Low-dose methotrexate-induced ulcerated psoriatic plaques: A rare case

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INTRODUCTION

Low-dose methotrexate is an effective and safe management for extensive and severe psoriasis. It may cause adverse reactions ranging from trivial to life threatening. Among them, hepatotoxicity and pancytopenia are the common serious side effects, whereas painful ulceration of psoriatic plaques as an early cutaneous manifestation of low-dose methotrexate toxicity has rarely been reported.[1-5] Here, we describe a case of psoriatic plaque ulceration induced by low-dose methotrexate and highlight the risk factors and possible mechanisms of toxicity.

CASE REPORT

A 34-year-old Taiwanese man was admitted to our inpatient ward for erythrodermic psoriasis. Although he had 14-year history of plaque psoriasis, he was never prescribed systemic medications except for etoricoxib and leflunomide, which had been used for psoriatic arthritis for 2 years and were discontinued because of abnormal liver function. In addition, amlodipine/benazepril and bisoprolol were taken for 4 years to control hypertension. After admission, celecoxib, 400 mg daily, was prescribed for joint pain along with the continuous use of amlodipine/benazepril and bisoprolol. Narrowband ultraviolet B, topical corticosteroids and vitamin D_3 analog were used initially, but the skin lesions responded little. Systemic treatment with low-dose methotrexate (15 mg/wk) and folate supplementation (5 mg daily) was started. Multiple painful ulcerations on his psoriatic plaques developed 1 week later. The patient was afebrile with normal vital signs. Dermatologic examination found several ulcerated erythematous plaques of different sizes on the trunk and limbs, with the groin and thighs being the most severely affected, showing a confluence of marked, bright red, moist erosions and ulcerations (Fig 1). The face, hands, feet, genitalia, and mucous membranes were spared.

Complete blood count and albumin level as well as renal and liver functions were all within the normal range. A skin biopsy section taken from the right flank area showed ulcers with fibrosis in the papillary dermis along with perivascular infiltration of lymphohistiocytes, neutrophils, and a few eosinophils (Fig 2). According to the clinical and histopathologic findings, the diagnosis of methotrexate toxicity was made, and the drug was, therefore, discontinued. Symptoms and signs soon resolved within 2 weeks after withdrawal of methotrexate.

DISCUSSION

Methotrexate, an analog of folate that competitively and irreversibly inhibits dihydrofolate reductase, is eliminated primarily by the kidneys, with 60% to 95% excreted unchanged. Therefore, the potential factors in the development of toxicity might include folate deficiency, drugs that impair folate absorption (eg, barbiturates, nitrofurantoin), drugs that inhibit dihydrofolate reductase (eg, trimethoprim-sulfamethoxazole, ethanol) or decrease glomerular filtration (eg, nonsteroidal anti-inflammatory drugs), or drugs that lower tubular secretion (eg, aspirin, penicillin, sulfonamides, colchicine). Also, approximately 50% of methotrexate within the blood is protein bound. Low serum albumin and medications

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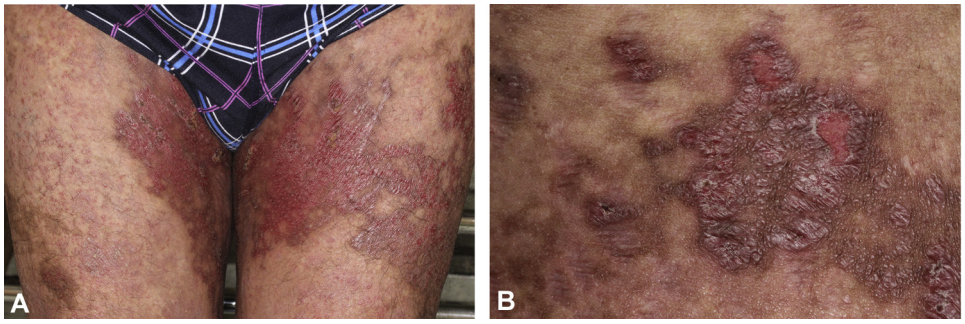

Fig 1. Clinical pictures of ulcerated psoriatic plaques. **A**, Erythematous psoriatic plaque with ulcerated surface on thighs. **B**, Ulceration of psoriatic plaques on the right flank.

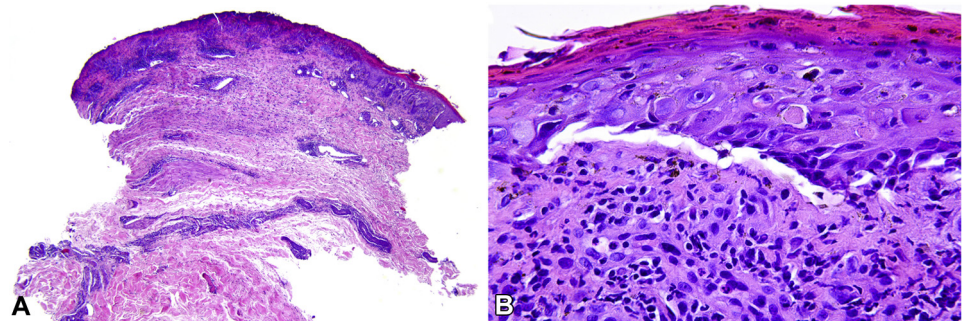

Fig 2. Histopathologic features of methotrexate-induced ulcerations. **A**, Skin biopsy section adjacent to an ulcerated lesion shows focal epidermal-dermal separation and ectatic vessels. **B**, Magnification shows an acanthotic epidermis with scattered dyskeratotic keratinocytes, overlying parakeratosis, and a superficial perivascular mixed inflammatory infiltrate. (Hematoxylin-eosin stain; **A**, low power; **B**, high power.)

that displace methotrexate from albumin (eg, phenytoin, tetracycline, sulfonamides, barbiturates, probenecid, salicylates, chloramphenicol, sulfonylureas) are likely to induce methotrexate toxicity. Other risk factors include alteration in dose (initiation, re-initiation, escalation in dose), advanced age, infections, diabetes mellitus,[6] and psoriatic flares.[4]

The exact incidence of methotrexate-induced ulcerated psoriatic plaques is unclear because of its rarity. A case of methotrexate-induced ulceration in patients without history of psoriasis has also been reported.[7] As reported by Jariwala et al,[3] the skin ulceration might develop at the onset of treatment or during longstanding treatment as a presenting feature of methotrexate overdose. It has also been described as a herald for impending pancytopenia in methotrexate toxicity.[1,2,4,5]

Surprisingly, most cases of methotrexate-induced ulceration were reported in patients treated with low-dose (7.5-25 mg/wk) instead of high-dose methotrexate (100-250 mg/m^2/wk), possibly because hyperproliferative psoriatic plaques are more susceptible to the effect of folate antagonism.[5] Unfortunately, painful, ulcerated, erythematous psoriatic plaques can sometimes be mistaken as an exacerbation of the psoriasis, which leads to erroneous increase in methotrexate dosage. Kivity et al[8] found that serum methotrexate concentrations, undetectable within 24 hours after administration, do not reflect or correlate with clinical toxicity, as prolonged low-dose methotrexate toxicity might be chiefly mediated by the intracellular polyglutamate derivatives, which cannot be measured. It is thus unnecessary to monitor routine methotrexate serum concentration, as there is currently no specific laboratory test effective enough to confirm the diagnosis, which is mainly based on clinical findings. Even a skin biopsy is rarely required. Histopathologic features include focal dermal-epidermal separation with dyskeratotic keratinocytes and a maturation defect related to a direct toxic antimetabolite effect on the epidermis. Other reported features are epidermal acanthosis, spongiosis, and focal parakeratosis in addition to a mild, superficial perivascular and interstitial mixed inflammatory infiltrate consisting of lymphocytes, histiocytes, neutrophils, and eosinophils with ectatic vessels within the dermis.[4] Nonspecific ulceration may also be present.[9] Treatment of choice for bone marrow suppression resulting from methotrexate toxicity is leucovorin

calcium (folinic acid), which should be administered intravenously or intramuscularly at a dose equivalent to or higher than the last methotrexate dose as soon as possible after exposure to methotrexate and every 6 hours until a significant clinical improvement is observed.[4,6] Nevertheless, treatment is usually supportive because the lesions may heal rapidly with complete re-epithelialization just a few days after discontinuation of methotrexate.

This case suggested 3 possible causes for the painful ulceration of psoriatic plaques including (1) administration of methotrexate for the first time, (2) psoriatic flare, and (3) increased methotrexate toxicity with the combined use of methotrexate and nonsteroidal anti-inflammatory drugs for joint pain. Although the laboratory parameters were all within normal limits, unexpected painful superficial ulceration and histopathologic results suggested methotrexate toxicity.

Increased erythema and ulceration of psoriatic plaques in the presence of normal laboratory profile should not always be considered an exacerbation of disease itself, as it could be an indicator of methotrexate toxicity. The awareness of the sequelae in methotrexate-induced skin ulceration is also important to prevent fatal bone marrow suppression by discontinuing the use of methotrexate in time. Proper monitoring and regular review of the concomitant medications are mandatory during methotrexate treatment.

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