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CASE REPORT

The Unseen Danger of Methotrexate Toxicity

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Abstract

Methotrexate is a commonly prescribed immunosuppressant and chemotherapy agent, which is closely monitored by healthcare providers for its adverse effects. As a result, methotrexate toxicity occurs infrequently. We present a case of a 51-year-old woman with a past medical history of rheumatoid arthritis on methotrexate and prednisone. She presented to the emergency room with altered mental status, jaundice, and mucosal ulceration. She was subsequently admitted to the intensive care unit for septic shock in the setting of severe pancytopenia, acute renal failure and acute liver failure. This case demonstrates the importance of recognizing the signs and symptoms of methotrexate toxicity due to its infrequent presentation.

Keywords: Methotrexate, Methotrexate toxicity, Myelosuppression, Pancytopenia, Sepsis, Septic shock

1. Introduction

Methotrexate is a folic acid antagonist that is used for the treatment of autoimmune diseases such as rheumatoid arthritis for its anti-inflammatory and immunomodulatory activity, when used at low doses. In higher doses, it can be used as a chemotherapy agent in various types of cancers by inhibiting DNA synthesis and thereby, emitting cytotoxic effects. Adverse effects of methotrexate include gastrointestinal effects such as nausea, vomiting, pancreatitis, fever, fatigue, alopecia, bone marrow suppression including aplastic anemia, infections, malignancy, and renal failure. Long term side effects can lead to both hepatic and pulmonary toxicity. With doses higher than 500 mg/m2, toxicity can occur. Development of mucosal ulceration can be a sign of imminent toxicity (1). Patients on methotrexate are closely monitored with routine labs and assessments. Therefore, toxicity is a rare occurrence, with only a few reported cases that have been fatal. Here we report an acute presentation of methotrexate toxicity (see Table 1).

2. Case presentation

A 51-year-old woman with a past medical history of rheumatoid arthritis on methotrexate (15 mg once weekly) and prednisone (5 mg daily), pulmonary embolism on apixaban, and alcohol use disorder was brought by ambulance to the emergency room with altered mental status. The patient had been drinking daily since the passing of her husband. On review of her medications, she had apparently been taking methotrexate on a daily basis instead of the usual weekly prescribed dose.

Approximately a week prior to her presentation, the patient developed swelling of her lips and oral mucosal lesions. She contacted her primary care physician, who attributed her symptoms to ill-fitting dentures and advised her to follow up with a dentist. On the day of presentation, the patient did not answer her sister's phone call which prompted a call to emergency medical personnel. When the paramedics arrived, the patient appeared to be confused and had blood oozing from her mouth. She was immediately rushed to the emergency department.

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Table 1. Labs revealed severe pancytopenia, a supratherapeutic INR, acute kidney injury and lactic acidosis.

Test	Laboratory value	Reference value
Venous blood pH	7.27	7.32–7.42
Venous blood carbon dioxide	36 mm hg	41–51 mm hg
Prothrombin time	>100 s	11.8–14.6 s
International normalized ratio	>13.6	0.8–1.2
Fibrinogen	638 mg/dl	216–537 mg/dl
Thyroid Stimulating Hormone	0.309 μIU/ml	0.5–4.7 μIU/ml
Free T4	0.83 ng/dl	0.89–1.76 ng/dl
CO2	18 mmol/L	20–31 mmol/L
Blood Urea Nitrogen	76 mg/dl	9–23 mg/dl
Creatinine	1.64 mg/dl	0.5–0.8 mg/dl
Bilirubin total	8.1 mg/dl	0.3–1.2 mg/dl
Direct bilirubin	6.24 mg/dl	0–0.3 mg/dl
Lactic acid	>12 mmol/L	0.5–2.2 mmol/L
Hemoglobin	9.3 gm/dl with repeat of 8.4 gm/dl	11.0–14.5 gm/dl
White blood cell count	0.8 k/μL	4.0–10.8 k/μL
Platelet count	2 k/μL	145-400 k/μL
Reticulocyte count	0.1%	0.5–2%
Absolute reticulocyte count	0.003 million/μL	0.020–0.10 million/μL
Haptoglobin	228 mg/dl	30–200 mg/dl
Cortisol	45.9 mcg/dl	3.4–22.5 mcg/dl
D-Dimer	<0.27 mcg/ml	≤0.50 mcg/ml
Glucose	72 mg/dl	65–140 mg/dl
Blood Alcohol level	<3 mg/dl	0–3 mg/dl
Urine toxicology screen	Positive for Benzodiazepines (Home medication)	
Methotrexate level	<0.04 μmol/L	<0.04 μmol/L

On arrival to the emergency department, she was afebrile (38.7 C), tachycardic (111 beats/min), tachypneic (32 breaths/min), hypotensive (76/46 mm Hg) and saturating at 94% on room air. Physical examination was significant for scleral icterus, oral mucosal ulcers, cardiac, respiratory and abdominal examination was unremarkable.

CT head showed chronic microvascular ischemic changes but no acute intracranial abnormality. Chest X-ray showed a mass like perihilar opacity in the perihilar region (Fig. 1). CT chest, abdomen and pelvis showed bilateral patchy pulmonary infiltrates, some of which are nodular in appearance, possible pneumonia or masses within the right lung, especially right lower lobe. It also showed thickened, dense gallbladder, fluid-filled esophagus, thickening and inflammatory changes in the cecum and ascending colon. While in the emergency room, she developed hypotension and eventually went into shock. She was initially administered 2.5 L of crystalloid fluids and was eventually started on norepinephrine due to persistent hypotension despite IV fluid resuscitation. Blood, sputum and urine cultures were drawn and she was empirically started on broad spectrum antibiotics with vancomycin and piperacillin-tazobactam. She was admitted to the intensive care unit.

Due to severe pancytopenia, she was transfused with 3 units each of fresh frozen plasma, packed red blood cells and 2 units of platelets. Hematology was consulted and she was started on Filgrastim. Overnight, her shock worsened despite being on the maximum doses of norepinephrine, vasopressin and epinephrine.

She eventually went into cardiac arrest with pulseless electrical activity approximately 16 h after presentation. She was brought back to sinus rhythm twice and her code status was changed to "do not resuscitate and do not intubate" by the family during the third cardiac arrest and she unfortunately passed away.

Upon follow up of her labs, her sputum culture came back positive for klebsiella aerogenes and blood cultures were positive for E coli. Methotrexate level was ordered and was within normal limits.

3. Discussion

Our case is an unfortunate presentation of a patient who is suspected to have had early signs of methotrexate toxicity with oral mucosal lesions. However, on presentation she had severe pancytopenia which was likely multifactorial related to methotrexate toxicity causing myelosuppression, compounded by increased alcohol intake. Patient's subsequent immunocompromised state led to the development of an infection, in this case, *E. coli* bacteremia and septic shock with development of persistent hypotension requiring vasopressors and lactic acidosis. She developed a gastrointestinal

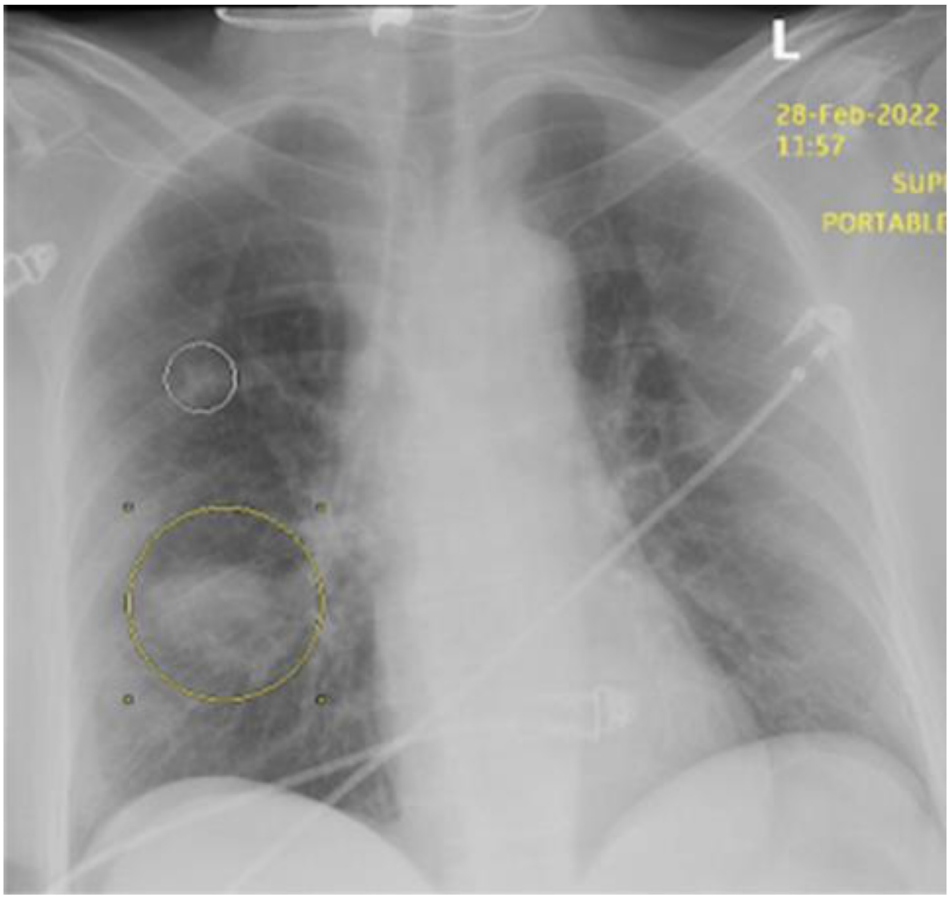

Fig. 1. Chest x-ray showed a mass-like opacity in the right perihilar region. (Yellow circle), an irregular nodular opacity in the right upper lobe (white circle) and increased interstitial markings bilaterally.

bleed worsened in the setting of pancytopenia. Her progressive shock finally led to cardiac arrest despite resuscitative interventions. She was unlikely to have disseminated intravascular coagulation or thrombotic thrombocytopenic purpura as she did not have any skin changes concerning purpura, or ecchymosis and her blood smear did not reveal schistocytes. Her fibrinogen and haptoglobin were elevated; however, these could be elevated acute phase reactants in the setting of her sepsis.

Folate is converted to tetrahydro folic acid in the body by dihydrofolate reductase. Tetrahydro folic acid (THF) is responsible for many biologic functions in the body and folate must be converted to THF in the body for it to effectively function in the body.[1]

Methotrexate (MTX) is an antimetabolite that competitively inhibits dihydrofolate reductase resulting in decreased thymidine monophosphate which is necessary for DNA synthesis. As it blocks DHFR, it also inhibits the synthesis of THF. The affinity of methotrexate to DHFR is about 1000 times higher than folate.[2]

MTX is used in the treatment of a wide variety of diseases including neoplastic and non-neoplastic conditions. It is commonly used in the treatment of rheumatoid arthritis, inflammatory bowel disease, psoriasis and is a component of various chemotherapy regimens.

Methotrexate is absorbed from the gastrointestinal tract and mostly eliminated by the kidney. Methotrexate toxicity leads to myelosuppression, hepatotoxicity, mucositis and pulmonary fibrosis.

The most common cause of methotrexate toxicity in adults is due to accidental daily intake of the medication as opposed to the prescribed once weekly dose. This was the case in our patient. Weekly administration of methotrexate, rather than daily intake, is recommended for management of rheumatoid arthritis due to more consistent plasma levels & reduced incidence of side effects compared to daily usage. Due to its high plasma protein binding, any drug that displaces methotrexate from protein also has the potential to elevate its levels in the bloodstream. Drugs such as non-steroidal anti-inflammatory drugs, salicylates warfarin,

trimethoprim can elevate blood levels of methotrexate. Heavy alcohol consumption has also been implicated as one of the risk factors causing methotrexate toxicity.[3,4] Other causes leading to methotrexate toxicity are dosage errors & renal impairment.

An interesting point to note is methotrexate toxicity does not occur due to acute oral overdosing in patients with normal kidney function due to saturable bioavailability and prompt renal excretion. Individuals at risk are patients who have staggered ingestion of the drug over a period and patients with significant renal impairment because it prolongs the duration of exposure due to a delay in excretion of the drug.[5] This patient did present with some renal impairment with a creatinine of 1.6 mg/dl (creatinine clearance of 35 ml/min) likely contributing to worsening methotrexate toxicity.

Serum methotrexate levels are not helpful in diagnosis of acute methotrexate toxicity due to rapid intracellular uptake and short distribution half-life of the drug. Levels are usually undetectable within 24 h post ingestion as seen in our patient.[6] Methotrexate accumulates intracellularly and exerts its toxic effect despite the serum levels within normal range.[7,8]

Leucovorin or folinic acid is used in the treatment of methotrexate toxicity. It is often termed as "Leucovorin rescue". Folinic acid bypasses the effect of methotrexate and provides reduced folate.[4,5] Supportive measures such as intravenous hydration and urine alkalization to increase the solubility of methotrexate and its metabolites in urine promoting excretion. Glucarpidase is a new FDA approved drug used in specific situations.

4. Conclusion

This case presentation shows the importance of monitoring patients on methotrexate closely to ensure they are taking medications as prescribed and are following up. It is also important that they are educated about the adverse effects of methotrexate to prompt early recognition of symptoms and understand factors such as increased alcohol intake that may increase the likelihood of toxicity.

Disclaimer

This report has neither been submitted to another journal for publication nor has it been presented at any conference or a meeting.

Conflict of interest

No conflicts of interest exist for this case report.

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