CASE REPORT

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Managing Methotrexate Toxicity – A Case Report

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ABSTRACT

Methotrexate, a folic acid analogue is being used globally in the treatment of neoplastic diseases and immunologically mediated disorders. MTX therapy is known to result in mucositis and myelosuppression. Methotrexate associated skin lesions are rare, but they serve as a forewarning signal for later-onset pancytopenia. Therefore, identification of mucosal and skin lesions might help to initiate treatment strategies at an incipient stage. Here we describe a case of methotrexate toxicity who developed mucocutaneous ulcerations and pancytopenia due to methotrexate being given for psoriasis. The provision of rescue therapy led to the amelioration of the symptoms showing the benefit of early recognition and treatment of MTX-induced toxicity.

KEYWORDS: Methotrexate toxicity, Psoriasis, Immunosuppression, Ulceration

INTRODUCTION

Methotrexate (MTX), an antimetabolite drug is being used since decades for a vast number of conditions. The mechanism of action points towards inhibition of dihydrofolic acid reductase and directing towards the synthesis of folic acid which is mandatory for DNA synthesis and repair. MTX, in lower doses, reduces cell proliferation and inhibits proliferation of lymphocytes and cytokine synthesis.[1] It works by inducing programmed cell death (apoptosis) and increasing the concentration of adenosine. It is also a component of chemotherapy regimens against breast and lung cancer, lymphomas or squamous cell cancer.[1,2] MTX can induce mild to severe side effects ranging from gastrointestinal symptoms to multi organ failure. Gastrointestinal toxicity, nausea, diarrhea, vomiting, mouth and lip sores, stomatitis, balanitis, anorexia, pharyngitis, enteritis, pneumonitis, hepatitis, pruritus, urticaria, ecchymosis, alopecia, ulcerations of psoriatic plaques, erosions of the mucosa and toxic epidermal necrolysis.[2,3,4] Subjects with methotrexate toxicity are more prone to infections and fever due to immunosuppression. Mucosal cells are more prone to get affected because of their highly replicative nature. Reports suggest that withdrawal of the drug show a positive dechallenge phenomena leading to complete resolution within a few days.[4] MTX can be administered via many routes. In human plasma, over 50% of MTX is bound to albumin[2,3] and any medication with a high plasma protein affinity can easily displace it. MTX is excreted via kidneys, with only a minor portion is metabolized in the liver.[2] Consequently, renal impairment and low

GFR may lead to accumulation, to higher blood levels and to toxicity.[3] As the cutaneous erosions tend to heal quickly within few weeks of stopping or decreasing the dose of methotrexate, the treatment required for these symptoms is mainly supportive.[5,6] Management with intravenous hydration, urine alkalinization, and high dose leucovorin are effective in the management of acute toxicity.[7] Leucovorin helps to replenishes the intracellular levels of reduced folate bypassing the dihydrofolic acid reductase and provides substrates needed for purine and thymidylate synthesis.[2] MTX toxicity can be fatal or life-threatening if not followed by adequate treatment strategies. So, it is recommended to initiate the rescue measures independently of drug blood levels if the patient shows evidence of toxicity related clinical symptoms.

CASE PRESENTATION

A 35-year-old man presented to our clinic with stomatitis and multiform exanthema. Ten months before the current presentation, the patient had noticed small red round patches covered by shiny scales on right elbow and wrist. During the following months, the lesions progressed and spread to the all the extremities and also involving the trunk to some extent. In October 2016, the patient visited his family doctor due to the progressive changes. The doctor suspected psoriasis vulgaris and started treatment with topical corticostroids and MTX at an dosage of 5 mg once a day for a week followed by 10 mg daily. A week later, the patient developed flu-like symptoms, throat pain, productive cough and difficulty in eating. His lips were fissured painfully swollen. His left foot showed erythema and swelling. The symptoms worsened gradually, involving different skin areas until presentation to us 2 weeks after initiation of MTX therapy. On admission, the patient had fever, night sweats and massive pain in all affected areas, On examination, the patient was febrile (body temperature 38.4°c) and in reduced overall general condition. Dermatological examination revealed multiple, ulcerated, erythematous plaques of 1–3 cm in diameter, distributed predominantly on all the extremities, with fewer lesions on the trunk. The ulcerations were surrounded by edematous areas. Erosive lesions were detected in the oral cavity. Swelling in the submandibular lymph nodes was evident, but other lymph nodes were unremarkable.

He was a non-alcoholic and a past smoker. His regular medication prior to admission was metformin for diabetes and MTX (10 mg daily).Once weekly, he took chewable Vitamin C. Based on the characteristic history and clinical presentation, we interpreted the clinical picture as a consequence of the excessive MTX intake. Due to the severe skin involvement, MTX was discontinued immediately.Laboratory investigations on admission showed elevated CRP. Haematological examination showed decrease in number of red blood cells, white blood cells and platelets pointing towards pancytopenia that might have been resulted because of the drug induced myelosuppression. Other laboratory findings including skin swab test and serological tests were unremarkable. The patient was put on broad spectrum antibiotics.

A histopathology of the representative skin lesion revealed hyperkeratosis, vacuolar alteration, apoptotic keratinocytes in the stratum basale of the epidermis. Moreover, it showed scanty lymphocytic peri-vascular infiltrates in the upper dermis with neutrophils and discrete intradermal erythrocyte extravasation. There were signs of lichenoid dermatitis and interface dermatitis. Topical therapy with triamcinolone and halometasone was started for cutaneous lesions and for mucosal lesions anesthetic gel was used along with triamcinolone tincture. Antiseptic baths (potassium permanganate) and analgesics were prescribed. No potential focus of infection was revealed in blood cultures, urine cultures and thoracic radiographic imaging. An antidote therapy with folinic acid was administered for 2 days. Adequate hydration and urinary alkalinization with sodium bicarbonate was done to increase MTX excretion. The patient healed gradually with regression of all lesions within few days after starting local and systemic therapy. After 11 days of treatment, the blood cell count reverted to normal with cessation of all the symptoms. The patient was dismissed in good general condition. During subsequent follow-ups, no drug toxicity related symptoms were detected.

DISCUSSION

We describe the clinical picture and management of a case of acute MTX toxicity. The most common causes leading to MTX intoxication are inappropriate dosage, impairment of renal function and thus decreased excretion, concomitant use of interacting drugs.[4] Methotrexate, a folic acid antagonist that inhibits DNA and RNA synthesis by binding to the enzyme dihydrofolate reductase ,is widely used in the treatment of proliferative disorders.[8] Methotrexate toxicity manifests itself in several forms including liver toxicity, lung toxicity, renal failure, gastrointestinal tract symptoms, and pancytopenia.[8,9] It can also cause more rare cutaneous side effects including burning sensation of the skin, sloughing over pressure points, severe mucositis, and Stevens-Johnson syndrome.[5,10,11] The histolpathological findings in the biopsy were in line with those of patients suffering from MTX intoxication. The histopathological study of eroded cutaneous lesions shows a microscopic image similar to that observed after intradermal administration of the drug, suggesting that the reaction is caused by a direct cytotoxic effect.[12] In case of acute MTX intoxication, cutaneous signs and symptoms may precede other serious adverse events as a warning sign. The treatment is made with immediate suspension of the drug and administration of folinic acid. In a review of the literature from 1951 to 1996, Pearce and Wilson[13] found 64 patients, who had experienced cutaneous erosions believed to be secondary to methotrexate toxicity. Drug interaction has also been counted as one of the potent causes of methotrexate induced toxicity. Daly et al[14] reported case of methotrexate toxicity which occurred due to co-administration of azapropazone. Ng et al[15] described a patient who developed necrotic skin ulceration and pancytopenia after concomitant administration of methotrexate, trimethoprim, and naproxen. Mucocutaneous ulceration on psoriatic plaques or previously healthy

skin due to MTX administration may indicate the development of other severe organ damage such as bone marrow suppression and multiorgan failure. However, perhaps due to the timely diagnosis and initiation of rescue therapy, our patient experienced a quick and complete recovery. He developed ulcerated livid plaques on previously healthy skin and ulceration of pre-existing psoriatic plaques, oral mucositis. The skin lesions preceded a severe pancytopenia. Under rescue therapy, both skin lesions and pancytopenia resolved within a few days. Physicians should be aware of the existence and morphology of MTX-induced skin lesions in order to take appropriate therapeutic action at an early stage and prevent the development of further complications.

CONCLUSION

In conclusion, this case depicts the importance of recognizing clinical signs of methotrexate toxicity and initiating therapy as soon as possible. Methotrexate is an option of great therapeutic value for countless disorders, yet it is not clear whether the benefits outweigh the risks or not. The healthcare professionals and the patients need to be thoroughly aware of the risks and side effects of methotrexate. MTX, being used worldwide, is a safe and effective drug, but the outcome may be fatal depending upon inappropriate use, dosage, concomitant medications and underlying medical condition of the subject. Prior workup and proper counseling regarding the drug interactions as well as self-medication should be enforced.

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