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Case report

Bone marrow aplasia and severe skin rash after a single low dose of methotrexate

Sitki Copur, William Dahut,[1] Edward Chu and Carmen J Allegra

NCI–Navy Medical Oncology Branch, National Cancer Institute, Bethesda, MD 20889-5105, USA. Tel: (+1) 301 402 1841; Fax: (+1) 301 496 0047. [1]Division of Hematology/Oncology, National Naval Medical Center, Bethesda, MD 20889-5600, USA.

A 64 year old man with recurrent metastatic squamous cell carcinoma of the head and neck developed severe skin rash and bone marrow aplasia 4 and 7 days, respectively, following a single dose of 40 mg/m^2 methotrexate (MTX). Skin rash involved regions of the face, lower abdomen, back, buttocks and both upper thighs. Biopsy of the skin rash demonstrated superficial perivascular lymphocytic infiltrate and was consistent with a drug reaction. Peripheral blood count revealed pancytopenia and a bone marrow biopsy was consistent with aplasia. Blood counts returned to normal 6 days after institution of granulocyte colony stimulating factor therapy. In the absence of mucositis or diarrhea, severe dermatologic toxicity following a single low dose of the drug suggests an 'allergic' or acute hypersensitivity reaction to MTX in this patient. Development of an extensive skin rash following a single dose of MTX may be an early warning sign for life-threatening bone marrow aplasia.

Key words: Hypersensitivity, methotrexate, pancytopenia, rash.

Introduction

Methotrexate (MTX) is a tight-binding inhibitor of dihydrofolate reductase (DHFR), a critical enzyme in intracellular folate metabolism. The importance of DHFR stems from its role in maintaining the intracellular folate pool in its fully reduced state as tetrahydrofolates. Since these compounds serve as one-carbon carriers for the *de novo* synthesis of pyrimidines and purines as well as for the synthesis of various amino acids, DHFR is a critical target enzyme in cancer chemotherapy.[1]

MTX is one of the most widely used antimetabolites in cancer chemotherapy and it remains an important agent in the treatment of locally advanced and metastatic head and neck cancer.[2,3] Myelosuppression is the dose-limiting toxicity following either bolus or continuous infusion therapy reaching a maximum after 5–14 days with rapid recovery thereafter. Other well characterized toxic side effects of MTX include mucositis, diarrhea, gastrointestinal ulceration, erythematous rashes, pruritus, urticaria, photosensitivity, alopecia, and, less commonly, liver dysfunction with potential risk for hepatic fibrosis and/or cirrhosis with chronic use, pneumonitis, immunosuppression and immune hemolytic anemia.

In this report, we present the case of a patient with squamous cell carcinoma of the pyriform sinus who developed a severe skin rash and bone marrow aplasia with pancytopenia following a single dose of MTX.

Correspondence to S Copur

Case report

A 64 year old man with recurrent metastatic squamous cell carcinoma of the pyriform sinus was evaluated at the National Naval Medical Center (Bethesda, MD). He originally presented to the National Naval Medical Center 2 years earlier with a $T_1N_2M_0$ lesion, treated with preoperative radiation of 7200 cGy and subsequent right modified radical neck dissection. One year later, he recurred locally and underwent total laryngectomy and partial pharyngectomy. Two months prior to evaluation, he developed biopsy proven metastatic disease to the scalp, chin and right hip. He received 3000 cGy to the right hip and proximal femur. Physical examination was otherwise normal except for 2 × 1 and 1 × 1.5 cm skin lesions on his scalp and chin, respectively. Pertinent laboratory values included leukocyte count 8.9 × 10^9/l, hemoglobin 13.9 g/dl, hematocrit 40.7%, platelets 387 × 10^9/l, blood urea

nitrogen 13 mg/dl, creatinine 1.1 mg/dl, AST 22 U/l, ALT 34 U/l, LDH 644 U/l, alkaline phosphatase 64 U/l and serum albumin 3.5 g/dl. The patient was started on intravenous MTX 40 mg/m^2 to be given on a weekly schedule.[3] He was given 10 mg prochlorperazine (compazine) intravenously before MTX for nausea. He was on no other medications. Four days after the administration of the first dose of methotrexate, he developed an extensive maculopapular rash involving regions of the face, lower abdomen, back, buttocks and both upper thighs. There were no complaints of mucositis or diarrhea. Three days later, the rash had crusted; however, his laboratory evaluation revealed a white blood cell count 0.3 × 10^9/l, hemoglobin 11.1 g/dl, platelets 101 × 10^9/l, blood urea nitrogen 51 mg/dl and creatinine 2.7 mg/dl. He was admitted to the hospital and treatment with intravenous fluids rapidly corrected his blood urea nitrogen and creatinine to baseline. Shortly after admission, he developed a fever requiring empiric antibiotics. All cultures remained sterile. A biopsy of the skin rash revealed a superficial perivascular lymphocytic infiltrate consistent with a drug reaction. Seventeen days after treatment with MTX, the patient had a white blood cell count of 0.1 × 10^9/l, hemoglobin of 6.7 g/dl and a platelet count of 16 × 10^9/l. Bone marrow biopsy revealed severe aplasia with only rare myeloid and erythroid precursors and a few megakaryocytes. A complete hepatitis panel and sugar water test were negative. The patient was then started on granulocyte colony stimulating factor (G-CSF) therapy (5 μg/kg/day) with return of his white blood cell count, hemoglobin and platelet count to baseline at day 24, 28 and 30, respectively (Figure 1).

Discussion

MTX toxicity may result from a variety of factors such as an increased concentration of free extracellular drug, increased plasma levels, and/or duration of exposure related to both dose and dosing schedule, renal impairment, or slow continuous release from reservoir sites such as ascites or pleural effusion. Pharmacokinetic studies have shown that MTX plasma levels decrease in a triphasic fashion after a single dose.[4] The initial half-life of 0.75 h appears to be secondary to drug distribution, while the second phase of 2–3.5 h reflects renal clearance. The terminal half-life of 10.4 h appears to be secondary to enterohepatic circulation.[5]

Clearance of MTX varies in proportion with creatinine clearance,[6] which gradually declines with age. The patient in this report had a normal baseline creatinine clearance of 70 ml/min. Although prerenal azotemia developed at the time of admission, this was rapidly corrected with hydration over a 2–3 day period. It appears unlikely that the severe pancytopenia with bone marrow aplasia was the result of increased drug levels secondary to impaired renal excretion. Normal initial renal function and rapid normalization of renal function with intravenous hydration argue against this possibility.

There was no evidence of third space fluid collection as evidenced by normal physical exam and

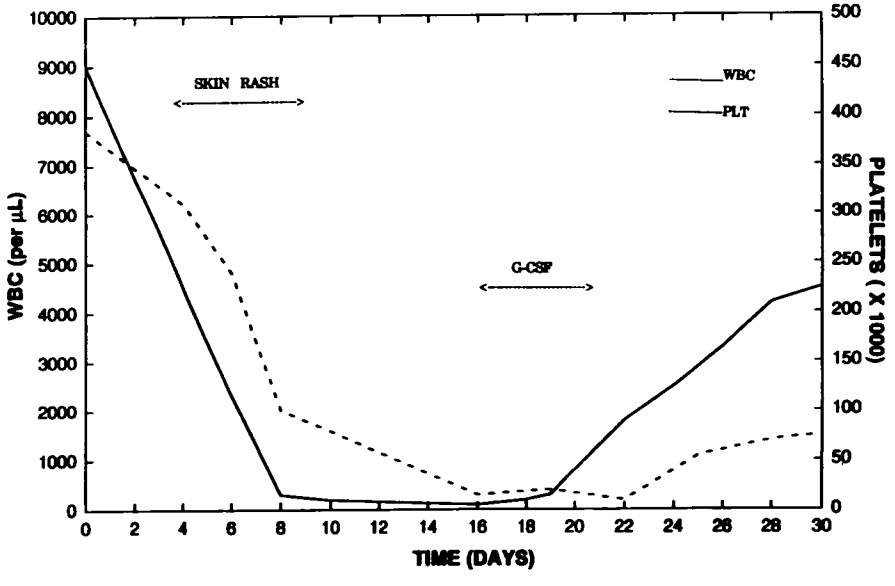

Figure 1.

unremarkable chest X-ray and abdominal ultrasound making the possibility of slow release of MTX from reservoir sites unlikely.

When MTX is given concomitantly with salicylates, probenecid, penicillin, piperacillin,[7,8] trimethoprim, trimethoprim with sulfamethoxazole[9] and non-steroidal anti-inflammatory drugs,[10] an alteration of MTX pharmacokinetics has been reported. There was no evidence to suggest use of these drugs by our patient either prior to or during his treatment with MTX. For this reason, the likelihood of a drug interaction leading to altered MTX drug clearance seems low.

There are factors other than absolute drug concentration which may be involved in the generation of hematologic toxicity. Diminished bone marrow reserve, intracellular folate deficiency and/or concurrent exposure to other marrow toxins including radiation may potentiate marrow toxicity. While the cellularity of the patient's pre-therapy bone marrow was not known, it is clear that his initial peripheral blood counts were normal. A normal red blood cell folate level of 833 mg/ml excludes the possibility of folate deficiency. Fatal aplastic anemia has been associated with viral hepatitis, predominantly non-A, non-B,[11] and paroxysmal nocturnal hemoglobinuria.[12] A negative hepatitis panel and negative sugar water test rule out these possibilities.

MTX-induced hypersensitivity reactions have been occasionally seen following intermediate or high-dose administration of MTX. The usual manifestations have been urticaria, anaphylaxis and photosensitivity.[13,14] Skin eruptions in previously normal skin have occurred in cancer patients given high-dose MTX and they have taken the form of a biopsy proven capillaritis[15,16] as well as a patchy, erythematous, macular eruption seen in approximately 15% of patients.[17,18] Pain and burning of the palms and soles and an erythematous desquamating eruption of the hand has been reported after infusion of high-dose MTX (1.5 g/m^2).[19] These were presumed to be toxic rather than allergic reactions because skin findings did not recur with dose reduction.[15–19] In our case, severe skin rash appeared following a single low dose of MTX. To date, severe anaphylactic reactions to high-dose MTX have been reported in eight patients.[20–23] There has been only one previous report of agranulocytosis after treatment with low-dose MTX (45 mg) due to an allergic pathogenesis[24] and one prior report of cutaneous vasculitis[25] developing after an intermediate dose of MTX (500 mg/m^2). Skin reactions have also been observed in association with treatment with other antifolates and they include transient erythema with piritrexim,[26] toxic dermatitis with 10-EdAM,[27] and generalized eruptions and erythroderma with trimetrexate.[28]

In conclusion, the severe toxicity experienced by our patient appears most likely to be the result of an 'allergic' or acute hypersensitivity drug reaction. The disproportionate involvement of the skin and the absence of extramedullary side effects make the possibility of a direct MTX-related toxicity highly unlikely. We wish to warn other physicians that the presence of an extensive skin rash following a single dose of MTX may portend the development of potentially life-threatening bone marrow aplasia.

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