The efficacy and safety of upadacitinib in the treatment of paradoxical amicrobial pustulosis and alopecia induced by infliximab in a patient with Crohn disease

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INTRODUCTION

Crohn disease (CD) is an immunologically mediated inflammatory gastrointestinal condition that can involve any region of the gastrointestinal tract. Pathogenesis derives from the interaction between the environmental factor, susceptibility genes, the immune system, and the microbiome. Chronic microscopic inflammation plays an important role in maintaining the disease active.[1]

Monoclonal antibodies have revolutionized treatment of this disease. Approved by US Food and Drug Administration in 1998, infliximab treats moderate to severe CD, ulcerative colitis, and other chronic inflammatory conditions by targeting soluble and transmembrane tumor necrosis factor (TNF), a key proinflammatory cytokine involved in mucosal immune dysregulation.[2,3] Despite its clinical benefit, infliximab may lead to possible adverse effects. An increased risk of de novo onset of neutrophilic dermatosis in patients with inflammatory bowel disease (IBD) has been recently demonstrated. This is due to a paradoxical skin reaction to treatment with TNF inhibitors.[4]

Abbreviations used:

APF: amicrobial pustulosis of the folds
CD: Crohn disease
IBD: inflammatory bowel disease
TNF: tumor necrosis factor

We report a case of a young female patient affected by CD, treated with infliximab, who experienced a diffused amicrobial pustulosis at the folds level with a great area of a nonscarring alopecia on the scalp.

Owing to the patient's condition, we proposed her to start a new therapy with upadacitinib, which had completely resolved the skin lesions with a good safety profile.

CASE REPORT

A 28-year-old woman, with a 2-year history of ileo-colonic, non-stricturing, non-penetrating CD with perianal involvement, came to our clinic in June 2024 with dermatologic complications. She had

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IRB approval status: Institutional review board approval was exempted as the study protocol did not deviate from standard clinical practice. The patient received upadacitinib as in good clinical practice, in accordance with guidelines. The patient provided written consent for retrospective study of data collected during routine clinical practice (demographics and clinical scores). The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Data collection and handling complied with applicable laws, regulations, and guidance regarding patient protection, including patient privacy.

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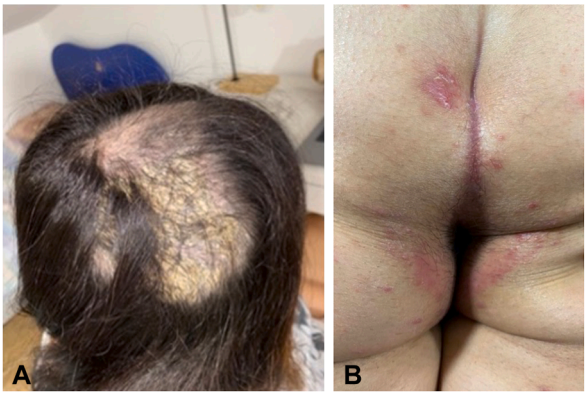

Fig 1. A, Scalp lesions before treatment with upadacitinib. **B,** Ano-genital lesions before treatment with upadacitinib.

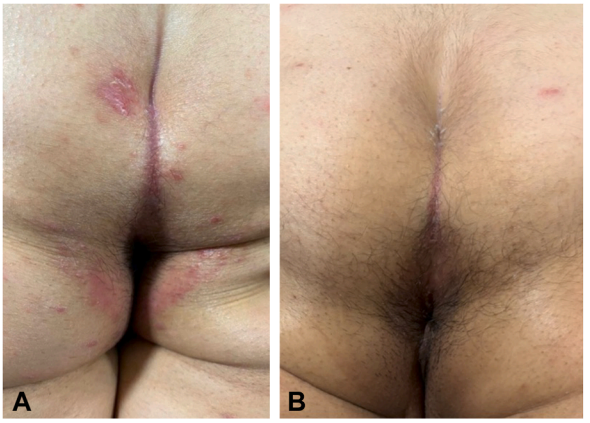

Fig 2. A, Scalp after 16 weeks of treatment with upadacitinib. **B,** Ano-genital area after 16 weeks of treatment with upadacitinib.

no history of smoking or alcohol consumption and no other comorbidities.

CD was diagnosed in July 2022 and clinical onset was characterized by chronic diarrhea and abdominal pain, low-grade fever and anal pain. An enteromagnetic resonance imaging and colonoscopy were performed allowing a diagnosis of ileo-colonic CD. Segmental intestinal biopsies from the ileum and the colon were compatible with the diagnosis of CD, showing crypt architectural distortion, inflammatory infiltrate composed of lymphocytes and plasma cells, presence of granulomas, and fibrosis involving the submucosa. The blood peripheral analysis indicated chronic intestinal inflammation, supported by both elevated inflammatory markers and high levels of fecal calprotectin.

The patient started therapy with infliximab in November 2022 achieving stable clinical remission until the end of 2023, when clinical signs of keratoconjunctivitis, otitis media, and inflammatory dermatosis appeared.

As reported by the patient, the first clinical appearance of cutaneous manifestations started in December 2023 with diffuse pustular eruptions in the armpits, groin, neck, scalp, and ear fold. On the scalp had concomitant nonscarring alopecia.

A consultant dermatologist prescribed to the patient oral methylprednisolone at a dosage of 32 mg per day (0.5 mg/kg/d). After an initial clinical improvement, a severe worsening of scalp involvement with progressive alopecia was observed in March 2024.

The patient came to our observation showing widespread pustules in the submammary folds, external auditory canal, and in ano-genital area. From the vertex of the scalp to the anterior region there was an extensive area of pustulosis and concomitant alopecia (Fig 1, *A, B*).

A comprehensive screening for infectious diseases was performed, which included taking skin swabs from affected areas; however, these swabs yielded a negative result for any infection.

Considering the global skin clinical presentation, the diagnosis was consistent with an amicrobial pustulosis of the folds (APF). Considering the skin condition and the bowel disease, we proposed to the patient to start the treatment with oral upadacitinib at dosage of 15 mg per day.

Two months later the patient experienced a complete clinical resolution of the skin lesions with sustained hair regrowth (Fig 2, *A*, *B*).

DISCUSSION

Extraintestinal manifestations could be present in up to 40% of cases of IBD.[5] Cutaneous dermatosis, which share a common pathogenetic pathway, are frequent and may occur in 22% to 75% of patients with CD[6] and in 5% to 11% of patients with ulcerative colitis.[7] Although TNF-α inhibitors have revolutionized CD treatment, inflammatory skin conditions occur twice as often with them than with other therapies. Common skin adverse reactions include paradoxical psoriasis, alopecia, lichen, and sterile pustulosis. Infliximab is the drug most frequently associated with alopecia.[8,9]

Autoinflammatory neutrophilic dermatosis has been very rare in patients with IBD treated with TNF-α inhibitors. Marzano et al[9] described 3 cases of APF under treatment with infliximab and adalimumab.

APF is a chronic neutrophilic dermatosis that presents sterile pustular lesions involving major skinfolds, the ano-genital region, and the scalp, and seems to almost exclusively affect young women.[9]

The autoinflammatory pathogenesis of anti-TNF-α induced APF, in the context of IBD, is well established.[10]

This clinical overlap is biologically plausible, as TNF-α blockade can lead to upregulation of interferon alfa, produced by plasmacytoid dendritic cells, which plays a key role in neutrophil recruitment and chemotaxis.[11]

Lewandowski et al[12] identified risk factors for APF identifying factors such as smoking, higher body mass index, small bowel lesions in CD and duration of treatment.

In our case report, the patient experienced a severe pustular dermatosis with associated severe alopecia after infliximab administration, suggesting a drug-induced cutaneous adverse reaction.

Clinical improvement observed in our patient, after discontinuation of infliximab and initiation of Janus kinase inhibitor treatment, highlights the reversibility of these immune-mediated pathways. By modulating cytokine signaling, neutrophil recruitment and activation, we observed resolution of pustular lesions and recovery of hair growth. In this patient, targeting the Janus kinase-signal transducers and activators of transcription pathway with upadacitinib, likely had contributed to concurrent improvement of both intestinal inflammation and APF.

This case underlines the mechanistic interplay between CD and autoinflammatory cutaneous manifestations, suggesting that effective management may depend on addressing the underlying immune dysregulation, rather than focusing on individual pharmacological agent.

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Conflicts of interest

Prof. Campione has received consulting fees, honoraria, and support for attending meetings from UCB, Almirall, Bristol Myers Squibb, Amgen, and LEO Pharma. Dr Bianchi has received consulting fees, honoraria, and support for attending meetings from UCB, Novartis, and AbbVie. The other authors have no conflicts of interest to declare.

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