

Methotrexate-induced cutaneous ulceration and necrosis in chronic atopic dermatitis



Malika A. Ladha, MD,^a Bryn Edgerton, BSc(Hons),^b Jonathan Levy, MD,^c Muhammad N. Mahmood, MD,^d Alim R. Devani, MD,^c Parbeer S. Grewal, MD,^c and Vimal H. Prajapati, MD^{a,c,f,g}
Edmonton and Calgary, Alberta, Canada

INTRODUCTION

Methotrexate is a folic acid antagonist used to treat malignant and inflammatory diseases.¹ Cutaneous ulceration and necrosis is a rare adverse event. Within dermatology, this phenomenon has occurred almost exclusively in psoriasis.² We present a case of methotrexate-induced cutaneous ulceration and necrosis in chronic atopic dermatitis.

CLINICAL CASE

A 56-year-old woman presented to the emergency department with fever and generalized skin eruption. Medical history was significant for congestive heart failure treated with furosemide and childhood-onset atopic dermatitis refractory to various topical corticosteroids. One week earlier, another practitioner had prescribed her oral methotrexate for erythroderma secondary to atopic dermatitis. Baseline laboratory investigation results were within normal limits. She misinterpreted the instructions and accidentally consumed 7.5 mg every 12 hours for 7 days (cumulative dosage 105 mg) without folic acid. Physical examination revealed widespread, well-demarcated, irregularly shaped, coalescing, superficial ulcers with overlying necrotic eschars arising within areas of scale and erythema on the trunk and extremities (Fig 1). There were no oral or genital ulcers. Atopic features such as lichenification and palmar hyperlinearity were noted. Scalp and nail abnormalities were not observed. Laboratory investigations demonstrated

Abbreviation used:

HSV: herpes simplex virus

pancytopenia and neutropenia, but normal liver and renal studies. The clinical differential diagnosis included methotrexate-induced necrotic skin ulceration or herpes simplex virus (HSV) infection.

Full septic evaluation (blood, urine, and skin cultures) plus studies for HSV (direct fluorescent antibody and polymerase chain reaction) were negative. Skin biopsy demonstrated sharply defined areas of epidermal ulceration and necrosis (Fig 2). HSV-induced cytopathic changes were absent and HSV immunohistochemistry was negative. Histopathology thus supported the clinical diagnosis of methotrexate-induced necrotic skin ulceration.

Initial treatment included methotrexate discontinuation, folic acid administration (10 mg/m² every 6 hours), wound care, and empirical intravenous acyclovir plus piperacillin-tazobactam. The latter 2 medications were discontinued with recovery of the neutrophil count. Folic acid and wound care were continued until complete epithelization of the necrotic ulcers, which took approximately 10 days (Fig 3).

DISCUSSION

Methotrexate is a synthetic folic acid analogue with both antiproliferative and anti-inflammatory

From the Division of Dermatology, Department of Medicine,^a Cumming School of Medicine,^b and Division of Community Pediatrics^f and Division of Pediatric Rheumatology,^g Department of Pediatrics, University of Calgary; Division of Dermatology, Department of Medicine^c; Department of Laboratory Medicine and Pathology, University of Alberta^d; and Dermatology Research Institute, Calgary.^e

Funding sources: None.

Conflicts of interest: None disclosed.

Correspondence to: Vimal H. Prajapati, MD, Dermatology Research Institute, Meadows Mile Professional Building, 330-8500

Blackfoot Trail S.E., Calgary, Alberta, Canada T2J 7E1. E-mail: vimal@dermatologyresearch.ca.

JAAD Case Reports 2020;6:864-7.

2352-5126

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<https://doi.org/10.1016/j.jidcr.2020.02.028>



Fig 1. Clinical findings at initial assessment: well-demarcated, irregularly shaped, necrotic, superficial ulcers of various shapes and sizes, scattered on the trunk.

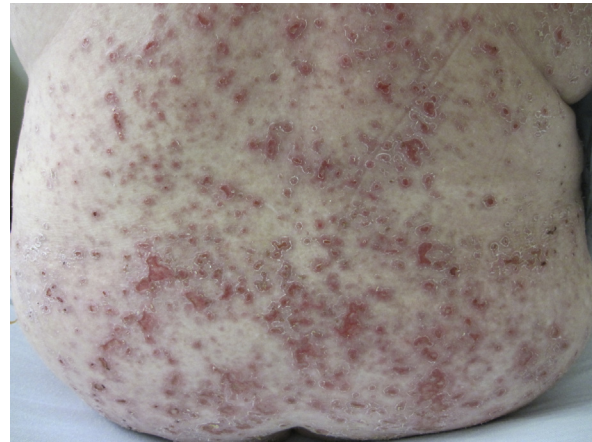


Fig 3. Clinical findings after 10 days of folic acid treatment and discontinuation of MTX: almost complete re-epithelization of ulcers on the trunk.

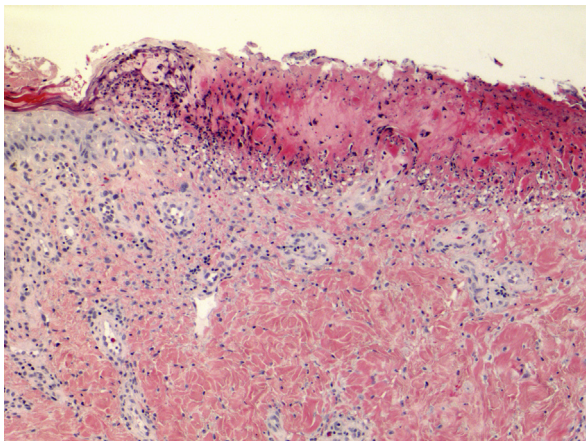


Fig 2. Histopathologic findings: well-demarcated epidermal ulceration and necrosis. No HSV-induced cytopathic changes were noted. (Hematoxylin-eosin stain; original magnification: $\times 100$.)

properties.¹ It inhibits dihydrofolate reductase to decrease folate, thereby interfering with DNA synthesis and cellular division.¹ The adverse events of methotrexate are classified as follows: type A, dose-dependent; type B, idiosyncratic; type C, resulting from long-term exposure; and type D, delayed even in the context of discontinuation.³ The most common adverse events include fatigue, malaise, nausea, emesis, and anorexia; these are dose-dependent and can be reduced with concurrent administration of folic acid.⁴ Methotrexate can also rarely cause severe, potentially life-threatening

adverse events, including hepatotoxicity and myelosuppression.⁴

Skin-related complications are type A and include cutaneous ulceration and necrosis. Within dermatology, this has occurred almost exclusively in the setting of psoriasis.² A potential explanation may be increased cell turnover, making these tissues particularly susceptible to cytotoxic effects.² There are only 8 reported cases in nonpsoriatic patients with an underlying primary dermatologic disease, either bullous pemphigoid or mycosis fungoides (Table I).^{2,5-8} To our knowledge, this is the first reported case of methotrexate-induced cutaneous ulceration and necrosis in atopic dermatitis. The latter is especially important because methotrexate is frequently used to treat pediatric and adult atopic dermatitis.⁹

Risk factors for cutaneous ulceration and necrosis secondary to methotrexate include alteration in methotrexate regimen (recent institution, high initial dose without folic acid supplementation, or resumption after brief hiatus), concurrent use of medications that impair renal tubular secretion of methotrexate, advanced age (especially ≥ 55 years), concomitant infection, chronic kidney disease or renal insufficiency, hypoalbuminemia, and increased mean cell volume.² Our patient's risk factors included recent institution of methotrexate, high initial dose of methotrexate without folic acid supplementation, advanced age, and concurrent use of a medication that impairs renal tubular secretion.

Table I. Reports of methotrexate-induced cutaneous or mucosal ulceration and necrosis in patients with nonpsoriatic primary dermatologic conditions

Author	Age, years	MTX dose/duration	Cause	Risk factors	Distribution of MTX-induced ulceration and necrosis	Mucosal involvement with MTX-induced ulceration and necrosis	Treatment (in addition to MTX discontinuation)
Bullous pemphigoid							
Borda et al ⁵	76	10 mg/wk PO for 4 mo; increased to 10 mg/day PO for preceding wk	Patient error	Alteration in MTX regimen, concurrent medication that impairs renal secretion, advanced age, concomitant infection (cellulitis), chronic kidney disease	Trunk, upper extremities, lower extremities	No	Folinic acid (PO), filgrastim (NS)
Chen et al ²	73	10 mg/wk PO for 10 d	NA	Advanced age	NS	No	Methylprednisolone (IV)
Delyon et al ⁶	92	2.5 mg/d PO, 5 d/wk for 3 wk	Patient error	Advanced age	Oral mucosa (gingiva and soft palate)	Yes	Folinic acid (NS)
Mycosis fungoides							
Breneman et al ⁷							
	81	10 mg/wk PO for 7 wk	NA	Advanced age	Axillae/inguinal regions, buttocks, lower extremities	No	Nil
	78	40 mg/wk IV for 3 wk	NA	Concurrent medication that impairs renal secretion, advanced age	Scalp, trunk, buttocks, upper extremities, lower extremities	No	Nil
	77	10 mg/wk PO increased to 40 mg/wk PO for 12 wk	NA	Alteration in MTX regimen, advanced age	Scalp, face, trunk, buttocks	No	Nil
	67	50 mg/wk IV for 6 mo; then increased to 60 mg/wk IV for 4.5 y	Acute renal failure	Alteration in MTX regimen, advanced age, renal insufficiency (postobstructive acute renal failure)	Axillary/inguinal regions, gluteal cleft	No	Fluid hydration (IV), folate (NS), folinic acid (NS)
Mna et al ⁸	57	10 mg/wk PO for 3 mo; then increased to 25 mg/wk PO	NA	Alteration in MTX regimen, advanced age	Scalp, face, trunk, upper extremities, lower extremities	No	Nil

IV, Intravenous; MTX, methotrexate; NA, not available; NS, not specified; PO, per os.

Clinicians should consider methotrexate-induced cutaneous necrosis and ulceration as a possible adverse event, especially if risk factors are present. High clinical suspicion for this diagnosis should prompt the following management: immediate discontinuation of methotrexate, administration of folinic acid, appropriate wound care, and monitoring of potential laboratory abnormalities, especially if myelosuppression is present.

CONCLUSION

Cutaneous ulceration and necrosis is a rare adverse event of methotrexate. Although most often limited to patients with psoriasis, this complication can occur in the setting of atopic dermatitis, as demonstrated by our patient.

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