

# Mucocutaneous Ulcerations Secondary to Methotrexate

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*Although methotrexate (MTX) is used in several medical specialties including dermatology, rheumatology, and oncology, drug-induced mucocutaneous ulcerations rarely are reported. We present a 36-year-old woman with plaque psoriasis and psoriatic arthritis being treated with oral MTX (12.5 mg weekly) and oral methoxsalen plus UVA. Following an increase in MTX dose, she developed erosions and ulcerations on her oral mucosa and within her psoriatic plaques. All erosions and ulcerations healed within 2 weeks upon discontinuation of MTX.*

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## Case Report

A 36-year-old woman with plaque psoriasis and psoriatic arthritis presented with complaints of worsening joint pain as well as mild pain and increased erythema within her psoriatic plaques (considered day 1 of her presentation). For 18 months, her psoriasis had been relatively stable on oral methotrexate (MTX) (12.5 mg weekly (5 mg the first morning, 5 mg 12 hours later, and 2.5 mg another 12 hours later) and concurrent oral methoxsalen plus UVA light treatments 2 to 3 times weekly. Her symptoms were attributed to a psoriatic flare and she was instructed to increase her next MTX dose from 12.5 mg to 17.5 mg. On the day the patient began taking the higher dose of MTX (day 3), she returned with worsening pain and burning within her psoriatic plaques, and she was started on azithromycin dihydrate for presumed cellulitis. The following morning (day 4), after

taking her third and final dose of MTX for the week, she presented to an outside emergency department with persistent psoriatic plaque pain and was admitted to the hospital (days 4 and 5) for pain control. During her hospitalization, azithromycin dihydrate was discontinued and she received a single dose of prednisone for a presumed psoriatic flare.

Three days after being discharged from the hospital (day 8), she returned with worsened pain within her psoriatic plaques, accompanied by new oral and cutaneous ulcerations. Review of systems revealed chills but no fever, nausea, vomiting, or diarrhea. Aside from psoriasis and psoriatic arthritis, the patient's prior medical history was notable only for hypertension. Her medications included furosemide, metoprolol tartrate, MTX, methoxsalen, and triamcinolone acetonide 0.1% and calcipotriol 0.005% ointments, all part of her treatment regimen for at least 6 months. The patient reported taking only one dose of azithromycin dihydrate prior to her hospitalization. She was unable to recall if she had taken nonsteroidal anti-inflammatory drugs (NSAIDs) since this recent episode of pain had begun. She did not think she had made any errors in the timing or dosing of her MTX.

On physical examination, the patient was found to have multiple 2- to 10-cm erythematous plaques involving the upper and lower extremities. Most of the plaques were eroded and covered with central black eschar and interspersed foci of yellowish exudate. She also had mucosal erosions limited to the upper and lower oral mucosa (Figure 1). The patient confirmed that all cutaneous ulcerations, with the exception of the oral mucosa, were in sites of former psoriatic lesions. Laboratory abnormalities included anemia (hemoglobin, 11 g/dL [reference range, 14.0–17.5 g/dL]) and mild transaminitis (aspartate aminotransferase, 38 U/L [reference range, 10–30 U/L]; alanine aminotransferase, 54 U/L [reference range, 10–40 U/L]); however, her platelet count, white blood cell count, and coagulation factors were within reference range; renal function test results were normal; and her MTX level was undetectable. A biopsy from a cutaneous ulceration

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**Figure 1.** Cutaneous erosions and ulcerations on the lower oral mucosa (A) and in psoriatic plaques on the hands (B) and legs (C) following treatment with methotrexate for plaque psoriasis.

was performed that later revealed psoriasiform dermatitis consistent with partially treated psoriasis, with prominent keratinocyte necrosis throughout the superficial epidermis.

The patient's development of erosions and ulcerations in the setting of a recent increase in MTX dose was most consistent with MTX toxicity. MTX was discontinued and she was hospitalized for pain control and wound care. All erosions and ulcerations healed completely within 2 weeks (Figure 2). She remained clear of psoriasis for nearly 2 months before experiencing gradual recurrence of psoriatic plaques.



**Figure 2.** Substantial improvement was seen in sites of former cutaneous erosions and ulcerations 2 weeks after discontinuation of methotrexate for plaque psoriasis (A–C).

### Comment

MTX is a folic acid antagonist with antiproliferative, antineoplastic, and anti-inflammatory properties that is commonly used to treat psoriasis, along with other various oncologic, rheumatologic, and dermatologic diseases. Acute toxicity for patients on low-dose oral therapy (7.5–15 mg weekly) primarily manifests as bone marrow suppression, occurring in 1% to 3% of patients, and oral and gastrointestinal

ulceration, seen in 3% to 10% of patients.<sup>1</sup> In addition, MTX can cause cutaneous reactions in up to 5% of treated patients.<sup>2</sup> Cutaneous findings such as skin desquamation, blistering, folliculitis, acral erythema, and mucosal erosion have been described in patients receiving high doses of MTX.<sup>3,4</sup> With lower doses, as used in the treatment of psoriasis, reactions ranging from urticaria to toxic epidermal necrolysis have been reported.<sup>5,6</sup> Erosions and ulcerations of psoriatic plaques have been described after short-term treatment with MTX and, less frequently, after chronic MTX therapy.<sup>4,7-9</sup>

Two distinct patterns of cutaneous ulcerations have been described in association with MTX. Type 2 ulcerations, which are less common, occur in nonpsoriatic, previously damaged skin, classically on the lower extremities of patients with stasis dermatitis. In contrast, type 1 mucocutaneous ulcerations typically erupt within psoriatic plaques after taking an increased dose of MTX,<sup>10</sup> as seen in our patient. A retrospective analysis of 47 cases from 1951 to 1996 identified alteration of the MTX dose and concomitant ingestion of NSAIDs as the greatest risk factors for mucocutaneous ulceration.<sup>9</sup>

There are several proposed mechanisms for the development of erosions and ulcerations. One mechanism attributes ulcerations to shortening the time between doses of MTX. With the weekly dosing schedule used in dermatology and rheumatology, pills are either taken as a single dose once weekly or divided into 2 to 3 doses, usually taken in 12-hour intervals; patients are told to always take the pills on the same day(s) of the week. If a patient were to accidentally take a MTX dose before the next scheduled time, the additional dose would theoretically stop proliferation of the small percentage of cells that escaped the initial MTX dose, thereby increasing the total number of cells affected by the drug.<sup>11</sup> Other mechanisms that may contribute to MTX-induced ulcerations include renal dysfunction, which leads to elevated MTX levels because of decreased renal clearance, and concomitant administration of medications such as NSAIDs, sulfonamides, and salicylates, which increase soluble MTX levels by displacing the protein-bound fraction.<sup>9</sup>

For our patient, the clinical course leading to MTX-induced cutaneous toxicity was somewhat unclear, as she had pain within her psoriatic plaques before she took the higher dose of MTX. In retrospect, we believe that the initial joint and plaque pain were caused by a psoriatic flare, with the higher MTX dose leading to superimposed toxicity-associated plaque pain and subsequent erosions and ulcerations. Cell turnover is increased in psoriatic

plaques and is particularly elevated during a flare, which may explain why ulcerations from MTX frequently occur in existing psoriatic plaques<sup>9</sup> and why this patient developed erosions and ulcerations during a flare.

In addition to taking a higher dose of MTX, unrecorded NSAID ingestion may have contributed to our patient's susceptibility to cutaneous toxicity. Although she did not recall taking any new medications such as NSAIDs prior to the onset of pain, we cannot rule out the possibility that she did indeed take ibuprofen as she reportedly had in the past for symptoms of a psoriatic flare. Azithromycin dihydrate and prednisone, which she began taking after the onset of pain, are not known to affect MTX levels or cause ulcerations.

Because the early signs of MTX-induced ulcerations can be subtle, a high clinical suspicion is critical in identifying this manifestation of MTX toxicity. The associated symptoms of pain, erythema, and erosions may be easily misdiagnosed as an infection and treated with antibiotics, or as a psoriatic flare and treated by increasing the dose of MTX, which can lead to worsened toxicity.<sup>9,10</sup> One clue of MTX toxicity is that the burning sensation within psoriatic plaques typically is out of proportion to the appearance of the lesions.<sup>3,7</sup>

Patients with suspected cutaneous MTX toxicity should have a complete blood count and chemistry panel to exclude the possibility of concurrent systemic toxicity. If MTX has been given within 24 hours, parenteral administration of leucovorin calcium may limit toxicity.<sup>12</sup> Reportedly, the majority of patients can resume taking MTX without further erosions<sup>10</sup>; however, we elected not to restart MTX in this patient and to treat her psoriasis with methoxsalen plus UVA and other topical antipsoriatic agents.

## REFERENCES

1. US Food and Drug Administration MedWatch. Methotrexate sodium for injection. [http://www.fda.gov/medwatch/SAFETY/2004/jan\\_PI/Methotrexate\\_PI.pdf](http://www.fda.gov/medwatch/SAFETY/2004/jan_PI/Methotrexate_PI.pdf). Accessed May 21, 2006.
2. Hani N, Casper C, Groth W, et al. Stevens-Johnson syndrome-like exanthema secondary to methotrexate histologically simulating acute graft-versus-host disease. *Eur J Dermatol*. 2000;10:548-550.
3. Methotrexate. RxList: Internet Drug Index. [http://www.rxlist.com/cgi/generic/mtx\\_ad.htm](http://www.rxlist.com/cgi/generic/mtx_ad.htm). Accessed March 20, 2008.
4. Kaplan DL, Olsen EA. Erosion of psoriatic plaques after chronic methotrexate administration. *Int J Dermatol*. 1988;27:59-62.

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5. Zachariae H. Methotrexate side-effects. *Br J Dermatol.* 1990;122(suppl 36):127-133.
6. Reed KM, Sober AJ. Methotrexate-induced necrolysis. *J Am Acad Dermatol.* 1983;8:677-679.
7. Kazlow DW, Federgrun D, Kurtin S, et al. Cutaneous ulceration caused by methotrexate. *J Am Acad Dermatol.* 2003;49(2 suppl Case Reports):S197-S198.
8. Del Pozo J, Martinez W, Garcia-Silva J, et al. Cutaneous ulceration as a sign of methotrexate toxicity. *Eur J Dermatol.* 2001;11:450-452.
9. Pearce HP, Wilson BB. Erosion of psoriatic plaques: an early sign of methotrexate toxicity. *J Am Acad Dermatol.* 1996;35(5, pt 2):835-838.
10. Lawrence CM, Dahl MG. Two patterns of skin ulceration induced by methotrexate in patients with psoriasis. *J Am Acad Dermatol.* 1984;11:1059-1065.
11. Bleyer WA. Methotrexate: clinical pharmacology, current status and therapeutic guidelines. *Cancer Treat Rev.* 1977;4:87-101.
12. Roenigk HH Jr, Auerbach R, Maiback HI, et al. Methotrexate guidelines—revised. *J Am Acad Dermatol.* 1982;6:145-155.