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Cutaneous Erosions: An Under-Recognised and Rare Side Effect of Methotrexate Treatment, in the Absence of Systemic Methotrexate Toxicity

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Abstract

Methotrexate is a potentially toxic anti-folate drug widely used in the treatment of skin disease. We describe here a case of cutaneous erosions occurring in previously erythrodermic skin after only four weeks of very low-dose therapy, in the absence of features of systemic methotrexate toxicity. We thus report that localised cutaneous toxicity can occur in isolation, and propose that cutaneous erosions be considered a rare but potentially serious side effect of methotrexate, rather than a sign of actual or impending systemic toxicity.

Introduction

Methotrexate is a potentially toxic anti-metabolite and anti-folate chemotherapy drug that is also frequently used in the treatment of psoriasis and other skin disorders. Recognised signs of toxicity include bone marrow suppression, hepatotoxicity and oral/gastrointestinal ulcerations [1]. In psoriatic patients treated with methotrexate, erosions within psoriatic plaques are a well-documented sign of systemic methotrexate toxicity, often alongside such other features as macrocytosis and mucosal ulceration [2]. Cutaneous erosions are more common in patients over 55 years, particularly following dose alterations [2]. Toxicity is usually dose-related and can be provoked by acute renal failure, since methotrexate is primarily renally-excreted, [3] or by drug interactions particularly with non-steroidal anti-inflammatory drugs [4].

In 1984, Lawrence and Dahl described two types of methotrexate-induced skin ulceration in psoriatic patients, [5] in type I ulceration, psoriatic plaques became painful and eroded shortly after starting methotrexate or restarting following a treatment-break (median time-period 10 days). Lesions then healed rapidly after the reduction or withdrawal of treatment (median 10 days). Conversely, type II ulceration occurred in non-psoriatic skin at sites of previous skin damage, particularly within areas of stasis dermatitis. The time period of onset of type II lesions was variable, three of their six cases developing within 22 days and the remaining three after prolonged treatment. Additionally, healing time after cessation of treatment was much longer (median 9 weeks; longer than 2 years in one patient).

The objective of this case report is to describe the occurrence of cutaneous erosions as a rare but potentially serious side effect of methotrexate in the absence of features of systemic toxicity including a high serum methotrexate level.

Case Report

A 79-year old lady presented with painful cutaneous erosions across the posterior neck and back (Figure 1) four weeks after commencing oral methotrexate five milligrams (5 mg) once weekly for erythrodermic psoriasis. Folic acid 5mg had been taken daily, except on the methotrexate day. Her mucosae were unaffected and she had no gastrointestinal symptoms. Blood count including haemoglobin and mean cell volume was normal except for slight lymphopenia of 1.0×109/L (1.5-4.0×109/L). Biochemical investigations revealed normal liver function, blood urea nitrogen and creatinine levels, with only slightly depressed estimated glomerular filtration rate at 86 ml/min (>90 ml/min).

Methotrexate toxicity was suspected but a tablet-count confirmed that there had not been an accidental overdose and indeed, when processed, her serum methotrexate levels were very low. This demonstrates the benefit of having prescribed methotrexate tablets of one only strength (i.e. 2.5 milligrams) [6]. Histology showed a large area of epidermal ulceration, with occasional apoptotic keratinocytes and evidence of re-epithelialisation.

There had been no recent change to her medications and she had not taken any over-the-counter drugs. Apart from aspirin, none of her medications interacted with methotrexate: Whilst aspirin may displace methotrexate from its plasma protein binding-sites and/or competitively inhibit its renal tubular secretion, [3] any such actions would be expected to have increased the serum levels. Our patient responded well to cessation of methotrexate therapy and application of topical steroids, with complete resolution in 2 weeks.

Discussion

This patient presented with cutaneous erosions suggestive of methotrexate toxicity but without gastrointestinal upset, significant bone marrow suppression or renal/hepatic dysfunction. Additionally,

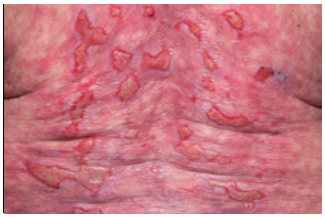

Figure 1: Cutaneous erosions. Numerous well-demarcated cutaneous erosions across the lower back.

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impending systemic toxicity would not be expected from such a short duration of low-dose therapy, and this was reflected by the low methotrexate level.

The lesions seen were more consistent with type I ulceration due to their early onset and rapid healing after methotrexate withdrawal but they did not develop within psoriatic plaques as would be expected, rather they developed in previously erythrodermic skin, overlapping between types I and II. We wish to highlight this side effect of methotrexate as ersosions may be misdiagnosed as deterioration of the underlying psoriasis, prompting an increase of methotrexate dosage, which could worsen symptoms.

We suggest that the erosions occurred in consequence of a direct toxic effect of methotrexate on keratinocytes, [5,7] Keratinocytes may sequester methotrexate, and with rapid cell turnover, more epidermal cells are thus in the S-phase of the cell cycle where methotrexate exerts its effects [8], so leading to local skin toxicity. Therefore we conclude that our patient was more susceptible to localized skin toxicity due to her preceding erythroderma.

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