Cutaneous manifestations of systemic methotrexate toxicity

To the Editor: Low-dose methotrexate as used in the treatment of autoimmune disease is generally well-tolerated and only rarely associated with life-threatening side effects.[1] Dose-dependent cutaneous complications of toxicity may portend impending life-threatening pancytopenia but remain poorly characterized.[2] Early recognition of cutaneous signs of toxicity is important to minimize morbidity. Here, we report mucocutaneous manifestations and circumstances surrounding toxicity in 10 patients presenting with methotrexate toxicity. Findings highlight the importance of recognizing cutaneous features to aid in early recognition of methotrexate toxicity.

Background characteristics, details of methotrexate usage, mucocutaneous findings, and presenting laboratory examinations are summarized in Table I. The mean (range) age of patients was 60 (43-83) years. Nine patients were female, and 1 patient was male.

Five patients had a methotrexate dose adjustment or initiation in the first month prior to presentation. Six patients were not taking methotrexate and folic acid as prescribed. In one such case, the patient's dermatologist had discontinued the prescription, but the patient's primary care physician had continued to refill. Two patients had recent prescriptions for ciprofloxacin. Two patients had recent hospital visits for dehydration. Two patients were using methotrexate in the context of decreased renal function. One patient had previous hospitalizations suspicious for undiagnosed chronic methotrexate toxicity.

Ten patients presented with any erosion or ulceration. Seven patients presented with cutaneous erosion or ulceration, and 9 patients presented with mucosal involvement. At time of presentation, 8 patients were pancytopenic, 7 patients had renal function abnormality, and 4 patients had liver function abnormality. All 10 patients were treated with leucovorin. Two patients died. Representative clinical images are shown in Fig 1.

The development of cutaneous erosion or ulceration in patients on methotrexate has previously been described as an indication of life-threatening pancytopenia.[3] Findings here agree with this association and demonstrate several other important patterns. Most patients presenting with methotrexate toxicity were not taking methotrexate and folic acid correctly, had been lost to follow-up, or were using methotrexate with decreased renal function. Several patients here were using methotrexate despite recent hospitalizations for dehydration or recent prescriptions for ciprofloxacin; a medication that may delay methotrexate clearance.[4] These findings underscore the importance of continued patient education for those prescribed methotrexate and regular medication review for agents that may interfere with methotrexate clearance or protein-binding.

Most patients clinically diagnosed with methotrexate toxicity in our cohort did not have a significant elevation in serum methotrexate concentration. In low-dose methotrexate regimens, serum methotrexate concentrations may not correlate with clinical or laboratory manifestations of toxicity, including degree of neutropenia, thrombocytopenia, or survival likelihood.[5] Altogether, results here and those of previous studies suggest that other signs of toxicity should guide clinical management in patients with suspected low-dose methotrexate toxicity.

Limitations of our data include its retrospective nature and small number of patients. However, results highlight the importance of careful multidisciplinary monitoring in patients prescribed methotrexate and the importance of recognizing cutaneous ulceration and erosion as signs of possible toxicity.

Shivani Jain, MPhil, MSc,[a] Hunter J. Pyle, MD,[a] Jessica C. Evans, MS,[a] Whitney Gao, MD,[a] and Melissa M. Mauskar, MD[a,b]

From the Department of Dermatology, University of Texas Southwestern Medical Center, Dallas, Texas[a]; Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center, Dallas, Texas.[b]

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Correspondence to: Melissa M. Mauskar, MD, Department of Dermatology and Obstetrics & Gynecology, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9069

Table I. Background characteristics and presenting findings of 10 patients with methotrexate toxicity

No./age/sex	MTX indication	MTX route	Involvement	1° exam	2° exam	Mucosal involvement	Initial serum MTX level, μM/L	Pancytopenia	Time to resolution	Disposition*
1/40s/F	Crohn's disease/RA	SQ	Hard palate, cheek, buccal mucosa, lower vermillion border, mucosal lower lip, bilateral arms, back, abdomen, thigh, labia minora	Papule	Erosion, serum, ulceration	Yes	0.05	Yes	>30 d	Resolved
2/40s/F	APML	PO	Hard palate, mucosal lips, tongue, vulvar mucosa	Papule	Erosion, fissure, serum	Yes	<0.02	Yes	40 d	Resolved
3/60s/F	PM	SQ	Hard palate, gingivae, cutaneous lips, abdomen, groin, feet	Macule, patch	Erosion, ulceration	Yes	0.77	Yes	8 d	Resolved
4/80s/F	PMR	PO	Scalp, hard palate, lower vermillion border, mucosal lips, chest, abdomen, upper back, mid back, clitoral hood	Macule, papule, patch, plaque, vesicle	Erosion, serum	Yes	<0.04	Yes	Did not resolve	Deceased
5/60s/F	SLE	PO	Vermillion border, cutaneous lips, upper arms, forearms, thighs, lower legs, foot	Plaque	Erosion, serum	No	<0.05	Yes	>70 d	Resolved
6/60s/F	RA	PO	Mucosal lip, lower legs, shin, malleolus	Macule, papule, patch	Erosion, scaling	Yes	0.05	No (bicytopenia)	>16 d	Resolved
7/50s/F	RA/SLE	PO	Hard palate, tongue, mucosal lips, chin, neck, chest, forearm, perianal area	Papule, plaque, pustule	Erosion, scaling	Yes	<0.04	No (bicytopenia)	~14 d	Resolved
8/60s/M	Psoriasis	PO	Nasal ala, vermillion border, mucosal lips, tongue, abdomen, back, forearms, hands, lower legs	Papule, plaque	Erosion, scaling, ulceration	Yes	0.38	Yes	Did not resolve	Deceased
9/50s/F	RA	PO	Buccal mucosa, tongue, oropharynx, chest, vagina, perianal area	Papule, plaque	Erosion	Yes	Unknown	Yes	Unknown	Unknown†
10/70s/F	Keratoacanthoma	ILES	Hard palate, buccal mucosa, mucosal lower lip	Vesicle	Ulceration	Yes	<0.04	Yes	30 d	Resolved

APML, Acute promyelocytic leukemia; *F*, female; *ILES*, intralesional; *M*, male; *MTX*, methotrexate; *NA*, not applicable; *PM*, polymyositis; *PMR*, polymyalgia rheumatica; *PO*, by mouth; *RA*, rheumatoid arthritis; *SLE*, systemic lupus erythematosus; *SQ*, subcutaneous.

*Deceased refers to death suspected secondary to methotrexate toxicity.

†Patient transferred to an outside hospital before full resolution.

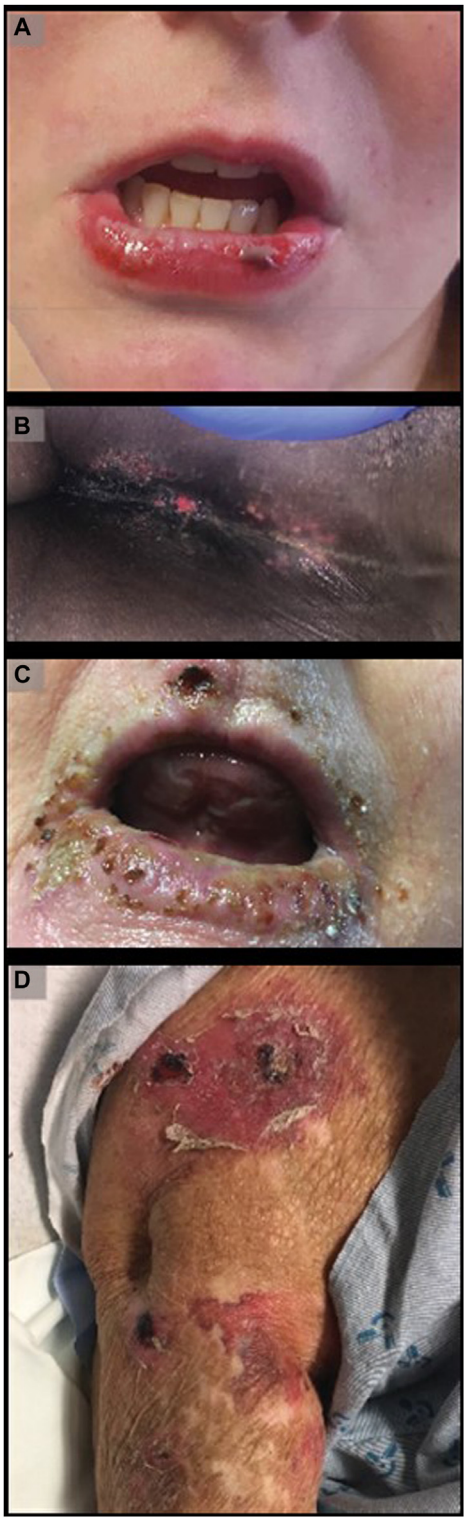

Fig 1. Representative clinical photographs of mucocutaneous manifestations of systemic methotrexate toxicity. **A,** Focal erosions of the oral mucosa (No. 2 in Table I). **B,** Perianal pink plaque with numerous erosions (No. 7 in Table I). **C,** Hemorrhagic ovoid erosion on upper right cutaneous lip and circumferential erosions on the mucosal lip (No. 5 in Table I). **D,** Several superficial broad geographic erythematous erosions on the dorsal upper arms (No. 5 in Table I).

E-mail: melissa.mauskar@utsouthwestern.edu

Conflicts of interest

None disclosed.

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