Refractory metastatic Crohn's disease responsive to ustekinumab dose intensification

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INTRODUCTION

Crohn's disease (CD) is often associated with extraintestinal manifestations, affecting up to 43% of patients in cohort studies.[1] Metastatic CD (MCD) is an uncommon manifestation of CD characterized by noncaseating granulomas at sites anatomically distinct from the gastrointestinal tract.[2] In this article, we present a case of a woman with refractory metastatic Crohn's disease with persistent fissuring abdominal and inguinal lesions and gluteal infiltrative nodules and plaques whose disease was responsive to ustekinumab dose–intensification.

Abbreviations used:

CD:	Crohn's disease
MCD:	Metastatic Crohn's disease
TNF:	tumor necrosis factor
UST:	ustekinumab

CASE REPORT

A 35-year-old woman with a 20-year history of CD presented with indurated skin lesions and chronic skin fissures. She had undergone a total abdominal colectomy with end ileostomy and completion proctectomy 7 years earlier. She had not received therapy for gastrointestinal CD since that time, and the intestinal disease was quiescent. She presented with persistent biopsy-confirmed CD skin lesions of >10 years of duration. There were pink-red linear fissures along the mons pubis at the incision sites of 2 previous Cesarean sections and a colectomy (Fig 1, *A*), as well as along the superior gluteal cleft. Pebbly erythematous papules coalescing into plaques were present on the medial buttocks. In addition, there was erythema along the outer labia.

Previous vaginal labial, vulvar, and buttock biopsy results from 5 years earlier had revealed nonnecrotizing granulomatous change consistent with MCD. The patient reported the lesions to be nonresolving with silver sulfadiazine cream; several months of oral metronidazole and ciprofloxacin; rifaximin and/or rifabutin; topical, intralesional, and oral corticosteroids; topical calcineurin inhibitors; and infliximab. Adalimumab had been trialed but discontinued due to the development of drug-induced lupus.

The patient underwent multidisciplinary evaluation with gynecology, gastroenterology, and plastic surgery. Intestinal reassessment by ileoscopy including biopsies, magnetic resonance enterography, and pelvic magnetic resonance imaging showed no evidence of gastrointestinal inflammation. The patient was started on ustekinumab (UST) maintained at the standard CD dose of 90 mg every 8 weeks.

After 6 months of UST, the patient noted resolution of her abdominal and inguinal fissures (Fig 1, *B*). However, the patient had persistent indurated gluteal plaque and nodular lesions, with fissuring and focal erosive change (Fig 2, *A*). A repeat biopsy result revealed granulomatous dermatitis again consistent with MCD. Methenamine silver, Fite, and Ziehl-Neelsen stains were negative. Trough UST

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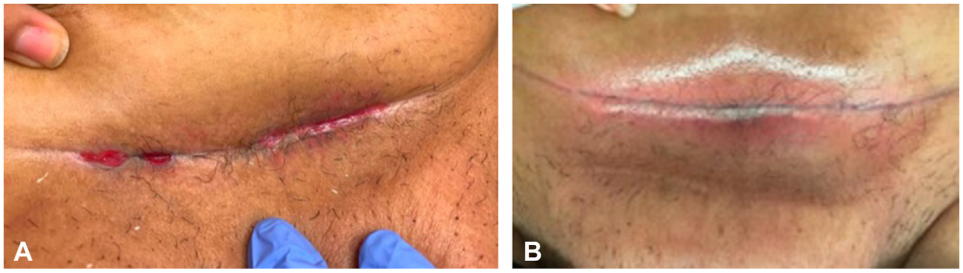

Fig 1. Knife-cut linear fissure along mons pubis (**A**) before and (**B**) after therapy with conventional dose ustekinumab.

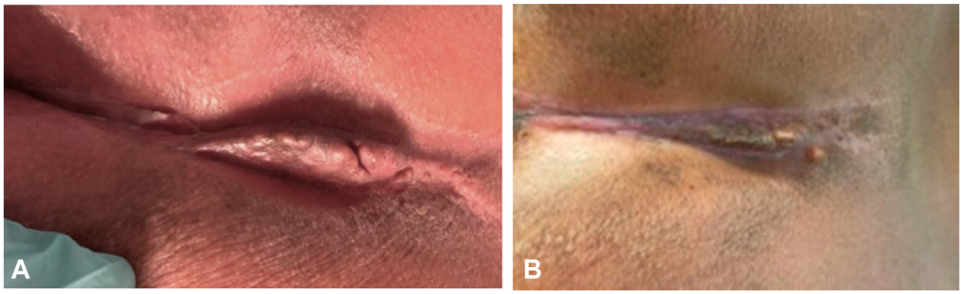

Fig 2. Persistent nodular plaque of the superior gluteal cleft (**A**) before and (**B**) after ustekinumab dose intensification.

levels were 1.8 mcg/mL (proposed therapeutic ranges vary from between 0.8 and 1.4 mcg/mL to >4.5 mcg/mL) with the absence[3] of detectable anti-UST antibodies. Given this level, the frequency of UST was increased to 90 mg every 4 weeks. Surveillance tuberculosis testing at this time was positive, having been negative at both 10 and 28 months earlier. Chest x-ray was negative and the patient began 4 months of rifampin for latent tuberculosis. Therapy with UST was not interrupted during antimycobacterial therapy, and after 3 additional months of dose-intensified UST, the patient noted resolution of all fissures and erosive change, with substantial involution of nodular lesions (Fig 2, *B*). Trough UST level with dose intensification was 6.5 mcg/mL.

DISCUSSION

MCD is an uncommon presentation of cutaneous CD. The pathogenesis is unknown; one hypothesis proposes that circulating antigens deposited in the skin trigger a type IV hypersensitivity reaction mediated by T lymphocytes. MCD is not related to the severity of CD and has been reported to precede intestinal involvement, although it commonly appears after the initial diagnosis in adults.[2] The most characteristic expression is knife-cut fissuring, but presentation commonly includes genital swelling, including vulvar edema (often with coexistent perianal CD for female patients) and nodules or plaques on the extremities.[2]

Guidelines for initial treatment of MCD include topical, intralesional, or systemic corticosteroids or topical calcineurin inhibitors. Lack of response often requires adjuvant treatments, including metronidazole or immunosuppression (eg, methotrexate and azathioprine).[4] Recalcitrant lesions are often treated with biologic agents that target inflammatory cytokine-dependent pathways implicated in inflammatory bowel disease. Common treatments include tumor necrosis factor inhibitors (anti—tumor necrosis factor [TNF]), such as adalimumab and infliximab. Rifampin has also been used in CD, but the experience has been relatively limited and its effect inconclusive.[5] MCD is difficult to treat, with partial improvement ranging from 30% for topical corticosteroids to 70% for anti-TNF, azathioprine, and systemic corticosteroids as monotherapy and in combination.[6]

Newer biologic agents for refractory MCD include UST, a monoclonal antibody that targets the common p40 subunit of interleukin 12 and interleukin 23 proinflammatory cytokines. This mechanism neutralizes the T-helper 1 and T-helper 17 cellular responses implicated in the pathogenesis of CD.[7] CD11c dendritic cells and CD68 macrophages in MCD (but not the granulomas) have also been shown to express interleukin 23.[6]

UST is approved for moderate to severe CD and may be effective for dermatologic manifestations of CD for patients who have failed anti-TNF medications or developed paradoxical reactions to other biologic agents.[8] In a retrospective case series of patients who had failed immunomodulator and anti-TNF therapy for MCD, UST therapy led to remission in 5 cases and partial response in 4 cases with a median time to remission of 5 months.[9] Here, we report a case of MCD having improved with UST that failed both infliximab and adalimumab.

Given the patient's incomplete response to UST, serum trough levels were measured and found to be on the lower end of some proposed targets (1.8 mcg/mL). The relationship between UST levels and CD clinical remission is unclear. In patients with intestinal CD, a median serum UST trough level of 1.9 μg/mL has been reported at 8 weeks in patients with clinical remission, decreasing to 0.3 μg/mL during maintenance therapy.[7] Prior studies have reported higher trough levels (3.3 μg/mL) associated with clinical remission.[10] Given the patient's persistent lesions, UST dosage was increased to every 4 weeks with notable improvement. The relative contribution of UST and rifampin to the response in our patient is uncertain. However, our patient's prior treatment with the rifamycin-group agents had been unsuccessful.

We present a case of recurrent MCD treated with ustekinumab-dose intensification in a patient that had failed numerous first-line treatments. Higher-dose ustekinumab may provide a new treatment option for patients that have failed other biologic agents, and therapeutic drug monitoring may play a role in drug dose titration.

Conflicts of interest

None disclosed.

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