Case Report

Methotrexate induced erythema multiforme: a rare case report

Hasan MM[a], Khalil MI[b], Haque MS[c], Rahman MR[d] , Yesmin S[e]

ABSTRACT

Methotrexate is commonly used in the treatment of inflammatory disorders and malignancies. Although it is an effective therapeutic agent, it may have serious adverse effects in both therapeutic dose and overdose. Here, we report a case of a 54-year-old lady with polyarthritis, who was prescribed 2 tablets of methotrexate (10 mg) orally once a week. However, mistakenly the patient started taking the drug daily. After 12 days of starting methotrexate, she presented with widespread skin lesions, sore mouth and dysphagia. A diagnosis of methotrexate induced erythema multiforme was made. Laboratory investigations revealed pancytopenia. She was managed conservatively. Although rare, methotrexate overdose should be considered along with other possibilities in a patient with erythema multiforme. This case report also focuses on the rational use of drugs as well as the importance of good communication between health care professionals and patients.

Key words: *adverse drug reactions, erythema multiforme, methotrexate.*

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INTRODUCTION

Methotrexate (MTX) is a disease-modifying anti-rheumatic drug (DMARD) used since 1980 as the first line treatment for rheumatoid arthritis (RA). MTX prevents cell proliferation by inhibiting the dihydrofolate reductase enzyme.[1] Skin and mucosal involvement may be a direct cytotoxic or cytostatic effect of MTX. Common adverse effects include mucositis, leukopenia, pancytopenia, nausea, malaise, fatigue, fever, chills, dizziness and low resistance to infections.[2-4] Erythema multiforme (EM) is an acute mucocutaneous immune reaction that can be triggered by infection, certain medications or antigenic stimuli.[5] Lesions of the oral mucosa are manifested as painful erosive blisters where thick hemorrhagic crusts can affect speech, diet and liquid intake.[6] In high doses, MTX may rarely cause EM.[7] The occurrence of typical EM along with mucositis and pancytopenia, in a patient with MTX toxicity was found to be rare[8-10] but in our case report, all these events were observed.

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CASE REPORT

A 54-year-old Bangladeshi woman got admitted with the complaints of itchy erythematous skin rash over whole body including palms and soles for 9 days, along with multiple painful oral ulcers, odynophagia which led her unable to eat or drink for last 3 days. She was a known case of diabetes mellitus, hypothyroidism, hypertension, ischemic heart disease (status post percutaneous coronary intervention) and was on appropriate management with regular follow-up. For last 3 years, she developed non-inflammatory type of pain in her both knee joints, later involved both shoulder and ankle joints. With these complaints recently she visited a physician and was prescribed MTX tablet 20

mg weekly but mistakenly the patient was having it daily. After 3 days of taking MTX 20 mg, she developed widespread itchy skin rash and painful oral ulcers. Initially, she neglected those symptoms and continued her medication. Her symptoms gradually worsened over a week. As she developed odynophagia, she got herself hospitalized.

Physical examination revealed widespread targetoid lesions (Figure 1) including palm and soles consistent with the diagnosis of EM with few pustules (Figures 2 & 3). Oral mucosa was found erythematous with multiple ulcers (Figure 4). After reviewing her medications, clinically we diagnosed her as a case of MTX induced EM.

Complete blood count (CBC) revealed pancytopenia. We excluded other possibilities of such findings clinically and planned for skin biopsy to confirm EM but our patient denied to do so. To exclude other possible etiologies of EM, we ran few other investigations and the reports were unremarkable. We stopped methotrexate and immediately started IV fluid, IV folinic acid, benzydamide mouth wash, triamcinolone oral paste, topical betamethasone, oral H_2-blocker and oral antihistamine. She gradually improved clinically but serial CBC revealed worsening pancytopenia (Table I). Then she was given subcutaneous filgrastim (granulocyte colony-stimulating factor) 300 mcg once daily for 3 days. Her blood picture improved by 7th inpatient day following admission (Table I).

She was diagnosed as a case of osteoarthritis for the joint pain and was managed conservatively with oral paracetamol and physiotherapy. On the 8th hospitalization day, the patient was discharged with significant improvement of the skin lesions, oral lesions and dysphagia with the advice to outpatient follow-up after 1 week. During follow-up she was found to have significant improvement both clinically and biochemically.

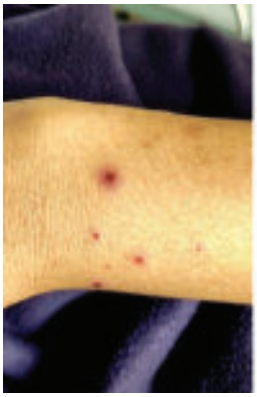

Figure 1. Targetoid lesions over extensor surface of right forearm

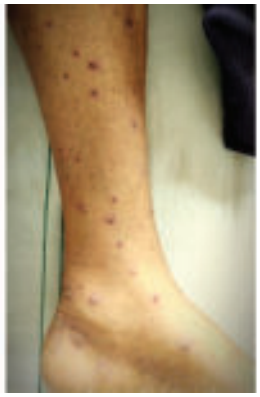

Figure 2. Targetoid lesions with few pustules over right leg and foot

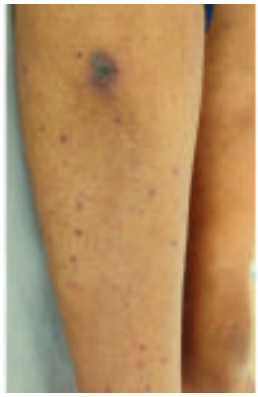

Figure 3. Ulcer with necrotic crust and few pustules over left leg

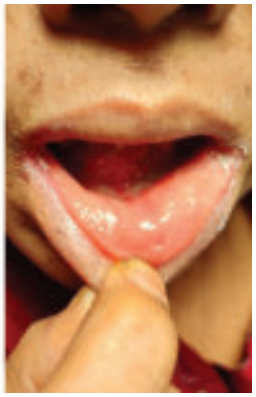

Figure 4. Mucositis of oral cavity

Table I. Laboratory values

CBC	Day-1	Day-3	Day-5	Day-7	Follow-up
Hb (g/dl)	9.2	8.7	8.6	9.5	10.9
Total WBC/cmm	1.15	0.85	2.14	13.06	9.07
Polymorph (%)	44.3	70.1	39.0	51.9	72.1
Lymphocyte (%)	44.3	24.1	65.4	23.5	26.3
Monocyte (%)	0.9	2.0	4.7	11.7	1.3
Eosinophil (%)	9.6	2.1	18.2	4.7	0.4
Platelet/cmm	172000	106000	70200	306000	410600

DISCUSSION

Reports of adverse events with the use of MTX are common, although it is important to discuss the context in which these effects were observed. In therapeutic dose, MTX is an effective medication but a wide range of adverse effects including bone marrow suppression, mucocutaneous damage, hepatic or renal dysfunction, gastrointestinal and neurotoxicity may occur in overdose. The toxicity usually occurs rapidly and often difficult to manage.[1,2] In most cases, bone marrow toxicity is dose dependent and responds to folinic acid administration. In a review, clinically significant pancytopenia was found in 1% to 2% of patients on MTX therapy.[3] Another cohort study revealed, pancytopenia is the most frequent systemic adverse effect of MTX toxicity (78%).[4]

EM is an acute mucocutaneous immune reaction, may be recurrent. The hallmark of EM is a target lesion described as rounded lesion that is regular with three concentric circles and a well-defined border. The peripheral ring is erythematous, the middle zone is often clearer, oedematous, palpable and the center is erythematous, covered by a blister. These different aspects evoke different stages of the evolving lesion. The lesions usually measure less than 3 centimeters and their location is mainly acral. They are symmetrical in the palms and soles and the limb extensors. The trunk is often spared but the face and ears can be involved. Usually there is no pruritus, rather sensation of burning in some patients. It shows variable mucous membrane involvement; usually limited to the oral mucosa. While skin lesions are painless, mucosal lesions are frequently painful. EM may be provoked by a range of systemic diseases, bacterial and viral infections but the majority of cases of EM are linked to medications. The diagnosis of EM is clinical. In case of doubt a punch skin biopsy can be used to confirm the diagnosis. The etiological assessment should be done according to the medication review and symptoms.[5] It is important to note the differential diagnosis of EM, which includes urticaria, fixed drug eruption, bullous pemphigoid, sweet's syndrome, rowell's syndrome and polymorphous light eruption. These various entities differ from EM clinically and pathologically.[6]

MTX induced adverse cutaneous drug eruptions may vary from benign maculopapular rash to Steven's-Johnson syndrome, which depends mainly on the host response to the drug. EM is a known adverse reaction of MTX although rare. We have found very few publications of such cases in our literature search.[7-9] Although the precise pathogenesis of MTX induced EM is still unknown, it appears to be the consequence of a cytotoxic immunological reaction against the keratinocytes expressing non-self antigens. The lesions can be numerous, with all typically appearing within 3 days and may persist up to 2 weeks. MTX induced EM is typically mild and self-limited but other systemic adverse effects may progress to multi-organ failure and ultimately death. Topical treatment is based on antiseptics for bullous lesions, antiseptic mouthwashes and anesthetic. Severe cases of EM will require admission to HDU or ICU to manage the complications along with dehydration and any infection. Folinic acid is the antidote of choice for treating MTX toxicity. Dosage of folinic acid is estimated according to the plasma concentration of MTX, however, the facility for serum MTX measurement is not widely available and most cases are managed on clinical grounds. Along with barrier nursing, broad spectrum parenteral antibiotic preferably a third generation cephalosporin should be instituted for neutropenic fever.[10] Recombinant granulocyte colony-stimulating factors (G-CSFs) therapy reduces the severity and duration of neutropenia and the consequent risk of febrile neutropenia. Recombinant human G-CSF acts on hematopoietic cells to stimulate production, maturation and activation of neutrophils.[11]

The most common cause of acute MTX toxicity is an accidental overdose of MTX tablets by the patient or physician's prescription error. In addition to correct prescription, it is necessary to ensure patient's understanding regarding the dose, duration and adverse effects of the medications. It is important to train and empower patients to manage their medication, particularly in chronic diseases.[12] Generally, MTX is prescribed at a dose of 7.5–25 mg once a week. Unfortunately, our patient misunderstood the prescription, which ended up with adverse events. Although it was clear that, not only MTX prescription was irrational in our case but also the patient's understanding regarding the medication dosage was inappropriate. In summary, the aforementioned case exemplifies the importance of good communication between the health professionals and the patient, as well as the rational use of drugs.

Authors' contribution: Md. Mehedi Hasan was involved in the diagnosis, patient management, manuscript writing and literature review. All authors were involved in evaluation and management of the case.

Consent: Informed consent was obtained from the patient after describing the method and purpose of the case report.

Conflict of interest: Nothing to declare.

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