

Oral Ulcer and Multiple Painful Eruption in a Patient with Chronic Psoriasis

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Case Report

A 69-year-old man had chronic plaque psoriasis for ten months. Many new psoriatic plaques and generalized exfoliation developed during a flare 2 months ago after treatment with herbs. MTX, 7.5 mg weekly in three divided doses 12 hours apart, was initiated since three weeks ago. Erythroderma resolved dramatically within one week. Oral ulcers and painful eruptions superimposing on psoriatic plaques developed over the whole body two weeks after the initiation of MTX. After admission, physical examination revealed multiple round or oval, bean to half-palm-sized, brownish, tender plaques with central shallow erosions over his extremities and trunk (Fig. 1). The laboratory data were all within normal limits. A biopsy specimen was taken from a lesion on his lower leg.

Histopathological examination revealed many dyskeratotic cells and ballooning keratinocytes with dysmaturation of the epidermis. Metaphase arrest in mitotic cells was also noted (Fig. 2) There was a dense lymphocytic infiltrate in the superficial dermis. Neither eosinophil nor evidence of vasculitis was noted. Bisbenzimidazole dye Hoechst 33258 (H33258) show nucleus of epidermal cells and TUNEL stain show apoptosis of epidermal cells (Fig. 3 A&B).



Fig. 1
Multiple brownish, tender plaques with central shallow erosions over his legs

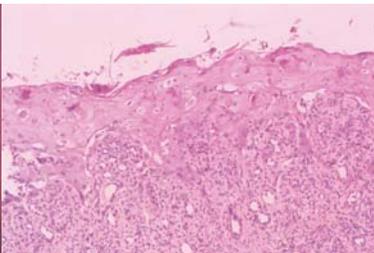


Fig. 2
Dyskeratotic cells and ballooning keratinocytes with dysmaturation of the epidermis. (H&E, 200x)

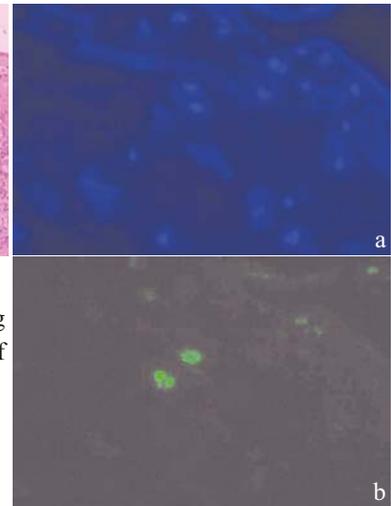


Fig. 3
(A) Bisbenzimidazole dye Hoechst 33258 (H33258) shows nuclei; of epidermal cells (400x)
(B) TUNEL stain shows apoptosis of epidermal cells (400x)

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Diagnosis : *Methotrexate-induced Cutaneous Necrolysis*

DISCUSSION

Methotrexate (MTX), a folic acid antagonist, is a standard systemic therapy for moderate to severe psoriasis today.¹ Usually, a single weekly dose or an oral schedule of three divided doses over a 24-hour period each week is used. The usual therapeutic dose is between 7.5-30 mg per week.¹ MTX inhibits DNA synthesis (S phase of the cell cycle) by competing as a substrate for dihydrofolate reductase. MTX may act through selective inhibition of rapidly proliferating psoriatic keratinocytes.² Though not fully elucidated, lymphocytes are also believed to be the main targets of MTX. Proliferating lymphoid cells in psoriatic lesions are over 1000 times more sensitive to the cytotoxic effects of MTX than keratinocytes.³ Most commonly, nausea, anorexia, fatigue, headaches, and alopecia are encountered as adverse effects. Development of leukopenia and thrombocytopenia indicates serious dysfunction of the bone marrow and may be a sign of MTX overdose. Hepatotoxicity is another major concern with MTX treatment. The risk of developing liver fibrosis or cirrhosis increases with the overall cumulative MTX dose. Adverse reactions to MTX are usually idiosyncratic or dose-related.

Reed and Sober introduced the term "**methotrexate-induced necrolysis**."⁴ Lawrence and Dahl further defined two separate patterns of ulceration associated with MTX.⁵ In type 1, redness, burning and then painful erosion or ulceration of psoriatic plaques develop shortly after MTX is initiated and lesions heal rapidly after withdrawal of MTX.^{2, 4, 5, 6} A toxic epidermal necrolysis-like pattern may be seen if the reaction is exaggerated.² Histologically, ballooning and dysmaturation of keratinocytes, dyskeratosis and overt necrosis are present in the epidermis with a lymphocytic dermal infiltrate.^{5, 6} Type 2 ulcerations occurred in clinically uninvolved skin affected by other pathology--stasis dermatitis in two and adjacent to an anal fistula in one and had a variable relationship to the duration of MTX treatment and take weeks to heal.⁶ Type 2 ulcers can mimic stasis ulcers and may be overlooked as evidence of MTX toxicity.⁶ Our case was a type 1 pattern and the lesions healed uneventfully within 14 days after withdrawal of

MTX.

Cutaneous ulcerations can be the only presentation of adverse effects. However, it may be accompanied by leukopenia, pancytopenia or oral ulcers.⁶ Painful erosion of psoriatic plaques has been often reported as an early sign of MTX toxicity mostly in psoriasis. However the necrosis may occur as an isolated early sign of MTX toxicity at as less as 7.5 mg of MTX in three divided doses.⁵ Cutaneous ulceration by MTX toxicity is a diagnosis by exclusion. The pathogenic mechanism may be multifactorial, including direct toxicity of the drug in addition to local factors. The most common risk factors for MTX-induced necrolysis are an alternation in MTX dosage and concomitant use of NSAIDs.^{4, 6} Other factors include renal insufficiency, infection, and a pustular flare of psoriasis.⁴ Burning and redness of the psoriatic lesions are an early warning sign of MTX toxicity and should not be confused with exacerbation of psoriasis. This may occur even with low dose of MTX, as less as 7.5 mg in this case without obvious risk factors. MTX should be reduced or discontinued promptly and can usually be restarted after reepithelialization.^{4, 6}

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