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Case Report

Mucous membrane ulcerations secondary to methotrexate in a patient with unruptured tubal ectopic pregnancy: a case report

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ABSTRACT

Ectopic pregnancy remains a significant contributor to first trimester maternal mortality, though early diagnosis now allows for successful medical management in hemodynamically stable unruptured ectopic patients. Methotrexate is the drug of choice in such scenarios, with known side effects including gastrointestinal discomfort and myelosuppression. We present a rare case of a 29-year-old primigravida with a right tubal unruptured ectopic pregnancy managed with multiple dose methotrexate regimen. Despite stable blood counts and normal organ function, the patient developed severe oral and vulvar mucositis by day 6 of the treatment. Examination revealed multiple painful aphthous ulcers and erythema affecting the buccal mucosa and labia minora. The mucositis resolved completely by day 25 with symptomatic treatment including antihistamines, topical agents and delayed vitamin supplementation. This case highlights an uncommon presentation of methotrexate toxicity with isolated orogenital ulceration occurring in the absence of pancytopenia or systemic toxicity. Early recognition of mucosal lesions is critical for prompt management and may prevent progression to more severe toxicity.

Keywords: Ectopic, Methotrexate, Orogenital ulcers, Mucositis

INTRODUCTION

Ectopic pregnancies are the leading cause of maternal mortality in the first trimester, with an incidence of 5-10% of all pregnancy-related deaths.[1] With better diagnostic tools for confirming ectopic pregnancy at an early gestation, many women are found in a clinically stable condition without risk of impending rupture, giving scope for medical management. The mainstay of medical management has been methotrexate, a folate antagonist that binds to dihydrofolate reductase leading to downstream inhibition of DNA synthesis and repair as well as in cell replication.[2,3] Well known adverse drug effects include gastro-intestinal discomfort, nausea and vomiting, pancytopenia, malaise and stomatitis. One of the rare manifestations of methotrexate toxicity is oral and vulval mucositis in the absence of known side effects.

CASE REPORT

A 29-year-old primigravida at 5 weeks 4 days of gestation presented with two episodes of spotting per vaginum and was diagnosed with unruptured right tubal ectopic pregnancy. The ultrasound report suggested a well-defined 12 mm gestational sac in the right fallopian tube with mild peripheral vascularity. A yolk sac and fetal pole was also visualized without fetal cardiac activity. The beta-human chorionic gonadotropin (β-hCG) levels were 6972 mIU/ml. Taking into consideration the stable condition, laboratory parameters and ultrasound findings, the patient was started on multiple dose methotrexate therapy. After baseline investigations, two doses of intramuscular 75 mg methotrexate were administrated on day 1 and day 3 with rescue therapy of 0.8 ml (~6 mg) leucovorin on day 2 and day 4. On day 4, serum levels β-hCG were repeated which

had increased to 14900 mIU/ml. A repeat ultrasound showed marginal increment in the gestational sac size with absence of cardiac activity. Taking into consideration the persistent stable condition, decision for further aggressive medical management was taken. The third and fourth dose of intramuscular 100 mg methotrexate was administered on day 5 and day 7 respectively. Serial complete blood count, renal and liver function tests were done which were within normal limits. Rescue doses of 1 ml (7.5 mg) leucovorin were given on day 6 and day 8. The patient had mild gastro-intestinal discomfort which was managed with oral anti-emetic and antacid medications.

However, on day 6 of initiation of methotrexate treatment, the patient complained of vulvar itching associated with erythema over the labia minora and majora. Despite oral antihistamines and local emollient application, patient complained of pain and increased sensitivity over vulva within 24 hours associated with complaints of increased sensitivity to spicy food and difficulty in eating and swallowing. Oral examination showed erythema along with few aphthous ulcers of size approximately 1×1 cm^2 over bilateral buccal mucosa. Genital mucosal examination revealed presence of multiple, tender well defined ulcers, approximately 3×2 cm^2 in size with overlying whitish slough and pustular discharge on minor manipulation overlying both labia minora. Cutaneous examination was unremarkable. A diagnosis of methotrexate induced mucositis was made and the patient was started on tablet fexofenadine (180 mg) in the morning, tablet hydroxyzine (25 mg) at night, tablet tramadol (50 mg) twice daily, lignocaine oral vicious before meals and mupirocin 2% ointment for the vulval ulcers. Multivitamins were withheld in view of the ectopic according to the risk benefit ratio. Serum β-hCG levels dropped serially, day 8-9279.12 mIU/ml, day 12-5953.13 mIU/ml and day 16-1578.28 mIU/ml. After confirming the decreasing trend of β-hCG values, she was started on oral riboflavin (10 mg thrice daily), folic acid (5 mg thrice daily) and niacinamide (500 mg twice daily) medication on day 13. Gradually the symptoms improved with complete resolution of the orogenital ulcerations on day 25 of the treatment.

The presence of orogenital ulcerations in the absence of pancytopenia reveals a novel presentation of methotrexate toxicity.

DISCUSSION

Methotrexate is an antimetabolite, DHFR reductase is commonly used to treat hematological, oncological and rheumatological disorders because of its effect on DNA synthesis and cellular reproduction.[4] The mechanism of acute toxicity is by inhibiting DNA synthesis in rapidly proliferating cells i.e., gastrointestinal tract, haematopoietic cells. As far as acute kidney injury (AKI) is concerned, MTX promotes intrarenal crystal formation, which impairs the renal clearance and consequently causes an increase in its serum levels.[5]

Toxicity can result from an idiosyncratic process or in a dose-dependent manner. The clinical manifestations of methotexate toxicity include mucositis, stomatitis, cutaneous ulceration, methotexate-induced epidermal necrosis, myelosuppression, acute hepatitis, diarrhea, AKI, and pneumonia.[6] Mucocutaneous ulcerations serve as an early indicator of impending systemic toxicity, and in some cases, patients may present solely with skin lesions. In a cohort study, pancytopenia emerged as the most frequent manifestation of low-dose methotrexate (MTX) toxicity, occurring in 78.5% of cases.[7] Systemic symptoms like diarrhoea and general weakness point toward multi-system involvement resulting from acute MTX toxicity.

Mucositis usually occurs within the first 7 days of administration, prior to the onset of pancytopenia, as the accumulation of MTX is higher in mucosal epithelial cells than in the bone marrow stem cells and cutaneous involvement usually appears with mucositis.[8] This could probably explain the occurrence of the ulcerations in our patient on a background of normal blood counts. However, isolated appearance of ulcerations in the absence of cutaneous lesions as well has not been reported yet.

CONCLUSION

This case underscores a rare but clinically significant presentation of methotrexate toxicity manifesting as isolated orogenital mucositis in the absence of pancytopenia or other systemic effects. It highlights the need for heightened clinical awareness of atypical adverse effects during methotrexate therapy, even in the presence of normal laboratory parameters. Prompt identification and symptomatic management of mucosal ulcerations can lead to complete resolution without requiring discontinuation of the treatment. Clinicians should maintain a high index of suspicion for mucositis as a potential early marker of methotrexate toxicity, particularly in patients undergoing multiple-dose regimens for ectopic pregnancy.

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