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METHOTREXATE INDUCED STEVENS JOHNSON SYNDROME: A RARE CASE REPORT

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ABSTRACT

Methotrexate (MTX) is a folic acid antagonist with cytotoxic and immunosuppressant activity andwith potent antirheumatic action. It is commonly a first choice Disease modifying antirheumatic drug (DMARD). There were some spurious reports of Adverse Drug Reaction (ADR) by this drug. Here we report a rare occurrence of Stevens-Johnson syndrome (SJS) / Toxic Epidermal Necrolysis (TEN) after the use of Methotrexate. Naranjo score for this adverse drug event was six, thereby making it a probable ADR. Symptomatic management of the patient was done and the offending drug was withdrawn. We are presenting this case to highlight the serious adverse reactions possible from a routinely prescribeddrug.

KEYWORD: Methotrexate, Stevens-Johnson syndrome, Rheumatoid arthritis, Adverse Drug Reaction.

INTRODUCTION

The World Health Organisation defines an adverse drug reaction (ADR) as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function." Methotrexate (MTX) is well-established as the "anchor drug" for patients with rheumatoid arthritis (RA), to be used early and aggressively, with higher long-term effectiveness, tolerability, and safety than any other disease-modifying antirheumatic drug (DMARD) (1). Methotrexate has greater affinity than folic acid for the dihydrofolate reductase enzyme. This mechanism of methotrexate reduces the tetrahydrofolate and attenuates the DNA synthesis in proliferating cells, making it an ideal disease modifying agent for rheumatoid arthritis. Methotrexate is metabolized into a series of polyglutamate derivatives that increase linearly with the concentration and duration of exposure. Therefore, higher doses of methotrexate administered for prolonged duration can result in greater toxicity(2).Other reported adverse effects are diarrhoea, dizziness, stomach pain, fever and chills. Stevens-Johnson Syndrome (SJS) is a life-threatening, bullous cutaneous disease considered as immune-mediated reactions to drugs characterized by epidermal necrosis, extensive detachment of the epidermis, erosions of mucous membranes and severe constitutional symptoms(3). Here, we report a case of methotrexate induced Stevens Johnson syndrome, a clinical association that has been previously reported in very few cases in Indian population.

CASE REPORT

A 46-year-old female came to Dermatology outpatient department with chief complaints of fever, swelling of lips, oral ulcers and blisters all over the body. Fever was of high grade 39.4 C (103F) and had a continuous pattern. Patient had noticed the rashes a few days after developing fever. She had been diagnosed with rheumatoid arthritis one month ago and had been taking oral methotrexate 7.5 mg per week for 2 weeks. No past history of allergic diathesis was reported. Gradually these rashes developed into bullae and blisters spreading all over the body from face to hands and legs, then to abdominal region and to the back. She also developed ulceration of buccal mucosa and desquamation of tongue.

She complained of pain in joints of both hands and legs. Physical examination revealed cutaneous involvement of trunk, face, lips, palms and soles. Patient had erythema and multiple vesicles in the oral mucosa and involving most of her face.Few disrupted vesicles with crusting were also present around the lips, nose and forehead. Conjunctival congestion was present. Bullous lesions with erosions and peeling were present bilaterally on both the legs and trunk. The vital signs recorded were as follows: temperature (axillary)-39.5ºC; pulse rate- 92/min; respiration rate-16/min. Blood Pressure (BP) was 160/80 mmHg. On taking history, patient's attendant told that she was

taking Tab. Methotrexate 7.5 mg per weekfor2 weeks as a treatment for Rheumatoid arthritis which was prescribed by a local practitioner. The patient was not suffering from any kind of infection or any other chronic disease. Patient was diagnosed with Drug Induced Stevens Johnson Syndrome. She was immediately admitted in emergency ward and given fluid resuscitation with normal saline, intravenous corticosteroids (Hydrocortisone Hemi succinate 100 mg I.V), antihistamines (Avil) andsupportive medication. (Ranitidine 50 mg i.v, Benzocaine gel for oral ulcerations). All the previous medications taken by the patient were discontinued. Laboratory investigations revealed haemoglobin 10.04 g/dl, white blood cell count 5890 mm3, platelet count 180,000 mm3, serum creatinine 1.1 mg/dl, blood urea nitrogen 17 mg/dl, liver function test was normal. Pus culture was positive for gram positive cocci and coagulase negative Staphylococcus. Blood and urine cultures were sterile. Chest X- ray and ultrasound abdomen were normal. Gradually the condition of the patient improved and after 3 days, crusting of rashes, bullae and blisters started developing and itching, oedemaand erythema subsided.

The Naranjo adverse drug reaction probability scale scoreof six indicated a 'Probable' relationship between Stevens Johnson Syndrome and Methotrexate therapy in this patient (4). WHO Uppsala Monitoring Centre Causality Assessment Criteria (5) also indicated a'Probable' association with Methotrexate.

Fig 1: Erosions and Peeling Present At The Back Of The Trunk

DISCUSSION

Stevens-Johnson syndrome (SJS) is a rare but severe cutaneous adverse reactions (SCARs) which cause significant morbidity and mortality (6). The aetiology of SJS and TEN is not clear and could be due to drug induced immunological mechanism. CD8 T-cells as well as the cytolytic molecules Fas ligand (FasL) and granulysin are key substances in the pathogenesis of SJS/TEN, but the manner in which a culprit drug regulates the function of these key substances in a patient who develops SJS/TEN is the subject of ongoing research (7). There are four causative categories which includes (a) infectious (b) drug-induced (c) malignancy-related (d) idiopathic (8).

SJS is classified as (7) –

- Stevens-Johnson syndrome: A minor form of toxic epidermal necrolysis (TEN), with less than 10% body surface area (BSA) detachment
- Overlapping Stevens-Johnson syndrome/toxic epidermal necrolysis: Detachment of 10-30% of the BSA. ·
- Toxic epidermal necrolysis: Detachment of more than 30% of the BSA

The most frequently involved groups of therapeutic agents cited in the literature that induce SJS include sulphonamides, anticonvulsants, non-steroidal anti-inflammatory drugs beta lactam antibiotics, carbamazepine, valproic acid, lamotrigine, barbiturates etc (8).It has been recognized that drug-induced SJS is a severe hypersensitivity reaction which involves major histocompatibility class -I (MHC) restricted drug presentation and cytotoxic T lymphocytes (CTLs) expansion, which further leads to extensive keratinocyte death in skin lesions. (9)

Methotrexate has greater affinity than folic acid for the dihydrofolate reductase enzyme. This mechanism of methotrexate reduces the tetrahydrofolate and attenuates the DNA synthesis in proliferating cells, making it an ideal disease modifying agent for rheumatoid arthritis. Methotrexate is metabolized into a series of polyglutamate derivatives that increase linearlywith the concentration and duration of exposure (2). Therefore, higher doses of methotrexate administered for prolonged duration can result in greater toxicity.Methotrexate induced SJS is a rare adverse drug reaction which we have highlighted in this case report.Cases of SJS/TEN are primarily induced by medications.

ALDEN (Algorithm for Drug causality in Epidermal Necrolysis) has been used to provide structured assistance for the assessment of culprit drugs in SJS/TEN patients(10).

A disease severity scoring system called SCORTEN (SCORE of Toxic Epidermal Necrolysis) built on seven independent variables (11) -

- Age more than 40 years
- Malignancy

- Heart rate >120/minute
- Initial epidermal detachment >10% of BSA
- Serum urea level >28 mg/dl (40 mg/dl in Indian settings)
- Serum glucose levels >250 mg/dl
- Serum bicarbonate levels <20 mEq/dl.

The probability of death predicted by this score is as follows: 0-1 points- 0.03; 2 points- 0.12; 3 points- 0.35; 4 points- 0.58; 5 to 7 points- 0.90. A probability of 0.90 means approximate 90 of 100 patients with TEN are expected to die.

SJS and TEN may be a dose dependent adverse drug reaction in susceptible individuals. In spite of MTX having a narrow therapeutic index, serum plasma concentration of MTX is not regularly monitored by the treating physicians. Folic acid should be supplemented along with methotrexate therapy is recommended by American College of Rheumatology to prevent the complications of methotrexate therapy (12).

CONCLUSION

The main intention of this case report of Methotrexate induced SJS is to make the clinicians as well as patients aware of this ADR occurrence. It is advocated that clinicians take a proper history before prescribing Methotrexate as a DMARD and early diagnosis and treatment might improve the outcome and decrease mortality in many patients of SJS. Patient education regarding the possibility of adverse drug reaction is essential to minimize the use of the drug.

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