International Journal of Health Sciences and Research
www.ijhsr.org ISSN: 2249-9571

Case Report

Methotrexate Induced Pancytopenia - An Unwanted Effect

Brij Mohan Kumar Singh[1], Barnini Banerjee[2]

[1]Assistant Professor, Dept of Immunohematology & Blood Transfusion, KMC Manipal, Manipal University.
[2]Assistant Professor, Department of Microbiology, KMC Manipal, Manipal University.

Corresponding Author: Brij Mohan Kumar singh

Received: 03/12/2015 *Revised: 14/04/2016* *Accepted: 15/04/2016*

ABSTRACT

Rheumatoid arthritis (RA) is a chronic, progressive multisystemic inflammatory disorder which affects approximately 0.5-1% of adult population. [1] Usually middle aged adult males are involved more than the females. This chronic inflammatory disorder results in the damage of articular cartilage with repeated attacks. Many a times the involvement is very symmetrical affecting both large and small joints. Thus, it is very important to introduce the effective treatment to inhibit the inflammation and destructive mechanisms as soon as the disease is diagnosed. Among the current management scheme of rheumatoid arthritis, Methotrexate (MTX) is the commonest disease-modifying ant rheumatic drug (DMARD). [2] Most of the time MTX is prescribed as monotherapy and also in combination with other DMARDs. The patients who are on long term treatment of RA are at great risk for the development of hematological toxicity, which includes leucopenia, thrombocytopenia, megaloblastic anaemia and pancytopenia, and their prevalence is estimated to be 3%. [3] The dreaded effect such as pancytopenia, which is a serious and unpredictable adverse effect of low-dose MTX, may be underestimated and sometimes results to be fatal for the patients. We report a case of severe bone marrow suppression in a rheumatoid arthritis patient on accidental intake of large dose of MTX.

Key words: Rheumatoid arthritis, DMARD, Bone marrow suppression.

CASE REPORT

68 years old female with known history of rheumatoid arthritis for 7 years with recent worsening of joint pain and swelling went to local doctor and was started on methotrexate, 7.5mg once a week, one month back. For no reason the patient inadvertently took the drug (MTX) daily, now presented to the tertiary care hospital with complaints of oral ulcer, loose stools, vomiting and decreased urine output. On clinical examination patient was conscious and oriented, vitals were stable. Chest examination showed bilateral crepitation. Patient showed pallor and features of volume overload.

Investigations: The coulter hemogram revealed pancytopenia (anemia, leukopenia and thrombocytopenia) with the following parameters: Hemoglobin- 6.6 g/dl, total WBC count- 600/µL, platelets- 10,000/µL. The peripheral smear confirmed the above findings. The differential count showed no atypical/abnormal cells. Liver function test was deranged. Renal function test showed mass abnormality with the following parameters: Serum Urea- 246mg/dl, Serum creatinine-11.6mg/dl, Uric acid- 12mg/dl. Serum amylase- 303U/L, Serum lipase- 379, Creatinine phosphokinase- 270 U/L. With the above smear findings, an impression of Pancytopenia? Cause was given, with an advice to perform bone marrow study.

Subsequently patient start presenting with altered sensorium after 3 days of admission for which CECT scan of brain

was done and for surprise it showed an intraparenchymal bleed. Bone marrow aspirate showed marked suppression of erythroid, myeloid and megakaryocytic component with relative increase in the lymphocyte and plasma cell count. In the aspirate macrophages were increased in number with marked platelet phagocytosis. Based on the above findings with correlation of clinical history the diagnosis of Hypoplastic marrow - Drug induced was given with advice to follow the counts on peripheral blood.

Bone marrow sample was also processed with BacT alert automated blood culture and found to have growth of *Candida tropicalis*. Gram stained urine sample was examined, there were numerous gram positive cocci was seen. On aerobic culture of the urine sample, growth of Enterococcus *faecium* was detected with colony count of 10^4CFU/ml. Blood sample was also processed with BacT alert and found to have *Enterococcus faecium*. Patient was negative for Hepatitis B surface antigen& Antibody to Hepatitis C.

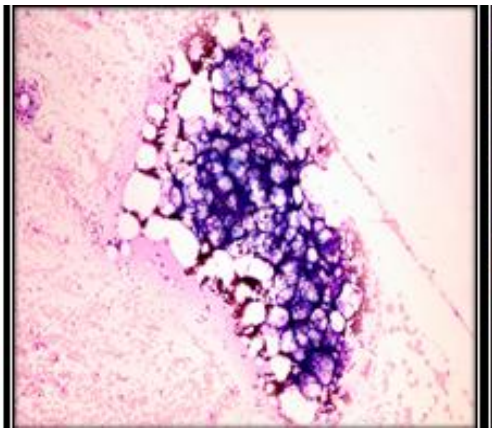

Fig I-Hypocellular marrow particle in aspirate (Leishman stain X40).

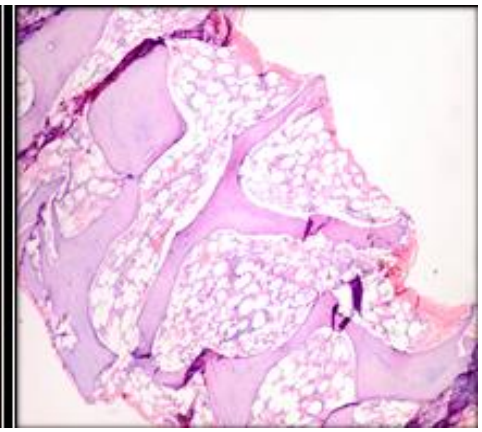

Fig II-Hypocellular marrow spaces in bone marrow biopsy (H&E X40).

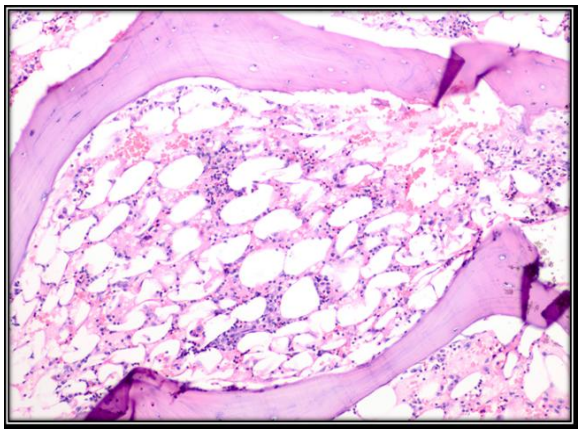

Fig III- Hypocellular marrow spaces in bone marrow biopsy (H&E X40).

DISCUSSION

A rare but potentially very fatal complication of MTX therapy is pancytopenia, it may develop suddenly and sometimes it may appear without any warning signs. The complication can occur as early as two months of starting MTX, as seen in the present case report. In many cases the hematological manifestation can develop independently of dose and route of administration. More commonly, however, it occurs late. [4] MTX is a selective competitive inhibitor of the enzyme dihydrofolate reductase and results in the reduced production of thymidylate and DNA synthesis. Tissues which are having their majority of cells in the synthetic phase of cell cycle (oral mucosa, gastrointestinal tract, bone marrow cells and testicular tissue) are the most susceptible to its killing effects. Similar symptoms are seen in cases of folate deficiency. Reduced levels of intracellular folic acid in the hepatocytes and peripheral blood lymphocytes of RA patients treated with MTX have been documented in various literatures. [5,6] With the above scenario it is clear that folic acid supplementation reduces the chances of liver function derangement [7] as well as mucosal and gastrointestinal side-effects. [8] But there is no study available to support the

protective effect of folate supplementation on MTX-related hematological toxicity.

In the present case the consequence of pancytopenia resulted in various infections leading to sepsis. Intraparenchymal bleed was a result of severe thrombocytopenia which left the patient debilitated.

With the long term use of Methotrexate, hematological effects are usually seen. It has also been reported in studies that elevation of Mean Corpuscular Volume (MCV) usually precedes the occurrence of Bone marrow suppression, [9] so this could alert the treating physician about the unforeseen event the patient would be developing. With the temporary removal of drug from the regimen for the treatment of rheumatoid arthritis can revert mild bone marrow suppression. Degree of pancytopenia can vary from mild to severe in patient with renal insufficiency and hypoalbuminemia receiving NSAID's (salicylates and probenecid). [10] It is well established that more than 90% of the drug is cleared within the first 24 hours after its administration. [11] So severe bone marrow suppression may be a cause of gradual accumulation of the drug in the body due to delayed plasma clearance of the drug.

CONCLUSION

The hematopoietic toxicity following low-dose methotrexate therapy in RA patients has been well established in the literature. [12,13] It has been estimated that 3-4% of the patients on MTX would experience pancytopenia as its side effect. [14]

Methotrexate is used widely in the treatment of early stage of rheumatoid arthritis with very little side effects, which if monitored rigorously can be managed with folic acid supplementation. Even though there should be a regular follow-up of the patients. According to the guidelines by the Health and Public Policy Committee, American College of Physicians, [14] laboratory studies (total and differential blood counts and platelet count, serum creatinine and liver enzymes) should be repeated every month. Treating physician should restrict the use of MTX for an unreliable patient who cannot come for follow up and utmost caution is needed when the patient, in addition to RA, has other metabolic disorders, such as diabetes mellitus2.

REFERENCES

1. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet 2010; 376(9746):1094-1108.
2. Cronstein BN. Molecular therapeutics. Methotrexate and its mechanism of action. Arthritis Rheum 1996; 39:1951-60.
3. Weinblatt ME. Toxicity of low dose methotrexate in rheumatoid arthritis. J Rheumatol 1985; (Suppl 12):35-9.
4. Grove ML, Hassell AB, Hay EM, Shad forth MF. Adverse reactions to disease-modifying anti-rheumatic drugs in clinical practice. Q J Med 2001; 94: 309-19.
5. Kremer J, Galivan J, Streckfuss A, Kamen B. Methotrexate metabolism analysis in blood and liver of rheumatoid arthritis patients. Association with hepatic folate deficiency and formation of polyglutamates. Arthritis Rheum 1986; 29:832-5.
6. Leeb B, Witzmann G, Ogris E et al. Folic acid and cyanocobalamin levels in serum and erythrocytes during low dose methotrexate therapy of rheumatoid arthritis and psoriatic arthritis patients. Clin Exp Rheumatol 1995; 13:459-63.
7. Van Ede AE, Laan RFJM, Rood MJ et al. Effect of folic or folinic acid supplementation on toxicity and efficacy of methotrexate in rheumatoid arthritis: a forty-eight-week, multicenter, randomised, double-blind, placebo-controlled study. Arthritis Rheum 2001; 44:1515-24.
8. Ortiz Z, Shea B, Suarez Almazor M, Moher D, Wells G, Tugwell P.Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. Cochrane Database Syst Rev 2000; 2:CD000951.

9. Basin KS, Escalate A, Beardmore TD. Severe pancytopenia in a patient taking low-dose methotrexate and probenecid. J Rheumatol 1991, 18: 609-10.
10. Brown MA, Corrigan AB. Pancytopenia after accidental overdose of methotrexate. A complication of low dose therapy for Rheumatoid Arthritis. Med J Aust 1991; 155:493-4.
11. Henderson, E.S., Adamson, RH. and Oliverio, V.T. The metabolic fate of tritiated methotrexate IL Absorption and excretion in man. Cancer Rea. 1965; 25:1018-23.
12. Mayall, B., Poggi, O. and Parkin, J.D. Neutropeniadue tolowdoae methotrexate therapy for psoriasis and rheumatoid arthritis maybe fatal. Med.J. Aust. , 1991;155:480-84.
13. Trenkwalder, P., Eisenlohr, H., Prechtel, K. and Lydtin, H. Three cases of malignant neoplasm, pneumonitis and pancytopenia during treatment with low-dose methotrexate. Clin. Investig. 1992; 70:951-55.
14. Health and Public Policy Committee, American College of Physicians. Methotrexate in rheumatoid arthritis. Ann. Intern. Med., 1987; 107:418-19.

How to cite this article: Singh BMK, Banerjee B. Methotrexate induced pancytopenia - an unwanted effect. Int J Health Sci Res. 2016; 6(5):412-415.

****