

coal tar products is necessary, with a larger patient population, grouping the patients according to time and duration of exposure, the percentage of body area treated, the compliance of the patient regarding the prescribed products, 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.

REFERENCES

1. Storer JS, DeLeon I, Millikan LE, Laseter JL, Grifing C. Human absorption of crude coal tar products. *Arch Dermatol* 1984; 120: 874–877.
2. Hansen AM, Poulsen OM, Menné T. Longitudinal study of excretion of metabolites of polycyclic aromatic hydrocarbons in urine from two psoriatic patients. *Acta Derm Venereol* 1993; 73: 188–190.
3. Mackenzie KM, Angevine DM. Infertility in mice exposed in utero to benzo(a)pyrene. *Biol Reprod* 1981; 24: 183–191.
4. Mattison DR, Nightingale MS. Oocyte destruction by polycyclic aromatic hydrocarbons is not linked to the inductability of ovarian aryl hydrocarbon hydroxylase activity in backcross mice. *Ped Pharmacol* 1982; 2: 11–21.
5. Zangar RC, Springer DL, Buschbom RL, Mahlum DD. Comparison of fetotoxic effects of a dermally applied complex organic mixture in rats and mice. *Fund Appl Toxicol* 1989; 13: 662–669.

Accepted January 15, 1999.

M.E.J. Franssen¹, G.J. van der Wilt², P.C.M. Pasker de Jong², R.P. Bos³ and W.P. Arnold⁴
 Departments of ¹Dermatology, ²Medical Epidemiology, ³Toxicology; University Hospital Nijmegen, PO Box 9101, NL-6500 HB Nijmegen, The Netherlands and ⁴Department of Dermatology, Hospital "Gelderse Vallei", Stationsweg 86, 6711 PV Ede, The Netherlands.
 (Correspondence to W. P. Arnold, MD, PhD).

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 (MST[®]) on a regular basis and the MTX treatment was changed to intravenous medication. He also required a wheelchair from this time on.

In February 1998, he again presented with erythroderma, pustulosis of his lower legs and generalized arthropathy under his current intravenous medication with 25 mg MTX per week. Surprisingly, when hospitalized, 12 h after intravenous MTX medication his skin symptoms were severely exacerbated, showing ulcerated psoriatic

plaques and wide areas of exfoliative dermatitis over his whole body. This exacerbation following MTX treatment was observed 3 times. MTX was discontinued and topical treatment with triamcinolone acetonide (Volon A[®]) and prednisolone pulse-therapy slowly led to an improvement of skin symptoms. At the same time treatment with mycophenolatomofetil (CellCept[®]) was started, but failed to have a lasting effect even after 5 weeks. The regimen was changed to azathioprin (Imurek[®]), acitretinate (Neotigason[®]) and prednisolone (Decortin H[®]). This led to a stable remission, so that the patient could finally be dismissed into rehabilitation.

DISCUSSION

After 5 years of low- and intermediate-dose MTX treatment, the patient developed acute extensive exfoliative dermatitis and ulcerated psoriatic plaques following intravenous administration of 25 mg MTX. Since psoriatic eruptions under immunosuppressive treatment with 25 mg MTX and topical steroids are extremely unlikely and the skin symptoms gradually improved after cessation of MTX medication, we interpreted his acute illness as MTX-induced skin lesions.

Unfortunately, the patient refused biopsy at that stage. Biopsy is helpful, as skin histology can support the diagnosis of cytotoxic drug-induced changes typically showing single cell necrosis of the epidermis and the acrosyringium.

Several cases of cutaneous adverse reactions of varying clinical patterns, including generalized desquamation, painful erythema and ulceration among others, have been ascribed to high-dose MTX (1–3) or MTX analogues (4, 5). Martins da Cunha et al. (1) described an erythematous skin rash followed by desquamation predominantly localized on the palms and soles after high-dose MTX infusion, but they also pointed out the difficulties in attributing a cutaneous reaction to a particular drug, as patients undergoing chemotherapy often receive many drugs at the same time. We recently observed a similar case of extended exfoliative dermatitis in a 51-year-old male, 10 days after he had received polychemotherapy including high-dose MTX (2.75 g MTX, with subsequent

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

- Martins da Cunha AC, Rappersberger K, Gadner H. Toxic skin reaction restricted to palms and soles after high-dose methotrexate. *Pediatr Hematol Oncol* 1991; 8: 277–280.
- Aractingi S, Briant E, Marolleau JP, Verola O, Brice P, Dubertret L, et al. Methotrexate-induced skin detachment. *Presse Med* 1992; 21: 1668–1670.
- Hellier I, Bessis D, Sotto A, Margueritte G, Guilhou JJ. High-dose methotrexate-induced bullous variant of acral erythema. *Arch Dermatol* 1996; 132: 590–591.
- Verweij J, Schornagel J, de Mulder P, Henzen-Logmans S, Cognetti F, Clavel M, et al. Toxic dermatitis induced by 10-ethyl-10-deaza-aminopterin (10-EdAM), a novel antifolate. *Cancer* 1990; 66: 1910–1913.
- Weiss RB, James WD, Major WB, Porter MB, Allegra CJ, Curt GA. Skin reactions induced by trimetrexate, an analog of methotrexate. *Invest New Drugs* 1986; 4: 159–163.
- Procter PR. Methotrexate-induced skin necrosis in psoriasis. *S Afr Med J* 1987; 72: 888.
- Lawrence CM, Dahl MGC. Two patterns of skin ulceration induced by methotrexate in patients with psoriasis. *J Am Acad Dermatol* 1984; 11: 1059–1065.
- Armstrong RB, Poh-Fitzpatrick MB. Methotrexate and ultraviolet radiation. *Arch Dermatol* 1982; 118: 177–178.
- Okamoto H, Fukuda A, Mizuno K, Matsuyoshi N, Fujii K, Imamura S. Reactivation of phototoxicity test for psoralen plus ultraviolet A by low-dose methotrexate. *Photodermatol Photoimmunol Photomed* 1994; 10: 134–136.
- Van Ede AE, Laan RF, Blom HJ, De Abreu RA, van de Putte LB. Methotrexate in rheumatoid arthritis: an update with focus on mechanisms involved in toxicity. *Semin Arthritis Rheum* 1999; 27: 277–292.
- Collins P, Rogers S. The efficacy of methotrexate in psoriasis—a review of 40 cases. *Clin Exp Dermatol* 1992; 17: 257–260.
- Van Dooren-Greebe RJ, Kuijpers AL, Termorshuizen F, van de Kerkhof PC. Interruption of long-term methotrexate treatment in psoriasis. *Acta Derm Venereol* 1995; 75: 393–396.

Accepted February 14, 1999

Thorsten Peters¹, Susanne Theile-Ochel¹, Jens Chemnitz², Dietmar Söhngen², Nicolas Hunzelmann¹ and Karin Scharffetter-Kochanek¹
Departments of ¹Dermatology and ²Internal Medicine I, University of Cologne, Joseph-Stelzmann-Str., D-50931 Cologne, Germany.