

# Methotrexate-induced cutaneous ulceration without pancytopenia in a patient treated for inflammatory arthritis



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## INTRODUCTION

Methotrexate (MTX) is a folic acid antagonist that is commonly prescribed at low doses for autoimmune conditions such as rheumatoid arthritis (RA) and psoriasis. Oral ulcerations are a common dose-dependent mucocutaneous side effect of MTX, particularly in patients receiving it at high doses and with inadequate folic acid supplementation.<sup>1</sup> Cutaneous ulcerations are less common and have been reported primarily in patients with psoriasis and as a cutaneous sign of marrow toxicity.<sup>2</sup> Herein, we present a rare case of MTX-induced mucocutaneous ulceration without concurrent pancytopenia in a patient with RA.

## CASE REPORT

A 54-year-old man who recently immigrated from Bangladesh presented with a 2-month history of a blistering rash on the lower extremities, which had progressed to painful ulcers. Oral ulcerations subsequently developed over the 3 weeks prior to presentation. The patient denied a history of similar lesions. Medical history was notable for RA, for which the patient had been taking a stable dose of MTX 10 mg per week and folic acid 1 mg daily for 2 years. The patient had no increased joint pain relative to baseline and endorsed minimal RA symptoms at the time of presentation.

Physical examination revealed numerous round ulcers with erythematous borders and collarettes of scale on the lower extremities and a large hypertrophic oral ulcer on the lower labial mucosa (Fig 1).

### Abbreviations used:

MTX: methotrexate  
RA: rheumatoid arthritis

Laboratory studies revealed a white blood cell count of 6.1 K/ $\mu$ L (reference range, 4.0-11.0 K/ $\mu$ L); platelets, 273 K/ $\mu$ L (reference range, 150-400 K/ $\mu$ L); hemoglobin, 9.3 K/ $\mu$ L (reference range, 13.5-17.5 K/ $\mu$ L); mean corpuscular volume, 87 fL (reference range, 80-100 fL); iron, 105  $\mu$ g/dL (reference range, 45-182  $\mu$ g/dL); transferrin, 200 mg/dL (reference range, 180-329 mg/dL); transferrin saturation, 38% (reference range, 20%-50%); ferritin, 78.2 ng/mL (reference range, 23.9-336.2 ng/mL); folate, 11.9 ng/mL (reference range, 5.9-24.8 ng/mL); creatinine, 0.96 mg/dL (reference range, 0.64-1.27 mg/dL); blood urea nitrogen, 10 mg/dL (reference range, 8-20 mg/dL); rheumatoid factor antibodies, >1000 IU/mL (reference value, <12.4 IU/mL); and cyclic citrullinated peptide antibodies, 132 (reference value, <19). Histopathology with hematoxylin-eosin staining from a biopsy performed on a lower extremity ulcer demonstrated focal subepidermal separation with dyskeratotic keratinocytes and rare eosinophils at the dermoepidermal junction and a dermal inflammatory cell infiltrate composed of lymphocytes, neutrophils, eosinophils, and rare plasma cells (Fig 2). Tissue cultures for aerobic bacteria, fungus, and mycobacteria were negative.

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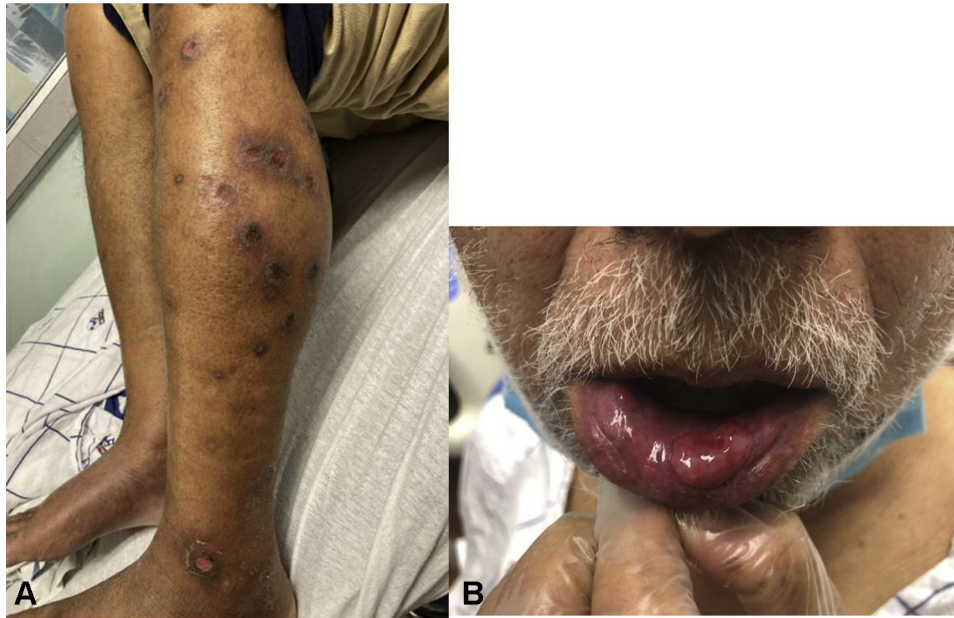
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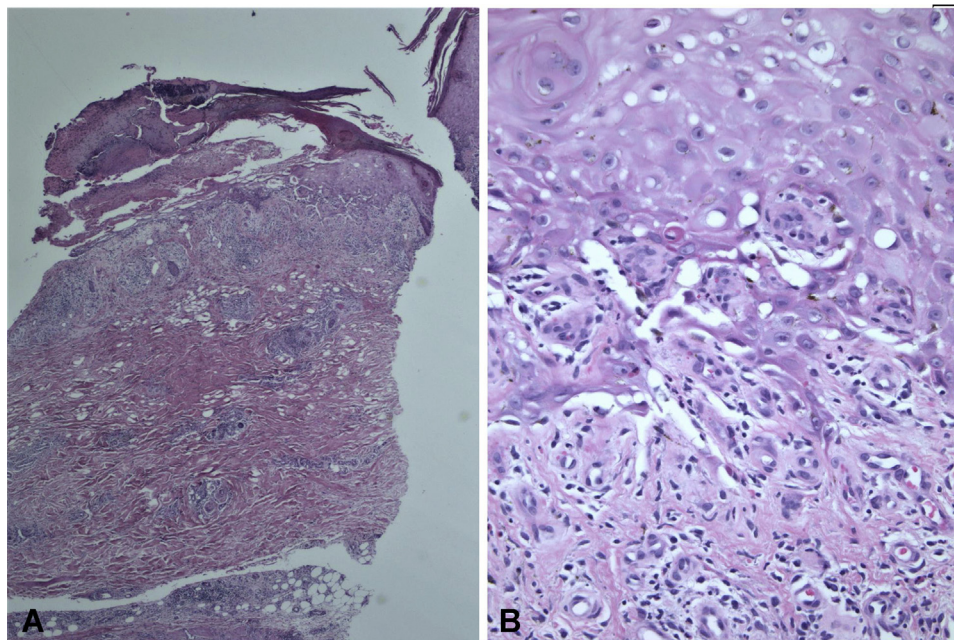
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**Fig 1.** **A**, Round ulcers with erythematous borders and collarettes of scale on the lower extremities. **B**, Hypertrophic oral ulcer on the lower labial mucosa.



**Fig 2.** Histopathology. **A**, Focal subepidermal separation with serum crust. **B**, Dyskeratotic keratinocytes in the epidermis and eosinophils in the superficial dermis.

A diagnosis of MTX-induced mucocutaneous ulcerations was made, and treatment with MTX was discontinued. The ulcerations on the lower extremities were treated with clobetasol and mupirocin

ointment and the oral ulcerations with dexamethasone solution. The patient had rapid reduction in pain over days and complete resolution of ulcerations at the 4-week follow-up (Fig 3). At 3 months,



**Fig 3.** **A**, Resolving ulcers of the lower extremity at the 4-week follow-up. **B**, Resolving hypertrophic oral ulcer on lower labial mucosa at the 4-week follow-up.

there was persistent postinflammatory hyperpigmentation with no signs of ulceration recurrence.

## DISCUSSION

MTX-induced cutaneous ulcerations were initially described as arising within psoriasis plaques as a harbinger of life-threatening pancytopenia, typically in the context of dose alterations or renal insufficiency.<sup>2</sup> More recently, MTX-induced ulcers have complicated treatment of other dermatologic conditions such as bullous pemphigoid, cutaneous T-cell lymphoma, and atopic dermatitis.<sup>3</sup> Ulcerations commonly present within involved skin and are accompanied by pancytopenia.<sup>3,4</sup> Morbidity from this medication toxicity can be high, and it has been associated with several deaths in patients with psoriasis and cutaneous T-cell lymphoma.<sup>2,4</sup>

More rarely, MTX can cause ulcerations in normal skin, such as in patients who are treated for RA, with the most common distributions being on the extremities or inguinal folds.<sup>5-9</sup> The presentation can be clinically difficult to distinguish from rheumatoid vasculitis when ulcers occur on the extremities. Similar to psoriasis, these cases have also been associated with pancytopenia.<sup>1</sup> Our patient had a unique presentation in that ulcers presented after 2 years of MTX therapy at a stable dose and at one of

the lowest doses that has been reported in the literature in a patient with normal renal function.<sup>10</sup> He had no associated pancytopenia with normal leukocytes, platelets, and normocytic anemia consistent with anemia of chronic disease. He had a mild course, with rapid ulcer healing after MTX cessation, without leucovorin rescue therapy.

The case demonstrated that MTX-induced mucocutaneous ulcerations can present in patients without skin disease and may occur independently of marrow toxicity. In these cases, MTX-induced ulcerations may be an idiosyncratic instead of dose-dependent toxicity or may considerably precede other signs of toxicity.<sup>2</sup> Clinically, the absence of marrow toxicity alone should not rule out MTX toxicity as a possible cause of cutaneous ulcerations in the appropriate clinical setting.

## Conflicts of interest

None disclosed.

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