Methotrexate-induced hyperpigmentation in a rheumatoid arthritis patient

Sirs,

Methotrexate (MTX) is a folic acid antagonist that is used in the treatment of neoplasias, skin diseases and rheumatic disorders. It is widely used in the treatment of rheumatoid arthritis (RA) (1-3). As with all chemotherapy agents, various adverse events have been reported, in the case of MTX mainly involving the liver, lung or bone marrow (1-3). Cutaneous reactions have also been noted with MTX but they appear to be uncommon (1, 2, 4). Here we report localized skin hyperpigmentation occurring during MTX therapy in an RA patient.

The patient, a 40-year-old woman, had nodular RA for 14 years. She was a native of Tunisia but had been living in France for 20 years. She had no other pertinent medical history. The treatments given for the rheumatic disease were non-steroidal antiinflammatory drugs (NSAIDs) and corticosteroids (prednisone). In November 1996 the patient received MTX, showing a good response. In 1997, her treatment was prednisone 10 mg per day and MTX 10 mg orally per week. She was taking no NSAIDs and no oral contraceptives.

In June 1997 she was exposed to the sun since she was on holiday in Tunisia. Five months later (November 1997), and one year follow-up (November 1998), she was receiving MTX, showing a good response. In 1997, her treatment was prednisone 10 mg per day and MTX 10 mg orally per week. She was taking no NSAIDs and no oral contraceptives.

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Fig. 1. Forehead skin hyperpigmentation.

morkable. The urine color was normal. Laboratory data showed an elevated erythrocyte sedimentation rate (28 mm/h), normal CRP level (6 mg/l) and positive rheumatoid factors (Latex: 800 UI; Waaler-Rose test: 640 UI). The white cell count was normal (7.0 x 10³/mm³) without eosinophilia, and antinuclear antibodies were negative. Liver investigations (serum transaminases) were normal as was the serum iron level. No skin biopsy was performed. MTX was discontinued but the localized skin pigmentation still had not resolved one year later.

This patient developed changes in skin pigmentation, mainly localized on the face (i.e., in sun-exposed area), during MTX therapy for RA and after exposure to the sun. These skin changes could suggest a cutaneous porphyria (porphyria cutanea tarda) but the patient’s urine was not dark in colour, and she had none of the risk factors for such a skin disease (no exposure to estrogens or excessive alcohol intake). Moreover, she showed no signs of liver involvement and no increase in her serum iron levels. For these reasons, urinary porphyrins were not evaluated. Furthermore, the association of cutaneous porphyria with RA has been reported (5), but is thought to be coincidental. A link between the administration of MTX and cutaneous porphyria has also been discussed but is unlikely (6).

Cutaneous reactions may be observed with MTX as they have been noted with other cytostatic agents (1, 4, 7). The mucocutaneous complications commonly observed with MTX therapy include stomatitis, transient alopecia, erythema, and macular and papular eruptions (1-4). Photosensitivity and pigmentation are uncommon, however (7, 8). Photosensitivity has been described in patients receiving weekly oral doses of MTX (9). This reaction resembles sunburn injury. Similarly, sun exposure in patients with cancer undergoing MTX therapy may induce reactivation of the sunburn reaction (9). The mechanism of this photosensitivity is assumed to result from enhancement of the ultraviolet-induced inflammatory reaction. Pigmentation has also been observed in a patient who received pulse MTX therapy for leukemia (4, 8). There are a number of drugs that have been described to cause epidermal hyperpigmentation by different mechanisms: heavy metal deposition in the dermis, or alteration or enhancement of melanin deposition. For instance, busulfan and cyclophosphamide may produce a diffuse pigmentation of the skin which is accentuated in exposed areas, particularly in non-Caucasoid patients with a dark complexion (8). Gold may also induce hyperpigmentation, a colour mainly due to the metal itself, and antimalarias such as hydroxychloroquine are capable of producing a similar hyperpigmentation. However, our patient had not been previously treated with these disease-modifying anti-rheumatic drugs. Moreover, being a native of Tunisia, she had a dark complexion. Before her skin condition became evident, she had been exposed to the sun while on holiday in Tunisia. This might have triggered a photosensitivity reaction that could have induced the changes in pigmentation. This is, to our knowledge, the first case of hyperpigmentation occurring in a RA patient with a weekly administration of MTX.

Thus, patients receiving MTX treatment should be advised to avoid significant exposure to the sun and this is particularly true for those with a dark complexion.

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References