

Acral Erosions and Ulcers: An Early Sign of Severe Acute Methotrexate Toxicity[☆]

Erosiones y úlceras acrales: manifestación precoz de toxicidad aguda grave por metrotexato

To the Editor:

Methotrexate (MTX) is a drug with a good safety profile that is frequently used in dermatology. Although serious complications due to acute MTX toxicity typically occur in the context of antineoplastic doses (up to 1-3 g/m² in some tumors), they occasionally occur in patients treated with considerably lower doses, and the early identification of these effects is essential. We present 3 patients who developed acute myelosuppression secondary to treatment with MTX. The initial signs in all the patients were similar forms of skin lesions; clinical observation of these lesions can be the key to the early diagnosis of this important condition.

The first patient was a woman of 65 years of age with rheumatoid arthritis. She had been on treatment for 1 month with MTX, 20 mg/24 h, ibuprofen, 600 mg/8 h, and prednisone, 10 mg/24 h. She came to the emergency department with a 3-day history of fever and mucositis associated with painful edema of the hands of sudden onset and ulcers on both feet (Fig. 1). After 48 hours of in-hospital observation, she developed severe pancytopenia with a neutrophil count of 400/ μ L (normal range, 1800-7600/ μ L), hemoglobin (Hb) of 9 g/dL (normal range, 11.4-15.1 g/dL), mean cell volume of 100 fL, and platelet count of 66 000/ μ L (normal range, 140 000-450 000/ μ L). Blood and urine cultures, microbiology study of the mucosae, and serology for human immunodeficiency virus, syphilis, hepatitis B and C viruses, parvovirus B19, cytomegalovirus, Epstein-Barr virus, and toxoplasma were negative.

The second case was a 60-year-old man and the third case a 55-year-old woman; both patients had a history of mycosis fungoides for which they had been treated with MTX, the man for 4 months at a dose of 20 mg/wk and the woman for 6 months at a dose of 25 mg/wk. For the previous month they had also been treated with sulfamethoxazole/trimethoprim (SMX/TMP) 800/160 mg 3 times a week as prophylaxis for sepsis of cutaneous origin. They were seen for very painful acral erosions that had been present for a week (Figs. 2 and 3). Blood tests in the man revealed a marked fall in the Hb to 7.9 g/dL from a value of 11.7 g/dL 2 weeks earlier, and in the woman revealed moderate bicytopenia that had not previously been detected (Hb of 10 g/dl and a white cell count of 2000/ μ L with 600 neutrophils/ μ L). Cultures of the skin lesions were negative for viruses and bacteria in both patients.

In all 3 patients, biopsy revealed reactive epidermal hyperplasia with areas of ulceration with a fibrin-covered base and dermal eosinophilia. The administration of MTX was



Figure 1 A, Swelling of both hands with poorly defined areas of violaceous erythema on the bony prominences of the fingers. B, Round superficial ulcers with a clean base and hyperpigmented borders on the sole of the right foot and on the left heel.



Figure 2 A and B, Bilateral, symmetrical, crusted erosive lesions with a retiform distribution on the dorsum of the feet and hands.

interrupted and symptomatic treatment was started, leading to resolution of the skin lesions in less than 1 month in all cases. In the first patient it was necessary to add specific treatment (folinic acid and granulocyte colony stimulating factor) because of the severe pancytopenia, which showed a favorable response.

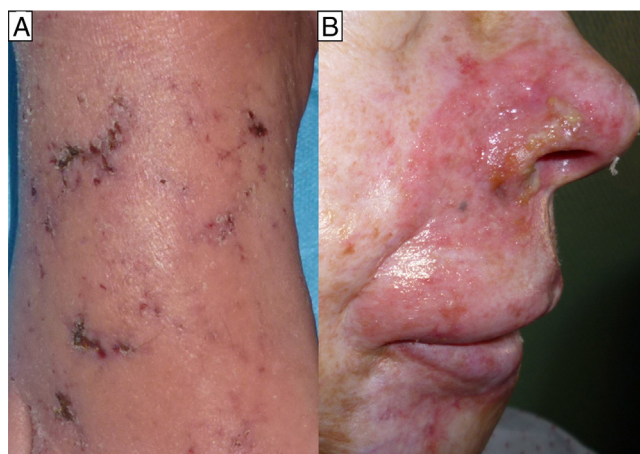


Figure 3 A, Clinical image of the lesions in the second patient: deep spiculated erosions covered by a hemorrhagic scab and with a peripheral violaceous halo. B, Erosive plaque with a crusted exudative surface on the right ala nasi.

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MTX is an antimetabolite. It is a folic acid analog that competitively and reversibly inhibits the enzyme dihydrofolate reductase (DHFR), a key enzyme for cell DNA synthesis. This mechanism explains its antiproliferative activity and the profile of adverse effects at high doses; acute myelosuppression is the manifestation that carries the greatest threat to life.¹ When used as at anti-inflammatory doses, the number of drug molecules bound to the enzyme is insufficient to achieve inhibition, and it is postulated that the effect a low doses may be related to the formation of intracellular polyglutamates.² However, the marked inter- and intraindividual variability in its metabolism³ and the possible coexistence of factors that increase its cellular availability means that, in practice, we must considered all patients on treatment with MTX to be susceptible to develop serious complications. Our 3 cases presented factors that could favor cytotoxicity: in the first patient, incorrect dosage (daily instead of weekly) leading to overdose, and treatment with ibuprofen, which interferes with the renal excretion of MTX and increases its free fraction in the plasma by displacing MTX from its protein binding sites; in the other patients, prophylaxis with SMX/TMP impeded the transformation of para-aminobenzoic acid into folic acid (SMX effect) and directly inhibited DHFR (TMP effect).

Skin erosions and/or ulcers as the manifestation of acute cytotoxicity due to MTX is very rare. In the medical literature reviewed, we found only 5 cases in patients with no previous dermatosis.⁴⁻⁸ All were men on low-dose treatment for rheumatoid arthritis and only one of them presented general manifestations with fever, mucositis, and acute severe pancytopenia, similar to our first patient.⁷ Cell turnover is increased in patients with psoriasis and/or mycosis fungoides, and this increases the cutaneous tropism of MTX.^{9,10} Lawrence et al.⁹ describe 2 distinct clinical patterns with different prognoses in patients with psoriasis: type I, with erosions and/or ulcers that develop on plaques and heal within a few days after the withdrawal of MTX; and type II, with lesions on healthy skin that take weeks to resolve despite the withdrawal of treatment. The clinical recognition of this condition is important, as it must be differentiated from treatment inefficacy or a flare-up of the dermatosis; this typically occurs at the beginning or end of treatment, which could lead either to an increase in the dose or to the reintroduction of MTX. The common factor in all the cases described, both in individuals with lesions on underlying skin disease and in those with lesions on healthy skin, was the disproportionate pain of the lesions and their characteristic distribution on acral areas, as was observed in our patients.

Based on all we have described, we believe that the appearance of painful acral erosions and/or ulcers in patients receiving treatment with MTX must lead us to consider severe underlying cytotoxicity. Two fundamental factors in the prevention of potentially lethal adverse effects are detailed evaluation of all the concomitant medication and ensuring that patients understand the indicated MTX regimen.

References

1. MacKendry RJ. The remarkable spectrum of methotrexate toxicities. *Rheum Dis Clin North Am*. 1997;23:939-54.
2. Carretero G, Puig L, Dehesa L, Carrascosa JM, Ribera M, Sánchez-Regaña M, et al. Metotrexato: guía de uso en psoriasis. *Actas Dermosifiliogr*. 2010;101:600-13.
3. Danila MI, Hughes LB, Brown EE, Morgan SL, Baggott JE, Arnett DK, et al. Measurement of erythrocyte methotrexate polyglutamate levels: ready for clinical use in rheumatoid arthritis? *Curr Rheumatol Rep*. 2010;12:342-7.
4. Ben-Amitai D, Hodak E, David M. Cutaneous ulceration: An unusual sign of methotrexate toxicity—first report in a patient without psoriasis. *Ann Pharmacother*. 1998;32:651-3.
5. Montero LC, Gómez RS, de Quirós JF. Cutaneous ulcerations in a patient with rheumatoid arthritis receiving treatment with methotrexate. *J Rheumatol*. 2000;27:2290-1.
6. Del Pozo J, Martínez W, García-Silva J, Almagro M, Peña-Penabad C, Fonseca E. Cutaneous ulceration as a sign of methotrexate toxicity. *Eur J Dermatol*. 2001;11:450-2.
7. Hocaoglu N, Atila R, Onen F, Tuncok Y. Early-onset pancytopenia and skin ulcer following low-dose methotrexate therapy. *Hum Exp Toxicol*. 2008;27:585-9.
8. Kurian A, Haber R. Methotrexate-induced cutaneous ulcers in a nonpsoriatic patient: Case report and review of the literature. *J Cutan Med Surg*. 2011;15:275-9.
9. Lawrence CM, Dahl MG. Two patterns of skin ulceration induced by methotrexate in patients with psoriasis. *J Am Acad Dermatol*. 1984;11:1059-65.
10. Breneman DL, Storer TJ, Breneman JC, Mutasim DF. Methotrexate-induced cutaneous ulceration in patients with erythrodermic mycosis fungoides. 2008;4:1135.

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