Case Report

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Methotrexate Induced Severe Bone Marrow Suppression with Low Dose

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ABSTRACT

Methotrexate is a first line drug for Rheumatoid arthritis. It is also being used for various autoimmune diseases and in cancer as a chemotherapeutic agent for decades. It works as a folic acid antagonist in cancer. However it works by inhibiting enzyme AICAR and thereby raising intracellular adenosine in autoimmune diseases. Adverse effects can range from mild gastrointestinal disturbance to severe life-threatening pancytopenia, hepatotoxicity, infection and lymphoproliferative disorders requiring hospital admission. Before initiating this drug physician should be aware of its potential harmful effects especially in old and co-morbid patients. Complete blood count, Liver and kidney function test and serology are essential before considering this drug.

Keywords: methotrexate; bone marrow suppression; rheumatoid arthritis.

INTRODUCTION

Methotrexate is an FDA approved folic acid antagonist commonly prescribed for various autoimmune diseases and malignancies. In cancer it acts as an antifolate antimetabolite. After entering the cell via human reduced folate carriers it inhibits the enzyme dihydrofolate reductase necessary for the conversion of dihydrofolate into tetrahydrofolate. As tetrahydrofolate has an important role in nucleotide synthesis, reduced production of it ultimately suppresses active cell division.

However in autoimmune disease it increases the level of adesoine inside the cell by inhibiting enzyme AICAR thereby repressing T-cell activation and down-regulation of B cells.[1] Despite the introduction of newer therapeutic agents like biologics methotrexate still remains the mainstay of treatment in rheumatoid arthritis. Major factor for widespread use of methotrexate as a disease modifying agent is its high efficacy and tolerability. Side effects are not uncommon in methotrexate therapy. Gastrointestinal manifestations including nausea, vomiting, mucosal ulcers, and loss of appetite are common and easily manageable. However hepatotoxicity, bone marrow suppression, pancreatitis, malignancy(lymphoproliferative disorders), infections, interstitial pneumonitis and renal failure are some other notable serious side effects which can be potentially life threatening.[2] In this case report we have presented a case of 83

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years old male with rheumatoid arthritis who developed severe bone marrow suppression after initiating treatment with single dose of methotrexate (Total cumulative dose of 15mg).

CASE PRESENTATION

A 83 years old male brought by his daughter with chief complaint of multiple joint pain in small joints of his hands (symmetrical polyarthritis) and knee along with fever, shortness of breath and pitting edema in bilateral legs. His blood pressure was 130/80 mmHg, Pulse 79/min, respiratory rate 23/min, Spo2 97%.He gave a history prolonged NSAID use for his unresolved joint pain.

On examination wheeze and mild splenomegaly was found. Investigations were requested and revealed positive CRP and RA. However, his anti CCP and ANA was negative splenomegaly with multiple splenic angiomas, Renal cortical cyst and grade 1 prostatomegaly in ultrasonography abdomen and pelvis and moderate aortic stenosis and regurgitation with mild mitral regurgitation and tricuspid regurgitation in Echocardiography was detected. Other blood investigations including complete blood count, liver and kidney function test, thyroid function test were found to be within normal limit. Based on his presentation and laboratory findings a diagnosis of Rheumatoid Arthritis was made and Methotrexate 15 mg/week, Hydrochlorothiazide 200 mg OD and Etoricoxib 90mg along with tapering dose of 15mg Prednisolone and 5mg folic acid was commenced and advised for follow up in 1 month.

After 9 days of initiating methotrexate patient was presented to OPD with complaints of painful mouth ulcer odynophagia, weakness and fever of 102F. Vitals were stable However, Blood investigation revealed TLC 530/ cmm (N 17%,L 78%,M 2%,E 2%,B 1%), Hb 9.9gm/dl, PCV 29.4, RBC 3.3 million/cmm, Platelet count 15000,CRP 130,ALT 80U/L, Creatinine 1.3. A diagnosis of Methotrexate induced Bone marrow suppression with Neutropenic fever was made and patient was admitted to ICU. He was managed with blood products-transfusion, antibiotics and IV fluids. He showed gradual improvements of his symptoms and was discharged on on 15 Nov 2021 with oral amoxiclav, hydroxychloroquine, leflunomide, fluconazole, and Vitamin B12 after 8 days of hospital admission.

DISCUSSION

Methotrexate is now the most popular drug worldwide for the treatment of rheumatoid arthritis. Low dose weekly methotrexate at the dose of 10- 25 mg/week as a single agent or in combination with other drugs is shown to be more effective.[3] Among various side effects pancytopenia is one that can be very serious and sometimes life threatening especially in old age. Pancytopenia in methotrexate is dose and duration dependent with over all manifestation of 1.4 % with slight female predominance (62.51%). It is more common in old aged population (59% patient above 60 years).[4] Symptoms of Methotrexate induced pancytopenia usually begins with stomatitis and later manifest as pancytopenia.[5]

Because of its potential life threatening side effects specially in old and comorbid patients a pre methotrexate evaluation is necessary before initiating medical therapy. This evaluation involves the blood tests, which include: complete blood count with differential, renal function tests include the serum creatinine, blood urea nitrogen, and urinalysis, and liver function tests include serum bilirubin, AST, ALT, serum albumin, hepatitis serology. HIV tests are also necessary, and if appropriate, the clinician should obtain a chest radiograph as well. [6]

CONCLUSIONS

Methotrexate is a first line drug in managing rheumatoid arthritis. It is one of the drug with high potency and tolerability. However its beneficial effects come with some potential harmful effects. Minor side effects can be managed easily but some serious side effects may need hospitalization and appropriate management. Before initiating this drug especially in geriatric population and in those with preexisting comorbidities physician should make clinical decision based on risk reward ratio. Blood tests including blood count, renal function test, liver function test and serology is highly advisable before starting methotrexate.

PATIENT CONSENT: A written consent was taken from patient for publication.

Conflicts of interest: None declared

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