

Low-dose methotrexate-induced vulvar edema

A case report

Guifeng Jia, MD, Wei Chai, PhD, Zhiwei He, PhD, Xiaojing Liu, PhD, Yan Wen, PhD, Lifeng Cui, PhD*, Fengyan Gong, PhD*

Abstract

Rationale: Methotrexate (MTX) is an antimetabolite of folic acid, which is used for management of ectopic pregnancy. MTX-related toxicity may include cutaneous mucosal damage, bone marrow suppression, gastrointestinal disorders (gastritis, diarrhea, hematitis), liver and kidney function damage, pulmonary toxicity, cardiac toxicity, and nerve toxicity. However, it is not usual for vulvar edema induced by low-dose methotrexate.

Patient concerns: In this case report, we described a patient with severe vulvar edema and oral cavity ulceration and scalp ulceration induced by low-dose MTX treatment for ectopic pregnancy. Her presenting complaints were pain in the vulva, oral cavity, and scalp.

Diagnoses: The patient was diagnosed based on clinical findings for MTX toxic reactions.

Interventions: Vulva was disinfected with iodide and Kangfuxin solution, her mouth was rinsed with mouthwash. Three compound glycyrrhizin tablets were orally administered (3 times/day). After 10 days, the broken skin and mucous membrane healed.

Outcomes: The vulvar edema and oral cavity ulceration and scalp ulceration healed.

Lessons: Our study demonstrated that even low-dose MTX can be induced skin and mucosal injury, patients and doctors should timely detection of drug toxicity reactions, immediately rescue, prompt discontinuation of medication, and symptomatic treatment to avoid accidental occurrence.

Abbreviation: MTX = methotrexate.

Keywords: ectopic pregnancy, methotrexate, ulceration, vulvar edema

1. Introduction

Low-dose methotrexate (MTX) is a common treatment for ectopic pregnancy. Although this treatment is usually safe and effective, due to individual differences, toxic reactions may develop, including skin mucosal damage, bone marrow suppression, gastrointestinal reaction, liver and kidney function damage, lung toxicity, and nerve toxicity^[1]; the adverse reactions may be life-threatening in serious cases. In the present report, we describe a case with severe ulceration and vulvar edema induced by low-dose MTX treatment for ectopic pregnancy, and review the relevant literature.

Editor: N/A.

Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images. Copy of the written consent is available for review by the Editor of this journal.

The authors have no funding and conflicts of interest to disclose.

Department of Gynecology and Obstetrics, The First Hospital of Jilin University, Changchun, Jilin, China.

*Correspondence: Lifeng Cui, Fengyan Gong, Department of Gynecology and Obstetrics, The First Hospital of Jilin University, 71 Xinmin Street, Chaoyang District, Changchun, Jilin Province 130021, China (e-mails: run1019@163.com, gongfengyan@sohu.com).

Copyright © 2019 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Medicine (2019) 98:35(e16895)

Received: 28 December 2018 / Received in final form: 18 June 2019 /

Accepted: 29 July 2019

<http://dx.doi.org/10.1097/MD.00000000000016895>

2. Case report

A 28-year-old Chinese woman presented to the department of obstetrics and gynecology of our hospital with a 10-day history of lower abdominal pain, along with vaginal bleeding, at 36 days of gestation. A transvaginal ultrasound examination indicated a normal intrauterine position, with the absence of the pregnancy sac in the uterine cavity. A 1.5 × 0.5 cm mixed echo was observed adjacent to the left ovary, and the free fluid in the pelvic cavity was found to be 3.5 cm deep. Her beta-human chorionic gonadotropin (β-hCG) level was 315.90 mIU/ml and progesterone level was 10.38 ng/ml. Her complete blood count, albumin level, and liver and kidney function were within the normal range. After 2 days, her β-hCG levels had increased to 1443.0 mIU/ml. She was definitively diagnosed with ectopic pregnancy. As her vital signs were stable, she was indicated to undergo the routine regimen for ectopic pregnancy, which includes 80 mg of intramuscular MTX. She was in good health, without any history of special medication or disease and drug allergy. On the third day after the initiation of MTX administration, vaginal discharge had increased. Examination of the vaginal discharge indicated trichomonas vaginitis, and hence, metronidazole was orally administered (400 mg, twice a day). Her itching symptoms significantly improved, and the vaginal discharge volume returned to normal. On the fourth day, her β-hCG levels were estimated as 3038 mIU/ml. Hence, she was administered another 50 mg intramuscular MTX injection. At 3 days after MTX re-administration, symmetrical edema and a 8.0 × 0.5 cm skin ulceration on both sides of the labia majora were observed, along with tenderness. Ulcer lesions and purulent secretions were noted locally, along with multiple oral cavity ulcer lesions and scalp ulceration lesions. We considered the toxic effect of MTX on the

mucocutaneous tissue, and hence, after disinfection of the vulva with iodide, Kangfuxin solution was applied topically and her mouth was rinsed with mouthwash. Three compound glycyrrhizin tablets were orally administered (3 times/day) as active symptomatic treatment. At 4 days after MTX re-administration, her β -hCG levels were recorded as 931.2 mIU/ml, and complete blood count and liver and kidney function were found to be normal. On the eighth day after MTX re-administration, her β -hCG levels were recorded as 106.1 mIU/ml. Transvaginal ultrasound examination indicated a normal intrauterine position, and the absence of a pregnancy sac in the uterine cavity. A 1.7×1.7 cm mixed echo was found adjacent to the left ovary, and the free fluid in the pelvic cavity was 2.8 cm deep. The patient was discharged from the hospital. After 10 days, we found that the broken mucous membrane of the vulva had healed. Her β -hCG levels had also reduced to normal after 3 weeks of follow-up.

3. Discussion

MTX is a folate analogue that strongly and persistently inhibits dihydrofolate reductase. When MTX is combined with an enzyme, the dihydrofolate cannot be converted to a tetrahydrofolate, resulting in a deficiency of 5, 10-formyl-tetrahydrofolate, and the consequent inhibition of deoxythoracic acid synthesis and DNA synthesis. MTX also prevents the synthesis of purine nucleotides, and thus inhibits DNA synthesis. When administered for the treatment of using ectopic pregnancy, MTX interferes with DNA synthesis, inhibits and trophoblast proliferation, which prevents embryo development and leads to absorption. The treatment does not have any adverse side effects on subsequent pregnancy, and does not increase the rate of abortion, fetal malformation, and tumor incidence.^[2]

MTX is a commonly used anti-metabolic anti-tumor drug in clinical practice, and is often used to treat childhood acute lymphoblastic leukemia, lymphoproliferative disorders, choriocarcinoma, ectopic pregnancy, various solid organ tumors, and autoimmune diseases. MTX-related toxicity may include cutaneous mucosal damage, bone marrow suppression, gastrointestinal disorders (gastritis, diarrhea, hematitis), liver and kidney function damage, pulmonary toxicity, cardiac toxicity, and nerve toxicity.^[1] In particular, mucocutaneous damage primarily involves oral cavity ulceration, nasal mucosal ulceration, gingivitis, labitis, annular erythema of the trunk and limbs, superficial erosion and ulceration, original psoriasis skin lesions, ulceration, and scabbing.^[3] Liguó et al reported a case of vulvar edema and ulceration induced by low-dose MTX. The patient underwent MTX treatment for ectopic pregnancy, 20 mg intramuscular injection, continuous use for 5 days, on the second day of methotrexate treatment, the patient felt uncomfortable in the vulva and did not stop taking the medicine. On the 4th day, the vulva pain was aggravated, and physical examination showed severe vulva edema, tenderness positive, ulcer foci and purulent secretions were seen in the labia majora and labia minora locally.

The incidence of ectopic pregnancy ranges from 1% to 2% in developed countries, higher than that in developing countries; however, the exact incidence remains unknown. At present, the treatment of ectopic pregnancy primarily involves expectant treatment, drug treatment, and surgical treatment (open or laparoscopic).^[4] With regard to drug treatment, MTX is non-invasive, simple, and retains fertility function. However, MTX has also found to lead to serious complications, even at low doses, that can be life-threatening. The serum protein binding rate of

MTX ranges from 46.5% to 54%, and the drug is mainly metabolized by the liver. It is excreted through the kidney, with 90% of the prototype excreted through the kidneys within 24 hours.^[5] In the present case, 130 mg MTX was used, and led to vulvar edema, ulceration, oral cavity ulceration, and scalp ulceration. MTX-induced toxicity was diagnosed based on the presentation of clinical features similar to those reported previously.^[6] At present, no sufficiently effective specific laboratory test is available for confirming the diagnosis of MTX toxicity, and hence, diagnosis is confirmed via clinical findings; a skin biopsy is also rarely conducted in these cases.^[7] Furthermore, no other cause of the mucocutaneous abnormalities was detected. Accordingly, our findings indicated that MTX may have induced the vulvar edema and ulceration. The risk factors for MTX toxicity events include drug dose error, simultaneous use of multiple drugs (non-steroidal anti-inflammatory drugs, phenobarbital, furantoin, etc.), hepatic and renal insufficiency, folate deficiency, abnormal pharmacogenetic metabolism of MTX, and excessive alcohol consumption.^[6] Therefore, the complete blood count and liver and kidney function of the patients should be completely evaluated prior to MTX use, and the dose should be carefully adjusted based on the patient's body surface area. The patient should also be monitored for toxicity during administration, as some patients may exhibit reactions in the absence of risk factors, which may be related to the individual differences in MTX absorption, distribution, metabolism, and excretion.

Following the toxic reaction, drug administration should be immediately discontinued, appropriate treatment should be given, and calcium subfolate should be administered as needed for intracellular rescue as an antagonist of MTX. In severe cases, hemodialysis is required to increase non-renal pathway metabolism and decrease the blood concentration; thereafter, extracellular rescue should be performed. The abnormalities noted are transient, and rapid and complete re-epithelialization of the lesions usually occurs a few hours after MTX discontinuation. In contrast to those treated with high-dose MTX chemotherapy who receive calcium treatment based on the MTX serum concentration and folic acid. Regardless of by what way to medicine when treated with low-dose MTX, MTX blood concentrations is about (0.09 ± 0.15) $\mu\text{mol/l}$, serum MTX concentration do not correlate with the degree of neutropenia or thrombocytopenia, the case fatality rate and death rate of patients with no linear correlation with serum concentration.^[8] Hence, monitoring of MTX plasma concentration may be of little significance in these cases.

Low-dose MTX is safe and effective for the treatment of ectopic pregnancy, and is administered at a markedly lower dose than that for the treatment of malignant tumors. However, due to the differences in the drug tolerances among individuals, the safety of low-dose MTX should be carefully considered. To achieve standard and rational drug use, patients should be educated and made aware of the importance of safe drug use, timely detection of drug toxicity reactions, immediately rescue, prompt discontinuation of medication, and symptomatic treatment with detoxification and nutritional support to avoid accidental occurrence.

Author contributions

Supervision: Lifeng Cui, Yan Wen, Fengyan Gong.

Validation: Xiaojing Liu.

Visualization: Zhiwei He.

Writing – original draft: Guifeng Jia.

Writing – review & editing: Wei Chai.

References

- [1] Delyon J, Ortonne N, Benayoun E, et al. Low-dose methotrexate-induced skin toxicity: keratinocyte dystrophy as a histologic marker. *J Am Acad Dermatol* 2015;73:484–90.
- [2] Li L, Yao D, Xia M, et al. Low-dose methotrexate-induced severe vulvar edema treated for ectopic pregnancy. *Chin J Obstet Gynecol* 2018;53:129–30.
- [3] Weidmann A, Foulkes AC, Kirkham N, et al. Methotrexate toxicity during treatment of chronic plaque psoriasis: a case report and review of the literature. *Dermatol Ther (Heidelb)* 2014;4:145–56.
- [4] Barash JH, Buchanan EM, Hillson C. Diagnosis and management of ectopic pregnancy. *Am Fam Physician* 2014;90:34–40.
- [5] Herfarth HH, Kappelman MD, Long MD, et al. Use of methotrexate in the treatment of inflammatory bowel disease (IBD). *Inflamm Bowel Dis* 2016;22:224–33.
- [6] Yélamos O, Català A, Vilarrasa E, et al. Acute severe methotrexate toxicity in patients with psoriasis: a case series and discussion. *Dermatology* 2014;229:306–9.
- [7] Ming-Chun Hsu, Chih-Chiang Chen. Low-dose methotrexate-induced ulcerated psoriatic plaques: a rare case. *J Am Acad Dermatol* 2015;1:264–6.
- [8] Kivity S, Zafrir Y, Loebstein R, et al. Clinical characteristics and risk factors for low dose methotrexate toxicity: a cohort of 28 patients. *Autoimmun Rev* 2014;13:1109–13.