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A Suppression of the Bone Marrow caused by Methotrexate among the most Serious and Intricate Adverse Effects: A Case Series

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Abstract

Methotrexate toxicities that have been well-reported are dependent on the drug's duration and cumulative dosage. The time of drug delivery may be used to anticipate the usual toxicities, where mucositis develops early and myelosuppression and pancytopenia's aftereffects develop later after Methotrexate administration. Even with these established hazards, low dosage Methotrexate treatment can still cause issues, especially in older patients who are more likely to experience severe myelosuppression. The American College of Rheumatology recommends performing complete blood count, serum creatinine, and transaminase tests before starting Methotrexate medication, followed by monitoring every 12 weeks for the next three months, and so on. We present a case of a 73-year-old male patient experienced mild tenderness, oral ulcer, decreased appetite, and increased bowel movement. He required intravenous antibiotic therapy and limited transfusion dependence due to low dose daily Methotrexate for rheumatoid arthritis. The other case is of a 68-year-old female patient experienced severe body-ache, weakness, stomatitis, and skin rashes, which were resolved with injection of Leucovorin and folic acid.

Keywords: Methotrexate, Myelosuppression, Pancytopenia, Stomatitis, DMARD

Introduction

The Disease-Modifying Antirheumatic Drug (DMARD) most frequently prescribed to treat rheumatoid arthritis (RA) is methotrexate (MTX). Both the American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) suggest it as a first and foremost DMARD, either on its own or in addition with other DMARDs and biological medications [1]. MTX is a dihydrofolate reductase inhibitor used to treat a range of malignancies. It also has anti-inflammatory and immunomodulatory properties. It inhibits the growth of cells that are newly formed [2]. Mouth ulcers, sore throats, fever, chills, new or persistent infections, greater bruising, or bleeding than normal, and anemia signs including pallor, dizziness, and shortness of breath are among the symptoms [3]. When low-dose MTX is used, gastrointestinal symptoms and raised liver enzymes are the most prevalent adverse effects. These are followed by neurological symptoms such as headache, tiredness, and dizziness, as well as cytopenias, predominantly leucopenia [4]. Like all medications, MTX has a side-effect profile. Medication-induced pancytopenia is one of the most severe and complex adverse events. Patients with MTX-induced pancytopenia should be closely monitored and treated with clinical judgment until the disease resolves, since the condition has a 17–44% fatality rate [5]. Here, we present two separate instances of patients whose bone marrow suppression resulted by using methotrexate.

Case 1

A 73-year-old male patient with a known case of rheumatoid arthritis of the right shoulder from 2 years on methotrexate 10 mg came with a complaint of watery diarrhea for 3 days. On admission patient was conscious, oriented and vitally stable but in systemic examination patient's abdomen system showed generalized mild tenderness and oral ulcer. In addition to patient have complaints of decrease appetite and increase bowel movement. On admission day, laboratory investigation data illustrated a decreased Hemoglobin (Hb) of 8.8 g/dL, a decreased White Blood Cells (WBC) count of 250/microliter, and a decreased platelet count of 8000/microliter, which is depicted as pancytopenia, that is describing in figure1,2 and 3. Also, elevated serum urea: 93.4 mg/dL; increased serum creatinine: 2.18 mg/dL; elevated total bilirubin: 3.1 mg/dL; and hypoalbuminemia (2.78

g/dL) were reported. Considering the possibility of methotrexate toxicity, the patient was admitted to rheumatology for further evaluation and folinic acid rescue therapy. The final diagnosis for the patient was methotrexate-induced bone marrow suppression. Upon admission, he was initiated on intravenous leucovorin rescue therapy, four units of Packed Red Cell (PRC) transfusion for 3 days, one unit of Packed Cell Volume (PCV) transfusion for 3 days, one unit of Inj. Nurokind (methylcobalamin) and filgrastim for throughout the treatment days and MTX were put on hold. He was symptomatically better and hemodynamically stable at discharge. On discharge Tab. Folvite (5 mg) was given for 15 days.

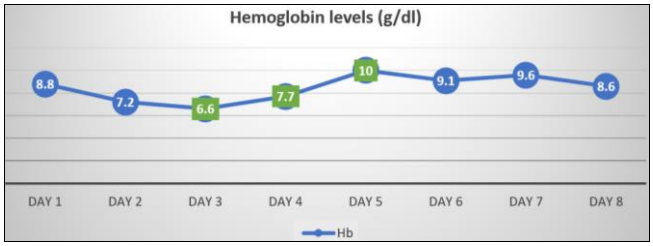

Fig 1: Hemoglobin level of case-1 (green boxes show PCV transfusion)

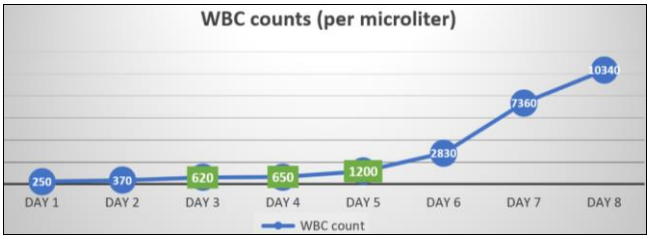

Fig 2: WBC counts of case-1(green boxes show PCV transfusion)

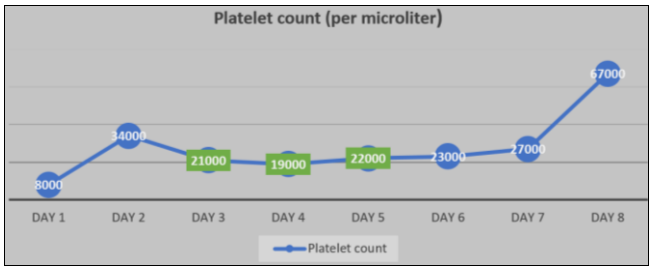

Fig 3: Platelets counts of case-1 (green boxes show PCV transfusion)

Case 2

A 68 years old female patient known case of rheumatoid arthritis and hypothyroidism on Tab. Methotraxate induced pancytopenia presented with complaints of severe bodyache, weakness, ulcer (Stomatitis) and skin rashes since 2-3 days. On examination blister and red laceration presented on both extremities. On admission day, laboratory investigation data illustrated a decreased Hb of 7.1 g/dL, a decreased WBC count of 440/microliter, and a decreased platelet count of 19000/microliter, which is depicted as pancytopenia and hypoalbuminemia (2.27 g/dL) were reported. Before the admission to the hospital, patient's reports showed low Hb (7.7 g/dL), low WBC (1100/microliter) and a low platelet count (13000/microliter). When all the reports were done, the physician stopped the MTX medication because the final diagnosis is methotrexate-induced pancytopenia was confirmed which shows in Table-1. A Possibility of MTX overdose was considered, 4 unit of PRC and 1 unit of PVC were transfused immediately. She was then started on Inj. Leucovorin and folic acid. She was also given Inj. Filgrastim 300 mcg for 2 days. She was also treated with proton pump inhibitors, probiotics, IV fluids, and other supportive medications. After that her blood reports improved gradually.

Table 1: Hb, platelet count and WBC count before and after admission in case-2

	Hb (g/dL)	Platelet count (/microliter)	WBC count (/microliter)	Result
Before admission	9.6	53000	1240	Due to MTX pancytopenia occurred.
	7.9	23000	1090	
	7.7	13000	1100	
After admission	7.1	19000	440	When MTX stopped, all counts improved gradually.
	9.3	35000	670	
	9.7	33000	1290	
	9.8	49000	5130	
	9.2	99000	22230	
	8.7	156000	24750	
	9.4	277000	14770	

Discussion

A folate antagonist used to treat autoimmune disorders and certain neoplasms is methotrexate. It prevents the formation of purines, thymidylic acids, and dihydrofolic acid reductase, all of which are inhibitory to DNA synthesis, repair, and cellular replication. Cells are eventually unable to multiply when DNA synthesis stops. Additionally, it prevents the skin's epithelial cells from proliferating quickly [6]. It has been observed that MTX toxicity can develop at any point during therapy, beginning with stomatitis and ending with pancytopenia. Although myelosuppression and pancytopenia are well-known side effects of MTX, there is little evidence that low doses of the medication can also cause these side effects. This is important to note because MTX is widely accepted by rheumatologists for its effectiveness and relatively safe therapeutic window in a range of inflammatory rheumatologic conditions [7, 8]. A dose- and duration-dependent adverse effect, MTX-induced pancytopenia is observed in 1.4% of documented cases, predominantly in females (62.51%), with roughly 59% of patients over 60 years old. Anemia, leukopenia, and thrombocytopenia are among the consequences of pancytopenia. Systemic symptoms include low hemoglobin-related lethargy, infections brought on by leukopenia or neutropenia, bleeding, and ecchymosis because of a lowered platelet count. It is important to keep an eye out for clinical pancytopenia signs and symptoms to determine when to stop treatment altogether or taper it down. Rescue medication, such as folinic acid or leucovorin, has also been shown to be somewhat effective in hastening recovery [5, 9]. Age and the age-related deterioration in renal function caused by elevated levels of MTX are potential risk factors. Because hypoalbuminemia results in higher amounts of free MTX than albumin-bound MTX, it also raises the risk of toxicity [10]. Before commencing MTX therapy, the American College of Rheumatology suggests baseline Complete Blood Count (CBC), serum creatinine, and transaminase tests. After that, monitoring should be done every 2-4 weeks for the first three months, every 8–12 weeks for the next three months, and once every 12 weeks after that [11]. Supplementing with folic acid may lessen the toxicity of

MTX. Additionally, research indicates that folic acid can provide cardioprotection by preventing hyperhomocysteinemia brought on by MTX. But as our patient's case illustrates, folic acid supplementation has also been linked to MTX toxicity. Leucovorin is believed to help speed up recuperation from toxic effects and avoid stomatitis. Research also documents the use of steroids and Granulocyte Colony-Stimulating Factor (G-CSF) to treat MTX-induced myelosuppression in patients suffering from RA [12].

Conclusion

Since most of these significant problems are preventable or may be recognized early, it is imperative that primary care physicians are aware of these issues and recommendations. Liver function tests and CBC should be performed on patients receiving MTX therapy on a frequent basis to detect myelosuppression and prevent pancytopenia's repercussions. Because this medication mostly excretes through the kidneys, renal function must also be monitored.

Table 2: Abbreviations

ACR	American College of Rheumatology
CBC	Complete Blood Count
DMARD	Disease-Modifying Antirheumatic Drug
EULAR	The European League Against Rheumatism
G-CSF	Granulocyte Colony-Stimulating Factor
Hb	Hemoglobin
MTX	Methotrexate
PCV	Packed Cell Volume
PRC	Packed Red Cells
WBC	White Blood Cells

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Conflict of Interest

The authors declare that there is no conflict of interests.

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