Methotrexate Cutaneous Toxicity following a Single Dose of 10 mg in a Case of Chronic Plaque Psoriasis: A Possible Idiosyncratic Reaction

Abstract

Low-dose methotrexate is a well-tolerated and inexpensive systemic immunosuppressive agent used commonly in dermatology. However, several adverse events such as pancytopenia, pneumonitis, mucositis, and cutaneous ulcerations may develop during acute toxicity with dose-dependent or idiosyncratic mechanisms. Risk factors for methotrexate toxicity include advanced age, hypoalbuminemia, renal dysfunction, and concomitant drugs increasing the level of methotrexate in the body. We present a case of methotrexate toxicity presenting with classical features along with mucocutaneous side-effects, such as ulceration of psoriatic plaques and acral erythema, following a single dose of methotrexate.

Keywords: *Cutaneous ulceration, low-dose methotrexate, methotrexate toxicity*

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Introduction

Methotrexate remains one of the most commonly prescribed systemic immunosuppressive agents in dermatology owing to its efficacy and low cost. Although uncommon and rarely reported, mucocutaneous side-effects such as ulceration of psoriatic plaques and mucositis can be seen with low-dose methotrexate therapy.[1] These toxic events are usually dose-dependent but may be idiosyncratic in nature. Here, we present a case of with cutaneous ulcerations, acral erythema, and severe pancytopenia following the administration of a single dose of methotrexate.

Case Report

A 60-year-old male, a known case of chronic plaque psoriasis for 10 years, presented with exacerbation of the disease (impending erythroderma) and pain in sacroiliac joints, left knee joint, both ankle joints, and small joints of hand for 15 days. The patient had hypertension which was controlled on tab. amlodipine 5 mg OD. The patient had received topical steroids and calcipotriol and systemic PUVA therapy 3 years back for his skin disease. On clinical examination, he had well-defined erythematous indurated plaques covered with silvery white scales involving the scalp and body, sparing the palms and soles, with a Psoriasis Area and Severity Index (PASI) of 25.5. The patient was febrile and had cough and difficulty in swallowing, and was diagnosed with as pharyngitis, and initiated on tab. amoxycillin-clavulanic acid 625 mg TDS, tab. paracetamol 500 mg SOS, and tab. ibuprofen 400 mg BD. The complete blood count prior to methotrexate administration was within normal limits with Hb – 10.2 g/dl, red blood cell count – 3.4 million/mm^3, WBC count – 10,800/mm^3, and platelet count – 4.4 lakh/mm^3. Serum biochemistry including serum albumin, kidney, and liver function tests were within normal limits. Urine analysis, chest X-ray, and electrocardiogram (ECG) were normal. After taking a medicine consultation, the patient was initiated on methotrexate 10 mg orally once every week. Three days later, the patient started complaining of nausea, vomiting, abdominal pain, and loss of appetite. Clinical examination revealed ulcerated painful psoriatic plaques present over the neck, chest, abdomen, and back [Figure 1] along with a burning sensation and painful erythematous macules and desquamation of skin present symmetrically on the palm and soles [Figure 2]. Oral mucosa examination showed stomatitis. Laboratory studies showed Hb – 7.8 g/dl, red blood cell

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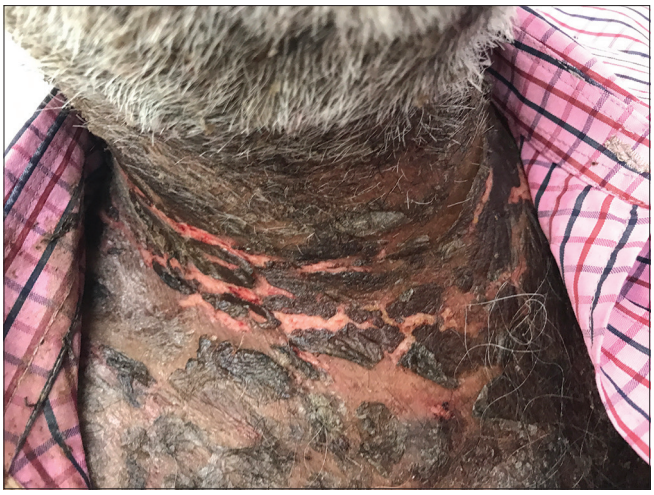

Figure 1: Ulceration of the psoriatic plaques present over the neck

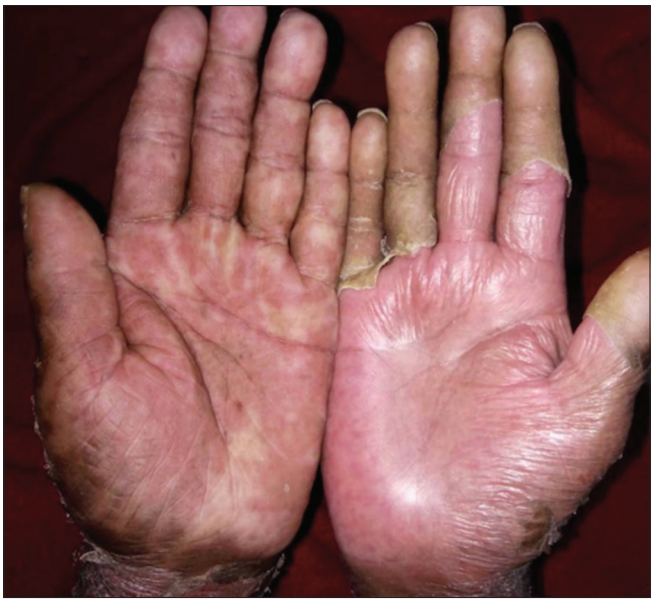

Figure 2: Painful erythematous macules with desquamation of the skin present on the palms and soles

count – 2.8 million/mm^3, WBC count – 4800/mm^3, platelet count – 80,000/mm^3. Biochemistry screen showed elevated liver enzymes with SGOT – 168 IU/L, SGPT – 89 IU/L, and alkaline phosphatase – 471 IU/L. Other investigations were normal. Skin biopsy done from the ulcerated plaque is depicted in Figure 3. Using Naranjo Adverse Drug Reaction Probability Scale and WHO-UMC causality criteria, a probable relationship was found between these cutaneous adverse effects and methotrexate therapy in this patient.[2,3] Based on the clinical and laboratory findings, a diagnosis of methotrexate toxicity was made. Methotrexate therapy was withheld and the patient was initiated on leucovorin rescue (Inj. leucovorin calcium 15 mg 6 hourly for 3 days) and Inj. pantoprazole 40 mg i.v. BD. Skin care consisted of cleaning the lesions with povidone-iodine followed by application of bland emollients and 2% mupirocin cream. Patient's general condition improved and lesions began to heal in 7 days.

Discussion

Low-dose methotrexate (7.5 mg to 25 mg/week) used in dermatology is usually well tolerated with mild adverse effects appearing within 48 hours after a weekly dose. However, several idiosyncratic or dose-dependent toxicities have been noted including pancytopenia, hepatotoxicity, severe mucositis, central nervous system complications, and pneumonitis. Of these, bone marrow toxicity has been reported to develop even after a single low dose of methotrexate.[4]

Cutaneous manifestations of methotrexate toxicity include dose-related mucositis, photosensitivity, and idiosyncratic immune reactions such as erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis. Methotrexate-induced cutaneous ulceration occurs in two patterns: in type 1, there is superficial ulceration of the existing psoriatic plaques and in type 2, ulceration involves nonpsoriatic skin. It develops because of increased susceptibility of the rapidly multiplying keratinocytes within the psoriatic plaques to the effects of folate-antagonism. Interestingly, it has been seen more frequently in patients on low-dose treatment than in high-dose chemotherapy regimens.[5] Jariwala *et al*. reported that the skin ulceration with methotrexate therapy can develop either at initiation of therapy or as a presenting feature of methotrexate toxicity during longstanding treatment.[6] Acral erythema or palmar plantar erythrodysesthesia is a side effect of high-dose chemotherapy, presenting clinically as dysaesthesia and tingling over the palms and soles followed by the development of symmetrical, well-defined, painful erythema, which may progress to bullae formation and desquamation.[7] Although the pathogenesis remains unclear, the most widely accepted hypothesis is direct cytotoxicity by chemotherapeutic agents on epidermal cells. The acral involvement in our case was suggestive of this reaction, which has not been noted with low-dose methotrexate used for dermatological diseases in the past.[8,9]

Our patient presented with signs of methotrexate toxicity (nausea, mucositis, cutaneous ulcerations, acral erythema, elevated liver enzymes, and pancytopenia) which developed after a single dose of methotrexate. Though acute toxicity with methotrexate has been reported previously with low-dose therapy, to our knowledge, mucocutaneous signs of methotrexate toxicity such as ulceration of psoriatic plaques and acral erythema have not been reported previously with a single low dose (10 mg) of methotrexate. Several risk factors have been implicated for the development of these severe adverse drug reactions [Table 1] including incorrect dosing, which is, taking methotrexate daily instead of weekly. However, because the patient developed toxicity during inpatient hospital treatment, the drug intake was supervised, ruling out any overdosing. In our case, it was

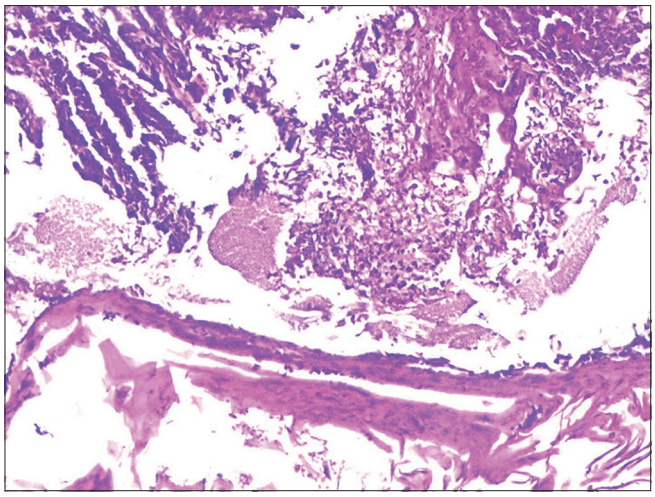

Figure 3: Skin biopsy from ulcerated plaque showing ulcerated epidermis and parakeratotic keratin along with necrotic debris and fibrinosuppurative exudate and perivascular inflammatory infiltrate in dermis. (H and E, ×100)

Table 1: Risk factors for the development of methotrexate toxicity

Risk factors	Explanation
Hypoalbuminemia	Methotrexate circulates in the bloodstream conjugated with albumin
Renal insufficiency	Methotrexate elimination depends on glomerular filtration and tubular secretion
Advanced age (>55 years)	Kidney function and cognition is often poor and they may be taking several medications
Concomitant infections	Antibiotics, such as penicillin and co-trimoxazole, increase the risk of drug interactions
Low folate levels and lack of folate supplementation	Methotrexate inhibits the enzyme dihydrofolate reductase, depleting the pool of reduced folates required for the formation of metabolic intermediates including purines required for DNA synthesis
Drug interactions	A. Drugs that diminish renal elimination of methotrexate (penicillin, aminoglycosides, nonsteroidal anti-inflammatory agents, salicylates, and sulfonamides)
	B. Those inhibiting dihydrofolate reductase (ethanol, trimethoprim-sulfamethoxazole)
	C. Drugs decreasing methotrexate protein binding (barbiturates, phenytoin)
Errors in drug administration	Taking methotrexate daily instead of weekly increases methotrexate level in the body
Genetic polymorphism	Methotrexate pharmacokinetics are highly variable due to gene polymorphisms in enzymes and transporters

probably the concomitant administration of nonsteroidal anti-inflammatory drugs (NSAIDS) and penicillin antibiotics and old age that may have played a role.[10,11]

Because the patient had not received methotrexate in the past and developed acute toxicity with a single low dose of methotrexate, it was possibly due to an idiosyncratic mechanism, which is dependent on an individual's genotype and the consequent metabolism of the drug.[12] Our case highlights the mucocutaneous signs of methotrexate toxicity, with a single low dose of methotrexate, and reiterates that, in predisposed individuals, even the first dose may cause toxicity.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical 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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Nil.

Conflicts of interest

There are no conflicts of interest.

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