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Case Report

An unusual case of acute methotrexate toxicity manifesting as ulcers on psoriatic plaques in an elderly male

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ARTICLE INFO

Article history:

Received 30 August 2012

Accepted 12 November 2012

Available online 23 February 2013

Keywords:

Methotrexate toxicity

Psoriasis

Skin ulceration

methotrexate for fast relief of psoriasis without realising its potential adverse effects.

Case report

An 83-year-old man, a known case of psoriasis vulgaris from last 20 years, was brought to a tertiary dermatological centre with alleged history of sudden onset inability to get up from bed, disorientation and development of ulcers on psoriatic plaques following injection of methotrexate which he was taking since the last three days. Present episode of psoriatic lesions existed from last 5 months for which he was on tab methotrexate 10 mg in once weekly dosage, with tablet folic acid 5 mg five times a week excluding the day of methotrexate and its following day. He was administered tablet methotrexate on multiple occasions in the past with good results. Cumulative dosage of methotrexate could not be calculated because of paucity of records. Two months ago, during OPD follow-up, he was found to have multiple mucosal erosions in the oral cavity following which methotrexate was stopped and gradually he was started on oral azathioprine and supportive topical therapy. He did not show satisfactory response to this therapy. He changed the doctor and requested for injectable methotrexate which he had taken for consecutive three days of 15 mg each.

Introduction

Systemic methotrexate, a potentially toxic antimetabolite, anticancer drug, first studied in the year 1978¹ remains a cornerstone of treatment of psoriasis even now when many modalities of treatment including biological agents are available in the armamentarium of psoriasis. Patients of psoriasis have very fast and satisfactory recovery with systemic methotrexate.² This prompts them to use this drug as self medication. Herein, we report one case of methotrexate toxicity presenting with ulceration of psoriatic plaques, severe weakness and mental confusion along with features of chronic methotrexate misuse. Our patient used injectable

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<http://dx.doi.org/10.1016/j.mjafi.2012.11.006>

There was past history of successful total hip transplant on the right side ten years ago. He was ambulatory without any support. He revealed taking tablet methotrexate of his own on many occasions for fast relief.

On examination he was febrile with max temperature of 101 °F, tachycardia with pulse of 110 beats per minute. There was marked pallor, glossitis (Fig. 1) and mild pedal oedema but there was no cyanosis, clubbing or lymphadenopathy. There was marked weakness of all four limbs with grade II power in the lower limbs and grade III in upper limbs. However, there was no sensory loss and his reflexes were preserved. There was no wasting, tenderness of muscle or any bone or joints pain, swelling or tenderness. He was disoriented in time, place, person and space. There was no neck rigidity. Dermatological examination revealed multiple, polysized, shallow, ulcers with well defined margin, at places covered with haemorrhagic crusts or serosanguinous discharge, present on the pre-existing psoriatic plaques, distributed on all four extremities, gluteal region; sparing face, palms, soles and genitalia (Fig. 2).

He was thoroughly investigated. His haemoglobin was 5.2 g/dL, red blood cell count 4.45 lac/ μ L, mean corpuscular volume 96 fL, white blood cell count (WBC) 4600/ μ L and the platelet count 3.5 lac/ μ L. Serum biochemistry showed a serum creatinine of 2.1 mg/dL, blood urea nitrogen of 102 mg/dL and total bilirubin of 2.4 mg/dL with direct bilirubin of 1.2 mg/dL, SGOT of 110 IU/L, SGPT of 96 IU/L, and alkaline phosphatase of 113 IU/L. Prothrombin time and partial thromboplastin time were within normal limits. Urine and stool analysis, chest X-ray, electrocardiogram and USG abdomen were normal. X-ray pelvis showed old prosthesis of total hip replacement in situ on right side. There were only spondylolythestic changes in lumbar vertebra L3, L4 and L5. Blood culture did not show any growth and CSF analysis were normal.

He was diagnosed as a case of acute methotrexate toxicity. He was started on intravenous leucovorin calcium (folinic acid), 25 mg every 6 h on day 1, followed by 10 mg every 6 h on day 2 and 3. Four units of packed RBC were transfused over two days. He was adequately hydrated with normal saline and empirically started on injectable broad spectrum antibiotic. Skin care consisted of twice daily

Fig. 1 – Glossitis due to chronic methotrexate use.

Fig. 2 – Ulcers on psoriatic plaques.

compresses of potassium permanganate solution in 1:10,000 dilution followed by application of topical Framycetin cream 1%. Orthopaedic consultation and psychiatric consultation were unremarkable.

He had shown dramatic response to the therapy. He became afebrile, well oriented next day. His ulcers on the psoriatic plaques healed totally over a period of three days (Fig. 3). He became ambulatory in 4 days. His haemoglobin was 9.8 g/dL after 7 days. Other parameters also returned to normal. He was discharged from the hospital after 7 days on supportive topical therapy and oral haematinics.

Discussion

Use of methotrexate (MTX) remains a systemic treatment of choice for moderate-to-severe psoriasis and has been widely used for more than 40 years.³ Treatment guidelines on the use of MTX in psoriasis have been published by Roenigk et al in 1973,⁴ 1982,⁵ 1998⁶ and updated by a group of experts from the United States National Psoriasis Foundation in 2009.⁷ Absolute or relative overdose of methotrexate can result in acute toxicity, manifested clinically by myelosuppression, mucosal ulceration (especially oral), and rarely cutaneous necrosis. Relative overdose is seen in cases where there is interference with renal excretion of methotrexate and certain drug interactions.⁸

Treatment of choice for bone marrow suppression secondary to methotrexate toxicity is leucovorin calcium (folinic acid)^{9,10} which is administered orally or intravenously every 6 h after an immediate loading dose of 20 mg (10 mg/m²) until plasma methotrexate concentration is 5×10^{-8} mol/L or less.^{9,11} However, leucovorin calcium must be administered within 12–24 h after the last dose of methotrexate for it to be effective. Folinic acid is a fully reduced folate coenzyme, which after intracellular metabolism can function in nucleic acid synthesis, thus bypassing the action of methotrexate. In acute methotrexate overdose, it can be life-saving and should be administered as early as possible, in serious cases, parenterally.⁸ It should therefore be readily available to any

Fig. 3 – Post treatment.

dermatologist prescribing methotrexate. Because folinic acid competes with methotrexate for membrane carrier sites to enter cells, high doses (equal to or higher than the dose of methotrexate) are more likely to be effective. Further, methotrexate levels can remain dangerously elevated for several days after an overdose in patients with poor drug excretion, and if plasma methotrexate levels are unavailable, folinic acid should be continued until the blood count has normalized and the mucosae have healed. It is also important to maintain adequate hydration and withdraw any drugs which the patient might be taking which may interact with methotrexate and/or delay its renal excretion. Supporting therapy such as blood transfusion and renal dialysis may be required.⁸ Clinical oncologists and haematologists familiar with high-dose methotrexate regimens may be useful sources of advice on the management of severe cases of overdose.¹²

Two types of cutaneous ulceration induced by methotrexate in patients with psoriasis have been described. Type 1 involves the painful erosion of psoriatic plaques which can take place shortly after initiation of the treatment or in the setting of dose alteration and drug interaction.¹⁰ This can be mistaken as an exacerbation of the condition itself. Type 2 describes ulceration in diseased skin, which has a variable correlation with treatment duration and thus may be overlooked as evidence of methotrexate toxicity.^{13,14} It has been reported that patients with multiple co-morbidities, on Weinstein regimen,¹⁵ on self medication or those suffering medical errors have ulceration of psoriatic plaques.¹⁶ Several factors have been identified which can precipitate methotrexate toxicity. The most common risk factors are an alteration in methotrexate dosage and the use of non-steroidal anti-inflammatory drugs.¹⁰ Other possible contributing factors are renal insufficiency, advanced age, lack of folate supplementation, methotrexate dosing errors, hypoalbuminemia, infection, pustular flare of psoriasis, greater than moderate alcohol intake and drug interaction.¹⁷ Reduced doses of methotrexate are effective in controlling psoriasis in the elderly, probably as a consequence of decreased renal clearance.¹⁸ Patients older than 80 years have been adequately controlled on only 2.5 mg of methotrexate per week.¹⁹

Discretion should be exercised when using methotrexate—some residual areas of psoriasis can be accepted to prevent relative overtreatment and the complete clearance of psoriasis should not be the primary goal of treatment. In addition, headaches, dizziness, fatigue and mood alterations usually occur at drug initiation and are dose dependent. However, they can also result from chronic use.²⁰

Our patient was very old who already had history suggestive of chronic methotrexate misuse in the form of glossitis, pallor and mucosal erosions and continued to take self medication on and off. Deranged renal parameter substantially increased the chance to develop methotrexate toxicity. Timely diagnosis of the case and prompt treatment enabled a dramatic recovery. When patient is started on methotrexate, it is essential that the treating dermatologist should devote considerable time to counsel the patients on severe adverse effects, importance of regular follow-up and avoidance of self medication to avoid such catastrophic event.

Conflicts of interest

All authors have none to declare.

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