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Case Report

Methotrexate-induced toxic epidermal necrolysis: A case report

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Methotrexate (MTX) is a folic acid antagonist that inhibits the enzyme dihydrofolate reductase resulting in decreased cell levels of tetrahydrofolate. Adverse cutaneous reactions to MTX are usually dose-related and have been mainly reported in patients receiving extremely large doses of chemotherapy. Toxicity can affect multiple organ systems including bone marrow, liver, intestinal tract, kidneys, lungs, skin, and blood vessels, resulting in death in severe cases. In this report we describe the case of a 9 year old boy who developed toxic epidermal necrolysis after high-dose MTX treatment and discuss the important clinical and therapeutic features of this condition.

Key words: Methotrexate, skin, toxicity, necrolysis.

INTRODUCTION

Methotrexate (MTX) is a potent competitive inhibitor of dihydrofolate reductase (DHFR), a key enzyme in the generation of reduced folates crucial for the biosynthesis of purines and thymidylic acid (Blakley and Benkovic, 1984; Blakley, 1995). Due to its substantial antiproliferative activity, MTX has been used effectively as a chemotherapeutic agent in the treatment of both hematopoietic and solid-organ neoplasms, particularly acute lymphoblastic leukemia, non-Hodgkin's lymphoma, Ewing's sarcoma, and osteosarcoma (Jolivet et al., 1983; Schornagel and McVie, 1983; Sorrentino et al., 1993). However, the usefulness of MTX as an antitumor agent is limited by the toxicity for highly proliferative normal cells and tissues of the hematopoietic system and gastrointestinal tract (Margolis et al., 1971; Rivera et al., 1985). Toxic epider-mal necrolysis (TEN) is a life-threatening disease characterized by extensive destruction of the epidermis. The mortality rate averages 25-30% following septicemia and various metabolic disturbances Fritsch, (2000). The generally recognized cause of TEN is an adverse drug reaction probably involving specific toxic metabolites (Fritsch and Sidoroff, 2000). We describe in this report a fatal case of high dose methotrexate toxicity.

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Case report

A 9 year old boy was referred to our department with a 7-month history of fever, vomiting, abdominal pain, edema of the lower limbs and loss of appetite. A diagnosis of Burkkit´s lymphoma was established. The patient was classified as Group C according to the LMB 2001 protocol. A one-week induction treatment using intrathecal chemotherapy (COPADM) was initiated combining daily doses of cyclophosphamide (1,500 mg/m^2), vincristine (2 mg/m^2), daunorubicine (60 mg/m^2), cytarabin (90 mg/m^2), prednisone (300 mg/m^2) and MTX (8 g/m^2).

Twenty four hours after the start of MTX infusion, leucovorin (15 mg, intravenous) rescue was initiated every 6 h for 3 days. Another preventive measure to prevent MTX toxicity included aggressive intravenous fluid replacement (3 L/m^2/day) and the addition of sodium bicarbonate to the intravenous fluid to alkalinize the urine. Four days after initiation of this treatment, the child developed pancytopenia, fever and sever kidney developed. At onset of pancytopenia, the patient was treated with supportive measures. A septic shock developed 10 days after completing the chemotherapy administration. This episode was treated by intravenous antibiotherapy associating ceftazidim (4 g/d), amikacine (15 mg/Kg/d) and vancomycin (2 g/d). Growth factors were administered also. Three days later, the patient developed an erythematous painful swelling on the fingers with subsequent large bulla

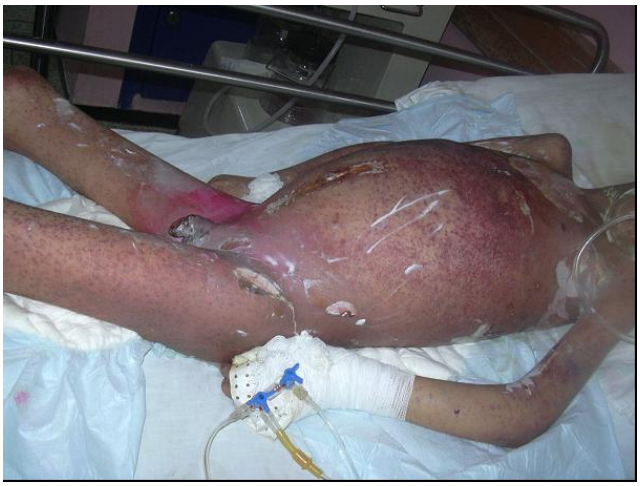

Figure 1. Toxic epidermal necrolysis involved the total body surface.

formation that progressed to palms, toes and soles of both feet. A few erythematous to hemorrhagic papules also appeared on the right elbow. Subsequently, diffuse erythema with extensive erosions and focal tiny pustules developed on the back, abdomen, proximal extremities and face (Figure 1). A positive Nikolsky's sign (denudation of the skin with gentle tangential pressure) was also present. The administration of amikacine and ceftazidim was stopped. Vancomycin therapy was maintained and supplemented with Imipenem (3g/d). The skin condition deteriorated rapidly and lesions involved roughly the total body surface. Mucositis, diarrhea, conjunctivis, oral lesions and chills were also noted. The general condition deteriorated rapidly and he died 4 days later due to septic shock and multiple organ failure.

DISCUSSION

MTX is a folic acid antagonist that has 100,000 times greater affinity than folic acid for dihydrofolate reductase enzyme (Weinstein et al., 1971). This mechanism effectively inhibits DNA synthesis in proliferating cells. The activity of this drug is augmented by polyglutamylation, and increases linearly with the concentration and duration of exposure. Therefore, higher doses or prolonged exposure to MTX result in greater toxicity than predicted by the drug dose alone. The half-life of MTX is approximately 10 h. Blood levels may vary according to the rate of absorption, exchange between plasma proteins and tissues, and excretion. Renal excretion is the major route of MTX elimination, and about 90% is excreted in an unchanged form within 24 h. Several factors can signifycantly influence MTX levels and toxicity (Olsen, 1991). Toxicity is increased by folic acid deficiency or by medications such as barbiturates and nitrofurantoin, which impair folic acid absorption. Trimethoprim-sulfamethoxazole, triamterene, and pyrimethamine are also dyhdrofolate reductase inhibitors and thus are clearly contraindicated in patients receiving MTX. Serum albumin binds between 50 to 70% of MTX; medications such as phenyltoin, probenecid, salicytates, and sulfonamides displace MTX and can increase its free level. Mucositis, urticaria, angioedema, photosensitivity, alopecia, maculopapular eruption, erythema, desquamation, Stevens-Johnson syndrome, toxic epidemrmal necrolysis and erosion of psoriatic plaques have been reported as adverse cutaneous reactions to MTX (Goldberg et al., 1978; Stiki et al., 1995; Cuthbert et al., 1993; Cuthbert et al., 1993; Hannah and Barbara, 1996; Doyle et al., 1983). Liver cirrhosis and bone marrow suppression are other well-known side-effects (Zachariae, 1990).

Whether the epidermal necrolysis is an allergic or dose-related toxicity reaction is still controversial. Stiki et al. (1995) presented a patient with generalized maculopapular eruption and bone marrow aplasia after a first MTX exposure, and assumed that it was an 'allergic' or acute hypersensitivity reaction in susceptible individuals (Stiki et al., 1995). Lawrence and Dahl (1984) described seven patients who developed skin ulceration on psoriatic plaques and pre-existing statis dermatitis after a low dose of MTX (Lawrence and Dahl, et al., 1984). Four of these patients received long-term MTX therapy and ulceration occured after increases in MTX dosage or after taking nonsteroidal anti inflammatory drugs (NSAIDs). All of these patients were receiving NSAIDs when skin ulceration occurred, and the ulceration of five patients healed after reducing the MTX dosage. Martins et al. (Martins et al., 1991) also reported palmoplantar erythema and desquamation in a child with ALL as a consequence of a high dose of MTX (5 g/m2). They suggested that the skin reaction was a result of direct toxicity due to the high MTX level. In our case, the patient presented an extensive skin necrolysis and bone marrow suppression occurring after high dose MTX administration. We believe that high-dose MTX schemes may arrest normal epidermal cell proliferation and cause direct cell toxicity. Thus, epidermal necrolysis may be a dose-dependent process, rather than an allergic reaction, in susceptible individuals. Careful monitoring of the hemogram for the possibility of bone marrow suppression, avoidance of the use of unnecessary concomitant medications, such as NSAIDs or contraindicated drugs such as, trimethoprim-sulfamethoxazole, sulfonamides, and salicylate, and reduction of MTX dosage when possible are required.

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