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METHOTREXATE OVERDOSE WITH BONE MARROW TOXICITY: A CASE REPORT

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ABSTRACT

Methotrexate (MTX) is a disease-modifying anti-rheumatic drug that has been used widely in dermatology, oncology and rheumatology fields. Our study concentrates on a fifty year old male patient who had developed MTX overdose with bone marrow toxicity by accidental intake of the drug continuously for a week. The patient developed neutropenic fever, oral mucosal ulcer and rashes along with increased serum aminotransferase and reduced count of leukocytes and platelets. With the diagnosis of MTX overdose, the drug was discontinued and the patient underwent treatment with leucovorin, granulocyte colony-stimulating factor and empiric broad spectrum antibiotics (Meropenem and Teicoplanin). Co-existing conditions were treated accordingly.

KEYWORDS: Methotrexate, toxicity, overdose, case report, treatment.

INTRODUCTION

Methotrexate (MTX) is an immunosuppressant drug that was developed in the 1950s.[1] It is a folic acid analogue and antagonist which binds to dihydrofolate reductase enzyme, thereby interfering with the conversion of dihydrofolate to tetrahydrofolate, resulting in inhibition of DNA synthesis.[1,2] Initially developed as an anticancer drug, MTX is currently the first line disease-modifying anti-rheumatic drug (DMARD) in the treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis, and psoriasis, and is also used in inflammatory bowel disease (IBD), multiple sclerosis (MS), vasculitis, systemic lupus erythematosus (SLE) and other connective tissue diseases, and transplantation due to its anti-inflammatory and immunomodulatory activities.[3]

MTX can be administered orally or as intramuscular, intravenous, intrathecal, or subcutaneous form of injections. After initiating therapy with MTX, follow-up tests involving monitoring of complete blood count (CBC), renal function test (RFT) and liver function tests (LFT) are advocated weekly for 4 weeks and then at least bi-monthly.[4] Even if the side effects are more common after administration of high dose MTX (HDMTX; > 500 mg/m2), they have also been reported after lower doses.[2] Factors such as age, drug interaction, individual susceptibility and co-morbid conditions can be conducive to the development of toxicity.[5] Leucovorin or folinic acid should be administered with MTX as a rescue to decrease the toxic effects like bone marrow suppression.[6]

CASE REPORT

A fifty year old male patient was admitted to the general medicine department of a tertiary care hospital with complaints of shivering, chills, odynophagia, oral mucosal ulcers and rashes over the head, face and back with itching for 2 days. His past medical history showed that he was on treatment with methotrexate (MTX) for rheumatoid arthritis (RA) and metformin for recently developed Type 2 Diabetes Mellitus. The patient claimed that he started developing rashes after metformin usage. Instead of taking MTX 10 mg once a week, he had inadvertently taken the drug daily for a week.

On examination, the patient had neutropenic fever (100.8ºF), increased heart rate (114bpm), phimosis and pus discharge. Laboratory investigation showed an elevation of CRP, SGOT, SGPT and ESR with a

reduction in leukocytes and platelet count. USG abdomen revealed grade 2 fatty infiltration of the liver, grade 1 prostatomegaly and cystitis. With the diagnosis of MTX overdose, the drug was discontinued and the patient underwent treatment with calcium leucovorin at a dose of 50mg intravenously. After collecting cultures, the patient started IV antibiotics: Meropenem (1gm), Teicoplanin (400mg) and granulocyte colony-stimulating factor, in view of neutropenia. Also, precipitating factors were treated accordingly. During the course of the treatment, the patient developed a further reduction in total count, ANC and platelet count. As there was not much improvement in the clinical condition of the patient and due to absence of a hematology department, the patient was referred to a higher centre.

DISCUSSION

MTX has been widely used as a DMARD for the treatment of RA. The dose varies from 7.5 to 30 mg/week.[7] Our patient had been prescribed with 10mg of MTX for weekly once administration, but he had taken the drug daily for a week by mistake which lead to toxicity.

Although a low dose of MTX is widely used, it is not free from side effects.[4,5] MTX toxicity is characterized by gastrointestinal symptoms, myelosuppression, pancytopenia, hepatotoxicity, acute renal failure (ARF), pulmonary toxicity, mucositis, stomatitis, ulceration of the gastrointestinal system and cutaneous ulcerations.[1,8,9] Elevation of serum aminotransferase levels, serum uric acid, leukopenia, thrombocytopenia, and anemia may be noticed in laboratory tests of MTX poisoned patients.[1] Our patient had almost all symptoms of MTX toxicity.

The three antidotes used for MTX toxicity are leucovorin, thymidine, and glucarpidase. Leucovorin is the reduced active form of folic acid which acts by rescuing normal cells from harmful results such as myelosuppression, gastrointestinal toxicity and neurotoxicity during MTX treatment. Thymidine acts by rescuing cells from the cytotoxic effects of MTX. Its use is still under investigation and is always given in conjunction with the other drugs. Glucarpidase acts by converting MTX into DAMPA and glutamate, thereby rapidly removing the drug in renal disease patients. Glucarpidase is commonly given in combination with leucovorin for MTX toxicity. Leucovorin therapy should continue for 48 hours after glucarpidase administration.[4]

CONCLUSION

Each patient should be aware of the relevance of medication usage which can be attained through patient counselling. As MTX toxicity is serious and potentially fatal, the patient should be properly educated by the medical practitioner about the proper intake of the medication, the right dose and the side effects to prevent potential adverse effects.

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