

Atypical COVID-19–related erythema nodosum in a patient with ulcerative colitis treated with upadacitinib

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Ulcerative colitis (UC) is an inflammatory bowel disease primarily affecting the large intestine. It is characterized by mucosal inflammation, with recurring episodes of flare-ups and remission. In recent years, a dynamic development in the therapeutic possibilities of UC has been observed. The approval of upadacitinib, an orally administered selective Janus kinase 1 inhibitor, has opened new opportunities for UC patients who do not respond to conventional medications and/or biologic agents.¹

A 28-year-old woman, diagnosed with left-sided UC in 2019, was hospitalized in November 2022 due to another disease flare. The patient experienced an unfavorable, steroid-dependent disease course, with multiple ineffective prior treatment attempts, including mesalamine, azathioprine, infliximab, vedolizumab, and ustekinumab.

On admission, she reported bloody diarrhea and fatigue. Physical examination indicated abdominal tenderness, tachycardia, and erythema nodosum on the right shin. Colonoscopy and laboratory tests confirmed severely active disease (FIGURE 1A). The patient declined surgical treatment and was subsequently administered upadacitinib at a dose of 45 mg daily. Just 2 days after initiating the treatment, clinical improvement was observed, with bowel movements gradually decreasing. After 8 weeks the dose was reduced to 30 mg daily, and remission was maintained over the next 2 months.

After 2.5 months of the treatment, the patient's husband was diagnosed with SARS-CoV-2 infection, and subsequently, our patient tested positive for COVID-19, although she did not have any respiratory symptoms. A week later, sudden pain, redness, and swelling appeared on her left shin and in the periankle region. Venous

Doppler ultrasound examination showed no signs of thrombosis. Another week later, similar symptoms appeared on the right lower extremity, limiting the patient's mobility (FIGURE 1B and 1C). Since the patient was in full UC clinical remission and a possible drug-induced adverse event was suspected, discontinuation of upadacitinib was advised. However, the skin lesions did not resolve, and the patient experienced a rapid severe flare of UC, resulting in another hospitalization. Repeated radiologic assessments of the lower extremities did not show any signs of venous thrombosis or arthritis. After multidisciplinary discussions, including a dermatological consultation, a diagnosis of COVID-19–related atypical erythema nodosum was established. Steroid therapy was initiated, and it was decided to continue upadacitinib at a dose of 30 mg. All symptoms gradually subsided, and UC remission was achieved.

Currently, after 7 months, the patient is in a sustained full clinical remission, with normal fecal calprotectin and serum C-reactive protein levels, no anemia, and healing of all ulcerations and erosions on colonoscopy (FIGURE 1D). She has resumed her professional activities.

To the best of our knowledge, this is the first case of COVID-19 in a patient with UC treated with upadacitinib.^{2,3} The COVID-19 course was benign, with a suspected extremely rare skin manifestation. The atypical erythema nodosum seemed to be secondary to SARS-CoV-2 infection, as the patient was in UC remission. However, the possible impact of upadacitinib—an immunomodulatory therapeutic molecule—on the atypical COVID-19 manifestation cannot be excluded.⁴ Additionally, our case reveals the rapidity of action and potent anti-inflammatory effects of upadacitinib in severe UC not responding to multiple targeted therapies.

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FIGURE 1 **A** – intraoperative image during colonoscopy performed before starting upadacitinib treatment, showing active colonic inflammatory lesions with multiple ulcerations and mucosal granularity corresponding to Mayo 3 endoscopic activity of ulcerative colitis; **B, C** – atypical erythema nodosum on lower extremities of a suspected etiology related to COVID-19; **D** – endoscopic remission of ulcerative colitis (Mayo 0) with complete healing of all ulcerations after 11 months of treatment with upadacitinib

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