Early onset pancytopenia in patient on methotrexate

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Abstract

A 30-years-old female presented to emergency department with a history of fever, epistaxis and bleeding gums since 3 days. She gave history of methotrexate (MTX) prescribed for joint pain (a cumulative dose of 20 mg in 3 days) prior to the presentation. Her blood counts were normal prior to MTX ingestion. But on the day of admission, all the three cell lines were low. She was given 5 units of fresh whole blood and antimicrobial and antifungal coverage during her total stay in the hospital. Her bone marrow finding was suggestive of aplastic anemia/drug induced bone marrow suppression. After 2 weeks of supportive therapy, her blood counts were normal. She was advised to repeat bone marrow examination, which she denied. Her anti-CCP levels were normal and did not meet the criteria for rheumatoid arthritis so advised to stop MTX. Although, pancytopenia associated with low-dose MTX therapy is not expected as early as 3 days after initiation of the therapy, physicians should also be aware of this life threatening adverse effect during the very first days of MTX therapy.

Key Words: Aplastic anemia, Bone marrow, Methotrexate, Pancytopenia

INTRODUCTION

Low dose methotrexate weekly has become accepted and widely prescribed disease modifying antirheumatic drug for rheumatoid arthritis with a greater toxicity in ealderly patients.[1] However we are reporting a case of early onset pancytopenia following MTX therapy in a young female of 30 years.

CASE REPORT

A 30 years old lady, mother of 2 children was admitted with the history of sore throat, epistaxis since 3 past days. She did not have any rashes or miscarriages in the near past. Her past history was not significant. She was prescribed methotrexate for arthritis by a local physician and the patient took a cumulative dose of 20 mg in 3 days. On examination she was asthenic with crusting in the lips with trismus and oral ulcers [Figure 1]. Her ENT examination showed features suggestive of pharyngitis. Her vitals were normal with and temperature of 102°F on admission. Rest of the general and systemic examination was unremarkable. On admission, her laboratory investigations revealed hemoglobin 8.3 gm/dl, normocytic normochromic red cell morphology, MCV 89 fl, total leukocyte count 1,600/ml with neutrophils 51%, lymphocytes 46%, eosinophils 2%, monocytoid cells 1% and platelet count of 0.6 lakhs/cumm. Her peripheral smear was negative for malaria parasite [Figure 2]. Liver and renal function tests, serum protein and albumin, urinalysis, radiograph of the chest and ultrasound of the abdomen were normal. Her blood and urine culture were sterile. Bone marrow examination showed diluted bone marrow suggestive of drug induced bone marrow suppression. She was treated with ceftazidime amikacin, parenteral fluconazole and folic acid. She was given 5 units of fresh whole blood and antimicrobial and antifungal coverage during her total stay in the hospital. Fever subsided after 10 days of admission and leucopenia and thrombocytopenia recovered completely by 14th day without growth factors. Her complete blood picture profile before and after the methotrexate treatment and on her discharge is given in Table 1. On discharge she was advised to take folic acid and vitamin B complex. Rheumatoid arthritis specific antibody anti-CCP was negative.

DISCUSSION

Methotrexate (MTX), an antimetabolite acts by inhibiting the enzyme dihydrofolate reductase. It is being increasingly used at low dose in the treatment of rheumatoid arthritis because of its efficacy and safe therapeutic window. Weekly

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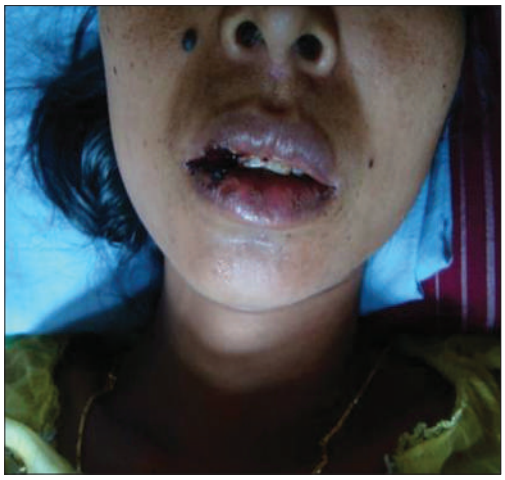

Figure 1: Photograph showing crusting of lips

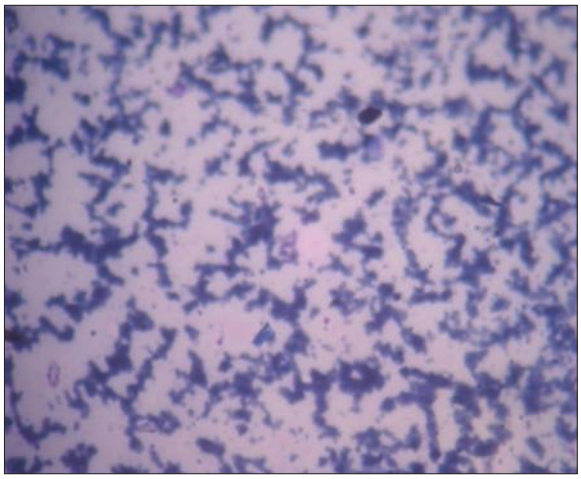

Figure 2: Photomicrograph showing pancytopenic picture on peripheral blood smear (Leishman stain, ×10)

Table 1: The improvement in the hematological parameters following withdrawal of methotrexate

	Hb (g %)	TLC/ cumm	DLC	PLATELETS/ cumm
On admission	8.3	1500	N-51, L-46, M-2, E-1	60000
2nd day	9	1800	P-67, L-30, M-1, E-2	80000
7th day	8.6	2000	P-5, L-44, Atypical-1	90000
14th day	12.4	7000	P-68, L-28, M-2, E-2	1.8 Lakhs

Hb: Hemoglobin, TLC: Total leucocyte count, DLC: Differential leucocyte count

low dose MTX therapy, especially in elderly patients appears to be safe.[1] However, a rare potentially lethal side effect is pancytopenia. The prevalence of hematological toxicity including leucopenia, thrombocytopenia, megaloblastic anemia and pancytopenia is estimated to be around 3%.[2] The potential risk factors for development of pancytopenia in MTX treated patients include increasing age, renal impairment, low serum albumin and concurrent anti folate medications.[3]

Pancytopenia is a condition when the hemoglobin is less than 9 g/dL; total leukocyte count (TLC) less than 4,000/cumm and platelet count less than 100,000/cumm.[4] But various studies and review article had been published regarding the pancytopenia due to prolong intake of MTX. Case reports of pancytopenia due to MTX within few days of its intake, is rarely reported in the literature.

As already mentioned, our patient had presented with the clinical and biochemical features of pancytopenia within 3 days of the ingestion of the MTX. Pancytopenia due to MTX is attributed to the patients with renal dysfunction, presence of infection, folic acid deficiency, hypoalbuminemia, concomitant use of drugs such as trimethoprim etc., and advanced age. But our patient's renal function was normal, peripheral smear did not show any features suggestive of folate deficiency and her blood/urine culture sensitivity was sterile. So our patient without any predisposing factor had pancytopenia after ingestion of 20 mg of MTX. She also recovered with symptomatic treatment for her pancytopenia without any colony stimulating factors within 2 weeks.

The MTX induced pancytopenia might be due to genetic predisposing factors like C677T polymorphism of the methylenetetrahydrofolate reductase (MTHFR) gene in RA patients.[5] Another study on C677T polymorphism on the toxicity of MTX showed that homozygous patients had increased oral mucositis and delayed platelet recovery or neutropenia.[6]

A study by Skibola *et al.*,[7] have shown that individuals with C677T MTHFR TT genotype, both homozygous recessive and heterozygous A1298C MTHFR genotypes have a decreased risk of acute lymphoblastic leukemia, indicating that folate depletion may play a role in the development of this malignancy. The permutation of folate nutritional status, common allelic variation in genes coding for folate-dependent enzymes, altered gene expression and impaired nucleic acid elaboration linked to folate metabolism possibly modulates the risk of developing pancytopenia secondary to MTX. More attention should be paid to patients' nutritional status before commencing MTX; we advocate caution in the elderly whose serum albumin is low and those with renal impairment. Folic acid supplementation at 5 mg weekly should be considered in all patients taking MTX.

Although, pancytopenia associated with low-dose MTX therapy is not expected as early as 3 days after initiation of the therapy, physicians should also be aware of this life threatening adverse effect during the very first days of MTX therapy for rheumatoid arthritis patients. We emphasize the need for a close monitoring of hematologic tests after onset of methotrexate particularly if some risk factors are present.

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