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Methotrexate-induced cutaneous ulceration in 3 nonpsoriatic patients: Report of a rare side effect



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Key words: cutaneous; methotrexate; toxicity; ulcers.

INTRODUCTION

Methotrexate (MTX) is a commonly prescribed medication in the treatment of autoimmune conditions such as rheumatoid arthritis (RA) and psoriasis. MTX is a folic acid analog and DNA synthesis inhibitor that competitively inhibits dihydrofolate reductase. Well-known side effects of MTX include diarrhea, nausea/vomiting, anorexia, stomatitis, fatigue, and malaise.¹ Cutaneous ulceration is a less commonly described sign of MTX toxicity in patients with psoriasis. Reported risk factors include relatively high MTX dosage, renal impairment, concurrent nonsteroidal anti-inflammatory drugs, age older than 55, folate deficiency, low serum albumin, and drug interactions.² MTX-induced cutaneous ulceration in nonpsoriatic patients is rare, with the first case reported in 1998. Since 2011, only 5 cases have been reported.³ In this case series, we report MTX-induced cutaneous ulceration in 3 nonpsoriatic patients.

CASE 1

A 52-year-old woman with RA, hypothyroidism, depression, alcohol abuse, and hepatitis C was admitted from an outside hospital for right hip pain and right thigh cellulitis, which developed 3 weeks after a fall and subsequent pubic rami fracture. On admission, the patient was found to have pancytopenia, acute kidney injury, and cholestatic transaminitis. MTX level was 0.07 $\mu\text{mol/L}$. She had been taking 15 mg/wk of MTX for RA for the last 6 months. The dermatology department was consulted for superficial ulcerations with crusting and scaling on

Abbreviations used:

H&E: hematoxylin-eosin stain
MTX: methotrexate
RA: rheumatoid arthritis

the patient's hands, digits, arms, legs, and upper chest of unclear duration (Fig 1). The primary team was concerned for an atypical infectious process, as the patient's cellulitis and skin lesions were not improving on intravenous vancomycin, meropenem, and clindamycin.

Punch biopsies for hematoxylin-eosin (H&E) stain and tissue culture on the left forearm and right thigh showed focal dermoepidermal separation (Fig 2) and epidermal dysmaturation (Fig 3). Tissue culture was negative for bacteria, fungus, and atypical mycobacteria. MTX was stopped, the hematology department was consulted, and the patient was administered 1 dose of leucovorin. Results of a bone marrow biopsy were normal. Given the negative tissue culture results and continued cellulitis of the right thigh, the patient was taken to the operating room for surgical debridement, which found pyomyositis, fasciitis, and a hematoma, likely incited from the pelvic fracture. Intraoperative cultures grew methicillin-resistant *Staphylococcus aureus*. The patient underwent several surgical washouts and debridements of the right thigh with eventual resolution on 6 weeks of intravenous vancomycin. Blood counts, creatinine, and liver enzymes all

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Fig 1. Superficial ulcerations with crusting and scaling on the hand, digits, arm, and shin.

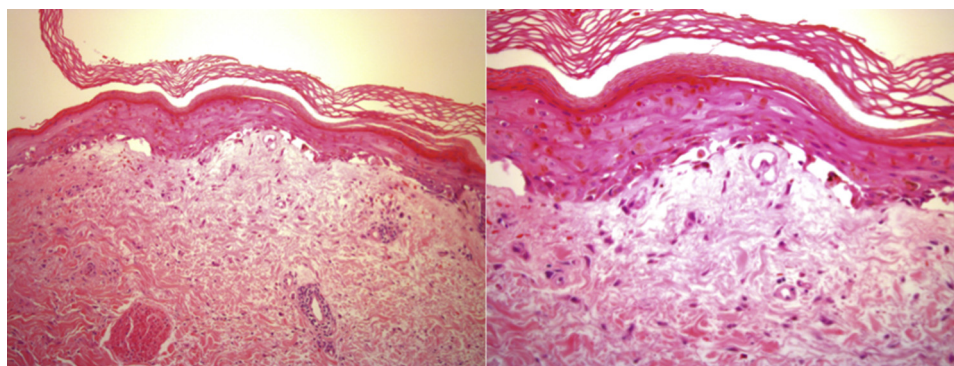


Fig 2. Histologic examination of a punch biopsy taken from the left forearm shows a focal subepidermal split with epidermal necrosis. (H&E; original magnifications: **left**, $\times 10$ and **right**, $\times 20$.)

normalized before discharge, and the patient's skin lesions slowly resolved off MTX.

CASE 2

A 56-year-old woman with RA presented to the hospital for new-onset pancytopenia and rash. She had been taking 20 mg/wk of MTX for RA for an unclear length of time. On presentation, there were necrotic, ulcerated nodules with surrounding erythema on the left second digit at the proximal interphalangeal joint, right knee, and left dorsal foot (Fig 4). The patient first noticed these painful, enlarging lesions 3 months prior after injuring her fingers on rose thorns in her garden. Before admission, the patient had received courses of amoxicillin, cephalexin, and sulfamethoxazole/trimethoprim without improvement.

Laboratory results showed pancytopenia, and an infectious workup was negative. MTX level was $0.05 \mu\text{mol/L}$. Two punch biopsies for H&E of the left knee showed prominent epidermal dysmaturations with nuclear pleomorphic and atypical mitotic figures (Fig 5). The patient's MTX was stopped, and leucovorin was administered, which resulted in resolution of the cutaneous ulcerations.

CASE 3

A 52-year-old woman with RA, type II diabetes, hypertension, and hyperlipidemia was admitted to the medical intensive care unit from an outside hospital for mouth ulcers, skin rash, fevers, acute kidney injury, and pancytopenia with an absolute neutrophil count of 0. On physical examination, the patient displayed periorbital scaling and thick hemorrhagic crusting of her hard and soft palates. The patient had thin, crusted ulcerations on the medial thighs and an eroded plaque underneath the pannus (Fig 6). At the outside hospital, the patient had received acyclovir, piperacillin/tazobactam, fluconazole, daptomycin, and anidulafungin.

The patient was unable to provide a history regarding symptoms or medications, but chart review found she had been taking adalimumab, leflunomide, and MTX, 25 mg/wk, for at least 2 months before presentation. A viral swab for herpes simplex virus polymerase chain reaction was negative. The patient's mucositis was attributed to MTX toxicity versus erosive lichen planus as a paradoxical effect of her recently initiated tumor necrosis factor inhibitor. MTX level was less than $0.04 \mu\text{mol/L}$. Punch biopsy findings for H&E of the

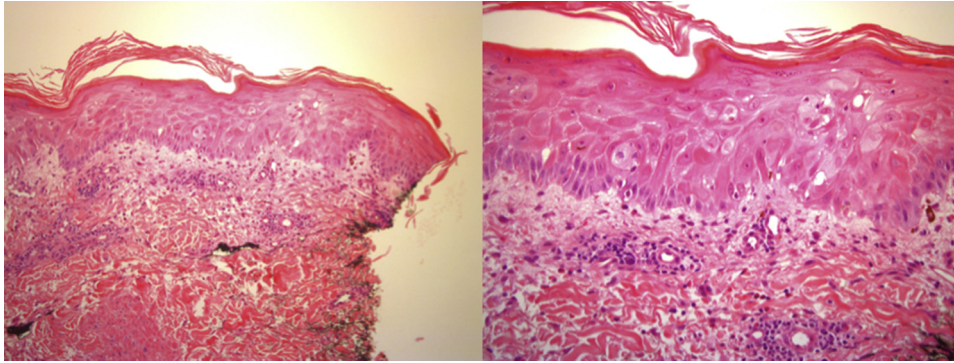


Fig 3. Histologic examination of a punch biopsy taken from the right thigh shows epidermal dysmaturation and a mixed dermal inflammatory infiltrate with eosinophils. (H&E; original magnifications: **left**, $\times 10$ and **right**, $\times 20$.)

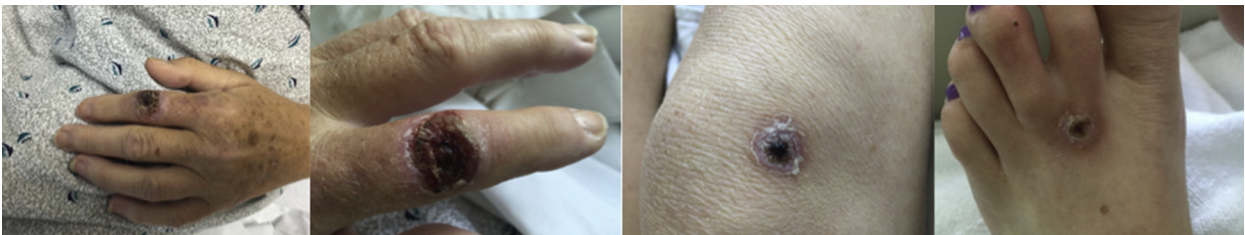


Fig 4. Necrotic, ulcerated nodules with surrounding erythema on the left second digit at the proximal interphalangeal joint, right knee, and left dorsal foot.

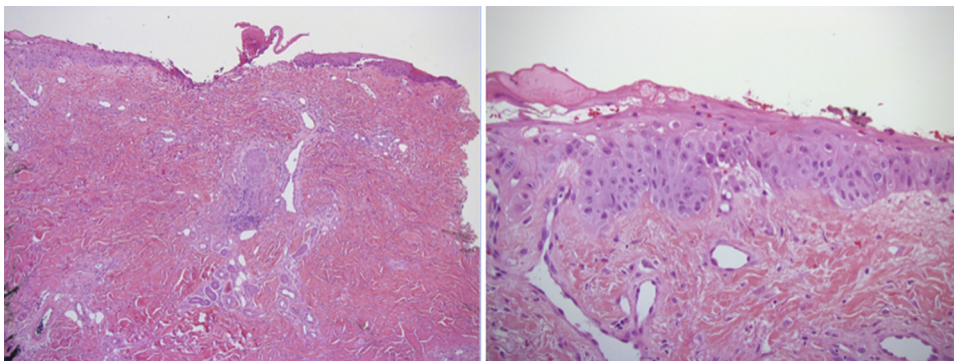


Fig 5. Histologic examination of a punch biopsy taken from the left knee shows epidermal dysmaturation with nuclear pleomorphism and atypical mitotic figures. (H&E; original magnifications: **left**, $\times 10$ and **right**, $\times 20$.)

right thigh displayed epidermal dysmaturation and dyskeratosis. Because of concern for MTX toxicity, leucovorin was administered, and MTX, leflunomide, and adalimumab were stopped. The patient's mucositis and cutaneous lesions improved throughout her hospital stay.

DISCUSSION

MTX-induced cutaneous ulceration in psoriatic patients is a rare side effect of low-dose MTX treatment and can be an indicator of life-threatening pancytopenia.⁴ Ulceration caused by MTX toxicity in nonpsoriatic patients is even more

rare. In this case series, we report MTX-induced cutaneous ulceration in 3 nonpsoriatic female patients with rheumatoid arthritis. Similar to previously reported cases, cutaneous ulceration resolved in our patients after discontinuation of MTX.^{1,2,5}

The histologic features of MTX-induced cutaneous toxicity are focal dermoepidermal separation with keratinocyte necrosis and dystrophy, specifically cytologic atypia and dysmaturation.^{2,6} Biopsies of lesions from all 3 patients displayed keratinocyte dystrophy. Case 1 also displayed focal dermoepidermal separation. These pathology findings confirm that the cutaneous ulcerations were

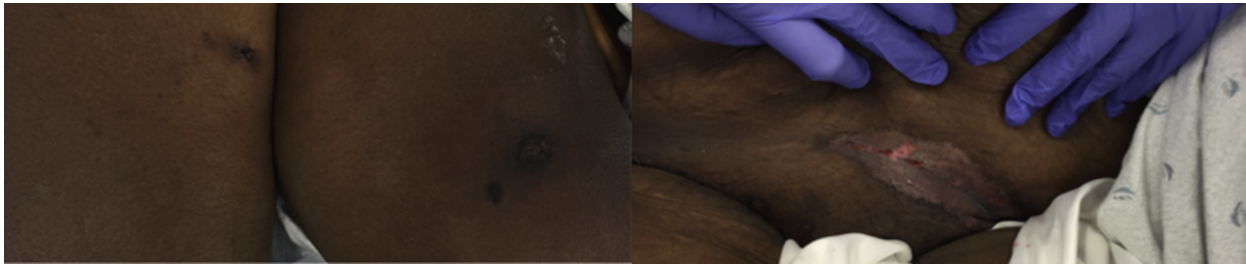


Fig 6. Thin, crusted ulcerations on the medial thighs and an eroded plaque underneath the pannus.

secondary to MTX toxicity and not infection, which was a suspected cause of ulceration in all 3 cases. Case 1 was complicated by right thigh pyomyositis; however, this finding could not explain the cutaneous ulcerations elsewhere on her body.

There is paucity of data on the correlation between cutaneous toxicity caused by low-dose MTX treatment (defined as $<50 \text{ mg/m}^2$) and serum MTX levels. Serum drug levels are monitored during high-dose therapy (defined as $>500 \text{ mg/m}^2$) for treatment of malignancies and are used to identify the need for leucovorin rescue. Serum MTX concentrations suggesting increased risk for toxicity after high-dose therapy are $10 \text{ } \mu\text{mol/L}$ after 24 hours, $1 \text{ } \mu\text{mol/L}$ after 48 hours, and $0.1 \text{ } \mu\text{mol/L}$ after 72 hours after MTX administration.⁷ Each of our 3 patients received leucovorin rescue and stopped MTX treatment after toxicity was suspected. This treatment subsequently led to the resolution of the cutaneous ulcerations; however, the highest serum MTX level recorded among our patients was $0.07 \text{ } \mu\text{mol/L}$, which is less than the 72-hour high-dose toxicity cutoff documented in the literature. This finding suggests that the serum drug levels measured during low-dose MTX treatment may be of undetermined significance, and interpretation of toxicity should be based on clinical status.

Although cutaneous ulcerations from MTX treatment are not life threatening, the pancytopenia caused by bone marrow suppression can be fatal.⁴ The appearance of eroded psoriatic plaques after low-dose MTX has been documented as an indicator of impending life-threatening pancytopenia and warrants the rapid cessation of MTX.^{4,8} All 3 of our patients had underlying pancytopenia in addition to cutaneous findings. Additionally, all 3 patients were treated with numerous antibiotics before a diagnosis was rendered. Thus, cutaneous ulceration in nonpsoriatic patients receiving low-dose MTX warrants drug discontinuation and further hematologic testing, especially when the infectious workup is inconclusive.

This case series illustrates 3 examples of MTX-induced cutaneous ulceration in nonpsoriatic patients. All 3 patients were women older than 50 years taking 15 to 25 mg of MTX per week, who presented with cutaneous ulcerations of the extremities mistaken for infection. All 3 patients subsequently responded to cessation of MTX and initiation of leucovorin rescue. In addition, our patients all had MTX serum levels less than $0.07 \text{ } \mu\text{mol/L}$ and underlying pancytopenia. Therefore, this case series suggests that cutaneous ulceration caused by low-dose MTX can be suggestive of underlying pancytopenia and that serum drug levels may be an unreliable marker of toxicity. This rare cutaneous side effect is an important forewarning for the more severe toxicities of MTX treatment.

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