bowel wall thickness of 3.9 mm (normal <3 mm) and hyperemia (modified Limberg score of 1) (Figure 2).

She received intravenous corticosteroids; however, this was deemed ineffective for both her skin and her bowel. Inpatient UPA was initiated, given its rapid pharmacokinetics and use as an induction and maintenance medication for UC. We initially used a dose of 30 mg orally daily due to decreased renal function until her kidney function normalized, and the dose was increased to the full induction dose of 45 mg. By day 3 of UPA, she had resolution of her bowel symptoms and improvement in her PG-related pain; IUS confirmed dramatic improvement, with normalization of her bowel wall thickness and no hyperemia, correlating with improvement in her diarrhea. After 7 days, CRP had decreased to 9 mg/L. She was discharged off of corticosteroids, and with additional PG therapy of topical triamcinolone and wound care.

After the standard 8 weeks of UPA 45 mg induction, she transitioned to standard maintenance dosing of 30 mg. At month 3 after UPA initiation, she had achieved stable clinical remission from her UC (normal stool frequency, no rectal bleeding, and no bowel urgency), and her PG was significantly healed without any drainage or associated pain (Figure 1).

DISCUSSION

We demonstrate the effectiveness of a selective JAK-1 inhibitor, UPA, in the treatment of steroid-refractory UC complicated by severe PG.

In PG, JAK-1/2/3 and its downstream targets STAT1-6 are overexpressed.[3] JAK inhibitors thus present as interesting pharmacotherapeutic agents for treatment. Tofacitinib (a nonselective JAK inhibitor), ruxolitinib (JAK-1/2 inhibitor), and UPA (JAK-1 inhibitor) have successfully treated PG in a handful of reported cases.[14,15] UPA 15 mg daily has been used to treat concomitant steroid-refractory PG and spondyloarthritis; the patient reached remission within 12 weeks of starting treatment.[13] A combination of biweekly monocyte adsorptive apheresis and UPA 45 mg daily that was later reduced to 30 mg due to anemia was also used for steroid-refractory UC and PG in a patient who experienced improvement within 10 weeks.[12] Our patient achieved clinical remission of both conditions with UPA 45 mg alone.

JAK inhibitors have a quick onset of action because they are rapidly absorbed after oral intake.[16] In clinical trials and real-world studies of UPA for the treatment of UC, the patients who responded to UPA did so within 2 weeks.[17,18] The most common adverse events associated with UPA include acne, nasopharyngitis, creatine kinase elevation, and a higher risk of cytomegalovirus and herpes zoster virus infections.[17] Therefore, patients are counselled to obtain the inactivated version of the herpes zoster vaccine before or at the start of treatment

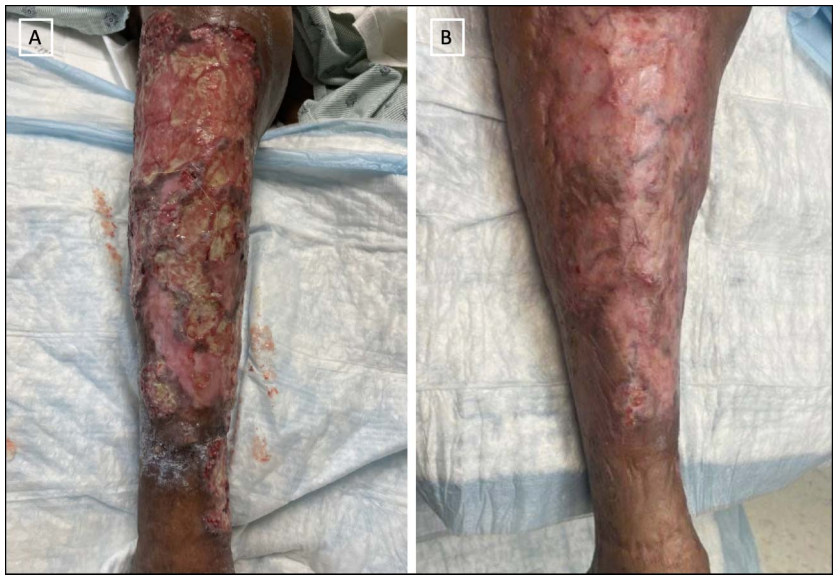

Figure 1. Appearance of the pyoderma gangrenosum-affected lower limb at the time of admission to hospital (A). Appearance of the same limb 3 months after upadacitinib initiation (B).

initiation. Though the incidence of venous thromboembolism was found to be higher with tofacitinib compared with tumor necrosis factor-β inhibitors in a phase 4 study, this has not been observed in patients with IBD or with UPA.[19,20]

Given the advantages of UPA therapy in IBD and the successful treatment seen in this case, we recommend future studies exploring the clinical and mechanistic benefits of this treatment for PG.

DISCLOSURES

Author contributions: S. Park, J. St. Pierre, and DT Rubin drafted the manuscript. All authors analyzed and interpreted

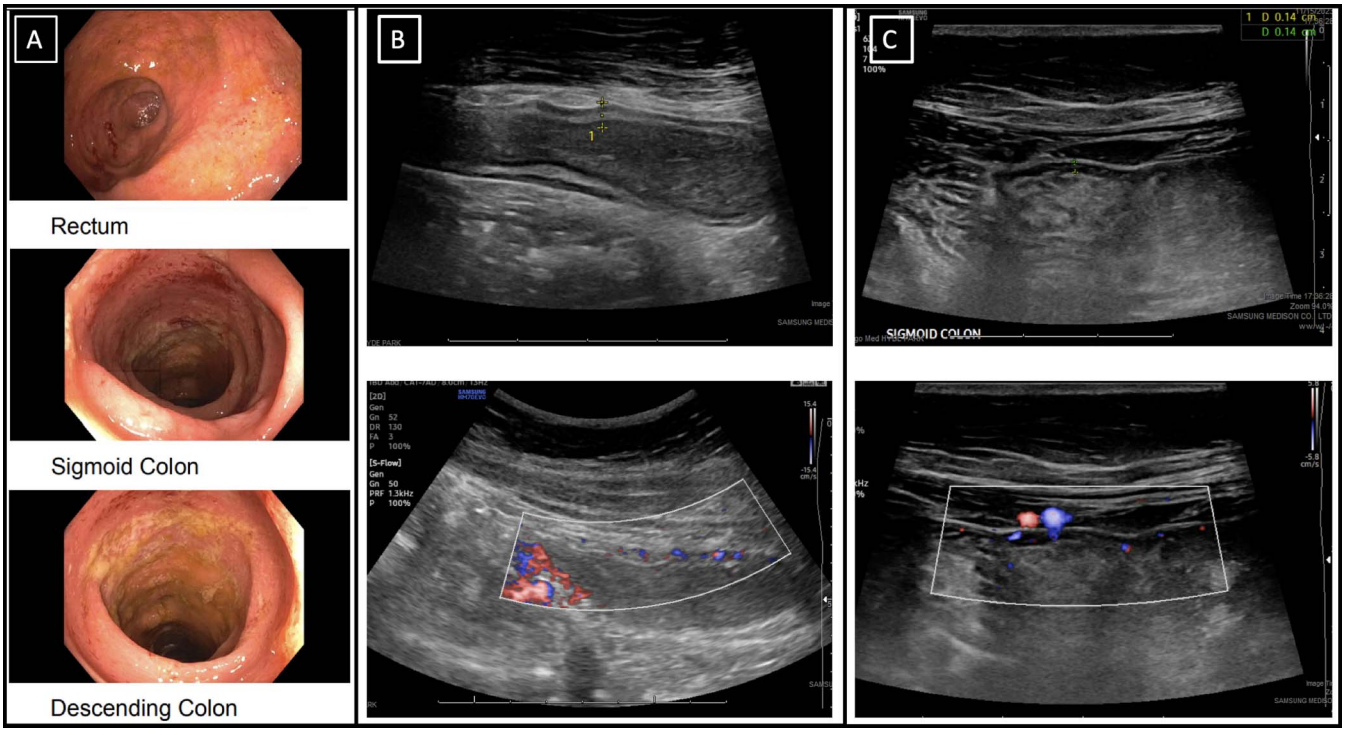

Figure 2. Baseline colonoscopy before UPA (A). IUS (intestinal ultrasound) before UPA showing increased bowel wall thickness and hyperemia consistent with inflammation (B). IUS at day 3 of UPA with improved bowel wall thickness and hyperemia (C). UPA, upadacitinib.

the data. All authors critically revised the manuscript for intellectual content. All authors approved the final version of the manuscript. DT Rubin is the article guarantor.

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Informed consent was obtained for this case report.

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