Methotrexate (MTX) Induced Pancytopenia - A Rare Serious Adverse Effect

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PRESENTATION OF CASE

A 65-year-old woman presented to us with complaints of fatigability and appearance of red spots on extremities since 6 days. She was a known case of rheumatoid arthritis since 5 years and was on tablet prednisolone 5 mg OD and tablet hydroxychloroquine 200 mg bid orally. Two months back she had exaggerated symptoms in the form of increased joint pains for which tablet methotrexate 7.5 mg was started weekly once and was increased to 7.5 mg bid (15 mg) per week 2 weeks back along with folic acid 5 mg per day.

Methotrexate (MTX) is a folate antagonist used to treat various malignancies, and autoimmune disorders including rheumatoid arthritis. It enters cell by an active cellular uptake and inhibits dihydrofolate reductase (DHFR) enzyme that converts dihydrofolate (DHF) to tetrahydrofolate (THF) affecting purine and ultimately DNA synthesis. Cell with capability of polyglutamylation like myeloblasts and lymphoblasts are most susceptible to the effects of MTX because polyglutamylation prolongs its intracellular presence.[1,2]

On Examination

Pulse - 112 / min, regular. BP - 100 / 66 mm of Hg, pallor was present. Icterus, cyanosis, clubbing, oedema feet were absent. JVP was normal. There were petechial spots in palate and oral cavity (Figure 1) and ecchymosis and petechiae in the upper and lower extremities. (Figure 2 & 3)

Lab Investigations

Hb - 5.2 gram %, TLC - 400 / mm 3, DLC - 12 % neutrophils, 68 % lymphocytes, absolute neutrophil count – 48 / mm^3, absolute platelet count – 11,000 / mm^3. Blood culture, urine culture were negative, CXR was normal. Serum procalcitonin was normal. Coagulation profile was normal. KFT and LFT were normal. A possibility of MTX induced pancytopenia was kept and the patient was treated with 3 units of PRC transfusions, 10 units of platelet transfusions, 3 doses of Granulocyte colony stimulating factor and IV antibiotics. Five days after therapy, her haemoglobin level became 9.8 gm %, TLC improved to 4,800 / mm^3 with 55 % neutrophils. MTX was stopped and she was discharged on 6th day.

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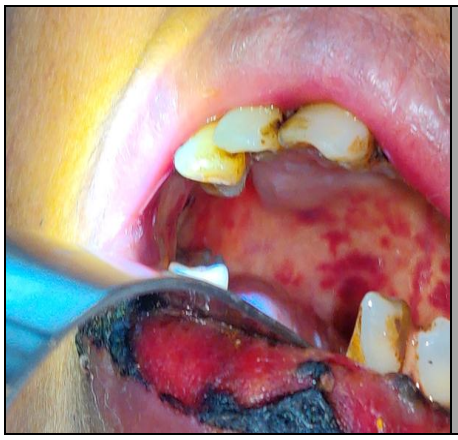

Figure 1. Petechial Spots on Palate and Bleeding in Oral Cavity

Figure 2. Bruising, Ecchymosis and Petechial Spots in Arm and Forearm

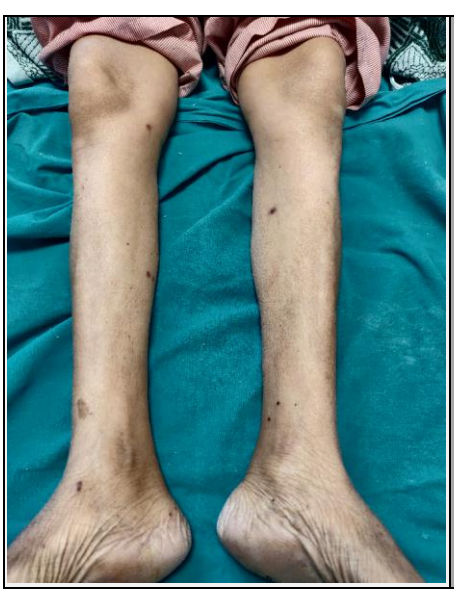

Figure 3. Petechial Spots in Lower Limbs

DISCUSSIONS

Adverse effects of MTX are pneumonitis, liver failure and myelosuppression as in this patient.[3] Oral mucositis appears early and later bleeding occurs. Renal impairment aggravates the toxic effects especially when NSAIDs are concomitantly used.[2] Routine blood count should be done every four to eight weeks.[4] Concomitant administration of folic acid (1 to 3 mg / day) decreases the frequency of toxicities.

In elderly patients aged more than 65 years, initial doses should be around 5 to 7.5 mg / wk. and should not exceed 20 mg / wk. Dosage adjustments for CrCl should be done and MTX should not be prescribed when CrCl is less than 10 mL / min. MTX dose should be gradually increased by no more than 2.5 mg every 1 to 2 weeks. In this case the dose was increased rather fast. Monitoring for toxicity should be done every 2 to 4 weeks for the first 3 months.[5] Bone marrow toxicity is dose dependent but overt pancytopenia is very rare. According to a review, clinically significant pancytopenia was found in 1 % to 2 % of RA patients on MTX therapy.[3]

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