

Letter to the Editor

Cutaneous ulceration as a manifestation of systemic methotrexate toxicity

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Dear Sir,

Methotrexate (MTX), introduced in the 1950s, remains a cornerstone in the systemic treatment of dermatological disorders due to its immunosuppressive properties.^[1] Although major adverse effects such as hepatotoxicity, bone marrow suppression, and pulmonary fibrosis are widely recognized and addressed in clinical protocols, cutaneous ulceration is an underreported and poorly described toxicity.^[1]

A 48-year-old female, known patient of psoriasis for the past 15 years, presented with complaints of erosions, crusted lesions, and ulcerations all over the body for the past 7 days. Along with cutaneous lesions, there was a history of fever, oral ulceration and gingival swelling, difficulty in swallowing, arthralgia, weight loss, and anorexia. There was a history of aggravation of psoriasis every winter for which she had been prescribed tablet MTX 7.5 mg every 5th day, and she continued to take it on her own in case of aggravation for the past 15 years. Approximate cumulative dose of MTX was 7.5 g. She gave a history of intake of MTX (7.5 mg, 1 tablet daily for the past 10 days). On examination, multiple erosions and ulcerations with crusting were present over the pre-existing psoriatic plaques [Figure 1]. Multiple erosions were also present in the oral mucosa. Genital, ocular, and nasal mucosae were not involved. Systemic examination was normal.

Skin biopsy showed focal keratotic plugging and irregular acanthosis [Figure 2a], with swollen keratinocytes demonstrating diminished nuclear and cytoplasmic staining, along with occasional vacuolated or dyskeratotic cells [Figure 2b]. The dermis exhibited pigment incontinence and a perivascular lymphocytic inflammatory infiltrate admixed with a few neutrophils and eosinophils [Figure 2c]. Dermis showed pigment incontinence and perivascular lymphocytic inflammatory infiltrate with few neutrophils and eosinophils [Figure 2]. Complete blood count revealed severe anemia (hemoglobin: 6.3 g/dL), leukopenia (total leukocyte counts: 3,000 mg/dL), thrombocytopenia (platelet counts: 90,000 cu/mm), and raised erythrocyte sedimentation rate (25 mm/h). Peripheral blood smear showed mild anisocytosis. Serum folate levels were low, and serum iron was raised. Liver function tests were mildly deranged. Kidney function tests were normal. MTX levels were normal. Ultrasonography of the abdomen was unremarkable except for mild splenomegaly. However, the fibro scan of the liver was graded as F2 (portal and periportal fibrosis with rare septa). The patient was given supportive treatment in the form of adequate hydration, prophylactic antibiotics, Condy's compresses, and antihistamines. A folic acid supplement was started. The patient started to improve within a week.

MTX is approved for psoriasis, psoriatic arthritis, rheumatoid arthritis, certain cancers, and is even used off-label for various dermatologic and autoimmune conditions. In addition, MTX is an

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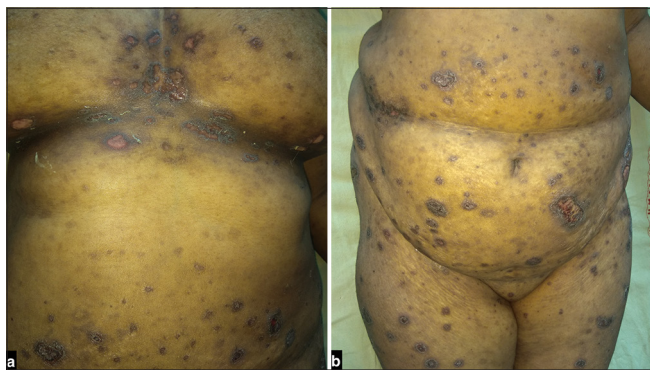


Figure 1: Cutaneous ulcerations over psoriatic plaques on (a) Inframammary region and upper part of abdomen; (b) lower part of abdomen and upper thigh.

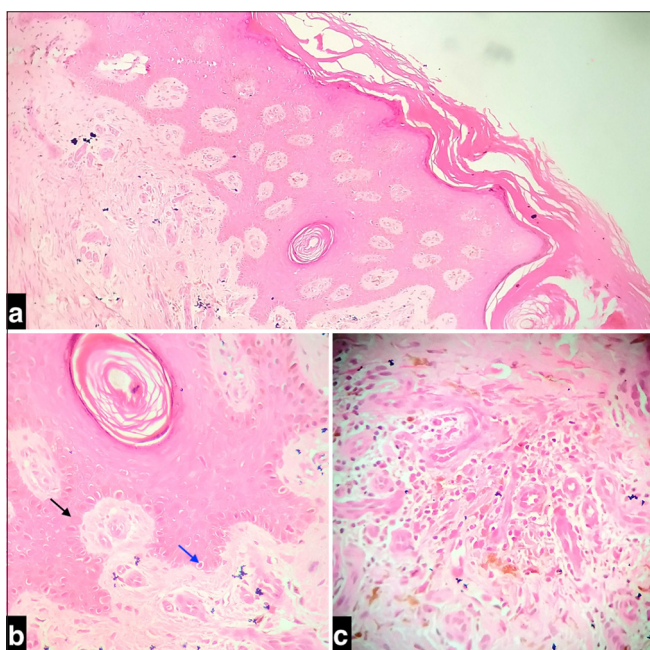


Figure 2: Histopathological examination showing (a) focal keratotic plugging and irregular acanthosis (H and E, 100x); (b) swollen keratinocytes (black arrow) demonstrating diminished nuclear and cytoplasmic staining, along with occasional vacuolated or dyskeratotic cells (blue arrow) (H and E, 400x); (c) the dermis exhibited pigment incontinence and a perivascular lymphocytic inflammatory infiltrate admixed with a few neutrophils and eosinophils (H and E, 400x).

abortifacient used in early and ectopic pregnancy and is used off-license in a host of dermatological conditions, including chronic urticaria, vasculitis, atopic dermatitis, pityriasis lichenoides, cutaneous sarcoidosis, and bullous pemphigoid, as well as in non-dermatological conditions, including Crohn's disease, systemic lupus erythematosus, and myositis.^[1] Toxicity can manifest in acute, chronic, idiosyncratic, or dose-dependent forms. Cutaneous toxicity may include erythema, necrosis, and ulceration, particularly over affected dermatoses. Ulceration

often signals impending systemic toxicity and may be overlooked or misinterpreted as a disease flare, leading to inappropriate dose escalation. Cutaneous ulceration is an early clinical sign of impending systemic toxicity to MTX.^[2] The exact incidence of MTX-induced skin ulceration is unknown; however, it is rarely seen. Roenigk *et al.*^[3] reported it in 6 out of 204 patients, while Lawrence and Dahl^[4] described two distinct ulceration patterns – type 1 over psoriatic plaques and type 2 on unaffected skin. It has been described soon after the onset of treatment^[2] or due to long-term use of MTX. Isolated cases of MTX-induced ulceration in patients without a history of psoriasis have been reported, including patients on low-dose treatment for rheumatoid arthritis and patients undergoing treatment for mycosis fungoides.^[5] Patients may present with isolated cutaneous lesions or with other signs of MTX toxicity, including mucositis, liver dysfunction, and/or myelosuppression. In patients with psoriasis, psoriatic plaques and/or normal skin become painful, erythematous, and superficially eroded. Early cutaneous ulceration may be mistaken for a flare-up of psoriasis, leading to an erroneous increase in the dose of MTX either by the patient or physician.^[3] Diagnosis is based on history and clinical examination, and biopsy is rarely required. Histology typically shows keratinocyte degeneration with signs of early necrosis and non-specific ulceration. Dermal findings often feature vascular dilation and lymphocytic infiltrates.^[4] Non-specific ulceration may also be present. Folic acid co-administration has proven beneficial in reducing toxicity and improving treatment adherence. In case of ulceration, withdrawal of MTX with supportive treatment usually leads to rapid improvement, with many patients showing signs of healing within a few days; however, in isolated cases, ulceration persists for years.^[4] Table 1 enlists the previous case reports of MTX toxicity.^[2,5-8] In our case, the patient presented with typical manifestations of MTX-induced ulceration on a background of psoriasis and, on further investigation, was found to have evidence of hepatic fibrosis. Early recognition of cutaneous findings as a marker of MTX toxicity in such cases allows prompt cessation of the drug, avoiding serious morbidity.

A recent systematic review by Berna *et al.*^[9] highlighted that MTX-induced cutaneous ulceration, although rare, is a significant early clinical marker of systemic toxicity. Cutaneous ulceration was often associated with mucosal involvement and myelosuppression and was frequently misdiagnosed as a flare-up of the underlying dermatosis, leading to inappropriate MTX escalation. Histological findings were generally non-specific, and management involved immediate drug cessation and supportive care. Most patients improved rapidly with folic acid supplementation and withdrawal of MTX.^[9]

Ethical approval: Institutional review board approval is not required.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical

Table 1: Previous case reports of MTX toxicity.

Study	Patient details	Mucosal involvement	Bone marrow involvement	Indication for MTX
Ben-Amitai <i>et al.</i> (1998) ^[6]	67-year-old man with recurrent leg ulcers over 3 years due to erroneous daily MTX dosing	Yes	No	Seronegative polyarthritis
Montero <i>et al.</i> (2000) ^[5]	52-year-old man with oral and leg ulcers after 19 months of MTX	Yes	No	Rheumatoid arthritis
Del Pozo <i>et al.</i> (2001) ^[7]	39-year-old woman with painless knuckle ulcers after MTX dose increase	No	No	Seronegative arthritis
Hocaoglu <i>et al.</i> (2008) ^[2]	64-year-old man mistakenly took weekly dose daily for 3 days; developed oral and foot ulcers	Yes	Yes	Rheumatoid arthritis
Kurian and Haber (2011) ^[8]	67-year-old man with hand, elbow, and leg ulcers after 3 years of MTX	No	Yes	Rheumatoid arthritis
Study	MTX dose	Coexisting conditions	Concomitant medications	Outcome
Ben-Amitai <i>et al.</i> (1998) ^[6]	5 mg/day	Coronary artery disease, duodenal ulcer	Prednisone, hydroxychloroquine	MTX discontinued; ulcers healed completely within 5 weeks
Montero <i>et al.</i> (2000) ^[5]	15 mg/week	Obesity, hypertension, type 2 diabetes, renal insufficiency	Deflazacort, flurbiprofen, folic acid	MTX stopped; complete healing of ulcers in 2 weeks
Del Pozo <i>et al.</i> (2001) ^[7]	15 mg/week	Demyelinating disease, non-Hodgkin lymphoma	Indomethacin	MTX stopped; ulcers resolved in 2 months
Hocaoglu <i>et al.</i> (2008) ^[2]	2.5 mg twice daily	None	None	MTX stopped; mucocutaneous ulcers and marrow suppression resolved in 16 days
Kurian and Haber (2011) ^[8]	25 mg/week	None	Prednisone, abatacept, diclofenac	MTX stopped; ulcers and marrow suppression resolved within 1 month

MTX: Methotrexate

information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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