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Authors

Mna, Amira Ben
Souissi, Asmahene
Halouani, Slim
et al.

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Letter

Methotrexate-induced necrosis in tumoral-stage mycosis fungoides: a challenging diagnosis

Amira Ben Mna¹, Asmahene Souissi¹, Slim Halouani¹, Dalenda El Euch¹, Alia Zahani², Nidham Kchir¹, Ines Zaraa¹, Mourad Mokni¹

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¹Dermatology Department, ²Pathology Department, La Rabta Hospital, Tunisia

Correspondence:

Amira Ben Mna
La Rabta Hospital
Tunisia

Introduction

Methotrexate-induced cutaneous ulceration is a rare but potentially serious drug adverse reaction. This adverse reaction of methotrexate therapy has been initially described in psoriasis patients and is unusual in patients with cutaneous T-cell lymphoma. In 1978, Mc Donald et al reported the first three cases of cutaneous ulcerations in patients treated for a mycosis fungoides with intravenous infusions of methotrexate [1]. Since then, few cases of methotrexate-induced skin ulcers in patients with mycosis fungoides have been published [2-5]. We report an additional patient with erythrodermic mycosis fungoides who developed cutaneous ulcerations as a sole manifestation of methotrexate toxicity.

Case synopsis

A 57-year-old man with a twenty year history of patch-stage mycosis fungoides (stage IB), had been treated by phototherapy, topical corticosteroids, and methotrexate (30 mg per week) with a good result. One year after the introduction of methotrexate, this drug was interrupted because of digestive intolerance. One year later, the patient presented with a new flare-up of the disease exhibiting exfoliative erythroderma with severe pruritus and multiple cutaneous nodules (stage III). We decided to reintroduce methotrexate at a lower dose (10 mg per week) associated with systemic corticosteroid therapy. Initially, we obtained mild improvement with disappearance of the nodules. Three months later, he noted multiple cutaneous erosions, which had been thought to be tumor ulcerations related to the progression of his cutaneous lymphoma. The dose of methotrexate was then gradually increased to 25 mg weekly.



Figure 1. Ulcerated plaques



Figure 2. The ulcers healed with scarring by 3 weeks. .

However, instead of obtaining improvement, the patient continued to develop other lesions. On examination, the patient had multiple 1 to 3 cm oval, bleeding, shallow and painful ulcers over the trunk, limbs, face, and scalp, with a 10 cm ulcer over his left leg. Laboratory investigations showed normal blood-cell-count, electrolytes, urea, serum creatinine concentration, and liver function. Biopsies of the ulcers revealed an almost complete epidermal necrosis with a mild inflammatory infiltrate of the dermis and a vasculitis, considered to be highly consistent with methotrexate-induced cutaneous toxicity. The methotrexate was discontinued. The ulcerated skin lesions began to heal within 5 days and complete re-epithelialization occurred after 3 weeks without further sequelae. The patient was subsequently placed on a combination of oral corticosteroid therapy and phototherapy with an excellent clinical response.

Discussion

In addition to psoriasis, cutaneous T-cell lymphoma is a well established dermatologic indication for methotrexate therapy. The most common side effects of this treatment are digestive and hepatic. Cutaneous reactions related to methotrexate toxicity, although numerous, are less frequent [6]. Skin ulceration has been rarely reported, especially in psoriatic patients [7-13]. Initially this event has been described by Gubner in 1951, in four psoriasis patients [14]. However, the term “methotrexate-induced necrosis” was introduced by Reed and Sober in 1983 [10]. The pathogenic mechanism of cutaneous necrosis leading to ulceration is thought to be direct toxicity of the drug via its anti-proliferative effect. Only a few cases associated with cutaneous T-cell lymphoma have been reported in the literature since 1978 [1-5]. As in our patient, it may be easily mistaken for tumor ulceration associated with the progression of the disease.

Most of the cases had erythrodermic mycosis fungoides [2, 3, 5]. Indeed, as methotrexate is an S-phase specific therapy, it mainly acts on rapidly dividing cells. This explains the fact that the existence of underlying cutaneous damage, especially if the cell turnover time is shortened (as in psoriasis or exfoliative erythroderma), increases the susceptibility to methotrexate-induced ulceration [5, 15-17]. Several other factors may precipitate methotrexate toxicity. The most common of them are older age (over 55 years) [18], impairment of renal function [5, 9], infections, and concomitant use of some other medications, which influence the metabolism of methotrexate or potentiate its toxicity [5, 9, 19]. In fact, a number of drugs can interact with methotrexate either by decreasing its renal excretion (aminoglycosides, cyclosporine, non-steroidal anti-inflammatory agents, sulfonamides, probenecid, salicylates, penicillins, colchicines, cisplatin, and other renotoxic drugs), or by displacing methotrexate from protein binding sites in the plasma and increasing its free level (salicylates, probenecid, sulfonamides, barbiturates, phenytoin, retinoids, sulfonyleureas, tetracyclines). Synergistic toxicity is also reported (trimethoprim and sulfamethoxazole, ethanol and pyrimethamine) [5, 20]. In our patient, the age over 55 years and the existence of an exfoliative erythroderma are the only two risk factors we noted. The onset of skin erosions or ulcerations usually occurs shortly after starting methotrexate therapy. However, it may follow chronic administration of the drug [5, 8, 11, 12]. Breneman et al found that cutaneous ulceration developed within the first three months after introducing the treatment in three of four patients and after five years of methotrexate therapy in the fourth case [5]. In our patient, a period of three months of methotrexate therapy preceded the onset of skin erosions and this period is compatible with a drug-induced reaction. Methotrexate-induced skin necrosis is dose dependent with an interpersonal variation of the toxic dosage [21]. Methotrexate dosage used at the onset of ulceration was 10 mg in our case. Breneman found a wide range of methotrexate dosage in his four patients with 10 mg being

the lowest dose and 60 mg being the highest dose administered. It is important for clinicians to be aware of any ulcerations or erosions occurring during methotrexate therapy and to remember the possibility of cutaneous methotrexate toxicity. When the diagnosis is suspected, the discontinuation of methotrexate therapy allows rapid healing within a period of about 10 to 12 days. Otherwise, more extensive ulcerations and potentially severe extracutaneous side effects can develop [5, 8].

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