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Case Report

Methotrexate-induced multi-organ chronic toxicity in a rheumatoid arthritis patient: a case report

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ABSTRACT

This case report highlights the clinical presentation, diagnosis, and management of a 48-year-old female diagnosed with rheumatoid arthritis (RA) who developed toxicity due to prolonged use of methotrexate (MTX) in combination with other immunomodulatory drugs. The patient exhibited erythematous rashes, skin peeling, angular stomatitis, oral candidiasis, symptoms of acute gastroenteritis and pancytopenia. This report discusses the importance of monitoring, managing polypharmacy in patients with chronic diseases, to prevent adverse events and management of drug-induced toxicity in RA patients and improve patient outcomes.

Keywords: MTX, RA, Drug toxicity

INTRODUCTION

Rheumatoid arthritis (RA) is a debilitating autoimmune disorder characterized by chronic inflammation, joint deformities, and systemic involvement. To manage the inflammatory cascade and halt the disease progression, immunomodulatory drugs such as MTX, Leflunomide, and corticosteroids are frequently employed as the treatment. However, it is important to select and adjusting the right combination of medications to achieve therapeutic benefits while minimizing adverse effects is a constant challenge in the treatment of RA and their potential adverse effects necessitates vigilant clinical management.

MTX serves as a folic acid antagonist, widely harnessed in oncology and the treatment of chronic inflammatory conditions due to its potent anti-inflammatory and immunosuppressive attributes. MTX has found extensive utilization as a disease-modifying antirheumatic drug (DMARD) in the therapeutic management of RA. The prescribed dosages typically range from 7.5 to 30 mg per week.[1,2]

At lower therapeutic doses, MTX is a mainstay in managing autoimmune diseases, encompassing RA, psoriasis, lupus, sarcoidosis, and eczema.[3] MTX exerts its effects predominantly through the inhibition of cellular proliferation, affecting cells characterized by high turnover rates or diminished half-lives. Consequently, the utilization of high-dose MTX can give rise to undesirable consequences, such as the development of microsites and cytopenias, heightening the susceptibility to bleeding and infections. Additionally, it can induce the production of macrocytic erythrocytes, further complicating the clinical scenario.[4] Accidental daily ingestion of MTX, instead of the prescribed weekly dosage, represents a frequently encountered etiological factor in the development of acute MTX toxicity.[5,6]

This case report illuminates the intricacies of managing RA through the lens of a 48-year-old female patient with a longstanding diagnosis of the disease. Her presentation is a stark reminder of the potential complications and toxicities associated with the use of immunomodulatory agents, especially when utilized continuously without proper monitoring. The occurrence of such multifaceted drug-induced toxicity in RA patients necessitates a deeper understanding of the risks and rewards of immunomodulatory therapies. This report aims to clear the Complicated interplay between immunomodulatory drugs and the multifaceted clinical manifestations observed in this case. By sharing this clinical experience, we hope to contribute to the existing knowledge base in the field of rheumatology, encouraging improved strategies for the management of RA and its associated complexities.

CASE REPORT

A 48-year-old female with a known history of RA presented with a constellation of distressing symptoms, prompting a complex diagnostic challenge. The patient had been managing her RA with a treatment regimen that included MTX at a dose of 7.5 mg weekly, tab. leflunomide 20 mg, and other medications for pain relief and RA management. Her medical history included a positive result for anti-CCP antibody, further confirming her RA diagnosis. The patient's chief complaints included erythematous rashes and extensive skin peeling, primarily concentrated on her hands and trunk region. Additionally, she exhibited angular stomatitis and oral candidiasis, causing considerable discomfort (Figure 1). These mucocutaneous manifestations were accompanied by symptoms suggestive of acute gastroenteritis, such as loose stools and abdominal pain, which had persisted for three days. She had taken her medications, including MTX, continuously for ten days, leading to the development of drug toxicity. This necessitated hospitalization, where her MTX and other medications were promptly withdrawn, and she received symptomatic treatment. Upon admission, the patient was conscious and oriented, with a blood pressure of 110/80 mmHg. A thorough oral cavity examination revealed ulcerated reddish mucosa, as well as skin peeling and erythema. Notably, reddish lesions were observed on both her upper and lower limbs. An abdominal ultrasound indicated a collapsed stomach with mild diffuse wall thickening. Laboratory investigations revealed the patient's blood counts and peripheral blood smear demonstrated normocytic normochromic anemia, leukopenia, and thrombocytopenia, with a total leukocyte count (TLC) of 700 cells/mm^3, hemoglobin (Hb) level of 9.3 g/dl, and a platelet count of 103,000/cu mm. Liver function tests (LFT) indicated mildly elevated liver enzymes with hypoalbuminemia, her albumin level measured at 2.5 g/dl. However, her renal function tests were within the normal range. Tests for infectious etiologies, including HIV, Hepatitis B, and Hepatitis C viruses, returned negative results, ruling out any underlying infections. The patient's complex clinical presentation, which included mucocutaneous lesions, pancytopenia, and liver enzyme abnormalities, strongly suggested MTX toxicity as the underlying cause. With the suspicion of MTX toxicity, the patient's treatment plan was revised. MTX was immediately discontinued, and a comprehensive management approach was initiated. This included the administration of Inj. Ofloxacin (200 mg) and Inj. ornidazole (100 ml), along with Tab. Hydroxychloroquine (HCQ) 200 mg. In addition, analgesics and antacids were provided, and the patient received intravenous fluids and multivitamins to support her overall health. Topical treatments, such as kenocort and propygenta NP cream, were used to manage the skin lesions. The patient's oral hygiene was maintained with candid mouth paint. Throughout the course of treatment, the patient's clinical condition gradually improved. The skin lesions began to heal, and her hematological parameters showed signs of recovery. Liver enzymes returned to normal levels. The patient was eventually discharged with a revised RA treatment plan, avoiding MTX to prevent further complications. Close follow-up and monitoring were strongly recommended to ensure the patient's sustained recovery and overall well-being.

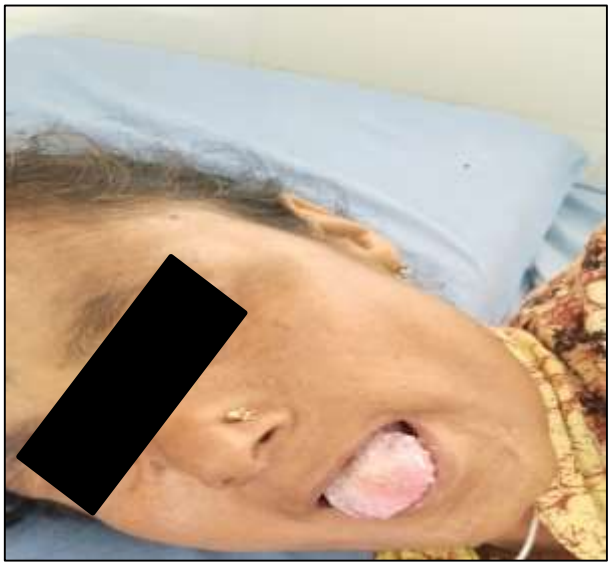

Figure 1: Oral candidiasis with angular stomatitis.

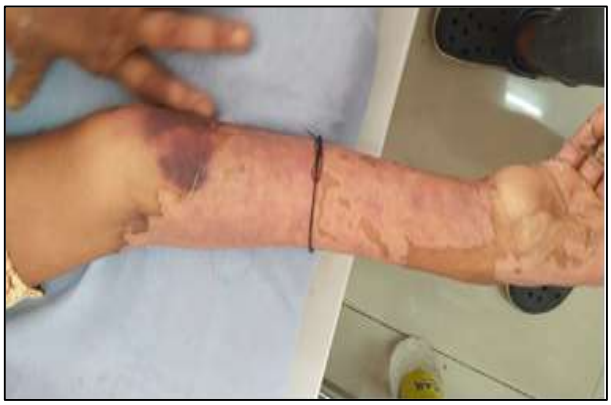

Figure 2: Erythematous rashes and skin peeling.

DISCUSSION

The presented case serves as a vivid illustration of the dual nature of MTX therapy in the management of RA. MTX, prescribed as a disease-modifying antirheumatic drug (DMARD), holds a pivotal role in the treatment of RA, particularly when administered at low doses, as it has demonstrated remarkable efficacy and stands as the preferred therapeutic choice in such cases. However, the benefits it offers in controlling the disease are balanced by the potential for severe toxic effects, particularly when dosing instructions are not meticulously followed.

MTX therapy, while efficacious, is not without its associated adverse effects, encompassing mucositis, hepatotoxicity, nephrotoxicity, and myelosuppression. Patients undergoing MTX therapy necessitate a rigorous regimen of laboratory assessments to monitor crucial parameters, including kidney function, liver function, and blood cell counts. Adhering to the guidelines outlined by the American college of rheumatology, patients receiving MTX are subjected to regular hematological analyses, which include complete blood counts, liver function assessments, and creatinine measurements. These assessments are recommended at 12-week intervals, particularly for patients with more than six months of MTX therapy.[7,8]

This case emphasizes the imperative nature of precise dosing and patient education in the context of MTX therapy. MTX therapy entails maintaining a delicate equilibrium between therapeutic efficacy and safety. The patient's inadvertent misunderstanding of the dosing regimen led to an unintentional overdose, culminating in a sequence of toxic effects that affected multiple organ systems. A similar case, reported by Kanishka et al detailed a patient who had been prescribed tablet MTX 7.5 mg and mistakenly consumed it daily for 15 days, ultimately resulting in MTX -induced pancytopenia and mouth ulcers.[1]

In this particular case, the patient's accidental MTX overdose resulted in a cascade of toxic effects that affected her skin, leading to erythematous rashes, skin peeling, angular stomatitis (Figure 2), oral candidiasis, and pancytopenia. These symptoms were further exacerbated by gastrointestinal distress, including loose stools and abdominal pain, mirroring the presentation of acute gastroenteritis. Kivity et al also observed a similar trend in a study involving 28 patients who experienced low-dose MTX overdose, with pancytopenia being the predominant presenting feature (78%).[9] Additionally, Singh and Handa reported a comparable case where prescription errors, akin to this scenario, led to the patient misunderstanding the frequency of dosing.[10] Recognition of MTX-induced toxic effects and the immediate discontinuation of the medication played a pivotal role in the patient's management. The comprehensive treatment approach, encompassing supportive care, antibiotics, analgesics, and topical therapies, ultimately resulted in clinical improvement, normalization of liver enzymes, and recovery from hematological abnormalities.

Healthcare providers assume a central role in patient education and monitoring in the context of MTX therapy. Patients undergoing MTX treatment must receive thorough education regarding the dosing regimen and potential side effects.[11] Vigilance in monitoring patients for early indications of toxicity is equally paramount. When complications manifest, as exemplified in this case, the timely recognition and discontinuation of MTX are critical for achieving favorable outcomes.

CONCLUSION

In conclusion, clinicians should remain vigilant and well-informed about the potential complications associated with MTX therapy in RA patients to ensure timely intervention and the optimization of treatment outcomes. This case stands as a poignant reminder of the importance of precision in MTX dosing and ongoing vigilance to prevent severe multi-organ toxicity and enhance patient care.

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