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Case in Point

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Correlation of Serum Methotrexate Levels with Drug Induced Side Effects

Saumya H Mittal, Tuhina Govil[1], Salony Mittal[2]

Department of Medicine, Indraprastha Apollo, Sarita Vihar, New Delhi, [1]Department of Pediatrics, Jagrani Hospital, Lucknow, Uttar Pradesh, [2]Department of Pathology, Yenepoya University, Mangalore, Karnataka, India

Abstract

Often employed in the treatment of malignancies with high cellular proliferation rates, including acute lymphoblastic leukemia, choriocarcinoma, trophoblastic tumours, and carcinomas of the breast, tongue, pharynx, and testis; and certain nonmalignant conditions like rheumatoid arthritis, psoriasis, asthma, sarcoidosis, and transplantation therapy, methotrexate is an antifolate agent. It works by inhibiting the enzyme dihydrofolate reductase. The molecule inhibits DNA synthesis by depletion of nucleotide precursors and is associated with a number of diverse side effects. The present series comprises of 4 patients: Each demonstrated significant drug-induced side effects even though their serum methotrexate levels were found to be normal.

Key words: Methotrexate, drug-induced side effects

Introduction

A 52-year-old lady presented with the complaints of oral ulcerations for 10 days at the time of presentation to the hospital. The ulcers had been gradually increasing for the past 7 days, in size and site. At presentation, they were present over the arms and legs also. She had associated complaints of bleeding per rectum, throat pain, difficulty in swallowing, and burning micturition for approximately 4 days at the presentation to the hospital. There had been generalized itching all over the body, in association to the ulcers. She also had a history of frequent episodes of loose stools. The patient, a known case of diabetes mellitus, hypertension, hypothyroidism, and rheumatoid arthritis had been taking 15 mg of methotrexate once a week, in view of her rheumatoid arthritis. Her joint pains had been increasing after the onset of winters. She therefore self prescribed herself to 15 mg of methotrexate twice a week. She presented with severe hemodynamic derangement. She had severe hypotension (systolic BP-70 mm Hg) with tachycardia (HR-128/min). Her oxygen saturation was normal. No pallor, clubbing, cyanosis, icterus, pedal oedema, or lymphadenopathy was noted. The systemic examination was unremarkable except for tachycardia. The patient presented with reports significant for low total leukocyte count (TLC-850/cumm), mild azotemia (creatinine–1.3 mg/dl) and hematuria (urine R/M-40–50 RBCs/hpf).

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The patient was kept in isolation and ICU initially in view of severe hypotension, generalized ulcerations and low TLC count. She was initiated on IV antibiotics and G-CSF. Ionotropes were added in view of persistent hypotension. She was found to have a ventricular dysfunction and therefore she was initiated on IV fluids at a slow rate. Her initial reports were suggestive of significant azotemia (Creat-2 mg/dl, Urea-76 mg/dl) and dyselectrolytemia (Na-134 meq/L, K-6.4 meq/L). Her urine output was found to be low. Her liver function tests (LFT) showed bilirubinemia (T Bil-2 mg/dL, D Bil-1.2 mg/dL). Methotrexate toxicity was considered and serum methotrexate levels were sent (Methotrexate levels-0.016 umol/L). Inj Folinic Acid was still added to her treatment. Initiated on the aforementioned treatment, her urine output gradually improved and her azotemia settled (Urea: 16 mg/dl, Creat: 0.6 mg/dl). Gradually her potassium levels reduced (2.4 meq/L), and she developed hypokalemia. The potassium levels didn't improve and she was found to have hypomagnesemia (1.4 mg/dL). The magnesium levels were also corrected (2.5 mg/dL), and thereafter her potassium levels gradually started improving (4.1 meq/L). The patient, improving otherwise, continued to have low TLC counts despite G-CSF being administered to her. She also received leukocyte concentrates. The patient gradually developed lowering of the platelet count. A bone marrow was therefore scheduled. The bone marrow biopsy report showed suppressed bone marrow.

Gradually, her TLC improved, and her ulcers healed. Her appetite improved and her burning micturition and abdominal

Address for correspondence: Dr. Saumya H Mittal, Department of Medicine, Indraprastha Apollo, Sarita Vihar, New Delhi
E-Mail: saumyamittal1@gmail.com

discomfort stopped. Her azotemia and hepatic derangements settled and she could thus be discharged.

A 48-year-old lady presented with complaints of generalized weakness. The patient, a known case of hypertension and rheumatoid arthritis was on long term steroid intake. The patient was tested for Anti CCP, CRP, and rheumatoid factor, which were found to be positive. She also had hypovitaminosis D. The other reports (LFT, kidney function tests (KFT), sugars and thyroid profile) were within normal range. Ultrasonography was significant for hepatomegaly. The patient was initiated on Methotrexate 5 mg once a week and her steroid dose was gradually tapered. When she tolerated the dose well, her methotrexate dose was stepped up to 7.5 mg once a week. She however developed oral ulcers. Her Methotrexate levels were found to be low (0.018 umol/L). In view of her symptoms, she was put back on the dose of methotrexate 5 mg once a week. Thereafter her oral ulcerations settled and she improved. She was thereafter continued on 5 mg of methotrexate.

A 55-year-old lady, a known case of hypertension, presented to the OPD with complaints of joint pains and stiffness affecting the joints of hands and fingers. She was found to have raised Anti CCP (81.4 units), raised CRP (121.3 mg/L) and her rheumatoid factor was positive. The patient was initiated on Methotrexate 5 mg once weekly. Her joint pains reduced further and her symptoms gradually improved and her levels of Anti CCP (50.3 units), and CRP (49.2 mg/L) reduced. However, on a further review a month later, she had complaints of loss of appetite and ghabharahat. The patient was therefore subjected to a repeat Complete Blood Count KFT and LFT. These revealed a deranged KFT (Urea-86 mg/dl, Creatinine-1.9 mg/dl, Sodium-139 meq/L, Potassium-5 meq/L). The CBC and LFT were normal. Her Methotrexate levels were found to be low (0.014 umol/L). Her methotrexate was stopped in view of deranged KFT.

Her KFT was reviewed within a week and was found to be within normal range again (Creat-1.1 mg/dl, Urea– 20 mg/dl, Sodium 140 meq/L, and Potassium-4.3 meq/L). She was restarted on Methotrexate 5 mg once a week again and she tolerated it well.

A 60-year-old gentleman, non smoker and non alcoholic, known case of diffuse large B cell lymphoma, presented with altered sensorium, with jerky movements of the right arm and right side of the face. His NCCT head showed ill defined hyper dense focus in right frontal and temporal lobe approximately 28 × 25 sq mm. The patient, who presented in a drowsy and arousable state, gradually regained his normal sensorium. His basic investigations were unremarkable. He was initiated on chemotherapy with methotrexate. The patient tolerated the chemotherapy well. However, after chemotherapy, the patient developed thrombocytopenia (50,000/cmm) and low TLC (900/cmm), azotemia (Creat-2 mg/dl, Urea-79 mg/dl), and deranged LFT (T Bil-1.3 mg/dL, SGOT-233 U/L, SGPT-557 U/L, GGTP-208 U/L). His methotrexate level was found to be 0.017. The patient was started on supportive care such as hydration with IV fluids, alkalinisation of urine, soda bicarbonate infusion, G-CSF, leucovorin and folate. He also needed platelet transfusions. The patient's azotemia and liver functions gradually normalized. His counts took longer to improve. He could be discharged after the improvement of the counts (Hb-11.7 g/dl, TLC-13000/cumm, Platelets-1, 30,000/cumm).

Methotrexate is an antifolate agent (inhibits the enzyme dihydrofolate reductase) that was synthesized in 1948. It is a commonly used medicine for certain cancers where high proliferation rates are known (e.g., acute lymphoblastic leukaemia, choriocarcinoma, trophoblastic tumours in women, and carcinomas of the breast, tongue, pharynx, and testis) and nonmalignant conditions such as rheumatoid arthritis (since 1970, after it was realized that it prevents joint deformity and precludes the progression of bony erosion), severe psoriasis, asthma, sarcoidosis, and transplantation therapy. The drug, in low doses as well as high doses, is known to cause numerous side effects. It inhibits DNA synthesis by depletion of nucleotide precursors.[1,2] Methotrexate is a teratogenic drug that affects multiple systems and has many side effects [Table 1]. Folate antagonism may be the cause of a few of the side effects.

The test of methotrexate levels detects the concentrations of methotrexate in the blood. A regular monitoring is required for high dose methotrexate levels. The levels of methotrexate are tested in patients on high dose methotrexate after 24, 48 and 72 h. Methotrexate levels are almost always tested when methotrexate induced side effects are suspected. Low dose methotrexate does not usually need methotrexate levels to be monitored and the levels of methotrexate are tested infrequently in these patients. Low dose methotrexate can be monitored by CBC, LFT, urea and creatinine.[3] Plasma methotrexate levels should be closely monitored during the infusion of methotrexate. They help detect any delay in methotrexate clearance at the earliest. This may also help adjust leucovorin doses and supportive measures like hydration and alkalinisation to ensure adequate urine output. The adjustment can be done till the target levels are <0.05-0.1 μg/ml.[4] The critical values of methotrexate, beyond which the side effects are more common, are <1 umol/L. Levels of more than 5 umol/L are known to occur 24 h after high dose therapy. The levels are considered abnormally high if they are more than 0.055 umol/L at 48 h or 0.02 umol/L at 72 h after infusion. And these levels may indicate the possibility of side effects of methotrexate.[2]

The levels of methotrexate are important to monitor as well as to guide the therapy to prevent and treat the side effects that can occur among these patients, whether on low dose or high dose methotrexate. However, as in the four cases described, the levels of methotrexate may not be able to guide the therapy

Table 1: Side Effects of Methotrexate

Methotrexate induced side effects

1 Acute Renal Failure
Caused by tubular necrosis due to
a. Accumulation of Methotrexate due to acidic pH
b. Direct effect of Methotrexate on tubules

2 Neurological Manifestations
Cause is not well established
a. Acute Neuropathy
Aseptic meningitis
Leucoencephalopathy
Headache
Nausea and vomiting
b. Subacute Neuropathy
Seizure
Paraplegia
Cerebellar dysfunction
c. Chronic Neuropathy
Necrotic leucoencephalopathy

3 Hematological Manifestations
More frequently seen in elderly, dehydrated, renal failure
Malnourished (hypoalbuminemia and decreased folate)
May occur as a hypersensitivity reaction also.
a. Megaloblastic Anaemia (due to folate antagonism)
b. Leucopenia (espeacially neutropenia- due to folate antagonism)
c. Thrombocytopenia
d. Pancytopenia or any combination of above

4 Cardiovascular Manifestations
a. Arterial thromboembolism
b. Hypotension
c. Pericarditis
d. Venous thromboemboli

5 Mucocutaneous Manifestations
Drug derived antigens expressed on keratinocytes
When detected by cytotoxic-T lymphocytes and
Mononuclear cells result in keratinocytes apoptosis
a. Oral ulcers and stomatitis (due to folate antagonism)
b. Ulcers of the skin
c. Urticaria
d. Erythema

6 Gastrointestinal and Hepatic Manifestations

Gastrointestinal	Hepatic
a. Vomiting	a. Hepatotoxicity, raised enzymes
b. Diarrhoea	b. Fatty liver
c. Abdominal pain	c. Liver cirrhosis

Liver involvement common in diabetics and alcoholics

7 Pulmonary Manifestations
Caused by
a. Activated T cells induced hypersensitivity reaction
b. Lung fibroblasts induced eosinophilia
May present as
a. Pneumonitis
b. Interstitial Lung Disease
Clinical features present
a. Non productive cough
b. Fever
c. Dyspnea
d. Malaise, Lethargy and Fatigue

8 Ophthalmic Manifestations
a. Blurred vision (transient visual changes)
b. Conjunctivitis

9 Vascular Manifestations
a. Vasculitis

correctly and one may have to look at the other tests such as complete hemogram, kidney and (LFT), and the clinical condition of the patient to guide the therapy and remedy of side effects.[3]

On our review of literature, only one report was found of 23 children who had received methotrexate for destructive polyarticular juvenile rheumatoid arthritis. In this report, the children were treated with methotrexate at a dose of 0.11-0.6 mg/kg/week. The children showed a rise in liver enzymes but no elevation in the serum methotrexate levels was found.[4] Outside of this study, in most other studies, serum methotrexate levels were either found to be high or had not been mentioned.

The levels of methotrexate may be low on account of a number of possibilities - The low levels of methotrexate levels may be due to errors in sample collection and transport. As has already been described, patients who are on high dose methotrexate show an initial rise followed by a decline in the levels of methotrexate. A patient with normal (KFT), may be able to excrete methotrexate. The levels of methotrexate therefore vary with time lapsed after the end of the therapy. So a sample of methotrexate collected and sent after 3 days of completion of methotrexate therapy may be found to be normal, while the side effects of methotrexate may last longer.[3]

It is already known that a person who is on methotrexate is more sensitive to light, natural as well as artificial. It should also be known that the sun degrades methotrexate. Therefore the blood collected for the methotrexate levels should be protected from the light and sent to the laboratory after wrapping the sample. The patients may have falsely low values if the collected sample is exposed to light because the light would degrade methotrexate.[2,3]

The patients who are suspected to develop tumour lysis syndrome are at a higher risk of developing high methotrexate levels. Tumour lysis syndrome can be well avoided by adequate hydration, use of allopurinol, and alkalinisation of urine using soda bicarbonate. Therefore, if tumour lysis syndrome is avoided after initiation of these protective measures, the levels of methotrexate may not rise.[3]

Methotrexate is excreted in the urine. It may accumulate in the acidic urine. Thereby the methotrexate levels rise. This rise may

lead to renal dysfunction. Dehydration and renal dysfunction predispose a patient to the development of haematological manifestations. The protective measure to avoid this is again adequate hydration and alkalinisation of urine. Thereby, the methotrexate is rapidly cleared from the renal tubules. Hence the levels of methotrexate may be low if supportive measures have been started prior to collection of sample.[1,3]

At times, the symptoms may appear late when the possibility of side effects is considered and preventive measures started beforehand.

Leucovorin is regarded highly in patients who have had methotrexate toxicity. Recommendations are it should be initiated after 24–36 h of completion of methotrexate infusion. So, a patient who has been empirically initiated leucovorin may show lower blood levels of methotrexate.[3]

Other supportive care measures include:

a. Hydration: IV fluids can be used to reduce the risk of methotrexate induced nephrotoxicity and to correct hypovolemia[5]
b. Urine Alkalinisation: Raised urine pH of 6–7 helps excretion of methotrexate and its metabolites[5]
c. Leucovorin and folate: This is effective in methotrexate induced side effects especially myelosuppression, gastrointestinal toxicity, and neurotoxicity. Patients should be advised to take these at least 12 h after administration of methotrexate so as to avoid diminishing its gastrointestinal and cellular uptake[5,6]
d. Glucarpidase: It cleaves methotrexate into inactive compounds that are no longer toxic. While the plasma levels are reduced within 15 min, the intracellular levels remain unaltered. It is however, not freely available[5]
e. Thymidine: An effective complement to glucarpidase and leucovorin, thymidine protects cells from cytotoxic effects[5]
f. Monitoring therapy: KFT, urine output, urine pH, and plasma methotrexate can be monitored[5]
g. Avoid nephrotoxic agents: Nephrotoxic agents such as NSAIDs, radiocontrast agents and aminoglycosides should be avoided[5]
h. Extracorporeal Measures: Hemodialysis and hemoperfusion may be utilized to remove methotrexate from the body[5]
i. CSF drainage and exchange: Useful in cases of intrathecal overdosing.[5]

The toxic effect of methotrexate on normal tissues is more a function of duration of exposure to high concentrations of drug rather than the peak level achieved. Although the risks of side effects and organ damage increase with increasing levels of methotrexate, a person may experience side effects from methotrexate use without having high blood levels of the drug.[3,7]

In our case series, we have shown 4 patients whose serum methotrexate levels were normal despite having side effects clinically. To the best of our knowledge, only 1 similar study was reported in 1989 where the patient's serum methotrexate levels were low despite liver enzymes being high. And none of these children had side effects clinically. Outside of this study, in most other studies, serum methotrexate levels were either found to be high or had not been mentioned. We therefore report the present case series where the patients were found to have normal serum methotrexate levels despite having clinical side effects and deranged laboratory parameters.

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