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CASE REPORT ON ACUTE METHOTREXATE TOXICITY

Bonish Romance[1], Devika Vijay R.[1], S. Jeni Sharon[1], Dr. Gopal S.[2], Dr. Shajahan O. M.[3], Dr. Aarthi Prakasam[4], Dr. N. Babu*[5]

[1]Pharm D Intern, K. K. College of Pharmacy, Gerugambakkam, Chennai.

[2]Senior Consultant, Dept. of General Medicine, Vijaya Hospital, Vadapalani, Chennai.

[3]MD Pharmacologist, Dept. of Emergency & Critical Care Medicine, Vijaya Hospital, Vadapalani, Chennai.

[4]Deputy Medical Director, Dept. of Emergency & Critical Care Medicine, Vijaya Hospital, Vadapalani, Chennai.

[5]*Head of the Department, Dept. of Emergency & Critical Care Medicine, Vijaya Hospital, Vadapalani, Chennai.

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***Corresponding Author**
Dr. N. Babu MBBS, MD
Head of the Department,
Dept. of Emergency &
Critical Care Medicine,
Vijaya Hospital,
Vadapalani, Chennai.
drbabu@vijayahospital.org

ABSTRACT

Background: Methotrexate is currently considered the first-line disease-modifying antirheumatic drugs (DMARDs). It is an antimetabolite that competitively inhibits the conversion of dihydrofolate to tetrahydrofolate by binding to dihydrofolate reductase. It has been widely and safely used in the treatment of rheumatoid arthritis, psoriasis, and many other rheumatologic diseases. The most common cause of acute MTX toxicity is an accidental overdose of MTX tablets by the patient or physician's prescription error. **Case presentation**: This is a case report of a 72 year old female patient who developed rashes all over the body with erythema, urticaria, followed by oral ulcers and bleeding from mouth. A detailed literature review found that pancytopenia, gastrointestinal (GI) mucositis, mouth ulcers and acute renal failure as warning signs of severe methotrexate toxicity. **Conclusion**: Methotrexate being an option of great therapeutic value for RA, its use should be well guided and counselled by the physician with strict warnings. This case instantiate the importance of recognizing clinical signs of MTX toxicity and to commence therapy as soon as possible. Although low-dose MTX turn up to be a safe medication, acute MTX toxicity can be fatal. So

it is important to use this medicine with much precautions by creating awareness about the ill effects of MTX if not taken as instructed, among the patients.

KEYWORDS: Methotrexate, Erythema, Pancytopenia.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, progressive, inflammatory systemic autoimmune disease that primarily affects synovial joints. The primary goals for managing RA are to relieve pain and discomfort and ameliorate symptoms; prevent or control joint damage, and avoid long-term loss of function. Disease-modifying antirheumatic drugs (DMARDs) are cornerstone treatments for controlling the symptoms and modifying its radiographic progression in RA.[1] Many DMARDs are available; however, since the reintroduction of methotrexate (MTX) in the early 1980s, it has become the most effective, fast-acting DMARD and the most widely used first-line treatment of RA.[2] Early treatment and adherence to disease modifying anti-rheumatic drugs (DMARDs) have an important impact on disease outcome in rheumatoid arthritis (RA) patients.[3,4]

Methotrexate (MTX) inhibits mitosis of the cells by antagonizing folic acid required for deoxyribonucleic acid (DNA) synthesis of cells. Once in the cell, MTX inhibits dihydrofolate (DHF) reductase, an enzyme responsible for the conversion of DHF to tetrahydrofolate (THF). Consequently, there is a reduction in thymidylate and purine biosynthesis. DNA synthesis eventually halts and cells can no longer divide. Polyglutamination of MTX prolongs its intracellular presence. Hence, cells with the capability of effective polyglutamination such as leukemic myeloblasts, synovial macrophages, lymphoblasts, and epithelia are more susceptible to the action of MTX.[5] Acute MTX toxicity presents as pancytopenia, gastrointestinal (GI) mucositis, hepatotoxicity, pulmonary toxicity, and acute renal failure.[6,7] Skin lesions due to acute MTX toxicity are rare.[7–11] The side effects of MTX therapy on the skin are manifold.[12–15] They include mild reactions and severe ones.[12,13,18,19] Identification of those cutaneous lesions might help to initiate rescue strategies at an early stage.[11] The most common cause of acute MTX toxicity is an accidental overdose of MTX tablets by the patient or physician's prescription error.

CLINICAL FEATURES

MTX toxicity targets vital organs and structures of the body namely skin, GI mucosa, kidney, liver, and bone marrow. Major toxic effects of MTX, such as hepatic, renal, pulmonary, and

bone marrow disorders, occur less frequently than the minor effects but may be life threatening. Signs and symptoms of acute MTX toxicity are based on extent and severity of organ involvement.[5] Methotrexate continues to be one of the most widely used systemic immunosuppressive agents in dermatology. In addition to the important, well-characterized adverse effects such as hepatotoxicity and myelosuppression, methotrexate may induce a number of rare cutaneous adverse events including methotrexate-induced ulceration.[18]

The present case highlights the above aspects and in addition clinical presentations, systemic complications, risk factors of methotrexate toxicity and outcome of the cases have been described.

CASE PRESENTATION

A 72 year old lady presented with complaints of rashes all over the body with severe erythema, urticaria, oral ulcers and bleeding from mouth. She had history of low grade fever for 3-4. she is a known case of hypertension and rheumatoid arthritis. She doesn't have any previous drug allergies. She was started on methotrexate in an outside hospital 10 days back. After enquiring the patient's attender, it was found that she was taking 7.5mg of methotrexate daily instead of weekly once thinking it was a pain killer.

On admission her vitals were as follows, temperature 99^0F, BP 130/80mmHg and respiratory rate 27/min. Her lab investigation at the time of admission showed **WBC- 120/cumm ; N-16.1; L- 52.5 E-28.7; Hb- 9.0g/dl; Platelet – 35000; ESR- 120; S.Cr - 1.4mg/dl; Urea -82.** Peripheral smear showed Normocytic normochromic anaemia with marked leukopenia and thrombocytopenia. RA Factor was 85.6 (Positive).

She was treated with parenteral antibiotics, follinic acid as an antidote, filgrastim to treat pancytopenia and with other supportive measures. She was improving symptomatically and discharged after 14 days of hospitalization with vitals stable and lab investigations were WBC-12000; platelets-1,25,000 and other parameters was also found to be normal. Her mouth ulcers were decreasing and cutaneous lesions also reduced.

DISCUSSION

This is a case of an elderly woman with known history of hypertension and recently diagnosed of rheumatoid arthritis and was prescribed with methotrexate 7.5mg once weekly in outside hospital. She took methotrexate once daily for 5 days and developed severe rashes

all over the body with erythema, urticaria, oral ulcers and bleeding from mouth and the clinical investigations showed that the patient is Normocytic Normochromic Anaemia with marked Leukopenia, Thrombocytopenia and found that it was methotrexate induced toxicity. Methotrexate is currently considered the first-line disease-modifying antirheumatic drugs (DMARDs).[19,20] It is an antimetabolite that competitively inhibits the conversion of dihydrofolate to tetrahydrofolate by binding to dihydrofolate reductase. Tetrahydrofolate is essential for the synthesis of thymidine and purines required for DNA synthesis. High-dose methotrexate treatment is defined as a dose greater than 500 mg/m2 given intravenously and is mostly used in the treatment of various malignancies.[21] Low-dose regimen (5 mg to 25 mg once weekly) has been widely and safely used in the treatment of rheumatoid arthritis, psoriasis, and many other rheumatologic diseases. prevalence of rheumatoid arthritis in elderly is increasing over last two decades, and in many countries, the prevalence can be as high as 40% in the elderly patient (older than 65 years).[22]

In the literature, most cases of cutaneous MTX toxicity have been reported in psoriatic patients.[18,23–26] In patients with RA MTX cutaneous toxicity was rarely reported[27-29] with the first case reported in 1998.[30] Yoon et al. have reported an acute cutaneous toxicity of MTX representing a Koebner-like phenomenon.[31] Gilani et al. have reported in their series of 140 adult RA patients receiving low dose MTX (10 mg/week) for at least 3 months mucocutaneous adverse effects of MTX in 3 cases.[27] MTX-induced panniculitis in a patient with RA have also been reported.[28] In our case the patient presented with severe extensive skin lesions which correlates with study reported by Aractingi et al., in which a case of male patient presenting with extensive skin erosions after intravenous infusion of a 5 gram total dose of MTX to treat high grade lymphoma.[30] The histology of skin biopsies taken from the edge of erosions, shows hyperkeratosis, hypergranulosis, and epidermal hyperplasia as well as changes consistent with a direct toxic effect on the epidermis, such as swollen epidermal cells with decreased nuclear and cytoplasmic staining, vacuolated or dyskeratotic cells, and even epidermal necrolysis.[23,32] In the skin biopsy there was numerous esinophils. Interestingly, eosinophilia is quite common in RA patients.[33] Keratinocyte dystrophy may help to diagnose skin toxicity of low-dose MTX, even in the absence of known risk factors or MTX administration errors.[34] Studies of the diagnostic performance of this histologic sign are needed.[35] Previous reports in the literature have described episodes of skin ulceration in patients who have recently started MTX or patients on chronic therapy who experience a dose escalation.[7,36]

Cutaneous erosions treatment is mostly supportive because it substantially tend to heal quickly within 1–2 weeks of stopping or reducing the dose of MTX.[14] Patients generally recovered following MTX withdrawal and intensive treatment.[23,10,24,18,26] Active treatment with folinic acid (calcium leucovorin) is required in patients presenting with cutaneous ulceration due to MTX.[18] Cutaneous ulcerations totally healed rapidly within two weeks and no recurrence has been observed for the 6 months of follow up in the case reported by Koçak et al.[26] These cases mentioned in the literatures chiefly parallels with the clinical course of our patient.

CONCLUSION

MTX is widely used drug for many conditions and its importance stand magnificent for many disease conditions. Inspite of its significant benefits, there are many side effects and toxic effects that are life threatening. So it is important to recognize the drug and discontinue immediately with rescue measures instituted. In conclusion, methotrexate being an option of great therapeutic value for RA, its use should be well guided and counselled by the physician with strict warnings. This case instantiate the importance of recognizing clinical signs of MTX toxicity and to commence therapy as soon as possible. Although low-dose MTX turn up to be a safe medication, acute MTX toxicity can be fatal. So it is important to use this medicine with much precautions by creating awareness about the ill effects of MTX if not taken as instructed, among the patients.

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