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Case Report

A case report on methotrexate induced pancytopenia

Meghana Devulapalli[1]*, T. S. Durga Prasad[1], G. V. Narasimha Kumar[2], B. Avanthi[1], S. K. Shabana Banu[1]

[1]Department of Pharmacy Practice, Sri Padmavathi School of Pharmacy, Tiruchanoor, Andhra Pradesh, India
[2]Department of Pharmacology, Siddha Central Research Institute, Arumbakkam, Chennai, Tamil Nadu, India

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***Correspondence to:**
Meghana Devulapalli,
Email:
megha.devulapalli@gmail.com

ABSTRACT

Systemic lupus erythematosus (SLE) is a non-specific systemic inflammatory disease that affects various organ systems in the body leading to a wide spectrum of clinical presentations. The management of SLE includes therapy with immunosuppressant agents who have a narrow safety range and a wide adverse effect profile. Methotrexate discussed in this case report is one of such drugs whose short term and long term usage has been associated with various adverse events that affect the individuals quality of life. So, it is always advisable to take prophylactic measures and to provide patient education to detect and prevent adverse events at the earliest.

Keywords: Adverse drug reaction, Drug induced pancytopenia, Drug related morbidity, Impaired quality of life

INTRODUCTION

Methotrexate (MTX) is a folate analogue having chemotherapeutic, immunosuppressant and anti-inflammatory effects. Methotrexate has multiple mechanism of actions and cancers are mainly affected by competitive inhibition of dihydrofolate reductase (DHFR), an enzyme that prevents purine and pyrimidine biosynthesis.1 In the management of auto immune and inflammatory disorders, inhibition of DHFR was not thought to be the key mechanism, but rather several mechanisms appear to be involved, including the inhibition of enzymes involved in purine metabolism, leading to accumulation of adenosine; inhibition of T cell activation and suppression of intercellular adhesion molecule expression by T cells; selective down-regulation of B cells; increasing CD95 sensitivity of activated T cells; and inhibition of methyltransferase activity, leading to deactivation of enzyme activity relevant to immune system function. The toxic effects of MTX such as bone marrow depression, stomatitis and liver dysfunction owes to inhibition of enzymes that require folate cofactors, including thymidylate synthetase (TS) and 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase.[1]

Various studies conducted revealed that MTX was effective in reducing the dose of steroids given for the

management of systemic lupus erythematosus (SLE), in decreasing arthritic, cutaneous, nephritic, neuropsychiatric and haematologic (thrombocytopenia) manifestations of SLE.[2,3] In a prospective open label study conducted by Nazrul Imran et al, low dose MTX was found to be as effective as Chloroquine in treating articular and cutaneous manifestations of SLE.[4] Thus despite of the toxicities, the use of MTX in various manifestations of SLE was beneficial.

Case details

A 55 year old male patients was admitted in the general medicine department with the chief complaints of non-radiating chest pain since two days and breathlessness since 10 days which progressed to grade IV as per New York Heart Association (NYHA) scale. The patient had a history of swelling of both lower limbs and facial puffiness which subsided on taking medication. He was a known diabetic since 3 years and is on Metformin 500mg twice daily. He was also using Levothyroxine 75µg once daily for the management of hypothyroidism. He was also under antitubercular therapy for pleural effusion which he was advised to stop 3 months prior to the current complaints.

The patient had a positive antinuclear antibody profile with ANA 148 IU/L and raised C-reactive protein 96mg/dl associated with negative rheumatoid antibody profile. Based on these laboratory assessments the patient was initiated with MTX 10mg once weekly and Prednisolone 2.5mg twice daily prior to three months. At the initiation of therapy patient had a haemoglobin count of 7.8 g/dL, packed cell volume (PCV) of 19%, a total count (TC) of 6,700 cells/mm3 with a differential count (DC) of N36% L56% E3% M5% B0%, platelets 1.5lakh cells/mm3 and peripheral smear revealed a microcytic hypochromic anemia with relative lymphocytosis.

On examination he was found to have pallor, clubbing, elevated jugular venous pressure (JVP), a pulse rate of 88 beats per minute with normal volume, and a blood pressure of 130/90 mmHg, His respiratory examination revealed presence of occasional wheeze with decreased breath sounds on both sides of infrascapular area (ISA) and inframammary area (IMA). The ocular examinations showed a normal fundus. The patient's medication chart during the entire stay at hospital was mentioned in the Table 1. A plan for the transfusion of one unit of packed cells was done on the fifth day.

Table 1: Patient medication chart during hospital stay for 9 days.

SN	Drugs given	Dose	Route	Frequency	D_1	D_{2-5}	D_6	D_7	D_8	D_9
1.	Tab Metformin	500mg	PO	Twice daily	Y*	Y	Y	Y	Y	Y
2.	Tab Thyroxine	75µg	PO	Once daily	Y	Y	Y	Y	Y	Y
3.	Inj Furosemide	40mg	IV	Once daily	Y	Y	Y	Y	Y	Y
4.	Inj Pantoprazole	40mg	IV	Once daily	Y	Y	Y	N	N	N
5.	Tab Iron Folic acid	200mg	PO	Twice daily	Y	Y	Y	Y	Y	Y
6.	Tab B complex		PO	Once daily	Y	Y	Y	Y	Y	Y
7.	Tab Enalapril	5mg	PO	Once daily	Y	Y	Y	Y	Y	Y
8.	Tab Paracetamol	500mg	PO	Twice daily	Y	Y	Y	Y	Y	Y
9.	Inj Ceftriaxone	1g	IV	Twice daily	Y	Y	Y	Y	Y	Y
10	Tab Methotrexate	10mg	PO	Once weekly	Y	N	N	N	N	N
11.	Tab Deriphylline	100mg	PO	Twice daily	Y	Y	Y	Y	Y	N
12.	Inj Hydrocortisone	100mg	IV	Twice daily	N#	N	Y	N	N	N
13.	Duolin Nebulization	200 mcg	Inh	Thrice daily	N	N	N	Y	Y	Y
14.	Tab Pantoprazole	40mg	PO	Once daily	N	N	N	Y	Y	Y
15.	Tab Aspirin	75mg	PO	Once daily	N	N	N	N	Y	Y
16.	Tab Atorvastatin	10mg	PO	Every night	N	N	N	N	Y	Y
17.	Tab Metoprolol	25mg	PO	Once daily	N	N	N	N	Y	Y
18.	Inj Deriphylline	1 amp	IM	Twice daily	N	N	N	N	N	Y

D = Day, *Y = Yes, # = No, Inh = Inhalation

The complaint of breathlessness was present throughout the length of hospital stay. The summary of laboratory examinations performed during the hospital is summarized in the Table 2.

The peripheral smear performed on day 2 testified the presence of microcytic hypochromic RBC with mild anisocytosis, total counts were decreased with marked leucopenia characterized by normal differential counts, mild thrombocytopenia with a reticulocyte count of 0.7%. Thus the impression obtained from these findings suggests pancytopenia. The patient was discharged on 10th day with medication mentioned in Table 3. He was advised to come for follow up after completing the course of medications or if condition gets aggravated or any new symptoms develop.

Table 2: Complete hemogram of patient performed on the day of admission.

SN	Components of hemogram	Observed value
1.	White blood cells	2100 cells/mm3
2.	Lymphocytes	1900 cells/mm3 (90.6%)
3.	Monocytes	100 cells/mm3 (4.7%)
4.	Granulocytes	100 cells/mm3 (4.7%)
5.	Red blood cells	3.20 lakh cells/mm3
6.	Hemoglobin	5.7 g/dL
7.	Hematocrit	18.6%
8.	Mean Cell Volume (MCV)	64.5 fl
9.	Mean Corpuscular Hemoglobin (MCH)	17.7 pg
10.	Mean Cell Hemoglobin Concentration (MCHC)	29.0%
11.	Platelets	1.16 lakhs cells/mm3
12.	Plateletcrit	11.3%

Table 3: Discharge summary of drugs.

SN	Drugs	Dose	Route	Frequency	Duration
1.	Tab Deriphylline	100mg	PO	Twice daily	30 days
2.	Tab Frusilac		PO	Once daily	
3.	Tab Metformin	500mg	PO	Twice daily	
4.	Tab Thyroxine	75µg	PO	Once daily	
5.	Tab Enalapril	5mg	PO		
6.	Tab Iron Folic acid	200mg	PO		
7.	Tab B complex		PO		
8.	Tab Aspirin	75mg	PO		
9.	Tab Metoprolol	25mg	PO		
10.	Tab Atorvastatin	20mg	PO	Every night	

DISCUSSION

Methotrexate is a DHFR inhibitor used in the management of SLE. Its use has been indicated in patients not being able to reduce steroids below the doses acceptable for chronic use (that is in non-responsive patients) as per the recommendations made by EULAR for the management of SLE5. The use of MTX in low doses, pulse doses or in long term use was associated with various ADRs such as hepatotoxicity, stomatitis, oral ulcers, anemia, neutropenia, pulmonary fibrosis, renal impairment, lethargy and fatigue.[1,6]

Case reports were extensively published on MTX induced pancytopenia in patients with rheumatoid arthritis but this case report illustrates MTX toxicity in a patient with SLE.[6-9] In the present scenario, the patient was diagnosed with SLE three months earlier and was on 10mg of MTX and Prednisolone 2.5mg twice daily. The haematological parameters measured at the time of diagnosis showed a decline after three months of therapy with MTX. The peripheral smear results also complied with decline in the blood indices reported in complete hemogram.

Usually SLE is also associated with increased leucocyte apoptosis and associated changes in blood indices due to failure in mechanisms that clear the autoantibodies.10 In this case; despite of the treatment with MTX the patient experienced a devastating deterioration in health condition requiring hospitalization which can be solely attributed to the drug intake. In their study Arvind Jain et al, reported that antineoplastic agents causing myelosuppression such as MTX, Cyclophosphamide, Vincristine and 5-Fluorouracil were the major causes of pancytopenia.[11]

The cytotoxic mechanism of MTX was explained on its ability to undergo polyglutamation. This mechanism enables prolonged intracellular exposure of leukemic myoblasts, synovial macrophages, lymphoblasts and epithelia increasing the risk of toxicity.[6,12] This mechanism also causes an alteration in the spectrum of enzymes inhibited by the drug.[6,12] Thus the altered immune cells and enzymes get reserved in liver and bone marrow myeloid precursor cell and fibroblasts leading to toxicities.[6,12] The tissues with the ability to undergo rapid multiplication such as in oral mucosa, gastrointestinal tract, bone marrow and testicular tissue were found to be most susceptible to cytocidal effects of MTX owing to a large spectrum of toxicities.[6,12]

Individuals taking immunosuppressants should be checked frequently for the presence of unexplained anemia, prolonged fever, and tendency to bleed.[10] The

incidence of stomatitis associated with any of the above mentioned symptoms should be considered as the prior indication of pancytopenia.[6] Escalations in serum alanine aminotransferase (ALT) levels and decline in peripheral lymphocyte levels were observed in individuals susceptible to MTX toxicity.[6,9] This should be considered as a warning sign and for performing specific diagnostic tests.

Various risk factors were associated with MTX toxicity such as renal dysfunction, hypoalbuminemia, low folate levels, concomitant infections, increased age, and concomitant use of more than five drugs and poor nutritional status.[6,7] Being male was also linked to increased risk of toxicity.11 In the present condition, the risk factors observed were increased age, polypharmacy, and male gender.

Apart from haematological investigations, bone marrow examinations should also be done to understand the underlying changes and mechanisms involved in toxicities.[10] Performing high profile studies such as immunophenotyping, cytogenic and molecular studies will aid in differentiating the drug toxicities from that of underlying disease conditions and will also aid in determining appropriate toxic mechanism of myelosuppression of the drugs.[13] In individuals, who are unable to undergo these type of studies should be followed up clinically by periodic monitoring.[13]

It is advised to supplement the usage of MTX with folic acid as a prophylactic measure to prevent drug toxicity.[1,6] Folic acid supplements should be given 12 hours after MTX as both the drugs share the same transporter, Reduced Folate Carrier 1 (RFC1) for absorption from the gastrointestinal tract and for cellular uptake.1 But this patient was not given any folic acid supplements during three months of therapy with MTX. This might be one of the contributing features for the development of MTX toxicity.

In some cases, though folic acid supplementation was given, pancytopenia may manifest suggesting a distinctive susceptibility to the tissues of bone marrow.[6] In such cases, susceptibility can be detected by performing in vitro studies on determining the response of suspected drugs on the colonies of Hemopoietic precursor cells. The number of colonies surviving the treatment based on the drug response dose curves gives an estimate of drug toxicity.[14]

In their study Syed Tanveer et al, reported that the cut off value of serum concentration of MTX to cause toxicity was about 0.71µmol/L.[9] So, it is suggested that therapeutic drug monitoring of drugs with increased toxicities should be carried out in settings with adequate facilities. Finally, the management of pancytopenia can be done with red blood cells transfusion, bleeding due to thrombocytopenia can be treated with Aminocaproic acid 50mg/kg six hourly, and antibiotic prophylaxis to prevent infections.[15] The specific management options include use of recombinant Granulocyte Colony Stimulating Factor (G-CSF), Granulocyte Macrophage Colony Stimulating Factor (GM-CSF), and recombinant erythropoietin (rhu EPO).[15] Administration of Folinic acid was also found to be beneficial in the management of pancytopenia caused by MTX.[7]

In this case, the patient was managed with packed cell transfusion, folic acid supplementation and antibiotic prophylaxis with ceftriaxone was also given. The offending agent i.e., MTX was stopped until further notice. The patient experienced symptomatic improvement and was discharged after ten days of hospital stay.

CONCLUSION

Though the use of MTX in various presentations of SLE was beneficial, its use was associated with wide range of toxicities. Various risk factors were also associated with the development of MTX toxicity. So, keeping this in view, it is of utmost importance to design criteria with scoring to make clinical decision at the initiation of MTX based on the severity of the disease, patient's clinical condition and drug profile. It is also essential to educate the patient regarding the most commonly observed symptoms of toxicity and to report to the physician immediately. Clinical monitoring of the patients with regular follow up check-ups and investigations might aid in early detection of drug related toxicities.

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