Austin Critical Care Journal

Open Access

Austin Publishing Group

Case Report

Medication Dosing Error Leading to Potentially Lethal Methotrexate Toxicity

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Received: January 24, 2022; **Accepted:** February 15, 2022; **Published:** February 22, 2022

Abstract

Pancytopenia is a rare consequence of rheumatoid arthritis treatment with low-dose methotrexate. Several literature reviews discovered earlier examples of severe pancytopenia caused by low- dose or dosage error of methotrexate. We discuss the case of a 67-year-old ACPA (Anti- citrullinated protein/peptide antibody) positive rheumatoid arthritis patient who had severe pancytopenia and oral mucositis as a result of methotrexate toxicity. To reduce medication dosing errors, we highlight its uncommon dose schedule.

Keywords: Folinic acid; Methotrexate; Medication Error; Pancytopenia

Abbreviations

CBC: Complete Blood Count IV- Intravenous; G-C SF: Granulocyte Colony-Stimulating Factor; ICU: Intensive Care Unit; PC: Platelet Concentrate; BM: Bone Marrow

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disorder characterized by chronic polyarticular synovial inflammation which can result in irreversible joint damage with disability and deformity. Traditional RA treatment combines corticosteroids with disease-modifying antirheumatic drugs (DMARD), most remarkably, methotrexate (MTX) [1].

Methotrexate (MTX) is an antimetabolite that was originally developed as a chemotherapeutic agent for cancer treatment. Only later did MTX at low doses gain popularity as a DMARD. Despite its high safety profile, there is a known risk of acute toxicity or long-term complications when used. Because of its favorable efficacy to toxicity ratio and rapid onset of action when compared to other second-line treatments, MTX has quickly become the rheumatologist's drug of choice for serious RA. When prescribed in the appropriate setting, the RA dose 5mg to 25mg weekly administered orally or subcutaneously is considered very safe [2].

The prevalence of hematological toxicity, including thrombocytopenia, leukopenia, megaloblastic anemia, and pancytopenia, in MTX-treated RA patients, is estimated to be around 3%. Pancytopenia can develop quickly, within 1-2 months after initiating MTX, and is thought to be an idiosyncratic reaction. Pancytopenia has been documented in 1.0-1.4% of cases, with a death rate ranging from 17-44% [3].

Case Presentation

Case details

A 67-year-old woman was admitted to the intensive care unit of a tertiary level hospital in Nepal for suspected methotrexate toxicity. She was diagnosed with an ACPA (Anti-citrullinated protein/peptide antibody) positive RA 2 year ago and was on methotrexate for 6 months. She was diabetic, hypertensive and had hypothyroidism. She was illiterate and could not read or write. She was on methotrexate at 17.5mg once weekly, folic acid 5mg twice weekly (except on methotrexate dose days), aceclofenac 100mg once daily, and esomeprazole 20mg once daily dosages. Her son would supervise her medications daily. Upon review of the patients' history, it was found that the patient had traveled to her village in the country's remote area, where she took the medicines unsupervised. She took methotrexate 17.5mg daily, instead of taking weekly, for 10 consecutive days as she couldn't read the prescriptions properly. She started having oral bleeding on and off for a week, as well as a loss of appetite, odynophagia, abdominal pain, and loose stool. She sought medical attention thereafter. There was a history of fever, chills, abdominal pain, and oral bleeding. Oral mucositis with oral ulcers was noted during a subsequent physical examination, which had gradually progressed to the point that the patient could no longer take foods orally. Complete blood counts, renal function tests, liver function tests, erythrocyte sedimentation rate, c-reactive protein, procalcitonin, INR, APTT, Vitamin B12, folic acid, and methotrexate blood levels, ECHO, EEG, CXR, and PBS were sent immediately.

Case management

Initial routine investigation revealed the patient to have pancytopenia. Methotrexate was discontinued immediately, and blood plasma levels were taken. Strict reverse isolation precaution measures were taken. BM suppressing drugs were avoided. Leucovorin (Folinic acid) was administered in an intermediate dose (50 mg eight hourly for 16 doses). Due to persistent fever, intravenous antibiotics (Piperacillin/tazobactam) and antifungal drugs (IV Voriconazole) were started. Granulocyte colony-stimulating factor (G-CSF) was started twice daily for hematopoiesis and leukocyte function modulation. Oral chlorhexidine and Clotrimazole mouth paint were given for mouth ulcers. Methotrexate-induced oral mucositis was treated with an Allopurinol gargle. A urinary alkalizer was given since the PH of the urine was 5.

As the patient's neutropenia worsened over next few days, the beta-lactam antibiotic (Piperacillin/tazobactam) was changed to Carbapenem (Meropenem) and Intravenous Teicoplanin was added for gram-positive coverage. Inj Folinic acid was converted to an oral dosage of 5mg once daily as gradual improvement was noticed. Inj.

Citation: Poudel S, Khadka B, Khanal K, Ghimire A and Regmi A. Medication Dosing Error Leading to Potentially Lethal Methotrexate Toxicity. Austin Crit Care J. 2022; 9(1): 1040.

Table 1: **Pre and Post treatment laboratory tests.**

Date\Test	17-Nov	5-Dec	6-Dec	7-Dec (DOA)	8-Dec	9-Dec	10-Dec	11-Dec	12-Dec	13-Dec	14-Dec
WBC (cells/Cumm)	7500	800	300	600	280	710	1240	840	970	2290	8660
Neutrophil (%)	60	30	20	20	2	0	6	19.6	34	60.8	81
Lymphocyte (%)	36	70	80	80	92	72	87	68.5	66	29.9	14.3
Platelets (cells/Cumm)	267000	49,000	45,000	21000	38,000	16,000	20,000	18,000	30,000	30,000	28,000
Hemoglobin (g/dl)	11.7	9.3	8.6	8.4	7.5	6.9	8	8.1	7.7	7.8	7.2
Serum creatinine (mg/dl)	1.1	0.9	0.8	0.7	0.7	0.7	0.7	0.8	N/A	0.6	0.5
Urea (mg/dl)	29	28	27	25	20	27	35	27	N/A	31	26
SGPT (ALT) (U/L)	16	132	83	70	N/A	N/A	N/A	26	N/A	29	N/A
SGOT (AST) (U/L)	14	73	31	28	N/A	N/A	N/A	20	N/A	30	N/A
Serum Albumin (g/dl)	N/A	2.5	2.4	2.8	N/A	N/A	N/A	2.3	N/A	2.1	N/A

Methylprednisolone 40mg daily was added. Oral mucositis resolved gradually. Platelet concentrate was transfused to target platelet count more than 20,000. Hydration was maintained with IV fluids.

Investigations

Laboratory investigations revealed that the absolute neutrophil count (ANC) on the 7th day was 1392/mm^3, the RT titer was 38.7IU/ml (0-20), ESR: 40mm, CRP: 4.8mg/L, Procalcitonin: 7.1ng/ml, aPTT: 23.5 seconds, INR: 1.3, Vit B12: >1000pg/ml, liver function and thyroid function tests were normal, except for mild hypoalbuminemia (2.5mg/dl). The echocardiogram (ECG) revealed sinus tachycardia with the poor progression of R wave with PVCs while echocardiography showed mild concentric LVH, Grade I LVDD, mild TR (PASP25mmHg), minimal pericardial effusion and ejection fraction of 60%. Chest x ray showed normal lung fields with cardiomegaly. A peripheral blood smear (PBS) showed normocytic, normochromic, with microcytic, hypochromic RBCs.

Follow Up and Outcome

Gradual improvement of CBC counts and neutrophils, along with platelet count was noticed with the start of the above-mentioned treatment therapy. The patient was afebrile. Oral mucositis was improved with good oral intake. The patient was discharged to the ward on the 8th day of ICU admission under the care of a physician. Serum methotrexate levels were reported to be 0.3umol/l (toxic level after 24 hours of high dose therapy of >=5). Methotrexate was restarted with specific and clear instructions on the dosing regimen of 17.5mg once weekly, and the frequency of intake was also explained to the patient and family members.

Discussion

MTX is a folate antagonist that inhibits dihydrofolate reductase (DHFR), preventing dihydrofolate conversion to tetrahydrofolate and thereby limiting purines and pyrimidines synthesis, thus inhibiting DNA, RNA, and protein synthesis. It inhibits the proinflammatory properties of major cell lineages involved in the development and pathogenesis of RA by altering cell-specific signaling pathways. Because of its disease-modifying properties and low-dose safety profile, it is considered the first-line treatment for RA. However, it is known to cause side effects such as pancytopenia, liver damage, and renal failure at larger doses [4]. Early toxicity is oral mucositis while severe toxicity includes bleeding, rash, and neurotoxicity (*via* the intrathecal route).

MTX should not be given more frequently than once a week due to increased toxicity risk. The MTX dose should be gradually increased by no more than 2.5mg every 1-2 weeks. Although myelosuppression and pancytopenia are well-known side effects of MTX, low doses have not been adequately studied. Though the prescription was correct in our case, the patient had taken a cumulative high dosage of the drug for more than a week, which led to myelosuppression.

The reasons behind MTX-induced pancytopenia are multifactorial. Because of their structural similarity, MTX and folates compete in several phases, including cellular absorption, cellular storage as polyglutamate, and enzyme binding. One of the numerous features that underlie cytotoxicity is MTX's potential to undergo polyglutamation, which modifies the spectrum of enzymes inhibited by the drug [7]. Pancytopenia caused by MTX is dose and duration dependent, occurring in about 1.4 percent of reported adverse effects, with a female predominance (62.51 percent) and around 59 percent in patients over the age of the 60 [5]. Leukopenia, thrombocytopenia, megaloblastic anemia, and pancytopenia are common symptoms, with a 17-44% mortality rate [6]. As in our case, the patient was female, over 60 years of age, and the incident occurred due to inappropriate dosing of the drug.

Folic acid supplementation can help to minimize MTX toxicity. Leucovorin is supposed to help in stomatitis prevention and recovery from harmful effects. Concomitant folic acid (1 to 3 mg/day) therapy reduces the incidence of toxicities such as mucositis, nausea, hematologic abnormalities, and liver enzyme increases while appearing to not affect clinical efficacy [9]. Complete blood count (CBC), serum creatinine, and transaminase tests should be performed at baseline before starting MTX therapy, with monitoring every 2-4 weeks for the first three months, 8-12 weeks for the next three months, and once every 12 weeks thereafter, according to the American College of Rheumatology [8]. In our case, the patient had visited a rural part of the country and no investigatory follow-up was made with an inappropriate intake of the drug. Folinic acid supplementation did help improve stomatitis and also helped encourage oral intake of food.

The diagnosis of MTX-induced pancytopenia was proven by the effective response to leucovorin and filgrastim therapy and by

withholding MTX. Improving cell counts and decreasing CRP were used as trends to monitor the effectiveness of therapy, as shown in the above table. The bone marrow biopsy was deferred given the positive response to therapy [10].

The National Coordinating Council for Medication Error Reporting and Prevention defines a medication error as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use" [11]. Medication errors can occur in choosing a medicine, writing the prescription, manufacturing the formulation to be used, dispensing the formulation, administering or taking the drug, and monitoring therapy. As in our case, there was incorrect patient action leading to the incorrect administration of the drug. Patient education is the only way to prevent this type of error.

Conclusion

Patients on MTX therapy should be regularly monitored with CBC and LFT to identify myelosuppression and avoid the sequelae of pancytopenia. Primary clinicians and pharmacists, however, need to remain vigilant over its use due to potential complications. There is a need for increased awareness among physicians to minimize prescribing errors. Dosing schedules should be printed on MTX drug envelopes, especially for elderly patients as medication error has usually been reported with MTX dosing.

Declaration

Acknowledgment: Department of Internal Medicine.

Human Ethics: Written and informed Consent taken.

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