Cutaneous toxicity of oral low-dose methotrexate

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ABSTRACT

Chemotherapy-induced acral erythema has been a known side effect of intravenous dosing but has not been reported with oral therapy. Herein we describe two patients receiving treatment with low-dose oral methotrexate who presented with acral erythema. Clinicians and rheumatologists should be aware of this potentially serious side effect of oral chemotherapy in various patient populations. This complication related to methotrexate, though rare, should be anticipated in patients on multiple medications who develop mucocutaneous toxicities.

KEYWORDS Acral erythema; adverse drug reaction; methotrexate; psoriasis; rheumatoid arthritis

Methotrexate administered weekly in low doses is a mainstay in the therapy of various rheumatoid diseases.¹ Its mechanism of action is due to its effects on inhibition of T cell proliferation via its effects on different cellular metabolic pathways.¹ Some of the common side effects of oral low-dose methotrexate therapy include gastrointestinal toxicity, stomatitis, alopecia, marrow suppression, and liver function abnormalities. Acral erythema,² a symmetric, painful erythema of the palms and soles with a prodrome of paresthesia and occasional bullous formation with desquamation upon resolution, is a rare side effect.³ It has been associated with a number of chemotherapeutic agents, including 5-fluorouracil,^{4,5} cytarabine,⁶ and cyclophosphamide.⁷ Intravenous methotrexate-induced acral erythema was initially described in 1983 and, since then, many reports have been published.^{8–15} Most affected patients have been older children and adults,^{16,17} with one reported case in a pediatric patient.² Here we describe two cases of acral erythema in adult patients taking weekly low-dose oral methotrexate.

CASE 1

A 53-year-old black woman with diabetes mellitus and hypertension presented with a rash in her palm and sole and new onset of rash in the perianal area. Twelve days before presentation, she was diagnosed with palmoplantar psoriasis and placed on methotrexate 7.5 mg weekly along with folic acid 1 mg daily. Her medications included hydralazine,

amlodipine, carvedilol, furosemide, insulin glargine, and lisinopril. Physical examination was remarkable for acral erythema on the palm and soles, mucosal membrane ulceration, and stomatitis. Laboratory results on admission and before treatment are shown in *Table 1*. Liver function tests were normal. The patient had chronic hepatitis C infection; anti-hepatitis B surface antigen was positive with negative Hepatitis B surface antigen (HBsAg). The patient's reticulocyte count was 0.1 and her folate level was >20 ng/mL. She was started on cefepime and vancomycin for febrile neutropenia and prednisone 80 mg and leucovorin 60 mg every 6 hours. Her methotrexate level was 0.05 on the second day after admission. (A serum methotrexate level below approximately 0.02 μ Mol/L has been indicated as necessary for resumption of DNA synthesis.) A bone marrow biopsy revealed hypocellular bone marrow, with a marrow-to-fat ratio of 20:80 and trilinear panhypoplasia of the erythroid, myeloid, and megakaryocytic cell lines; no metastatic tumor or granuloma was seen. Her pancytopenia did not improve with prednisone. She was given three doses of Neupogen for severe leucopenia. Ten days after admission, the acral erythema on her palm and sole had improved (*Figure 1*). Pancytopenia improved markedly on the day of discharge.

CASE 2

A 62-year-old black woman diagnosed with rheumatoid arthritis at age 30, with a past medical history of hypertension, depression, and osteoarthritis, presented with severe mouth soreness and a painful rash on both hands that

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Table 1. Pertinent features of the two hypertensive black women

Variable	Case 1			Case 2		
Age (years)	53			62		
Underlying diseases	Psoriasis			Rheumatoid arthritis		
Methotrexate dose (mg weekly)	7.5			25		
Primary presentation	Palm, sole, and perianal			Oral ulcers and hand rash		
Laboratory tests	Pretreatment	Admission	Discharge	Pretreatment	Admission	Discharge
White cell count (mm ³)	5400	1000	13,100	3600	1700	5400
Hemoglobin (g/dL)	10	10.1	8	8.1	6.9	10.7
Platelets (/mm ³)	142,000	54,000	146,000	172,000	159,000	332,000
Absolute neutrophil count	3.4	0.3	10.6	2.8	0.8	8
Eosinophils (%)	3.2	14.6	—	6.9	—	—

started 4 days before admission. Her medications at the time of admission included methotrexate 25 mg weekly, leflunomide 10 mg daily, esomeprazole, prednisone 5 mg daily, folic acid 1 mg daily, and mirtazapine. Physical examination revealed stomatitis with painful, erythematous rash on her hands. Laboratory results are shown in *Table 1*. After 5 days of admission, her albumin level was 3.1 g/dL. Methotrexate was discontinued. Her treatment included local wound care, two units of blood transfusion, and a single dose of Neupogen. Her pancytopenia improved after Neupogen administration upon discharge.

DISCUSSION

Chemotherapy-induced acral erythema is a painful, symmetric, well-defined erythema and edema over the palms and soles. The clinical manifestations usually begin 1 day to 3 weeks after drug initiation and resolve 1 to 2 weeks after discontinuation of chemotherapy.^{3,18} A literature search revealed reports of two adult patients with methotrexate-induced acral erythema.^{16,17} Both of our patients were on low-dose oral methotrexate, and there are no case reports of acral erythema induced in adults with

weekly low-dose oral methotrexate. Treatment of acral erythema has generally been supportive and included compresses, sodium chloride soaks, and general wound care. Topical and systemic corticosteroids have been used with variable results,^{13,19} and pyridoxine has been associated with decreased pain.⁵ Other systemic side effects caused by weekly oral low-dose methotrexate are gastrointestinal toxicity, stomatitis, alopecia, marrow suppression, and liver function abnormalities. Both cases presented here had systemic side effects from weekly oral low-dose methotrexate.

Folinic acid administration may help as a competitive folate agonist. Hemodialysis and peritoneal dialysis were compared by Diskin et al when tackling methotrexate toxicity in a renal failure patient who was put on peritoneal dialysis before the episode of methotrexate toxicity.²⁰ It was concluded that hemodialysis has a greater methotrexate removal effect than peritoneal dialysis after the first hour of dialysis.

Other risk factors reported for pancytopenia with low-dose methotrexate therapy include hypoalbuminemia, advanced age, low serum folate level, elevated mean corpuscular volume, concurrent use of nonsteroidal antiinflammatory drugs, and polypharmacy with more than five drugs.^{21–23} A recent report

Figure 1. Case 1: Erythema on the (a, b) palms and (c) soles while on methotrexate. Resolution of erythema on the (d, e) palms and (f) sole after treatment.

has suggested that co-administration of proton pump inhibitors decreases methotrexate clearance, resulting in delayed plasma methotrexate elimination. The mechanisms of this delayed elimination, including the genetic factors and the contribution of other methotrexate transporters, remain to be clarified in further investigations.²⁴

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