Exfoliative Dermatitis after Long-term Methotrexate Treatment of Severe Psoriasis

Sir,

Severe cutaneous adverse reactions to high-dose methotrexate (MTX) regimens occur occasionally and are rarely misinterpreted. By contrast, low- and intermediate-dose MTX therapy, as frequently used for treatment of severe psoriasis and psoriatic arthropathy, is relatively well tolerated. Skin reactions are rare and when they occur they are often not interpreted as causally related to MTX. Consequently, because of deteriorating skin symptoms that can be interpreted as exacerbating psoriasis, MTX dosage may be increased rather than reduced or discontinued. We present here a case of exfoliative dermatitis following long-term low- to intermediate-dose MTX treatment for severe psoriasis and progressive psoriatic arthropathy.

CASE REPORT

A 37-year-old man with a 7-year history of chronic stationary plaque-type psoriasis had been treated with cignoline, topical and oral corticosteroids, acitretinate and cyclosporin A, as well as with concomitant UVB, photochemotherapy (PUVA) and selective UVB (SUP) radiation because of exacerbated psoriasis and psoriatic arthropathy between 1991 and 1998. Despite intensified treatment and several periods of hospitalization his skin symptoms and arthropathy were progressive. He eventually developed psoriatic erythroderma with pustulosis of his lower legs and generalized arthropathy of the distal and proximal joints. In August 1993, MTX treatment was started at 15 mg per os and subsequently increased to 25 mg weekly. At that time, his weight was 107 kg at a height of 195 cm. In January 1995, he presented with an extremely painful, fluoride arthritis of his fingers and ankle joints. Consecutively, he was administered morphine sulphate (MST1) on a regular basis and the use of coal tar products by the fathers. It would also be of value to extend the research with the question as to whether PL-containing products lead to an increase in intrauterine mortality in humans.

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citrovorum factor rescue) for angioimmunoblastic lymphadenopathy (AILD). Histology supported our diagnosis of drug-induced toxic dermatitis with MTX as most likely candidate. Nevertheless, the potential of concomitant chemotherapy to enhance MTX skin toxicity also has to be considered (1).

However, severe cutaneous adverse reactions following low- or intermediate-dose MTX treatment are rare in the literature. Similar cases have rarely been reported. In fact, diagnosis is often hindered, as adverse cutaneous reactions may vary in morphology (6–9) and even imitate psoriatic eruptions (7). In the case described here we found severely ulcerated psoriatic plaques as well as extensive exfoliative dermatitis, which had, in slightly milder manifestations, already been seen in former episodes of the patient’s illness. Only the therapeutic context revealed an association with MTX therapy and led us successfully to discontinue the drug.

In addition, cases of erythema after MTX administration and concurrent UV radiation (8) as well as reactivation of sunburn by MTX medication 1 month after exposure to the sun (9) have been reported. As our patient received selective UVB phototherapy (SUP) until 4 weeks before his cutaneous adverse reaction, aggravated recall of UV-induced erythema by MTX cannot strictly be excluded. However, the patient had tolerated phototherapy well concurrently with MTX treatment for a long period of time previously and thus, it seems unlikely that UV-associated skin toxicity should have appeared more than 4 weeks after SUP was discontinued. After all, consequences would have been the same, namely to stop MTX administration, only with the possible option to continue MTX treatment after a sufficient break in case of UV-aggravated toxicity.

At this point, it should be mentioned that phototherapy including SUP combined with MTX treatment constitutes a potential increase in carcinogenicity of non-melanoma skin cancer (predominantly squamous cell cancer) and, therefore, is not a preferred combination. However, our patient neither tolerated systemic PUVA therapy, because of its gastrointestinal side-effects, nor did systemic PUVA lead to a sufficient remission of psoriatic skin symptoms. MTX medication, on the other hand, was effective in improving his psoriatic arthropathy, but as sole treatment did not clear the cutaneous manifestation of his disease. Thus, we used this delicate combination of phototherapy and MTX judiciously.

Regarding MTX toxicity, adverse effects of low- or intermediate-dose MTX therapy most frequently afflict the gastrointestinal tract, the liver, the bone marrow or may lead to pneumonitis, whereas dermatitis is rare (10). Severe cutaneous adverse reactions seem to depend on the cumulative MTX dose and thus, are more likely to appear when MTX is administered in long-term regimens for years (11). In our case, the cumulative total MTX dose was as high as 4 g by the time the patient developed exfoliative dermatitis. Van Dooren-Greebe et al. (12) suggested an interval MTX treatment as a possible strategy to diminish high long-term cumulative doses. In their therapy scheme weekly low-dose MTX regimens are periodically followed by MTX-free intervals.

A further therapeutic concept, which is indispensable for high-dose MTX regimens and is constantly used in oncology as “rescue“ medication, comprises additional administration of folic or folinic acid to decrease MTX toxicity (10).

Concomitant medication to MTX should be carefully controlled, as several drugs are known to enhance MTX toxicity, the most important of which are trimethoprim-sulfamethoxazole, probenecid and furosemide (10, 11). In this respect, the effect of NSAIDs is discussed controversially in literature and uncertain (10). However, our patient’s medication did not contain any of the drugs mentioned above.

Awareness of the above-described severe cutaneous adverse reaction of MTX which may be veiled by imitating severe psoriasis is particularly important when treating patients with low- or intermediate-dose regimens for psoriasis. Long-term administration may lead to a respectable cumulative total dose with serious toxic effects, not only concerning the liver and bone marrow, but also leading to severe lesions of various patterns at the skin. These should be recognized as early as possible.

REFERENCES


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