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To the Editor.—The principal toxicities of methotrexate sodium are myelosuppression, oral and gastrointestinal tract mucositis, and hepatitis. Other uncommon toxicities also include liver cirrhosis, interstitial pneumonitis, osteoporosis, alopecia, and immune dysfunction.[1,2] Over the past several years, high-dose methotrexate and leucovorin calcium–containing regimens have been introduced in the treat-

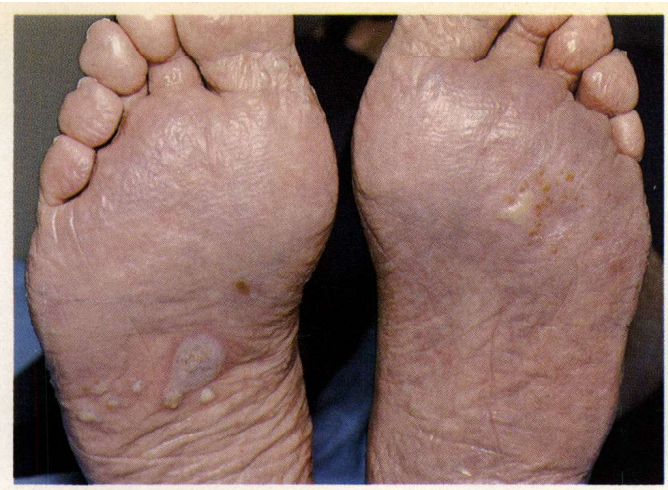

Fig 1.—Acute bullous lesions in sole of foot in patient 1. Note that lesions are well demarcated and unilocular without surrounding erythema or papule. Size of lesions are variable.

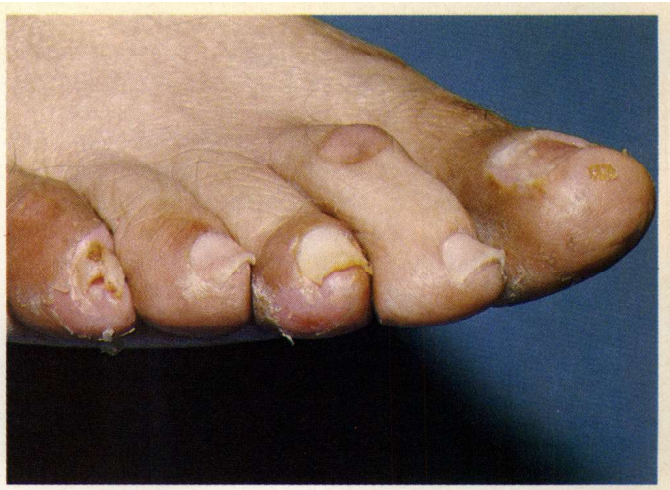

Fig 2.—Result of severe onycholysis in patient 2. Some toenails have fallen off, and others have become loose. Healing bullous lesions characterized by progressive desquamation of epidermis are also present.

ment of histiocytic lymphoma with an eye toward its cure, and their superior value to conventional regimens has been well demonstrated.[3-5] With high-dose methotrexate therapy, the toxicities have been more frequent and severe, and other side effects such as renal dysfunction, vasculitis, conjunctivitis, rhinorrhea, headache, hypertension, and seizure also have been observed.[2,6,7]

In this communication, three patients are described in whom the previously unreported side effects of severe multiple bullous dermatosis and onycholysis developed due to high-dose methotrexate and leucovorin calcium administration, which were serious enough to disrupt their chemotherapy schedules.

Report of Cases.—**Case 1.**—A 74-year-old man was diagnosed as having poorly differentiated lymphocytic lymphoma of the diffuse type when multiple cervical, axillary, and inguinal adenopathy and right tonsillar swelling developed. A biopsy specimen of the tonsil was obtained. The bone marrow biopsy specimen was normal. The patient was treated with eight cycles of the combination chemotherapy of cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (CHOP) and achieved a complete remission. The disease relapsed in four months with bilateral cervical adenopathy. A new regimen, prednisone, high-dose methotrexate and leucovorin calcium, doxorubicin hydrochloride, cyclophosphamide, etoposide mechlorethamine hydrochloride, vincristine sulfate, and procarbazine hydrochloride (ProMACE-MOPP)[4] was begun. The methotrexate sodium dosage was 1.0 g intravenously, and the leucovorin calcium dosage was 100 mg intravenously every six hours for five doses beginning 24 hours after the methotrexate administration. The treatment was repeated at five weekly intervals with the administration of other drugs between the schedule. After each treatment of methotrexate and leucovorin calcium, usually in about one week, multiple bullous lesions developed in the soles, palms, and dorsa of the hands and feet (Fig 1). The lesions generally were unilocular, subepidermal bullae without surrounding erythema or papule and filled with clear fluid when aspirated. Initially, the lesions were small and few in number, and they healed gradually, leaving crust formation and thickening of the skin. The lesions became more numerous and larger, and they ulcerated after each methotrexate administration. Because of this toxicity, administration of methotrexate and leucovorin calcium was discontinued from the patient's regimen. No further cutaneous toxicity occurred, and a complete remission of the non-Hodgkin's lymphoma was achieved.

Case 2.—A 69-year-old man was begun on the combination chemotherapy of bleomycin sulfate, high-dose methotrexate sodium and leucovorin calcium, doxorubicin hydrochloride, cyclophosphamide, vincristine sulfate, and prednisone (MACOP-B)[6] for a rapidly advancing diffuse histiocytic lymphoma with generalized lymphadenopathy. The methotrexate sodium dosage was 600 mg intravenously and, 24 hours later, eight doses of leucovorin calcium (25 mg) were given orally at six-hour intervals. A complete remission of the non-Hodgkin's lymphoma was achieved. After the second methotrexate treatment, extensive bullous lesions developed in the palms and dorsa of the hands, forearms, and soles and the dorsa of the feet in about ten days. In addition, extensive onycholysis began to occur. Most of the toenails and fingernails became loose, and some eventually fell off from their beds (Fig 2). The chemotherapy regimen was discontinued, and gradual healing took place over the next five weeks. Several nails were lost, and severe desquamation of the skin followed.

Case 3.—A 59-year-old male with stage III recurrent histiocytic lymphoma of the diffuse type was begun on the chemotherapy regimen of ProMACE-MOPP. The methotrexate sodium dosage was 1.0 g intravenously over 24 hours, followed by 12 doses of leucovorin calcium, 50 mg intravenously every six hours. Initially, no cutaneous toxicity occurred. After the third cycle of methotrexate and leucovorin calcium, in about one week, a modest number of bullous lesions developed on the plantar surface of both feet. The high-dose methotrexate and leucovorin calcium dosages were deleted from the patient's regimen. Although doxorubicin, etoposide, and cyclophosphamide therapy was continued, the cutaneous lesions gradually cleared up.

Comment.—Dermatologic manifestation of metho-

trexate toxicity is rare, although side effects such as reactivation of solar dermatitis, acute desquamative dermatitis, papular skin rashes that were slightly elevated, acute paronychia have been described,28" and it still is considered to be uncommon even with high-dose methotrexate-containing regimens. Recent investigations in the treatment of non-Hodgkin's lymphoma have reported no serious cutaneous toxicity.35 Blistering skin reaction was described in the regimens containing high-dose methotrexate, but it was thought to be caused by the administration of bleomycin rather than the administration of methotrexate.5

My experience indicates that a high-dose methotrexate and leucovorin calcium regimen can cause acute severe bullous dermatosis and onycholysis, which can be serious enough to demand a modification of the treatment program. The fact that the cutaneous lesions disappeared when methotrexate administration was not resumed, even though administration of the other drugs in the various regimens was continued, further supports the cause-and-effect relationship. To discount the side effect of bleomycin administration, two patients did not receive the drug and, in one patient, the cutaneous lesions cleared up while bleomycin administration continued.

No life-threatening complication occurred from the toxicity in the short run. The long-term effect of the cutaneous side effects of high-dose methotrexate and leucovorin calcium should be examined closely. At this time, it seems to be appropriate to recommend a modification of the regimen should severe cutaneous bullous lesions or onycholysis occur during an intensive chemotherapy regimen containing high-dose methotrexate and leucovorin calcium.

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