CASE REPORT

LOW–DOSE METHOTREXATE (MTX) INDUCED PANCYTOPENIA AND MUCOCUTANEOUS ULCERATIONS: A CASE REPORT OF RARE SERIOUS ADVERSE EFFECT.

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ABSTRACT:

Methotrexate (MTX) is a folate analogue having chemotherapeutic, immunosuppressant and antiinflammatory effects which is commonly used in rheumatoid arthritis (RA), psoriasis, lupus, sarcoidosis and eczema. The development of MTX toxicity are also associated with various risk factors. We present a case of a 54year old female with pancytopenia causing severe neutropenia, multiple oral mucocutaneous lesions and requiring intravenous antibiotic therapy, platelet transfusion as a result of continuous usage of low dose MTX for rheumatoid arthritis.

KEYWORDS: Methotrexate, Immunosuppressant, Anti-Inflammatory, Pancytopenia, Mucocutaneous lesions.

INTRODUCTION:

Methotrexate is an antimetabolite, antiinflammatory and an immune modulating drug. It is a folate analogue which inhibits dihydrofolate reductase (DHFR), an enzyme that catalyzes dihydrofolic acid to tetrahydrofolic acid and as a result it inhibits the synthesis of folic acid, which is indispensable essential for DNA synthesis, repair and methylation. MTX reduces cell proliferation and inhibit proliferation of B,T lymphocytes, cytokine synthesis and methyltransferase activity.[2,4] Initially it was developed to treat certain types of cancer, hence high dose of the drug acts as a chemotherapeutic agent.[11] At lower doses, it is usually used disease-modifying anti-rheumatic drug (DMARD) for the treatment of rheumatoid arthritis to control chronic inflammation.[4,8]

Methotrexate can develop toxicity on tissues especially with high proliferative capacity such as mucosal layer, gastrointestinal tract and bone marrow.[9] The prevalance of MTX-induced hematological toxicity and pancytopenia in patients treated with rheumatoid arthritis is estimated to be 3% and 1.0-1.4% respectively. Among the adverse effect nausea, vomiting, urticarial, pruritus, reversible alopecia, ecchymosis are commonest and in severe cases mucosal erosions, reactivation of phototoxic responses, toxic epidermal necrolysis, pancytopenia, skin erosions and ulcerations are seen.[5,6] MTX-induced pancytopenia is usually dose-dependent, but occasionally

it may occur by an idiosyncratic reaction. However, the prevalance and the exact mechanism of idiosyncratic pancytopenia induced by MTX is unkown.[9] It is shown that low dose of methotrexate administration may cause severe pancytopenia and sometimes even fatal, in such cases oral mucositis and fever are the precursors of hematological toxicity.[9] Here we report a 54 years old female patient of RA who had developed severe pancytopenia and oral mucocutaneous ulceration.

CASE REPORT:

A 54 year old female patient was admitted under emergency unit with complaints of mouth ulcers associated with difficulty to open mouth, fever and decreased appetite since seven days. The patient has a history of rheumatoid arthritis since 3 years and on Tab. Methotrexate 15mg (once in a week), Tab. Leucovorin 15mg, Tab. Leflunomide 20mg and Tab. Cholecalciferol 1gm. She had no history of hypertension, type 2 diabetes mellitus, hyperthyroidism. On the day of admission patient was conscious, oriented with a pulse rate of 96 bpm, blood pressure of 140/80 mmHg and respiratory rate was 20 cpm. Oral cavity examination showed reddish inflamed multiple mucocutaneous lesions without bleeding, chapped dry lips and also scar like lesions seen in upper limbs. Laboratory testing on admission showed pancytopenia (red blood cell 9.0gm/dl, total count 270 cells/cumm, platelet count 0.21 lakhs/cumm), neutropenia (4%). Her liver function tests (LFT) were significantly elevated and renal function tests (RFT) were quite normal. Testing for HIV, hepatitis, dengue viruses were negative. Patient was further referred to dermatologist for the opinion and they confirmed to be cheilitis.

Based on characteristic history, clinical presentation of multiple mucocutaneous lesions with pancytopenia and increased liver enzymes, methotrexate toxicity was suspected due to

continuous intake of it. Hence, its dose was reduced and was administered. The treatment advised to patient includes Inj. Combitum (Ceftazidine + Tazobactum) given for bacterial infection, Inj. Walcobal forte (Nicotinamide + Cynacobalamin +Folic acid) in 100ml NS given for vitamin B12 deficiency, Inj. Filgrastim helps to treat neutropenia, Tab. Leflunomide and Tab. Methotrexate are given to treat inflammation and rheumatoid arthritis, Tab. Leucovorin (Folinic acid), 1 pint of platelet transfusion. Therefore in this case, it was seen patient developed multiple oral mucocutaneous lesions with pancytopenia resulting severe neutropenia due to development of acute toxic side effects exhibited by methotrexate.

DISCUSSION:

Methotrexate is a dihydrofolate reductase inhibitor used in low weekly doses is a first-line therapy for inflammatory diseases such as psoriasis and rheumatoid arthritis and also in the management of SLE due to its effectiveness, low cost and ease of use. It is generally administered at doses ranging from 7.5-25mg/week.[1,5] It was first approved by US Food and Drug Administration in the year 1999. A variety of risk factors were associated with MTX toxicity such as renal dysfunction, hepatotoxicity, hypoalbuminemia, low folate levels, concomitant infections, increased age, and concomitant use of more than five drugs and poor nutritional.[1,3] This drug is contraindicated in any patient with e GFR < 30 ml/min. In this case, the risk factors observed were increased age, deprived nutrition. Methotrexate has numerous side effects such as hyperuricemia, gingivitis, leucopenia, and thrombocytopenia, in rare circumstances, leads to cutaneous ulceration. [6] Even low doses of methotrexate can cause early-onset pancytopenia and skin ulcers.[6] It is advised to give folic acid with MTX as a prophylactic measure to prevent drug toxicity.[1]

The findings from other cases [2,5], our patient suffered from both pancytopenia and ulcerations.[2] The adverse effects of methotrexate may be classified as type A, dose dependent (methotrexate toxicity); type B, idiosyncratic (e.g. methotrexate pneumonitis); type C, resulting from long-term therapy but anticipated, based on overall drug exposure (e.g. methotrexate hepatotoxicity); and type D, delayed effects persisting even after drug discontinuation (e.g. methotrexate in the first trimester of pregnancy, inducing teratogenesis). Cutaneous ulceration due to methotrexate is regarded as a hazardous side effect and a rare Type A occurrence.[6]

Haematological toxicity induced by MTX can be managed by stopping or reducing the dose of that drug followed by supportive treatment to give adequate hydration, intravenous leucovorin, recombinant growth factors, transfusion of blood and its components along with antibiotics due to high risk of infection. The maintenance of, mucocutaneous and dental hygiene is also essential.[5] In our patient MTX dosage was reduced and was monitored, started on intravenous folinic acid. Additionally, granulocyte colony stimulating factor (G-CSF) was given in view of worsening leucopenia. Thereby severe thrombocytopenia and leukopenia was treated with platelet transfusion and injection Filgrastim. These findings were similar to other case study reported by Brunda et.al.

CONCLUSION:

Patients on MTX treatment should have routine liver function tests and complete blood counts (CBC) to identify myelosuppression and prevent the consequences of pancytopenia. As this medication mostly relies on the kidneys for excretion, renal function must also be monitored. It is crucial that primary care physicians are aware of these complications and recommendations, because the majority of these severe complications can be diagnosed early on and even

prevented. Various risk factors were also linked to the emergence of MTX toxicity. By careful monitoring and effective prevention, many of these adverse effects can be prevented**.** Additionally, it is crucial to inform the patient of the most typical poisoning signs and to report to the physician immediately.

CONFLICT OF INTEREST:

The author declares that there is no conflict of interest to disclose.

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