Dreaded adverse events due to overdose of methotrexate: a case report

Anil Prakash Gosavi, MD
Ravindranath Brahmadeo Chavan, MD*
Rahul Narendra Jaiswal, MD
Vijay Deepak Joshi, MD

Department of Skin and V.D, B.J. Government Medical College and Sassoon General Hospitals, Pune, Maharashtra, India

**Corresponding author: Ravindranath Brahmadeo Chavan, MD, Department of Skin and V.D., B.J.G.M.C and Sassoon General Hospitals, Pune, Maharashtra, India Email: drravindranathchavan@gmail.com*

Received: 28 August 2020
Accepted: 19 October 2020

Methotrexate, an anti-psoriatic drug possessing immunoregulatory, antiproliferative, and anti-inflammatory properties, acts by blocking deoxyribonucleic acid and ribonucleic acid synthesis. It acts especially on rapidly dividing bone marrow cells and proliferating epithelia and mucosae. The toxicity of this double-edged sword occurs due to accidental excessive intake or daily dosing instead of weekly dosing. We report the case of a 31-year-old male with acute methotrexate toxicity presenting with ulcerations over pre-existing psoriatic plaques with foci of bleeding. Oral mucosal involvement in the form of buccal and palatal ulceration was present in the setting of sepsis, pancytopenia, and acute kidney injury. It is worth emphasizing the role of adequate prescription guidelines, patient education, stringent monitoring, early recognition of tell-tale signs of toxicity, timely leucovorin rescue, and the need for strict enforcement of regulations regarding the over-the-counter availability of such drugs, especially in developing countries.

Keywords: methotrexate toxicity, psoriasis, leucovorin

Iran J Dermatol 2022; 25: 178-182

DOI: 10.22034/ijd.2020.245779.1201

INTRODUCTION

Methotrexate, an anti-psoriatic drug recognized in 1951, is a structural analog of folic acid. It acts by blocking deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis. Owing to its cytotoxic, immunosuppressive, anti-inflammatory (due to increased intracellular adenosine accumulation), and antiproliferative (on T cells and epidermal keratinocytes) properties, it is commonly used in psoriasis [1,2]. The cells most susceptible to methotrexate include leukemic myeloblasts, lymphoblasts, synovial macrophages, and proliferating epithelia [3]. This is due to polyglutamination, a process that makes the drug persist intracellularly for a long time [1,2]. The recommended weekly doses of this drug range from 7.5 to 30 mg per week [2]. Dermatologists prefer standard doses in the range of 0.3–0.5 mg/kg/week and later tapering the dose till a Psoriasis Area Severity Index (PASI) score of 75 is achieved. The toxicity of methotrexate is due to the inhibition of DNA synthesis in actively proliferating cells [3], which manifests as pancytopenia, mucocutaneous ulcerations, and systemic signs and symptoms.

CASE PRESENTATION

A 31-year-old rural alcoholic male known to have had plaque psoriasis for the past seven years consumed 15 mg daily methotrexate tablets for ten consecutive days. He started having nausea, vomiting, and diarrhea, and subsequently developed raw areas on pre-existing psoriatic skin lesions, intolerance to spicy food, and an inability to swallow. On examination, his general condition was serious. He had pallor and icterus. Dermatological examination revealed multiple ulcerations on pre-existing keratotic, scaly psoriatic

plaques on the elbows, forearms, hands, knees, feet, and gluteal region, with focal areas of bleeding and oozing (Figures. 1–4). Hemorrhagic crusting was present at places. The lesions showed a predilection for the extensor regions, with relative sparing of the trunk. The PASI score was 10.5. Fingernails showed irregular pitting. He had multiple irregular

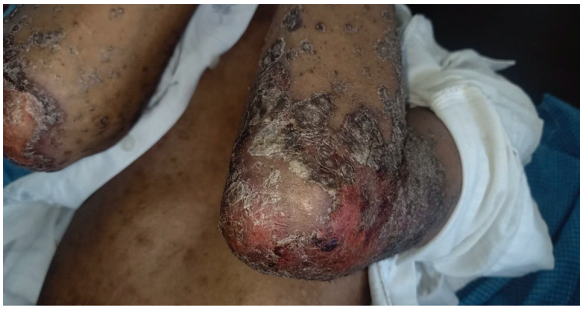

Figure 1. Ulcerated, psoriatic plaques over bilateral elbows.

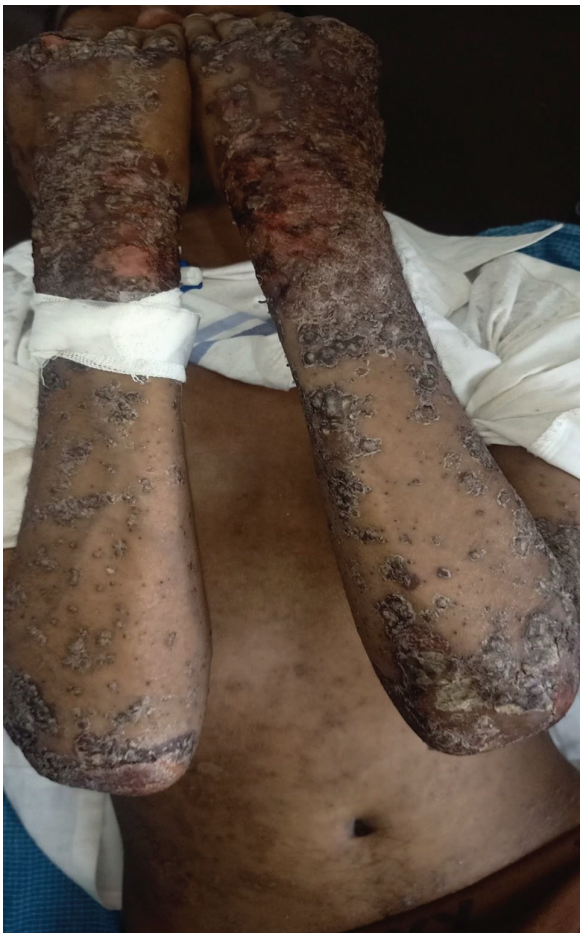

Figure 2. Bilateral forearms and hands showing keratotic crusted plaques with erosions.

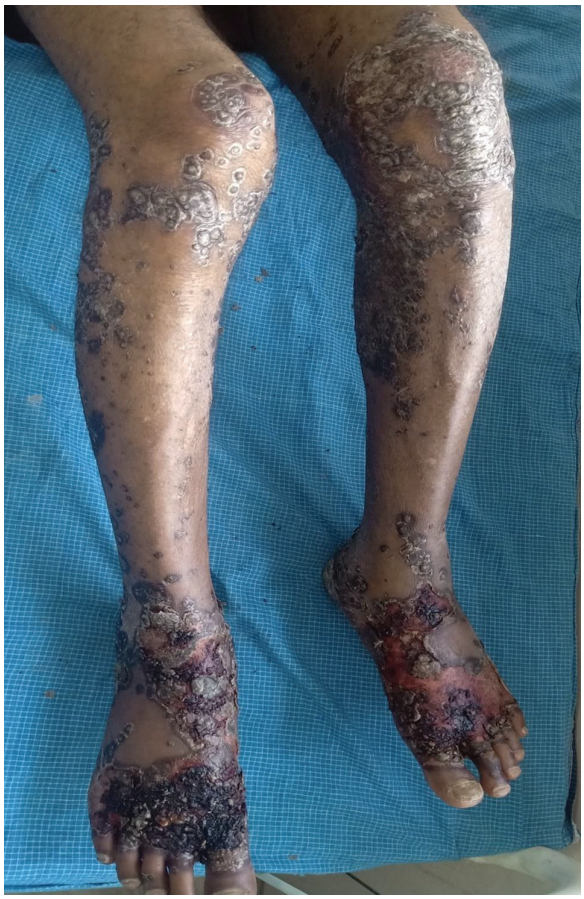

Figure 3. Bilateral lower limbs with extensor-predominant, crusted, keratotic plaques conspicuously presenting on knees and feet with focal erosions.

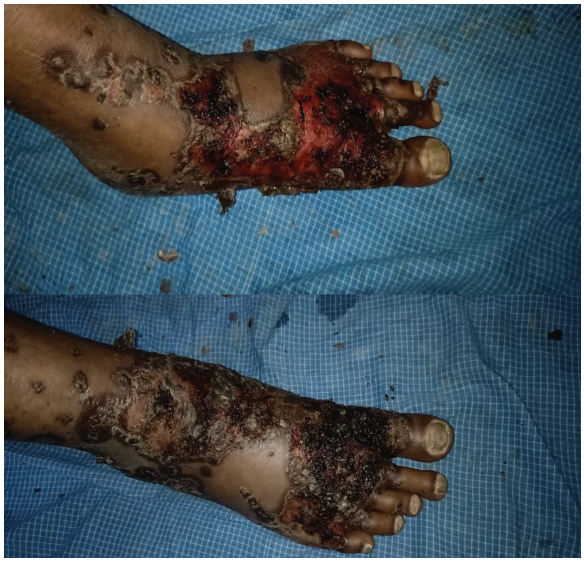

Figure 4. Feet showing ulcerated plaques with foci of bleeding and hemorrhagic crusting on the pre-existing hyperkeratotic, scaly psoriatic lesions.

confluent erosions on the palate, buccal mucosa, and lips, with hemorrhagic crusting on the lips (Figure 5). The patient showed systemic signs of fever, tachycardia, tachypnea, and hypotension. Based on the history and clinical findings, a probable diagnosis of acute methotrexate toxicity in a case of plaque psoriasis was made. Hematological investigations were suggestive of pancytopenia (Hb: 8.5 g/dl, WBC: 500/mm^3, platelets: 10,000/mm^3) with a low reticulocyte count (0.2%), indicative of bone marrow insult. Renal and liver function tests returned abnormal results (urea 151 mg/dl, creatinine 4.4 mg/dl, bilirubin 3.5 mg/dl, aspartate transaminase 280 IU/l, alanine transaminase 96 IU/l, alkaline phosphatase 156 IU/l). Urine analysis depicted the presence of albumin and bile pigments. Blood culture showed the presence of coagulase negative staphylococcus aureus, sensitive to amoxicillin-clavulanic acid. Radiological investigations were normal. His baseline serum methotrexate level measured within first 24 hours of admission was 0.3 µmol/l, with subsequent measurement after 72 hours showing the level of 0.11 µmol/l. The patient was admitted under intensive care unit and his general condition was stabilized. Methotrexate tablets were stopped immediately. 15 mg/m^2 of leucovorin was injected intravenously every 6 hours, the first dose of which was given within 3 hours of presentation (Table 1). It was continued for three days, after which it was stopped when the serum methotrexate level dropped to 0.11 µmol/l. Folic acid tablets in a dose of 5 mg once a day were started. Intravenous fluids with 5% dextrose and antibiotics were given. Adequate urine output maintenance and urine alkalinization were ensured. Platelet and packed red cell transfusions were given as corrective measures for pancytopenia. Topical antibiotics were administered to prevent secondary infections of the erosions. Nonetheless, the patient's clinical condition, blood counts, and liver and kidney functions deteriorated. In spite of timely interventions, the patient

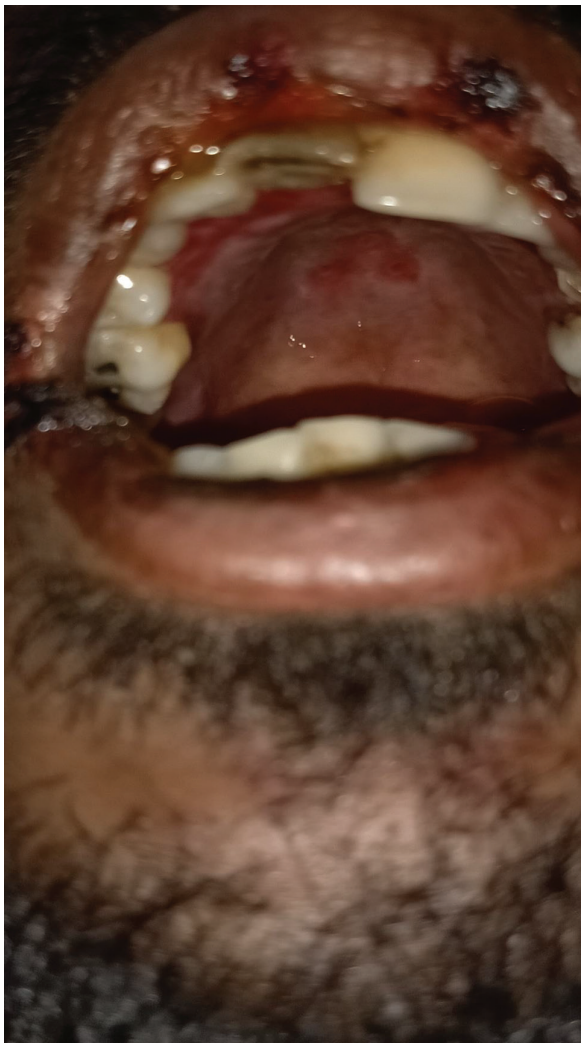

Figure 5. Multiple, reddish, irregular, confluent erosions on palatal and buccal mucosa with hemorrhagic crusting on lips.

Table 1. Dosage of folinic acid according to methotrexate plasma concentration (µmol/l) [9]

Timing after last methotrexate dose	Methotrexate plasma concenteration					
	< 0.2 µmol/l	0.2–0.7 µmol/l	0.71–2 µmol/l	2.1–19.9 µmol/l	20–100 µmol/l	> 100 µmol/l
24 hours	None	15 mg/m^2, 6 hourly	15 mg/m^2, 6 hourly	15 mg/m^2, 6 hourly	60 mg/m^2, 6 hourly	According to the formula
48 hours	None	15 mg/m^2, 6 hourly	15 mg/m^2, 6 hourly	150 mg/m^2, 6 hourly	300 mg/m^2, 6 hourly	According to the formula
72 hours	None	30 mg/m^2, 6 hourly	150 mg/m^2, 6 hourly	750 mg/m^2, 6 hourly	3000 mg/m^2, 6 hourly	According to the formula

Formula: Total daily dose of folinic acid = (Patient's actual serum methotrexate standard daily dose of folinic acid) ÷ Upper limit of serum methotrexate for the actual day and time (20 µmol/l at 24 h, 2 µmol/l at 48 h, and 0.2 µmol/l at 72 h)

succumbed to type-1 respiratory failure with sepsis due to pancytopenia, complicated by acute kidney injury.

DISCUSSION

Psoriasis is a chronic, autoimmune, inflammatory skin disease with polygenic predisposition combined with environmental triggers such as trauma, infection, or medication. To inhibit the excessive and unregulated keratinocyte proliferation, systemic immunosuppressants like methotrexate are used. It is the preferred immunosuppressant due to its low cost, easy availability, and favorable safety profile. It is used in widespread and recalcitrant psoriasis, erythrodermic psoriasis, recalcitrant psoriatic arthritis, and psoriasis unresponsive to retinoids and phototherapy [2]. The drug was approved by the Food and Drug Administration to treat psoriasis in 1972 [2]. It is a potent, competitive, and irreversible inhibitor of the enzyme dihydrofolate reductase required for DNA synthesis in proliferating cells.

Methotrexate toxicity in the acute form occurs due to wrong dosing patterns, drug interactions, and fallacious escalation of doses in an attempt to control flared-up skin lesions. The drugs enhancing the risk of methotrexate toxicity include those that either decrease its renal elimination (aminoglycosides, non-steroidal anti-inflammatory drugs, probenecid, sulphonamides, salicylates, colchicine, cisplatin, penicillin) or those that displace methotrexate from protein binding sites (barbiturates, salicylates, sulphonamides, phenytoin, sulfonylureas, tetracyclines, retinoids) [4]. Other predisposing causes include age greater than 55 years, infections, alcoholism, pustular psoriasis flares, hypoalbuminemia, and acute renal failure [4].

The toxicity presents itself with maculopapular skin rashes, mucocutaneous ulcerations, mucositis, diarrhea, vomiting, melena, pancytopenia, hepatotoxicity, acute renal failure, and pulmonary toxicity [4]. Cutaneous ulcerations are observed in hyperproliferative epithelia, especially on the psoriatic plaques (type I) or pre-existing dermatoses (type II), and rarely on healthy skin [5]. Ulceration and necrosis of cutaneous psoriasis plaques may signal the impending development of life-threatening pancytopenia in patients with acute methotrexate toxicity [6]. Mucosal ulcerations are observed after 3–7 days, preceding the onset of cytopenia. Although the exact cumulative doses causing acute methotrexate toxicity are not clear, doses of 35-150 mg taken over 3-7 days have been shown to induce this condition [7].

Most patients resort to self-medication due to the over-the-counter availability of methotrexate [7]. This results in untoward toxicity due to accidental overdosing, which can also result from prescription error or in a self-attempt to heal the flares of psoriasis [8]. In case of such an event, it should be properly managed with adequate hydration, urine alkalinization, glucarpidase (carboxypeptidase) as supportive therapy, and leucovorin rescue and granulocyte monocyte colony-stimulating factor (GM-CSF) for pancytopenia as specific therapy [9]. Our case had risk factors of wrongly self-administered daily doses of methotrexate, lack of physician's guidelines about the dosage, lack of folic acid supplementation, and alcoholism.

CONCLUSION

Methotrexate toxicity presenting as mucocutaneous ulcerations should be promptly recognized and treated to prevent fatal occurrences. It is preventable if one ensures patient education about appropriate dosing guidelines, prescription of only limited tablets till further follow-up, stringent monitoring, and strict enforcement of drug availability and purchasing regulations.

Conflict of interest: None declared.

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