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Case Study *Medical research*

Methotrexate induced oral ulcer: a case report

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ABSTRACT

Methotrexate (MTX) is well known in the treatment of various neoplastic diseases and autoimmune disorders. Methotrexate is known as antimetabolite of the antifolate type. Prolonged use of low dose Methotrexate develop sores in gums, cheeks, and tongue. Folic acid supplements can be used to avoid such conditions. About 11-17% of patients receiving Methotrexate has been diagnosed as oral ulcer. In this case report we are discussing about Oral ulcer induced by Methotrexate.

Keywords: Methotrexate, Folic acid, Oral ulcer, Dihydrofolate reductase

INTRODUCTION

Methotrexate (MTX) is an antimetabolite which blocks intracellular DNA synthesis, it acts as a DHP reductase inhibitor [1] it can modulate the function of immune cells and reduce the production of cytokines like interleukins, tumour-necrosis factor, and interferon [2]. It was in 1999 where MTX was approved as an antirheumatic drug [3], used for the treatment of both benign condition's rheumatoid arthritis, psoriasis, atopic dermatitis, psoriatic arthritis, collagen vascular disease [4] and malignancies, Leukaemia, Non-Hodgkin's Lymphoma, cutaneous T cell lymphoma, choriocarcinoma [5]. Low dose MTX has been used as a disease modifying antirheumatic drug for Rheumatoid arthritis[6] whereas High doses MTX shows antiproliferative activity and is used for the treatment of cancer [7].
MTX is a folic acid and dicarboxylic acid analogue that inhibits dihydrofolate-reductase the key enzyme to produce tetrahydrofolates required for the synthesis of purines and pyrimidines [8]. Inhibition of DHFR prevents the reduction of folic acid to THF, reducing the nucleotide synthesis and homocysteine remethylation. Also, it directly inhibits other enzymes in the folate pathway, thymidylate synthetase required for pyrimidine synthesis and amino-imidazole carboxamide ribosyl-5-phosphate (AICAR) transformylase required for purine synthesis [9] Blockage of the folate pathway thus inhibits the synthesis of AMP, GMP, DNA, and RNA hence inhibiting the cell cycle [10]. This can cause folic acid deficiency and hence cause ulceration in mouth, as the accumulation of MTX is higher in mucosal epithelial cells than in bone marrow stem cells in the following case there is a clear example of methotrexate induced oral ulcer in a 75-year-old female patient.

CASE PRESENTATION

A 75-year-old female patient was admitted with complaints of oral ulcer for 5 days and decreased food intake. She had a

known case of Rheumatoid arthritis (RA) and Interstitial lung disease on treatment. On admission time the vitals of the patient were normal. Laboratory investigation showed elevated levels of WBC count (12400 cells/cumm), ESR (92mm/hr) and CRP (78.5).

She had a dermatology consultation and diagnosed the case as Methotrexate induced oral ulcer. No other skin lesions were present. The physician prescribed Folic acid 5mg once daily for 3 weeks, chlorhexidine mouth wash and candid mouth paint once daily for one week.

On the 2nd day patient had complaints of breathing difficulty hence prescribed Nebulization with Duolin (Levosalbutamol and Ipratropium Bromide) Q8H and nebulization with Budecort (Budesonide) twice daily. On 3rd day the ulcerative lesions were healing and had a dermatology consultation and advised to continue the same. The patient was admitted for 6 days for completing the course of antibiotic given and to observe whether the ulcer is curing.

She was treated with IV antibiotics, IV pantoprazole for treating gastric irritations, nebulization's to treat breathing difficulty and clearing the chest also folic acid, chlorhexidine mouth wash and candid mouth paint to decrease the intensity of mouth ulcer.During the discharge elevated levels of WBC, ESR and CRP was normal, vitals were stable and hence discharged.

Advice on discharge include Tab. Defcort (Deflazacort) 6mg once daily in the morning, Tab. Sazo (Sulfasalazine) 500mg twice daily, Tab. HCQ (Hydroxychloroquine) 200mg once daily in the morning, Tab. Folitrax (Methotrexate) 15mg weekly once (thursday), Tab. Qfol (Folic acid) 5mg once daily, Tab. Pantop (Pantoprazole) 40mg once daily in the morning before food, Tab. Augmentin (Amoxicillin and Potassium clavulanate) 625mg thrice daily for five days.

Table 1: Laboratory Investigations

LABORATORY DATA	VALUES
↓ HB	11 gm/dL
↑ ESR	92→37 mm/hr
↑ TOTAL COUNT	17270 → 12400cells/cumm
↓ SERUM SODIUM	127→135 mEq/L
↑ CRP	236→34.5 mg/L
URINE RE ALBUMIN	Nil
↑ PUS CELLS	14-16 → 3-4
↑ RBCs	1-2 → Nil
↑ EPITHELIAL	3-5 → 1-2

DISCUSSIONS

Rheumatoid arthritis is an inflammatory disorder characterized by joint inflammation, synovial proliferation, and destruction of articular cartilage. RA result from the dysregulation of humoral and cell mediated immunity. Immunoglobulins activate the complex system which enhances chemotaxis, phagocytosis, and release of lymphokines by mononuclear cells and are then presented to T lymphocytes. The activated T cells then produce cytotoxins and cytokines which stimulate further activation of inflammatory mediators. Activated B cells produce plasma cells which produce antibodies that result in the accumulation of polymorphonuclear leukocytes, these leukocytes release hydroxyl radicles, cytotoxins, oxygen free radicals which damages the synovium and bone. The release of vasoactive substances like histamines, kinins and prostaglandins occurs in the inflammatory site hence increases the blood flow and vascular permeability and it further causes edema, warmth, erythema, and pain at the site.

Methotrexate is an immunosuppressive drug which is used to treat RA. This dihydrofolate reductase inhibitor has prominent immunosuppressant and anti-inflammatory property. The beneficial effect of MTX in RA is probably related to inhibition of cytokine production, chemotaxis and cell mediated immune reaction. Methotrexate is preferred for initial treatment in RA because the onset of symptom relief is relatively rapid i.e., 3-6 weeks. Methotrexate is now the DMARD of first choice and the standard treatment for RA. The major drawback while using methotrexate is folic acid deficiency hence concomitant folic acid may reduce the adverse effect without loss of efficacy.

Methotrexate induced oral ulcer is seen in up to 11%-17% of RA patients due to folic acid deficiency. Here the patient was not given concomitant folic acid and due to the lack of folic acid consumption, it leaded to oral ulcer and decreased food intake due to pain and difficulty. Diagnosis is done by physical examination which showed painful sores in the inner lips, tongue, roof of the mouth, throat, gums, and cheeks.

The major treatment for methotrexate induced oral ulcer is giving folic acid supplements to the patient and providing ointments, creams, or mouth paints to cure the ulcer lesions in the mouth. Here the patient was treated with 5mg Folic acid, chlorhexidine mouth wash, candid mouth paint and Metronidazole oral gel.

CONCLUSION

It was in 1999, Methotrexate was approved as an antirheumatic drug. About 60,000 patients were using MTX and was having a very positive response. Mouth ulcers, cirrhosis and hepatitis are the major effect caused by prolonged use of Methotrexate, so concomitant folic acid administration and monitoring of

liver function test periodically is important to stay healthy. More than discontinuation of MTX, the concomitant use of folic acid daily is advised. RA can occur to any generation and the first line therapy is Methotrexate, while given in combination also. Also, the increased screening for oral signs and symptoms is also beneficial in preventing ulcers. So, to avoid the negative symptoms due to MTX is taking prophylactic treatment and doing periodic checkups.

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