Methotrexate induced Pancytopenia in a Patient of Rheumatoid Arthritis: A Case Report

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Introduction:

Methotrexate is the commonest disease modifying antirheumatic drug (DMARD) used in the treatment of rheumatoid arthritis (RA). It may be prescribed as monotherapy, or in combination with other DMARD or biological agents. In methotrexate treated RA patients, the prevalence of haematological toxicity, including leucopenia, thrombocytopenia, megaloblastic anæmia and pancytopenia is uncommon and is estimated to be less than 5%[1]. The extent of pancytopenia, a serious and unpredictable adverse effect of methotexate, may be underestimated. A case of RA patient presenting with methotrexate induced pancytopenia due to inadvertent dosing of the drug is reported here.

Case Report:

A 70-year-old man diagnosed case of RA for 1 year who was on combination therapy of DMARDs viz. methotrexate (15mg/week with folic acid supplementation), salfasalazine (1gm twice daily) and hydroxychloroquine (200mg once daily) for 1 month. On routine follow-up methotrexate dose was raised to 20mg per week. He came back after 2 weeks with complaints of painful eruptive rashes all over the trunk (Fig 1), bleeding gum and melaena for 4 days. On further enquiry there was a history of daily intake of methotrexate 20 mg for 12 days continuous by mistake.

On examination, the patient looked weak, pale and there was active bleeding of gum and throat. Oral candidiasis was present, and the urine output was normal. There were multiple eruptive rashes present all over the trunk both anterior and posteriorly. Blood pressure was 110/70mm Hg with a pulse rate of 90/minute. Chest, cardiovascular, and abdominal examinations were normal clinically.

On investigation, Hb-9gm/dl, TLC-2300/ cumm, DLC N59L37M4E0, ESR 5mm/1st hour, platelets 12,000 / cumm (severe thrombocytopenia), RBC 2.91 million / cumm, MCV 91, RBC morphology-normocytic, normochromic. Liver function test and kidney function test were normal.

Bone marrow examination revealed reduced erythropoiesis with many megaloblasts, suppressed myelopoiesis with markedly suppressed megakaryopoiesis consistent with features of bone marrow suppression (Fig 2, Leishman, x1000).

All ongoing DMARDS were stopped immediately. The patient was given supportive treatment with IV fluid infusion and daily transfusion of platelet concentrate. Antibiotic coverage with systemic antifungal therapy was started and recombinant granulocyte colony stimulating factors (G-CSF) i.e filgrastim 300 µgm subcutaneous injection was given daily for 5 days. Oral hygiene was maintained with antiseptic mouthwash. Packed red blood cell supplement was given from third day of admission besides platelet concentrate because of reducing haemoglobin concentration by third day of admission (i.e. 6.8 gm/dl). Peripheral haematological examination became normal with improvement in general condition after 2 weeks of admission, and patient was kept on follow-up programme for treatment of RA.

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Discussion:

Pancytopenia, a rare but potentially fatal complication of methotrexate therapy, may develop suddenly without any warning signs. It can occur early within 1–2 months of starting methotrexate, independently of dose and route of administration, this type of toxicity is called idiosyncratic. More commonly, however, it occurs late, suggesting a cumulative effect[2]. Risk factors for this cumulative toxicity include use of the drug in the setting of renal insufficiency, folic acid deficiency, acute infection such as parvo virus infection, dosing errors such as daily therapy, and concomitant use of selected drugs including probenecid and cotrimoxazole[1].

Methotrexate by its action as a folic acid antagonist, blocks the synthesis of purines and pyrimidines by inhibiting several key enzymes. The half-life of methotrexate in the serum is in the range of 6 to 8 hours after administration of the drug, and methotrexate is undetectable in the serum by 24 hours. Once taken-up by cells, methotrexate is metabolised to polyglutamate derivatives. Methotrexate polyglutamates (MTXglu) are stored in the tissues, including liver and erythrocytes, for long periods[3]. The estimated median half-life of MTXglu is around 3 weeks (range 2-4 weeks)[4].

The accumulation of MTXglu in the tissues viz liver, erythrocytes, etc reduces the polyglutamation of natural folates and may account for the chronic toxicity associated with methotrexate in patients of RA taking this drug[5].

Exposure to prolonged suprathreshold concentration of methotrexate is responsible for the toxic effect of this drug on tissues rather than achieving the peak level of the drug at one time. Lim *et al*,[6] in their review of 25 cases of methotrexate induced pancytopenia, observed that daily dosing of the drug had enhanced toxic affect than weekly dosing. In their case series, 1 patient had reportedly taken 2.5mg methotrexate daily for 6 days and 5mg on the 7th day of the week making a total intake of 20mg. The patient had been reported with enhanced toxicity. Kar and Ghosh[7] also reported a case of methotrexate induced pancytopenia in a patient of RA taking methotrexate 2.5mg daily unsupervised for ten weeks.

We have observed the enhanced toxicity of methotrexate by inadvertent daily intake of the drug in the present case, with the patient taking 20mg methotrexate daily for 2 weeks leading to accumulation of suprathreshold concentration of the drug in the tissues leading to stomatitis with bleeding gums and oropharyngeal mucositis with pancytopenia with possibility of mucositis in gastro-intestinal tract.

The management of methotrexate induced pancytopenia is in line of supportive treatment. Stopping of the drug, then supportive treatment with fluid rehydration, nutritional status improvement, blood and its components transfusion is important, along with antibiotic and antifungal coverage. Careful maintenance of skin hygiene, good dental care, and rectal hygiene is essential.

Folinic acid (leucovorin) should be given in a suspected methotrexate toxicity. It should be administered at a dose equal to methotrexate dose every 4 to 6 hours until there is no detectable serum level of methotrexate. But folinic acid is most effective when administered within 24 to 48 hours after the last dose of methotrexate[1]. After this folinic acid is ineffective to counteract methotrexate toxicity since cellular uptake of methotrexate is already finished.[3] For this reason our patient was not given leucovorine therapy as the patient reported to us with the drug toxicity due to daily inadvertent consumption of the drug.

Methotrexate being weak acid is poorly water soluble at low pH and may precipitate in the kidney during and after high dose bolus infusion. The subsequent nephrotoxicity decreases the elimination, and may increase the toxicity. For this reason, pre- and post infusion hydration and urinary alkalinisation are routinely used in case of high bolus dose methotrexate infusion to minimise renal toxicity from methotrexate precipitation in the kidney tubules[8]. But here in our case the toxicity was due to daily cumulative effect and so hydration and alkalinisation was not considered.

Recombinant growth factors like granulocyte colony stimulating factor (G-CSF) or granulocyte macrophage colony stimulating factor (GM-CSF), and recombinant erythropoietin (rhu EPO) have enabled more specific management with improved outcome in the pancytopenia treatment[9]. Recombinant human G-CSF, acts on hematopoietic cells to stimulate production, maturation and activation of neutrophils. These recombinant growth factors are usually used in treatment of leucopenia from different causes[10]. It is also reported to be effective in management of methotexate induced pancytopenia[11].

Conclusion:

The hepatoxicity of methotrexate is well known and established. But the more fatal condition methotrexate

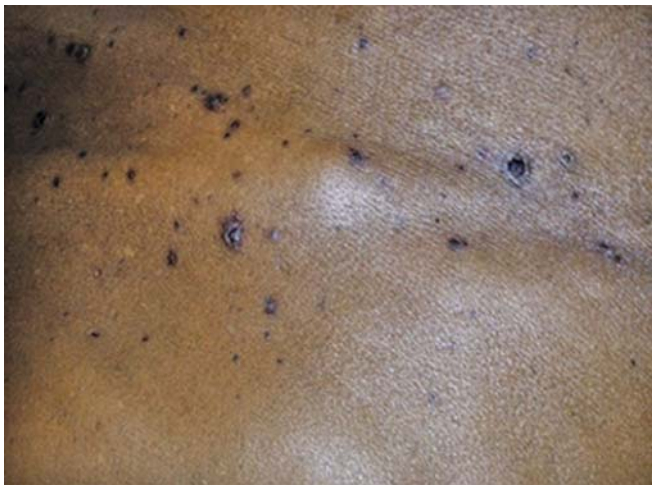

Fig 1- *Showing Petechial Skin Haemorrhage on the Trunk of Patient*

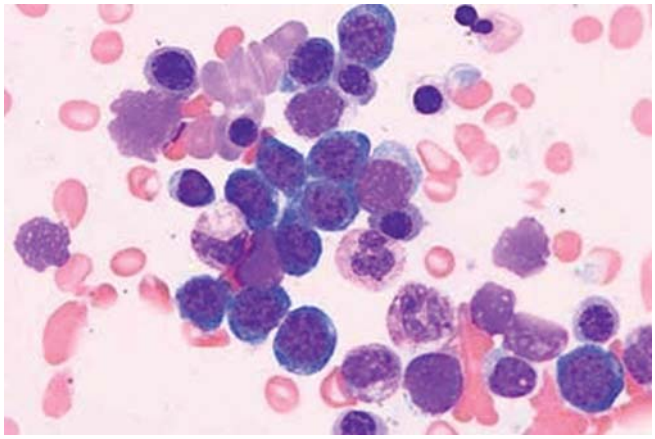

Fig 2- *Showing Decreased Cellularity with Features of Megaloblastoid Erythropoiesis, Suppressed Myelopoiesis Consistent with MTX induced Bone Marrow Suppression*

induced pancytopenia might be more common than expected and is probably under-reported. The methotrexate induced pancytopenia following wrong daily dosing of the drug causing a cumulative effect can lead to serious complication including death. Vigilance is required to identify this and prompt supportive management is essential to avoid fatal complications. Proper counselling about dosing of the drug is important in patients taking the drug to avoid such complications. Supportive treatment with blood and its components, recombinant growth factors like G-CSF, GM-CSF and rhu EPO along with measures for prevention of infections are the mainstay of management for methotrexate induced pancytopenia.

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