METHOTREXATE INTOXICATION IN THE ELDERLY POPULATION: A REPORT OF TWO CASES

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Abstract
Methotrexate (MTX), a folate antagonist, is the anchor drug in rheumatoid arthritis (RA) treatment. The low dose is the most preferred therapeutic management, considered safe and generally well-tolerated in many rheumatic patients. Despite being rarely seen, life threatening severe toxicities such as bone marrow suppression may occur especially in the elderly population, most associated with certain risk factors. Management of this event may sometimes be challenging with relatively high mortality rates because of infectious complications. Treatment approach should be including folinic acid replacement, granulocyte-colony stimulation factor as required and antibiotics as well as supportive care. Herein, we report two elderly cases of MTX intoxication (one due to improper usage of MTX and the latter because of forgetting to take folate supplement) and discuss treatment options in the light of literature data.

Keywords: methotrexate; elderly population; toxicity; management

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Key Messages for Research and Practice

- Low dose methotrexate (MTX) can cause severe toxicity in patients with certain risk factors such as old age, decreased renal functions and concomitant drug use.
- Toxicity can be fatal if not recognized early and treated properly.
- Rescue therapy with leucovorin is vital in terms of decreasing hospital stay and mortality rates.
Introduction

Methotrexate (MTX) constitutes a cornerstone in rheumatology practice, particularly for the treatment of rheumatoid arthritis (RA), with low-dose MTX being the gold standard. The adverse reactions of MTX vary depending on the dosage and proper usage. At lower doses, MTX functions as an anti-inflammatory agent through the elevation of tissue adenosine levels, whereas high-dose MTX provides an antiproliferative cytotoxic effect [1]. Although the use of considerably higher doses for malignancies is widely considered to be associated with severe toxicities, low doses may lead to life-threatening adverse effects [2]. Most common adverse reactions during low-dose MTX include gastrointestinal disturbances, hepatotoxicity, dermatological manifestations (rash and alopecia) as well as alterations in blood cells. Some risk factors for the development of MTX intoxication have been described such as advanced age, renal impairment, hypoalbuminemia, inadvertent daily intake contrary to weekly prescription, inadequate folic acid supplementation, and polypharmacy [3]. Currently, no consensus or standardized guidelines regarding therapeutic approach of these patients are available. Existing literature highlights the utilization of folic acid, folinic acid/leucovorin rescue therapy, granulocyte-colony stimulating factor (G-CSF) if needed. Our aim with this case series is to attract attention to the importance of the proper usage of MTX in elderly population.

Clinical cases

Case 1

A 74-year-old female patient with a RA diagnosis manifested by skin rashes in her arms, decreased oral intake due to widespread oral lesions, abdominal pain, and diarrhea. Past medical history was remarkable also for diabetes mellitus, appendectomy, and right hip arthroplasty. Her medications included MTX, folic acid, prednisolone, and metformin. She stated that diagnosis of RA was made three months ago based on bilateral symmetrical arthritis in hands and high titers of autoantibodies (rheumatoid factor and anti-CCP) and the combination of leflunomide and prednisolone was given initially. Two months later, due to persistent alterations in liver function tests, MTX was prescribed with a dose of 7.5 mg per week per oral in line with 5 mg of folic acid supplementation once a week and daily prednisolone of 5 mg. On a detailed questionnaire, she mentioned using the drug on a daily basis and her symptoms started two weeks after starting treatment, showing gradual deterioration. Physical examination showed bullous skin lesions in both arms, widespread mucositis in the oral cavity with some of bullous and hemorrhagic, decreased skin turgor, tenderness on abdominal examination. Her vital signs were fever, normal blood pressure and increased heart rate. Laboratory findings were as follows: leukopenia (white blood cell count 1.7 x 10^3/µL), neutropenia (absolute neutrophil count 0.8 x 10^3/µL), thrombocytopenia (56 x 10^3/µL) and hemoglobin level 12.6 g/dL, CRP (15 mg/dL), serum creatinine level of 1.5 mg/dl. Peripheral blood smear was consistent with cytopenia, but no pathogenic cells. Blood, stool and urine culture examination were noncontributory and radiography investigations were normal. MTX was stopped and empirical treatment with piperacillin-tazobactam commenced due to fever and neutropenia in conjunction with intravenous folinic acid, oral nystatin and intravenous fluid administration. In the following days, neutrophil (absolute neutrophil count 0.1 x 10^3/µL) and platelet counts showed a marked decrease. Up on hematology evaluation, bone marrow examination demonstrated approximately cellularity of 15% with tri-lineage hematopoiesis and no blasts, therefore daily filgrastim administration was recommended. On day four, the antibiotic regimen was replaced with imipenem due to persistent fever and severe neutropenia. The patient started to show clinical and laboratory improvement on day 10 of hospitalization. She was discharged two weeks after initial admission.

Case 2

A 76-year-old male with a long-term diagnosis of RA presented with abdominal pain and painful blisters in his mouth. His past medical history showed that he was given sulfasalazine, prednisolone, MTX, leflunomide, etanercept and tocilizumab at different times during the last 20 years. He reported that he was recently started to take MTX again with the dose of 15 mg per week via subcutaneous route and folate replacement twice a week, however, forgot to take folate as recommended. Physical examination showed widespread mucositis in the buccal and oropharyngeal mucosa, white plaques on the tongue consistent with thrush and tenderness in the abdomen. Laboratory investigations revealed pancytopenia (hemoglobin of 7.0 g/dL, absolute neutrophil count of 6 x 10^3/µL and platelets of 9 x 10^3/µL), serum creatinine level of 1.96 mg/dL, and elevated acute phase reactants (CRP: 22.4 mg/dL). Diagnosis of MTX related intoxication was considered, and the drug was stopped. The peripheral blood smear examination was nonrevealing. Bone marrow biopsy showed
increased eosinophilic precursors, histiocytes but no hemophagocytes, with decreased cellularity. Leucovorin infusion (4x15 mg/day for 3 days) commenced together with intravenous fluid administration. During follow up, he developed fever and hematochezia. Empirical intravenous piperacillin-tazobactam was started in line with erythrocyte and thrombocyte transfusions as needed. Throughout this period, microbiologic examinations were non-revealing and radiologic evaluation was non-contributory for an infectious focus. Due to persistent fever, antibiotic regimen was revised with meropenem and granulocyte-colony stimulating factor (G-CSF) was initiated. Gastrointestinal bleeding stopped on day 7 and hematologic parameters returned to normal reference values on day 14. He was discharged 3 weeks after admission.

Discussion

Its proven efficacy and good tolerability in low doses have placed MTX as the first line option in RA and other inflammatory arthritis conditions. Gastrointestinal intolerance, alterations in liver function tests and blood cell counts are well-known, easily manageable adverse events. It is widely expected to assess any drug related toxicity in the context of various aspects: age of drug initiation (especially elderly population), renal functions, metabolic profile and/or comorbid conditions and concomitant drug usage which can alter the pharmacodynamic of the drug [4].

To date, data regarding severe toxicity related to low dose MTX in the rheumatology literature are of limited numbers with all of which recruited small numbers of patients [5-8]. The first report was a systematic review of case reports and data from prospective studies by Gutierrez et al. [3]. According to analysis of 70 cases in this study, most of them had impaired renal function, hypoalbuminemia, concurrent infection, and/or concomitant medication with more than 5 drugs, suggesting these as potential risk factors [3]. In Kivity et al, pancytopenia related to low dose MTX was reported in 78.5% among 28 patients. They have found that acute renal failure, hypoalbuminemia, concurrent use of drugs known to interact with MTX, and dose errors seem to be potential risk factors for toxicity [5]. Ajmani et al have also demonstrated similar results [6]. In elderly population, a previous report described decreased renal functions, alterations in pharmacokinetics of the drug by aging and alimentary problems as potential risk factors for MTX related bone marrow toxicity [9].

It is widely considered that severe toxicity is associated with the usage of higher dose. In Gutierres et al, the dose for fatal toxicity can be as low as 10 mg weekly [3]. Kivity et al have demonstrated that there is no correlation between serum MTX concentrations (studied in 20 patients) and the degree of cytopenia (either neutropenia (p=0.18) or thrombocytopenia (p=0.10)) [5]. Moreover, serum MTX concentrations did not show significant difference between the dead and surviving patients from MTX toxicity [5]. In our cases, we were not able to study serum MTX level in our institution.

In recent years, concomitant usage of certain drugs was found to increase MTX toxicity risk. Dalkılıç et al described certain concomitant drugs as a potential risk, with nonsteroidal anti-inflammatory agents (12/14) being the most common followed by omeprazole (3/14) [7]. This observation was supported by Kumar et al. They have recently demonstrated that toxicity is significantly associated with the usage of diuretic (6/12 vs 24/168), proton pump inhibitors (PPIs; 10/12 vs 70/168) and levetiracetam (2/12 vs 1/168) [8]. However, these results should be carefully handled as the study recruited only 12 patients. The reasons in our cases were as follows: improper usage of MTX and not taking folate supplementation. Management in the setting of severe bone marrow toxicity is challenging because the patients are prone to infectious complications due to suppression in the bone marrow. Intravenous folinic acid supplementation is the vital step in terms of rescue therapy in MTX related severe toxicity. Besides, it is sometimes needed to commence granulocyte-colony stimulating factor and empirical antibiotic administration as supportive agents [3,7]. In Dalkılıç et al, 93.5%, 87.1%, and 90.3% were treated with calcium folinate, filgrastim and antibiotic, respectively [7]. Twenty-seven patients (87.1%) were discharged after treatment [3]. Üsküdar Cansu et al have demonstrated that use of folinic acid/leucovorin either with or without G-CSF shortens the recovery time [2]. However, it is not well-identified whether combination of folinic acid/leucovorin and G-CSF has an impact on survival rate and hospital stay. Further studies with large numbers of patients are required to assess this approach.

Despite all therapeutic interventions, toxicity can be fatal with mortality being reported between 5 to 25% [3-7]. The most common cause of dead is infectious complications due to severe bone marrow suppression. Ajmani et al have shown that white blood cell count at admission was found to determine survival (P < 0.05) [6].
Our cases have fully recovered within two weeks of hospitalization.

Conclusion

In conclusion, severe toxicity is still a concern in the elderly population. Clinicians should be aware of identified risk factors related to the toxicity before initiating MTX in this patient group. The most vital step is to make sure the proper usage of the drug as well as folate supplementation.

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REFERENCES

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CONFLICT OF INTEREST
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