PANCYTOPENIA WITH THE FIRST DOSE OF METHOTREXATE IN A PATIENT WITH PSORIATIC ARTHRITIS

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Abstract: A 21-year-old Muslim male developed severe pancytopenia, fever and oral mucositis after 4 days of first dose of low-dose methotrexate (MTX) therapy for psoriatic arthritis. He did not have any of the known risk factors for MTX toxicity like renal insufficiency, folate deficiency or hypoalbuminemia. With the prompt use of broad-spectrum antibiotics and leucovorin rescue, he recovered completely in two weeks time. Severe pancytopenia associated with low-dose MTX therapy is a potentially serious complication that may occur at any time during therapy. Commonly, MTX induced pancytopenia occurs late suggesting a cumulative effect, however, it may occur early, as was seen in the present case, possibly reflecting an idiosyncratic reaction. Case is presented to sensitize the physicians regarding idiosyncratic reaction to MTX.

Key words: Neutropenia, Renal insufficiency, Idiosyncratic reaction

In methotrexate (MTX) treated rheumatoid arthritis (RA) patients, the prevalence of hematological toxicity is estimated to be 3%1. Pancytopenia is defined as total leucocyte count below 3500/mm$^3$, hemoglobin below 10g/dl and platelet count below 1,500,000/mm$^3$. Serious pancytopenia has been reported to occur in around 1.4% of the cases2. Usually, it is dose dependent but occasionally it may be idiosyncratic. Herein we present one such case of psoriatic arthritis that developed severe pancytopenia following administration of the very first dose of methotrexate.

Case summary

A 21-year-old Muslim male, with asymmetric polyarthritis and spondylitis of 15 years duration, presented with history of erythematous silvery plaques all over the body and worsening of joint pains for 6 weeks and fever and oral mucositis for 10 days duration. Two weeks back, he was initiated on indomethoacin 75 mg/day, methotrexate (MTX) 7.5 mg/week along with prednisolone 10 mg/day, elsewhere. He received only one dose of MTX. There was no family history of seronegative spondylo arthropathies. Examination showed asthenic built male with thoracic kyphosis with normal vitals and temperature of 102°F. He had disseminated silvery white plaques all over the body including the face and scalp, active arthritis of left ankle, bilateral knee, wrists and proximal interphalangeal joints, modified Schober’s of <1cm, finger floor distance of 54 cm, occiput-wall distance of 24 cm and chest expansion of 1.3 cm. There were flexion deformities (15-20°) of both the knee and ankylosis of the left wrist. Rest of the general and systemic examination was unremarkable.

Laboratory investigations revealed hemoglobin 6.5gm/dl, normocytic normochromic red cell morphology, MCV 89 fl, total leukocyte count 1,300/ml with neutrophils 13%, lymphocytes 62%, eosinophils 7%, monocytoid cells 18% and platelet count of 0.5 lacs/ml. Malarial parasite were not seen in the peripheral blood smear. Liver and renal function tests, serum protein and albumin, urinalysis, radiograph of the chest and ultrasound of the abdomen were normal. Multiple cultures of blood, throat and urine were sterile. Bone marrow examination showed maturation arrest in the myeloid series of cells. On radiography there was pancarpal fusion of the left wrist and erosions at the metacarpal heads, bilateral grade III sacroiliitis with loss of joint space in the left hip and loss of height of the D6 vertebra posteriorly with sclerosis of margins. A diagnosis of psoriatic arthritis with idiosyncratic reaction to methotrexate leading to pancytopenia was made and he was treated with ceftazidime amikacin and leucovorin rescue (15 mg IVI 6 hourly for 3 days). Fever subsided in 3 days time and leucopenia and thrombocytopenia recovered completely by 14th day. However, mild anemia persisted.
Discussion

Our case was unique in the sense that firstly, psoriasis developed after 15 years of arthritis and spondylitis; secondly with the very first dose of low dose methotrexate he developed severe pancytopenia.

Two recent reports, one from Finland and another from United Kingdom reported their data about the incidence of MTX related pancytopenia in patients with various rheumatic diseases but predominantly with rheumatoid arthritis. In the Scandinavian study, there were 18 cases with pancytopenia, 14 had severe infections (septicemia, pneumonia and pyelonephritis), 12 had significant bleeding manifestations and 8 patients died due to infections. In all the cases pancytopenia started abruptly. Cumulative dose of MTX varied from 12.5 to 3000 mg. Serum creatinine concentration prior to pancytopenia was available in 12 cases and 8 patients had deranged renal functions. Authors identified renal dysfunction, presence of infection, folic acid deficiency and advanced age as factors predisposing to hematological toxicity. Duration of leucopenia was found to determine the outcome of patients in this study. In the study from United Kingdom, there were 25 patients with MTX related pancytopenia, 11 were receiving folic acid supplementation prior to pancytopenia and there were 8 deaths. Besides already known factors predisposing to MTX related pancytopenia, dosing errors in 18 and polypharmacy in 15 patients were conspicuous.

In a review of 70 patients with pancytopenia related to methotrexate therapy, renal dysfunction, hypoalbuminemia, low folate levels, concomitant infection, advanced age, concomitant use of >5 drugs, and lack of folate supplementation were identified as risk factors. Patients with mucositis and neutropenia have a higher risk of septicemia. Few cases were precipitated by concomitant use of drugs especially, Trimethoprim-sulfamethoxazole and sulfasalazine.

Our patient did not have any of the above-mentioned risk factors or drug interactions. Development of severe pancytopenia following the first dose of MTX points towards an idiosyncratic reaction. With the expanding field of pharmacogenomics, it is possible to predict the efficacy or toxicity profile of a particular drug for an individual patient. For MTX toxicity, C677T polymorphism of the methylene tetrahydrofolate reductase (MTHFR) gene has been identified as a risk factor for elevated alanine transaminase values in RA patients. Similar studies on C677T polymorphism on the toxicity of MTX showed that homozygous patients had increased oral mucositis and delayed platelet recovery or neutropenia.

In another study, 1298CC polymorphism of the MTHFR gene was found to be protective, while the 1298AA genotype was associated with adverse effects despite higher doses of folate supplementation.

Though idiosyncratic reactions cannot be predicted beforehand vigilance and prompt identification of the toxicity and treatment with leucovorin rescue and antibiotics may prevent an adverse outcome.

References