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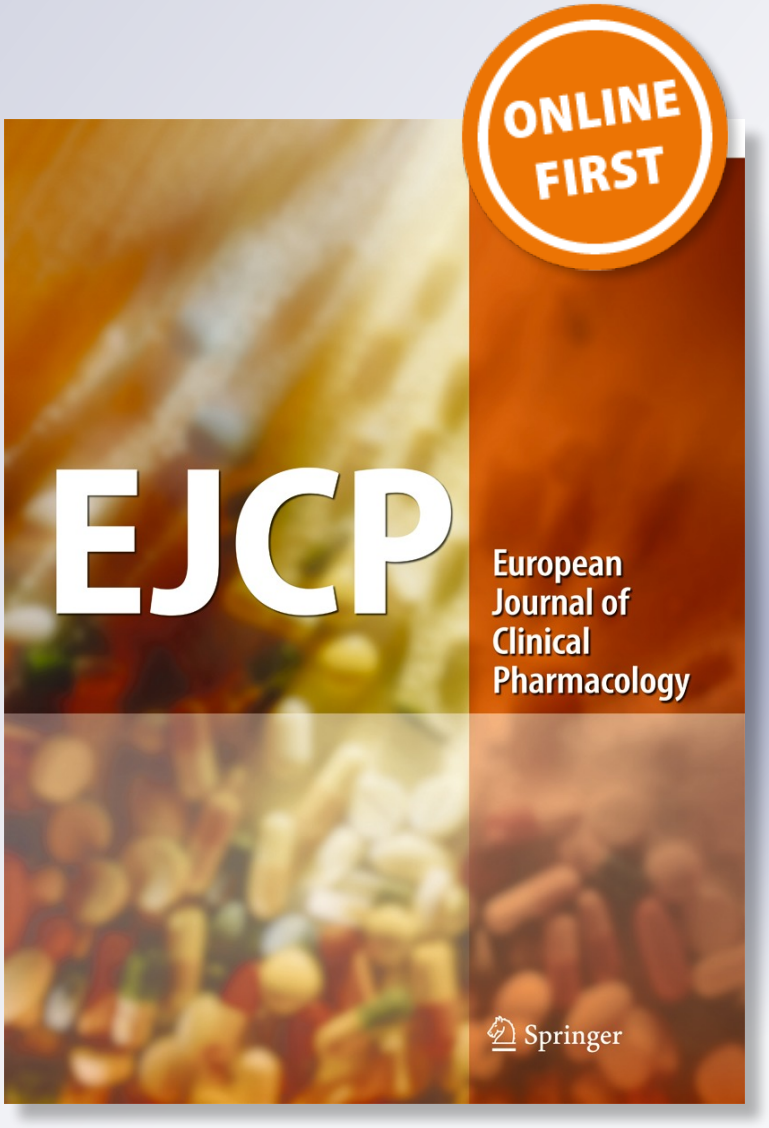


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LETTER TO THE EDITOR

# Acute methotrexate toxicity presenting with bullous lesions: an unusual presentation

**Sarita Sanke**[1] · **Pravesh Yadav**[1] · **Ram Chander**[1] · **Jagdish Chandra**[1]

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Sir,

Methotrexate (MTX) toxicity can be acute as well as delayed and idiosyncratic as well as dose dependent. Cutaneous presentation of acute MTX toxicity varies from acral erythema to necrosis and ulceration over pre-existing dermatological pathology.

A 7-year-old boy, a known case of acute T cell lymphocytic leukemia (ALL) on treatment, was referred for generalized redness of skin and blistering over the dorsa of the hands and scrotum since 2 days. He had received an induction regimen (prednisolone 60 mg/m$^2$ orally, intravenous vincristine 1.5 mg/m$^2$, asparaginase 10,000 units/m$^2$ intramuscularly for 5 weeks) and a consolidation regimen (6-mercaptopurine 60 mg/m$^2$/day orally for 3 weeks). In addition, oral trimethoprim-sulfamethoxazole was given regularly to prevent *Pneumocystis carinii* infection. He was then started on interim maintenance regimen comprising methotrexate weekly (5 g/m$^2$, i.e. 3250 mg) along with 6-mercaptopurine (25 mg/m$^2$) daily. This dose was given over a period of 24 h, every 3 hourly in 5% dextrose (240 ml). Folinic acid (15 mg/m$^2$) rescue was given the next day every 6 hourly as per the protocol. Three days after the first dose of MTX, he developed erosions in mouth followed by edema and erythema over the face, trunk, and extremities and blisters over the dorsa of the hands and scrotal area. There was no gastrointestinal, urinary, ocular, or upper respiratory involvement. There was no history of seizures, palpitations, or sudden respiratory distress. On examination, the child was irritable and febrile (99 °F) with tachycardia (104/min) and hypotension (90/68 mmHg). Submandibular and inguinal lymphadenopathy with facial edema was present. Cutaneous examination revealed erythema of face, upper limbs (distal > proximal), and lower limbs with skip areas. Multiple, flaccid bullae (0.6 to 2 cm) over erythematous skin were present over the bilateral dorsa of the hands and scrotum, filled with clear to minimally turbid fluid (Fig. 1). Nikolsky sign was negative. The bulla over the scrotum ruptured to reveal frank superficial erosion (Fig. 2). Examination of oral mucosa revealed ill-defined erosions and hemorrhagic crusts. Genital, ocular, and nasal mucosae were not involved. There was no involvement of palms and soles. Systemic examination was normal. Gram and Giemsa stain showed neutrophils with no acantholytic cells. Blood and pus cultures were sterile. The laboratory parameters revealed gradual deterioration in the blood counts (hemoglobin, total leucocyte count, platelets), rapid increase in total bilirubin (0.5 to 1.8 mg/dl), and aspartate transaminase (AST) (70 to 240) suggesting liver dysfunction. Urea increased from 22 to 42 mg/dl and creatinine from 0.3 to 0.9 mg/dl within 3 days. Ultrasound of abdomen and radiograph of chest were normal. The biopsy was not done; however, three differentials were kept, which included staphylococcal scalded skin syndrome (SSSS), Steven Johnson syndrome (SJS), and acute MTX toxicity. SSSS was ruled out, as oral mucosal involvement is not seen in SSSS and as Giemsa stain did not reveal any acantholytic cells. Presence of frank bullae, absence of targetoid lesions or frank necrosis of skin, and no rapid worsening of skin lesions ruled out SJS/TEN. Thus, the final diagnosis of acute MTX toxicity was considered.

The patient was given adequate hydration, prophylactic antibiotics (vancomycin and colistin), mouth wash and symptomatic treatment. The patient was also started on high-dose

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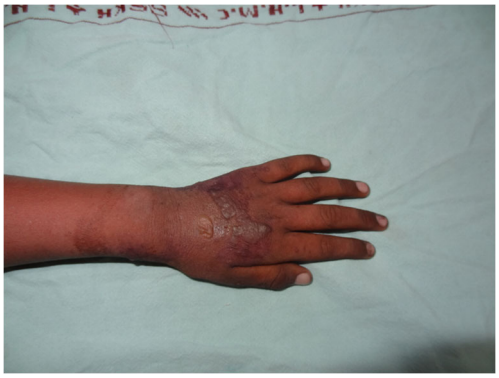

**Fig. 1** Bullae present over the bilateral dorsa of the hands

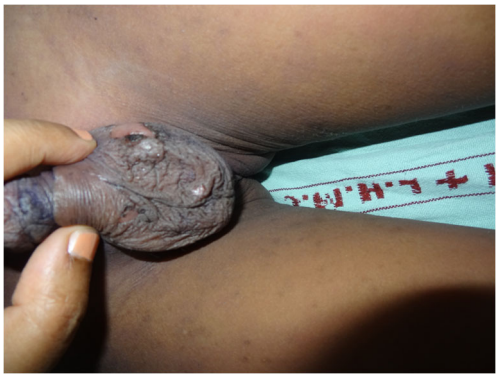

**Fig. 2** Erosions present over the scrotum

leucovorin. The MTX level was <0.10 μmol/l, following which leucovorin was stopped. Gradually, the erythema and edema improved along with improvement in general condition of the patient. Oral erosions showed hemorrhagic crusting followed by gradual healing. On day 10, there was improvement in the hematological parameters as well as liver and renal function tests. The patient was given a lower dose of MTX in the next cycle (2.5 g/m$^2$) to which the patient developed only mild oral erosions, while there was no derangement in the hematological parameters and renal or liver function tests.

High-dose MTX (HD-MTX) is defined as more than 1 g/m$^2$ [1]. Dermatologic toxicities are idiosyncratic reactions occurring in up to 10% of patients and range from mild acral erythema and necrosis to acral ulceration [1]. Cutaneous blistering by MTX toxicity is a diagnosis of exclusion, and its pathogenic mechanism may be multifactorial, including direct toxicity of the drug. Aractingi et al. reported a similar report of skin necrosis in a male receiving 5 g of MTX for high-grade lymphoma. The skin disease was accompanied by renal, hepatic, and mucosal lesions, as well as bone marrow aplasia. Direct toxicity of epidermis by MTX was considered the probable mechanism [2]. Toxic epidermal necrolysis-like lesions involving 90% of the total body surface after MTX infusion for ALL were reported by Yang et al. However, this patient succumbed to death [3]. The development of toxicity in our patient can be explained on the basis of various genetic associations between folate metabolic pathway and MTX pharmacokinetics [4]. MTX clearance has been found to be decreased in patients with the MTHFR 677TT, and its polymorphism is associated with an increased incidence of mucositis which might be the probable factor responsible in our patient [4]. However, genetic polymorphism could not be studied due to lack of resources. In addition to its role in the prevention of MTX toxicity, high-dose leucovorin (0.24 to 8 g/d) is standard care for patients with delayed MTX clearance and renal injury [5]. Hence, our patient was given further dose of leucovorin on diagnosis, which led to his improvement. For patients receiving high doses of MTX, the terminal half-life of MTX is 8 to 15 h. However, toxicity may continue for up to 24 h after serum concentrations fall. This explains the delayed presentation of signs of toxicity in our patient on day 3, which might be due to the trapped polyglutamated forms of MTX inside the cells. Moreover, leucovorin is particularly effective in the prevention of myelosuppression, GI toxicity, and neurotoxicity as compared to cutaneous toxicity [6]. This explains the predominant cutaneous toxicity in our patient as compared to other toxicities. Acute MTX toxicity presenting as acral and perineal blisters associated with generalized erythema and severe oral mucositis with minimal systemic toxicity in the absence of any underlying dermatological pathology makes our case unique. Early identification of these signs can prevent morbidity and possible mortality in cases of MTX toxicity.

**Compliance with ethical standards**

**Conflict of interest** None.

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