

Febrile Neutropenia Following Single Dose Methotrexate for Medical Management of Ectopic Pregnancy: Case Report

Ektopik Gebeliğin İlaçla Tedavisinde Tek Doz Metotreksat Sonrasında Febril Nötropeni

Funda GÜNGÖR UĞURLUCAN,^a
Ahmet Cem İYİBOZKURT,^a
Selen GÜRSOY,^a
Samet TOPUZ^a

^aDepartment of Obstetrics and Gynecology, İstanbul University Faculty of İstanbul Medicine, İstanbul

Geliş Tarihi/Received: 18.12.2012
Kabul Tarihi/Accepted: 15.04.2013

This case report was presented as a poster at 8th National Obstetrics and Gynecology Congress, 18-23 May 2010, Antalya, Turkey.

Yazışma Adresi/Correspondence:
Funda GÜNGÖR UĞURLUCAN
İstanbul University
Faculty of İstanbul Medicine,
Department of Obstetrics and Gynecology, İstanbul,
TÜRKİYE/TURKEY
fgungor@yahoo.com

ABSTRACT Methotrexate is a folic acid antagonist and can be used as single or multi-dose regimen for the medical management of ectopic pregnancy. Rarely, side effects are observed during or after methotrexate treatment. Febrile neutropenia is one of these rare complications. We report a 33-year old patient suffering from unruptured ectopic pregnancy and treated with single dose methotrexate treatment and developed febrile neutropenia, thrombocytopenia, dermatitis, diarrhea, stomatitis and alopecia. She was managed with folic acid (leucovorin), granulocyte colony stimulating factor, fresh frozen plasma, and thrombocyte suspensions in addition to intravenous antibiotics. She responded well to treatment; the clinical state and laboratory values normalized in 12 days.

Key Words: Pregnancy, ectopic; 3',5'-dichloromethotrexate; acquired agranulocytosis

ÖZET Metotreksat folik asit antagonistidir. Ektopik gebeliğin medikal tedavisinde tek doz veya multidoz şeklinde uygulanabilir. Nadiren de olsa metotreksata bağlı yan etkiler görülebilir. Febril nötropeni de bu nadir komplikasyonlardan biridir. 33 yaşında, ektopik gebelik nedeniyle tek doz metotreksat tedavisi sonrasında febril nötropeni, trombositopeni, dermatit, diyare, stomatit ve alopesi gelişen vakayı takdim ediyoruz. Tedavide folinik asit (lökovorin), granülosit koloni stimülan faktör, taze donmuş plazma, trombosit süspansiyonu ve intravenöz antibiyotikler kullanılmıştır. Vaka tedaviye iyi yanıt vermiş, klinik durumu ve laboratuvar değerleri 12 günde normale dönmüştür.

Anahtar Kelimeler: Gebelik, ektopik; 3',5'-diklorometotreksat; kazanılmış agranülositoz

Türkiye Klinikleri J Gynecol Obst 2013;23(4):258-60

Ectopic pregnancy is observed in 1-2% of all pregnancies.¹ While the incidence and mortality/morbidity rate of ruptured ectopic pregnancy is high, almost all of the patients diagnosed with ectopic pregnancy are treated either with surgery or medical treatment. Till 1980's, with the introduction of early diagnosis of ectopic pregnancy, medical management with methotrexate (MTX) has been performed.²

MTX is a folic acid antagonist, it inhibits DNA synthesis and cell proliferation. It is used in the treatment of neoplasias, psoriasis, and rheumatoid arthritis. It may be used parenterally or locally, with single dose or multidose regimens in the management of ectopic pregnancy. Main side effects are mild side effects such as mucositis, stomatitis, diarrhea.

Myelosuppression is the major dose-limiting side effect of high-dose MTX. Rarely, with low-dose treatment, as used in rheumatoid arthritis, pancytopenia may develop.³ Occasionally, anemia, leukopenia, or thrombocytopenia may occur without significant reductions in other cell lines.

The definition of neutropenia varies from institution to institution, but severe neutropenia is usually defined as absolute neutrophil count less than 500 cells/microL.⁴ The Infectious Diseases Society of America defines fever in neutropenic patients as a single oral temperature of $>38.3^{\circ}\text{C}$ or a temperature of $>38.0^{\circ}\text{C}$ sustained for >1 hour.⁴

Here we report a case of febrile neutropenia after single dose MTX therapy for medical management of ectopic pregnancy for the first time in the literature as far as we know.

CASE REPORT

33-year-old gravida 5 para 2 patient, applied with delay in the menstrual period and vaginal spotting. Her medical history was unremarkable except for three ectopic pregnancies treated laparoscopically. Gynecologic examination revealed minimal vaginal spotting and pelvic tenderness. Transvaginal sonography showed an endometrium 4 mm in thickness and a 3-cm mass in the right adnexal area without any fetal pole and no free fluid. β -hCG was 2080 mIU/mL, hematocrit 34.3%, leukocyte 6.400/mL, thrombocyte 325 000, blood urea nitrogen (BUN): 17 mg/dL, creatinine 0.8 mg/dL, aspartate aminotransferase (AST): 16 IU/L, alanine aminotransferase (ALT): 10 IU/L, lactate dehydrogenase (LDH): 493 IU/L. The treatment options were discussed and the patient preferred medical treatment with single dose MTX. The weight and height of the patient was 55 kg and 1.65 m, respectively and intramuscular 75 mg single dose MTX according to 50-mg/m² regimen was administered. On the fifth day of the MTX treatment, oral ulcers, dermatitis on the scalp and face, alopecia, and diarrhea developed. β -hCG was 1799 mIU/mL. No pathology was observed in the blood count. Intravenous 40-mg/day methylprednisolone and oral diphenoxylate hydrochloride were begun in addition to intramuscular 7.5 mg

folinic acid. On the ninth day of MTX treatment, the patient developed fever up to 39.4°C ; hematocrit was 24.8%, leukocyte 600/mL, and thrombocytes 92 000/mL. Liver and renal function tests were normal. Subcutaneous thirty million units of filgrastim (granulocyte colony stimulating factor) twice a day was begun with the diagnosis of febrile neutropenia in addition to intramuscular calcium folinate 4x15 mg, intravenous meropenem 3x500 mg and teicoplanin 1x400 mg, and oral nystatin 4x1. On the 12th day of MTX treatment, as the patient still had intermittent fever and hematocrit was 22.4%, leukocyte 500/mL, thrombocyte 10 000/mL and the blood, urine and stool cultures were sterile, bone marrow biopsy was performed. β -hCG was 141.8 mIU/mL at this time. Bone marrow biopsy revealed agranulocytosis and cellular hypoplasia in all three cell lines and folic acid deficiency. Fresh frozen plasma and thrombocyte suspensions were administered three times a day and six days afterwards the fever subsided and laboratory results normalized and the β -hCG was negative.

DISCUSSION

With the introduction and common use of early pregnancy ultrasonography, the early detection of ectopic pregnancy before rupture and its medical treatment has been possible. The success of medical treatment is as high as 90% in hemodynamically stable cases with β -hCG less than 5000 mIU/mL and without fetal cardiac activity.^{5,6}

MTX treatment can be administered as a single dose or multidose regimen. The dosage used for the treatment of ectopic pregnancy is far less than used for other indications; usually doses are given intramuscularly in 50 mg/m² or 1 mg/kg regimens.⁷ MTX is eliminated from the kidneys.⁸ Contraindications to MTX treatment are being hemodynamically unstable, ruptured ectopic pregnancy, hematologic, hepatic, and renal pathologies, immune insufficiency, active pulmonary disease, peptic ulcer, hypersensitivity to MTX, coexistent viable intrauterine pregnancy, and lactation.⁷

Side effects related to MTX are generally mild and rarely observed. Multidose protocol leads to

more side effects when compared to single dose protocol.⁵ 40% of the cases receiving multidose protocol develop side effects as compared to 30% of cases receiving single dose protocol. Single dose protocol is cheaper, requires less monitorization, and there is no need for folinic acid administration.

Myelosuppression is mostly observed in high dose MTX treatment as used in the treatment of rheumatoid arthritis.³ There is only one case of myelosuppression following multidose treatment for medical management of ectopic pregnancy reported in the literature.⁸ This case developed high-grade fever, vomiting, melena, oral ulcerations, pneumonitis, subconjunctival haemorrhages and skin pigmentation, even severe third space fluid collection and shock. Her hematological picture showed severe neutropenia and thrombocytopenia. She was managed in the intensive care unit with ventilatory support, high-dose leucovorin and injection filgastrim.

Our case is unique in that, she developed febrile neutropenia and thrombocytopenia after single dose MTX treatment for medical management of ectopic pregnancy. Folinic acid in addition to granulocyte colony stimulating factor administration is critical in the treatment of this pathology. Folinic acid diminishes the toxicity of

MTX; however may decrease the efficacy of MTX in high doses.⁹

Association between MTX side effects and methylenetetrahydrofolate reductase (MTHFR) polymorphism have been evaluated. In a meta-analysis of 14 studies investigating MTHFR C677T polymorphism in patients with acute lymphoblastic leukemia, MTHFR C677T polymorphism was significantly associated with increased risk of MTX-induced liver toxicity, myelosuppression, oral mucositis, gastrointestinal toxicity, and skin toxicity.¹⁰ The authors suggested that genotyping of MTHFR polymorphism prior to treatment with MTX is likely to be useful with the aim of tailoring MTX therapy and thus reducing the MTX-related toxicities. We did not analyze MTHFR polymorphism in our patient, but it may be speculated that this might be a reason for this complication despite single dose MTX treatment. However, we believe that it is not feasible to check MTHFR polymorphism prior to treatment with MTX for ectopic pregnancy in order to assess the risk of complications.

In conclusion, single dose MTX treatment used for the medical management of ectopic pregnancy is highly successful; but may lead to life-threatening complications, especially in patients with MTHFR polymorphism.

REFERENCES

- Centers for Disease Control and Prevention (CDC). Ectopic pregnancy--United States, 1990-1992. *MMWR Morb Mortal Wkly Rep* 1995;44(3):46-8.
- Lipscomb GH. Medical therapy for ectopic pregnancy. *Semin Reprod Med* 2007;25(2): 93-8.
- Gutierrez-Ureña S, Molina JF, García CO, Cuéllar ML, Espinoza LR. Pancytopenia secondary to methotrexate therapy in rheumatoid arthritis. *Arthritis Rheum* 1996;39(2):272-6.
- Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al.; Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. *Clin Infect Dis* 2011;52(4):e56-93.
- Barnhart KT, Gosman G, Ashby R, Sammel M. The medical management of ectopic pregnancy: a meta-analysis comparing "single dose" and "multidose" regimens. *Obstet Gynecol* 2003;101(4):778-84.
- Morlock RJ, Lafata JE, Eisenstein D. Cost-effectiveness of single-dose methotrexate compared with laparoscopic treatment of ectopic pregnancy. *Obstet Gynecol* 2000;95(3):407-12.
- Practice Committee of the American Society for Reproductive Medicine. Medical treatment of ectopic pregnancy. *Fertil Steril* 2006;86(5 Suppl 1):S96-102.
- Dasari P, Sagili H. Life-threatening complications following multidose methotrexate for medical management of ectopic pregnancy. *BMJ Case Rep* 2012;2012.
- Shiroky JB, Neville C, Esdaile JM, Choquette D, Zummer M, Hazeltine M, et al. Low-dose methotrexate with leucovorin (folinic acid) in the management of rheumatoid arthritis. Results of a multicenter randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 1993;36(6):795-803.
- Yang L, Hu X, Xu L. Impact of methylenetetrahydrofolate reductase (MTHFR) polymorphisms on methotrexate-induced toxicities in acute lymphoblastic leukemia: a meta-analysis. *Tumour Biol* 2012;33(5):1445-54.