Original Research Paper

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Emergency Medicine

PRESCRIPTION DICTUM; CASE REPORT ON UNINTENTIONAL OVERDOSE OF METHOTREXATE

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ABSTRACT Methotrexate is used to treat a range of adult and childhood cancers. High dose methotrexate can cause significant toxicity, including acute kidney injury (AKI) in 2%-12% of patients. Crystallization of methotrexate deposits in renal tubules causing nephrotoxicity causing decreased clearance and increasing level of serum methotrexate causing myelosuppression, mucositis, dermatologic toxicity, and hepatotoxicity. Monitoring RFT, LFT serum creatinine, urine output, and serum methotrexate concentration are closely monitored. Treatment includes adequate hydration, urinary alkalinization, and leucovorin rescue to prevent complications. When delayed methotrexate excretion or AKI occurs despite preventive strategies, increased hydration, high-dose leucovorin, and glucarpidase are usually sufficient to allow renal recovery without the need for dialysis. Refractory cases require hemodialysis if the patient not improving to the above-mentioned strategies.1

KEYWORDS : Methotrexate, nephrotoxicity, leucovorin.

INTRODUCTION

In normal clinical practice methotrexate (folic-acid antagonist) is widely used. Educating the patients is very important regarding the dosing, frequency, and adverse events they must watch out for. Adverse effects include bone marrow suppression, hepatic or renal dysfunction, gastrointestinal distress, mucocutaneous damage, and neurotoxicity. The toxicity usually occurs rapidly and leads to severe neutropenia, sepsis, and advanced renal failure that are difficult to manage[2]. The use of methotrexate has been markedly increased in the field of dermatology due to its anti-proliferative and anti-inflammatory properties. Apart from the original property of immune-modifying agents, it is used for the treatment of steroid-resistant inflammatory diseases. This case report portrays a 52-year-old man who took methotrexate for psoriasis at higher doses over a period of 3 months more than prescribed by his dermatologist, who later presented to our emergency department with worsened skin lesions and oral ulcers associated with dysphagia and persistent high-grade fever.

Low-dose methotrexate (MTX) is one of the classical agents and is still one of the most frequently used systemic treatments for psoriasis worldwide. Low-dose MTX is also effective in treatment of psoriatic arthritis. The mechanism of action is not fully understood, but MTX is suggested to act primarily as an anti-inflammatory and immunosuppressant drug. A favorable efficacy and safety profile has been established for MTX in a large number of clinical trials, as well as in common practice[3]

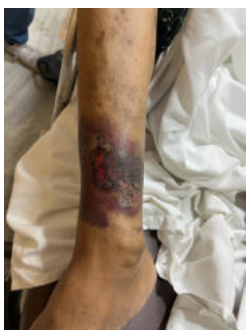

Figure 1 Psoriatic lesion for which patient started taking methotrexate

Antifolate methotrexate is widely used in the treatment of hematological malignancies. Even when given identical methotrexate doses, patients vary significantly in their response and pattern of toxicities and clinical manifestations vary in different patients attributed to genes involved in drug absorption, metabolism, excretion, cellular transport, and effector targets or target pathways. Pharmacogenomics is expected to bring individualized therapy with methotrexate. Major challenge to dissect out which of these have the strongest impact on efficacy and toxicity and hence should be the targets for intervention.[4]

Case Presentation

54 year old gentleman presented with fever for 5 days, lower lips ulcer for past 4 days with dysphagia (secondary to intra oral ulcers) and painful skin lesions appearing over bilateral upper and lower limbs, along with lesions over anterior abdominal wall and groin(as given below). He gives past history of being diagnosed with lichenified psoriatic type of lesion in (R) leg four months back for which he was prescribed Tab.Methotrexate 5 mg once weekly but he accidentally took it daily.

On examination-vitals stable. Blood investigations showed Pancytopenia (Platelet 5000, TLC-240, Hb-7.4), Serum methotrexate level-1.3 micromole/L (>1 –toxic level).

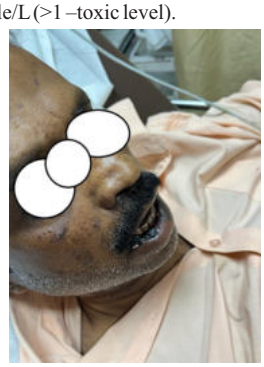

Figure 2 : Oral lesions

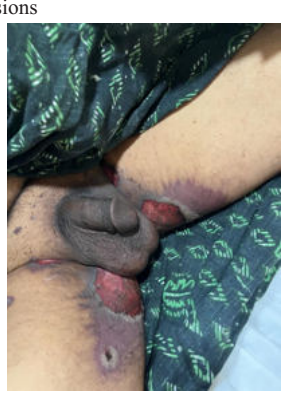

Figure 3 : Skin lesions over groin

Figure 4 : Skin lesions over abdomen

Management :
Patient was started on Inj Leucovorin 30 mg IV BD, transfused 4-unit RDP and 1 unit SDP on day 1 and 2 respectively and started on Inj G-CSM 300 mg IV daily. On Day 5, repeat CBC was taken, shows TLC-4100, Platelet-1,76 lakhs. Vitals stable and patient shifted to ward. On day 7, skin lesions subsided, hence discharged with the advice to continue Tab leucovorin 30 mg twice daily with monthly serum methotrexate level monitoring.

On follow up patient was non complaint with medications. Serum methotrexate levels came to nil after 3 months and was continued on medications for the lesions as prescribed by the dermatologist.

DISCUSSION

Literature is very limited regarding the total cumulative dose, duration of intake, or serum level of MTX. In the case report though the patient thought to took methotrexate daily, he was not compliant to medication, which might have avoided life threatening complications in this case. Identification of minimum total cumulative dose helps in assessing toxicity and complications is needed in such patients.[5]

High-dose methotrexate followed by leucovorin (LV) rescue is an important component in the treatment of childhood and adult cancers.[6] HDMTX can be safely administered to patients with normal renal function by the use of alkalinization and hydration In addition to conventional approaches, dialysis have been used to remove MTX with limited effectiveness.Carboxypeptidase-G (2) (CPDG (2)), a recombinant bacterial enzyme that rapidly hydrolyses MTX to inactive metabolites, has become available for the treatment of HDMTX-induced renal dysfunction.[7]

Methotrexate is an antifolate drug that competitively inhibits the enzyme dihydrofolate reductase and thymidylate synthetase and thus reducing the synthesis of DNA and RNA. Skin lesions secondary to methotrexate overdose is not common, however pancytopenia can cause skin erosions and ulcers associated with high doses.[8] In most of the cases there are cutaneous diseases prior to ulceration, mainly psoriasis. In the absence of underlying dermatitis, the presence of ulcerations is very rare.

Methotrexate (MTX) remains the backbone of psoriasis management in dermatological practice. The widespread usage as well as over the counter availability of drug in India has led to frequent incidents of overdosing, resulting in toxicity. Gautam Kumar Singh Et al conducted a multicentric, retrospective study including all cases of psoriasis who were treated for MTX toxicity in the last 5 years. Complete information including demographic details, drug history, detailed clinical evaluation, laboratory parameters, management protocol, and outcome were studied and analyzed. A total of 21 patients of psoriasis with MTX toxicity were included, of which 20 had mucocutaneous ulcerations and hematological abnormalities were found in 76% patients. All cases were treated with folinic acid and 85% patients recovered within 7-14 days. Three out of 21 patients succumbed to their illness despite the best possible treatment. Overdosing was found to be the most common cause (66%) of drug toxicity, either inadvertent or due to self-medication. Patients must be counseled regarding course of the disease, drug regimen, and dreaded side effects prior to initiating the drug. In case the symptoms of toxicity appear, a prompt medical advice must be sought.[9]

CONCLUSION

An analogue of folate with excellent therapeutic efficacy in the management of autoimmune disorders and malignancies is methotrexate (MTX). Genes involved in the MTX metabolic pathway have mutations that can influence the toxicity and effectiveness of the drug. Gene polymorphisms-based personalized pharmacotherapy makes patient treatment more effective, compatible, and economical. There is debate on the effects of single-nucleotide polymorphisms, or in the genes connected to the MTX pathway. Numerous pharmacogenetic relationships are racial and illness specific. Current research has largely focused on a small number of specific diseases and ethnic groups. The evidence from these investigations is insufficient to make firm judgments regarding the suitability of MTX pharmacogenetics in clinical settings. Large-scale, multicentre studies are required in the future.[10]

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