**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 thymidylate. 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 epidermal 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 and Sidoroff, 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.

**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 Burkitt'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/m²), vincristine (2 mg/m²), daunorubicine (60 mg/m²), cytarabin (90 mg/m²), prednisone (300 mg/m²) and MTX (8 g/m²).

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/m²/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 pan-cytopenia, fever, and severe kidney development. 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...
Toxicity is increased by folic acid deficiency or by medications such as barbiturates and nitrofurantoin, which im-
zole, triamterene, and pyrimethamine are also dyhydrofol-
etically inhibits DNA synthesis in proliferating cells. The ac-
tration of skin with gentle tangential pressure) was also pres-
concentration and duration of exposure. Therefore, higher doses or prolonged expo-
sure to MTX result in greater toxicity than predicted by the drug dose alone. The half-life of MTX is approxi-
ately 10 h. Blood levels may vary according to the rate of ab-
sorption, exchange between plasma proteins and tis-
sues, and excretion. Renal excretion is the major route of MTX elimination, and about 90% is excreted in an un-
changed form within 24 h. Several factors can significa-
cantly influence MTX levels and toxicity (Olsen, 1991).

Whether the epidermal necrosis is an allergic or dose-
related toxicity reaction is still controversial. Stiki et al.
(1995) presented a patient with generalized maculopa-
pular 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 stasis dermatitis after a low dose
of MTX (Lawrence and Dahl, et al., 1984). Four of these
patients received long-term MTX therapy and ulceration
occurred 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 des-
quamation 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 exten-
sive skin necrosis and bone marrow suppression occur-
ing after high dose MTX administration. We believe that
high-dose MTX schemes may arrest normal epidermal
cell proliferation and cause direct cell toxicity. Thus, epi-
dermal necrosis may be a dose-dependent process, ra-
than an allergic reaction, in susceptible individuals.

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 effect-
vively inhibits DNA synthesis in proliferating cells. The ac-
tivity of this drug is augmented by polyglutamylation, and
increases linearly with the concentration and duration of
exposure. Therefore, higher doses or prolonged expo-
sure to MTX result in greater toxicity than predicted by
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cantly influence MTX levels and toxicity (Olsen, 1991).

Toxicity is increased by folic acid deficiency or by medi-
cations such as barbiturates and nitrofurantoin, which im-
pair folic acid absorption. Trimethoprim-sulfamethoxa-
zole, triamterene, and pyrimethamine are also dyhydrofol-
ate reductase inhibitors and thus are clearly contrain-
dicated in patients receiving MTX. Serum albumin binds
between 50 to 70% of MTX; medications such as phenyl-
toin, probenecid, salicylates, and sulfonamides displace
MTX and can increase its free level. Mucositis, urticaria,
angioedema, photosensitivity, alopecia, maculopapular
eruption, erythema, desquamation, Stevens-Johnson
syndrome, toxic epidermal necrosis and erosion of psoriatic plaques have been reported as adverse cuta-
neous 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 cir-
rhosis and bone marrow suppression are other well-
known side-effects (Zachariae, 1990).

REFERENCES

Blakley RL and Benkovic SJ (1984). Chemistry and biochemistry of
folates, in Folates and Pterins, John Wiley and Sons, New York. 1:
191-253
Cuthbert RJ, Craig JIO, Ludlam, CA (1993). Stevens-Johnson
syndrome associated with methotrexate treatment for non-Hodgkin's