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CASE SERIES ON METHOTREXATE INDUCED BONE MARROW SUPPRESSION

Internal Medicine

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ABSTRACT

Methotrexate is a widely used drug, as an antimetabolite in cancer chemotherapy, immunosuppressant in graft-versus-host disease after bone-marrow transplantation and in the treatment of rheumatoid arthritis and psoriasis. However the hepatotoxicity caused by methotrexate is well known, there are still concerns about its bone marrow toxicity, with pancytopenia being a rare but potentially fatal consequence. Monitoring of MTX serum level is an effective tool in managing the toxicity profile. We report a case series of methotrexate induced bone marrow suppression, as it is important for differential diagnosis and management of MTX toxicity from other hematological abnormalities.

KEYWORDS

Methotrexate, Bone marrow suppression, Hematological complications

INTRODUCTION

Methotrexate (MTX) is a folate antagonist with anti-inflammatory and immunomodulatory characteristics and also used in a variety of cancers. It prevents the multiplication of cells. Therefore, cells with a high turnover rate or a short half-life are more vulnerable to its effects. [(1)] So it is common in highly proliferative tissues (e.g. mucosal layers, gastrointestinal tract and bone marrow). Symptoms involve mouth ulcers, sore throat, fever or chills, new or non-resolving infections, bruising or bleeding more easily than usual, anemia symptoms such as shortness of breath, dizziness and pallor [(2)]. In side-effect profile, methotrexate-induced pancytopenia being one of the most severe and complex adverse effects, careful monitoring and clinical discretion should be used in patients as the condition carries a mortality of around 17-44% [(3)]. Here, we discuss a case series on methotrexate induced bone-marrow suppression

CASE 1

A 69 yr old female who is a known case of Seropositive Rheumatoid Arthritis, presented to the emergency department with complaints of persistent oral ulcers for 6 days along with a history of vomiting (2 days ago). She is a known case of Seropositive RA and was on multiple DMARDs (HCQ 200 mg BD/ Lefno 20 mg OD). In view of high disease activity, she was initiated on Methotrexate 10 mg, Leflunomide 20 mg and oral steroids. After the first dose of methotrexate, the patient started complaining of numbness in the mouth, which was followed by oral mucosal erosion on the 2nd dose of Methotrexate. She also complains of headache and maculopapular rashes on legs. She had difficulty in swallowing along with painful mouth ulcers. She gives a history of 1 episode of vomiting (small amount, contained food, non-bilious). Considering the possibility of Methotrexate toxicity, the patient was admitted under Rheumatology for further evaluation and folinic acid rescue therapy. Her initial blood investigations revealed leucopenia (TLC- 1800), thrombocytopenia (0.94), low hemoglobin (8.9), hypoalbuminemia (3.23), elevated creatinine (1.39) and elevated inflammatory markers (ESR- 55, CRP- 73.9). Upon admission, she was initiated on intravenous leucovorin rescue therapy along with granulocyte colony stimulating factor (G-CSF) and all DMARDs (MTX/ Lefno) were put on hold. Subsequently, leukopenia with neutropenia improved and G-CSF was stopped and steroids were tapered to oral formulations. Later, CBC showed decreased Hemoglobin levels (7.3mg/dL). Blood grouping and cross-matching was done, and 1 unit PRBC transfusion was given. She was symptomatically better and hemodynamically stable at discharge

CASE 2

A 63 year old female, case of Rheumatoid Arthritis, who was on Oral methotrexate therapy presented in Emergency Department with complaints of multiple erosions over oral mucosa, tongue and lips for 1 week associated with difficulty in opening mouth and intermittent oral cavity bleeding, which gradually progressed to swelling of lips and difficulty swallowing. She also complained of abdominal pain and loose stools (coffee coloured) for 1 week .She gives no history of fever, vomiting, myalgia, dizziness or drug overdose. Hence was admitted for further evaluation and management. Her initial laboratory tests showed pancytopenia (TLC-2700, Platelet-1.04, HB-9.6) and elevated inflammatory markers (CRP -74.3, ESR-53). In view of pancytopenia, Methotrexate and Colchicine was stopped. Upon enquiry it was found that there were missing doses of methotrexate from her stock medicines. A Possibility of MTX overdose was considered and she was then started on Inj. Leucovorin and folic acid . She was also given Inj. Filgrastim 300 mcg for 2 days. For oral ulcers,she was started on sucralfate with oxetacaine syrup which provided transient relief and was also initiated on antibiotic (Doxycycline 500 mg OD) empirically. She was clinically stable with treatment and hence was discharged.

CASE 3

A 52 year old male, a known case of Psoriatic Arthritis, has accidentally taken 10 mg of Methotrexate twice daily, instead of weekly dose, for almost 7 consecutive days. He developed abdominal pain and loose stools (coffee colored) for the last 1 week along with oral mucositis. He gives a history of fever but not of any vomiting, myalgia, or dizziness. His initial laboratory tests showed bicytopenia (TLC-1400, Platelet- 0.48) and elevated CRP (52.6). On admission he was started on Inj. Leucovorin, folic acid and Inj. Filgrastim. For oral ulcers, he was started on sucralfate with oxetacaine syrup which provided transient relief and was started on antibiotic (Levofloxacin 500 mg OD + Cefaperazone Sulbactum 1.5gm BD) empirically. Despite initial measures he continued to have worsening of cytopenia and hence was subjected to G-CSF injection twice daily along with platelet transfusions. Even though he had melena, there was no Hb drop hence OGD/ colonoscopy was withheld. With daily colony stimulating factors, his counts improved and became clinically stable and hence discharged.

CASE 4

A 62 year old male came with complaints of multiple joint pain and swelling, multiple oral ulcers and multiple episodes of loose stools after intake of methotrexate for 4 days. He is a known case of Rheumatoid Arthritis and was initiated on MTX 5 days back. On routine examination he was found to have severe neutropenia (TLC : 700) thrombocytopenia (0.69) and anemia (9.2). Peripheral blood smear reports showed leucopenia with severe neutropenia, left shift in neutrophilic series with toxic granulation, thrombocytopenia and hence impression was pancytopenia. The serum methotrexate level of the patient was 0.13. He was initially started on antibiotics (Inj.Piptaz 4.5 gm IV Q6H X 4 days).He was also treated with proton pump inhibitors, probiotics, IV fluids, and other supportive medications. He was symptomatically better, hemodynamically stable on discharge.

CASE 5

A 63 year old male patient presented with c/o abdominal pain centered around epigastric pain for 2 days which aggravated after recent outside food intake, relieves on sitting. Patient also had c/o left sided shoulder pain, nausea and hiccups since present day morning. No history of fever, vomiting, loose stools, seizures, abdominal pain, nausea, breathlessness, chest discomfort, hematemesis or melena. He was a known case of psoriasis, chronic pancreatitis, CKD, Type 2 diabetes mellitus, systemic hypertension, dyslipidemia, benign prostatic hypertrophy, complex partial seizures. He was on regular medication with methotrexate 10 mg weekly. But took on consecutive days resulting in toxicity. Routine blood investigations were sent which showed pancytopenia with severe thrombocytopenia (TC - 3100, Hb-7.10, platelets - 0.05) and hematology consultation was sent and was advised to start on granulocyte colony stimulating factors and thrombopoietin receptor agonist. His pancreatic enzymes were also elevated (amylase - 133.7 , lipase - 322) and a gastro-medicine consultation was sent and was advised to give panlipase. 2 pints of platelets were transfused and his platelet count improved gradually. 1 pint of PRBC was also transfused in view of low Hb (6.9). Dermatology consultation sought out i/v/o hyperpigmented skin lesions and advised for topical drugs. On following days, patient was symptomatically better, vitals within normal limits, pain subsided, hence discharged

DISCUSSION

Methotrexate is a folate antagonist, used to treat a variety of neoplasm and autoimmune diseases. It inhibits dihydrofolic acid reductase, inhibits purine and thymidylic acid synthesis, which in turn interfere with DNA synthesis, repair and cellular replication. DNA synthesis eventually halts and cells can no longer replicate. It also inhibits rapid proliferation of epithelial cells in skin [4]. Polyglutamination with this drug occurs resulting in intracellular accumulation and hence risk of toxicity increases [5]. Severe dermatological reactions, GI toxicity (abdominal distress, diarrhea, GI hemorrhage), hematological effects like bone marrow depression with agranulocytosis, anemia, neutropenia, leucopenia, pancytopenia and thrombocytopenia, hepatotoxicity, infection, nephrotoxicity, neurotoxicity and pulmonary toxicity has been reported with methotrexate use. [6] Pancytopenia, an uncommon but possibly fatal side effect of MTX medication which can appear suddenly and without any prior symptoms.[7] Hematologic toxicity induced by low dose is rare with an incidence of 3% [8]. Although the exact reason for the hematologic toxicity brought on by MTX is still unknown, some theories propose that methotrexate's delayed elimination causes severe neutropenia and thrombocytopenia[9]. Due to an increased risk of toxicity, MTX should not be used more frequently than once per week and dose escalation should be done gradually by no more than 2.5 mg every 1 to 2 weeks[10]. Monitoring for toxicity should be done every 2 -4 weeks for the first 3 months of therapy. Most of the time, dose-dependent bone marrow damage is responsive to folic acid treatment. [1]

CONCLUSION

MTX induced myelosuppression is more common than expected and usually underreported. It is crucial that primary care physicians should be aware of these complications and recommendations, as the majority of these consequences can be diagnosed early on and even prevented. Patients receiving MTX medication should undergo routine liver function tests and complete blood counts, for detection of myelosuppression and preventing the effects of pancytopenia. As this medication mostly relies on the kidneys for excretion, renal function must also be monitored. It is also important to educate the patient about when to seek medical attention if they notice symptoms of bone marrow suppression. We recommend vigilance for this late and potentially fatal complication of MTX therapy. Pharmacovigilance should be actively involved in providing the knowledge on these adverse drug reactions and publishing it to spread the awareness.

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Conflicts Of Interest

There is no conflicts of interest

Abbreviations

MTX – Methotrexate
TC – Total count
Hb – Hemoglobin
CKD – Chronic Kidney Disease
CRP – C-reactive protein
G-CSF - Granulocyte-colony stimulating factor
DMARDS - Disease-modifying anti-rheumatic drugs
ESR – Erythrocyte sedimentation rate
HCQ - Hydroxychloroquine

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