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Case Report

When low-dose Isn't Low-risk: Methotrexate-Induced Pancytopenia and Mucositis in a Rheumatoid Arthritis Patient

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Abstract

Methotrexate (MTX) has long served as a mainstay treatment for rheumatoid arthritis. While high dose methotrexate is associated with significant side effect, low dose methotrexate toxicity rarely occurs. We present a case of an 81-year-old male patient with a recent diagnosis of rheumatoid arthritis who deliberately took daily methotrexate (cumulative dose of 40mg) instead of weekly dose of 5mg for his flare-up and presented with mucositis, pancytopenia (platelet nadir of 14000/mm^3, hemoglobin level of 9g/l and white blood cell count of 2530/mm^3) and normal renal and hepatic function. After ruling out hematological emergencies, malignancies and infectious causes, the patient was diagnosed with low dose methotrexate (LDMTX) toxicity. The patient's advanced age, daily methotrexate intake, alcohol use, smoking history, and possible folate pathway polymorphisms were considered contributing factors. Methotrexate was stopped and the patient was treated with leucovorin, filgrastim, and supportive care resulting in progressive and complete hematological recovery. Follow-up at one week, one month and six months showed full resolution of the cytopenia. This case underscores that LDMTX toxicity can occur even at minimal doses when taken consecutively and may be exacerbated by folate deficiency, age-related vulnerability, and genetic susceptibility. Early recognition, prompt cessation of MTX, and appropriate rescue therapy with leucovorin and G-CSF are crucial to achieving a good outcome. This case emphasizes the necessity of clear patient education regarding weekly MTX dosing to avoid dosing errors and subsequent toxicity.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder characterized by persistent inflammation that primarily affects the joints and surrounding soft tissues. It typically presents with a gradual, symmetrical onset of polyarthritis. The therapeutic objective in RA management is to attain and maintain either complete clinical remission or consistently low disease activity for each individual patient [1].

Methotrexate (MTX), a conventional synthetic disease-modifying antirheumatic drug (csDMARD), has remained the cornerstone of RA therapy since its introduction in 1951. As a 4-amino-10-methyl folic acid derivative, MTX demonstrates superior efficacy in controlling RA progression—whether used as monotherapy or in combination regimens [2,3]. MTX shares structural similarities with folate, enabling it to competitively block key folate-dependent enzymes, thereby disrupting DNA and RNA synthesis while increasing extracellular adenosine levels. Its antifolate properties are largely responsible for the adverse effects associated with its long-term use, most of which arise from MTX suppression of cellular proliferation. Although they are more common after administration of high dose methotrexate (HDMTX) (HDMTX, >500-1000mg/m2), they have also been reported after low doses. Because available data are sparse and predominantly drawn from observational studies, case series, and case reports, the precise incidence of low dose methotrexate (LDMTX)– related adverse effects is still undetermined [4].

For most treatment-naïve patients with early RA, oral MTX is initiated at 7.5–25 mg weekly. However, the optimal dose must be individualized to balance efficacy with tolerability while ensuring personalized treatment [2].

We report a case of LDMTX toxicity in a RA patient who developed severe pancytopenia and stomatitis after inadvertently taking consecutive daily low doses of MTX, despite concurrent folic acid supplementation with multiple possible contributing factors for his toxicity.

Case presentation

An 81-year-old male presented to the emergency department with a one-week history of gingival bleeding and difficulty swallowing that worsened over the past two days. Past medical history is significant for hypertension and a recent diagnosis of rheumatoid arthritis. He has been prescribed methotrexate (MTX) at a dose of 5 mg weekly, along with daily folic acid supplementation. Ten days prior to his presentation, the patient experienced a flare-up of his disease and started taking MTX 5mg daily on his own initiative thinking that it will resolve his pain faster (40mg per week). The patient is a smoker (80 pack-years), and alcoholic (4-5 glasses per day).

Upon presentation, the patient was afebrile, with a heart rate of 114 beats per minute. Physical examination

revealed a dry mucous membrane, severe mucositis, bleeding of the gums and no active synovitis of the hands or knees. The patient denied hematuria, rectorrhagia or hematochezia, rashes, pruritis and abdominal pain. Initial laboratory studies were significant for pancytopenia with a platelet count of 34,000/mm3 reaching a nadir of 14,000/mm3 later that day. Hemoglobin level was 9g/dl and WBC count of 2530/mm3(Table 1.) Last complete blood count that was done by the patient was one month prior to his presentation and was completely normal. Liver and kidney function were normal. Peripheral smear didn't reveal any schistocytes, blasts, dysplastic cells or other abnormal cells. Anemia workup was significant for anemia of chronic disease. Inflammatory markers were elevated, as demonstrated in Table2. MTX was stopped upon admission and the patient received one unit of platelets. Serologic testing for cytomegalovirus, Epstein-Barr virus, and Brucella was negative, as was his auto-immune workup (Table2.). A computer tomography (CT) of the chest, abdomen and pelvis with intravenous contrast was unremarkable. The decision was made to proceed with a bone marrow biopsy that showed hypocellular marrow (20% cellularity) with the presence of all three lineage. Bone marrow cytology and flow cytometry showed no abnormal or immature cells. On hospital day four, the patient received another unit of platelets for a further drop in platelet count to 18,000/mm3 and was placed in verse isolation for a moderate neutropenia (absolute neutrophilic count 700/mm3). Given the aforementioned findings, a provisional diagnosis of MTX-induced pancytopenia was made. The patient was started on leucovorin and injection filgrastim 300mg subcutaneously once daily. As cell count improved over the next days, the patient was discharged home. Follow-up at one week and one and six months, revealed complete resolution of his pancytopenia (Table1.).

	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6 ***	**Day 7**	**Day 8**	**One week follow-up**	**Two-week follow-up**	**Six-month follow-up**
Hemoglobin (g/dL)	10	9.5	9	8.4	8.3	8.5	8.5	8.6	9	10	11.5
White blood cell count (/mm^3)	2531	3210	2305	2010	2303	3320	3400	3320	3400	3700	4200
Platelets (/mm^3)	34000	14000	45000	18000	40000	50000	99000	100000	120000	160000	210000

Table 1: cell count differential trend, *Day of leucovorin and filgrastim injection

Investigation	Results	Normal values
Serum Immunoglobulin (Ig)		
IgA (g/L)	5	0.8-3
IgM (g/L)	1.01	0.4-2.5
IgG (g/L)	12	6-16
ANA	1/100	Not Available
C3 (g/L)	1.2	0.9-1.8
C4 (g/L)	0.12	0.1-0.4
C-reactive protein (mg/L)	300	<6
Erythrocyte sedimentation rate	97	Age/2
Coombs Direct and Indirect	Negative	Negative
LDH (IU/L)	236	
Vitamin B12 (pg/mL)	195	160-950
Folic acid (ng/mL)	2	2.7-17
Ferritin (ng/mL)	1310	24-300
Fibrinogen (mg)	684	180-350

Table 2: Laboratory investigation

Discussion

The initial presentation of gingival bleeding, mucositis, and pancytopenia required evaluation for life-threatening etiologies, including thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, hemophagocytic lymphohistiocytosis, and hematologic malignancies; including leukemia, and myelodysplastic syndrome which were excluded through normal coagulation studies, absence of hemolysis and bone marrow biopsy demonstrating hypocellularity and no dysplastic or malignant cells. Our patient was ultimately diagnosed with low-dose methotrexate (LDMTX)-induced pancytopenia and mucositis, resulting from inadvertent daily administration (instead of weekly), advanced age and the possibility of genetic polymorphism. The toxicity here stemmed from daily dosing; a well-established risk factor. Although single low-dose MTX overdoses (≤1g) are rarely toxic due to saturable absorption, daily administration bypasses this mechanism, leading to cumulative drug exposure and toxicity [5,6]. Moreover, our patient's pancytopenia may have been partially attributable to insufficient folic acid supplementation, as folate deficiency is a recognized factor in MTX-associated adverse effects [7].

Multiple studies also linked genetic polymorphism to susceptibility to MTX toxicity. Genetic polymorphisms affecting folate metabolism and MTX transport may predispose some individuals to heightened MTX toxicity [8]. Variants in enzymes such as MTHFR have been linked to enhanced risk of MTX-induced mucositis and hematologic toxicity, particularly in RA populations [9].

MTX toxicity can manifest as mucositis, hepatotoxicity (fibrosis, hepatitis), pneumonitis, alopecia, and

metabolic disturbances like hyperglycemia. However, severe myelosuppression represents the most serious adverse effect and is the primary cause of MTX-related fatalities [10]. Although it is rare with acute single LMTX poisoning, a retrospective cohort of 28 patients receiving consecutive daily LDMTX found that approximately 79% developed pancytopenia. Furthermore, MTX levels don't correlate with clinical manifestations in LDMTX toxicities [11].

Both cytopenia and mucositis were successfully managed with folinic acid, a rescue strategy adapted from high-dose MTX toxicity protocols, and supported by the existing literature [12]. As a MTX antidote, folinic acid (leucovorin) exploits identical cellular uptake pathways but bypasses MTX's blockade of dihydrofolate reductase, thereby replenishing intracellular folate stores and reversing metabolic disruption. Dosing regimens vary substantially by toxicity pattern; acute low-dose MTX exposure rarely requires treatment due to saturable absorption kinetics, whereas chronic toxicity often demands extended, low-dose folinic acid administration until hematologic recovery is achieved [12].

Our case mirrored complications observed in similar cases of MTX toxicity due to dosing errors. Like the patient in Yildiz et al. [13], our case exhibited advanced age and omission of folic acid as key risk factors for MTX-induced myelosuppression. Both patients presented with oral mucositis and pancytopenia, though our patient's thrombocytopenia (nadir: 14,000/mm³) was more severe. Notably, Yildiz et al.'s patient showed rapid hematologic recovery with folic acid and filgrastim alone, whereas our patient required leucovorin rescue.

Furthermore, this case aligns with prior reports of MTX toxicity by Hassan et al. [14] and Amissah-Arthur et al. [12] due to dosing errors and underscores the life-threatening consequences of improper MTX use, particularly in elderly patients with comorbidities (e.g., smoking, alcoholism) that may exacerbate toxicity.

Our case of MTX-induced pancytopenia in an 81-year-old male, along with comparable reports [12-14] demonstrates that filgrastim (G-CSF) has been consistently employed in severe cases at a standard dose of 300 μg/day until hematologic recovery, typically showing rapid neutrophil improvement within 2–5 days. While Yildiz et al. [13] achieved resolution with a single filgrastim dose plus folic acid, most cases- including our patient- combined filgrastim with leucovorin, particularly in profound cytopenia or high-risk patients (e.g., elderly, hypoalbuminemia, or renal impairment). The exception- Amissah-Arthur et al. [12]-relied solely on leucovorin, suggesting filgrastim may be omitted in mild presentations. Our patient's severe thrombocytopenia (14,000/mm³) and alcohol-related folate deficiency warranted this dual approach, aligning with evidence that filgrastim accelerates neutrophil recovery, while leucovorin is critical for counteracting MTX's folate antagonism. These findings support filgrastim's role as first-line therapy for MTX-induced neutropenia, with leucovorin reserved for pancytopenia or mucosal toxicity, though dosing duration should be tailored to serial CBC trends. Notably, all filgrastim-treated cases reported full recovery, reinforcing its efficacy when initiated

promptly. Future studies might clarify optimal treatment duration and whether prophylactic G-CSF benefits high-risk patients on long-term MTX.

Notably, chronic MTX toxicity does not require monitoring of serum MTX levels, as serum concentrations do not correlate with the severity of neutropenia or thrombocytopenia [15]. Several factors—renal insufficiency, hypoalbuminemia, advanced age (>75 years), baseline folate deficiency, and polypharmacy—may precipitate chronic LDMTX toxicity. In a cohort of 28 patients with chronic LDMTX overdosing, approximately half had concurrent use of medications (e.g., esomeprazole, NSAIDs) known to reduce renal MTX excretion [15]. Although impaired renal function is one of the strongest predictors of toxicity, it was not a contributing factor in this case.

This case highlights the potentially life-threatening consequences of improper MTX use, particularly among elderly individuals with comorbidities such as smoking and heavy alcohol consumption that may exacerbate toxicity, despite normal renal function and minimal weekly dose escalation. Prompt recognition, immediate MTX cessation, early leucovorin rescue, and G-CSF support are critical for favorable outcomes. Prevention through patient education thoroughly regarding the weekly dosing of MTX and differentiate this from the daily folate dose remains the most effective strategy to avoid similar dosing errors.

Conflict of Interest: Authors declare no conflict of interest.

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