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Case Report

Successful treatment of MTHFR A1298C and C677T mutant ectopic pregnant woman with extremely high serum β-hCG levels using single dose methotrexate

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Abstract

Ectopic pregnancy is a life threatening condition in the first trimester. Medical treatment with methotrexate can be administered in selected cases. Methotrexate (MTX) inhibits folate cycle in which 5,10-methylenetetrahydrofolatereductase (MTHFR) enzyme involved. Polymorphisms in the MTHFR enzyme gene is associated with changes in cellular composition of folates and may lead to toxicity of MTX. Herein we present a case report of successful treatment with single dose MTX in MTHFR mutant [C677T (rs1801133) and A1298C (rs1801131)] ectopic pregnant woman with extremely high serum beta fraction of human chorionic gonadotropin (β-hCG) levels with guidance of current literature. A 32 years old primary infertile patient was diagnosed as ectopic pregnancy with a β-hCG level of 18598 mIU/ml. Despite the extremely high levels of β-hCG, the decrease in β-hCG level was uneventful after only single dose MTX administration. She was followed up in outpatient clinical setting without any complication. To the best of our knowledge, This is the first case report in the literature describing a deal with MTX treatment and MTHFR mutancy in ectopic pregnancy treatment.

Key words:

Ectopic pregnancy, methotrexate, MTHFR polymorphism, methylenetetrahydrofolatereductase

Introduction

Ectopic pregnancy (EP) is a potentially life-threatening condition in the first trimester accounting for 6–13 % of all pregnancy-related deaths [1]. With improvements in imaging facilities and serial use of β-hCG levels, EP can be diagnosed early and MTX administration can be a choice of treatment in selected cases. Medical treatment with MTX has a success rate of 90% [2]. MTX inhibits folate cycle in which MTHFR enzyme involved. Polymorphism in the MTHFR gene is associated with changes in cellular composition of folates. The two most commonly identified MTHFR polymorphisms are the single nucleotide substitutions C677T (rs1801133) and A1298C (rs1801131). The C to T change at nucleotide 677 reduces MTHFR activity, and is associated with elevated plasma homocysteine levels [3] and MTFHR activity and plasma homocysteine levels might be affected by the A1298C polymorphism [4]. MTX treatment and the toxicity of this drug is a part of concern in hematology and rheumatology. We also hypothesized that if an ectopic pregnant woman with MTHFR polymorphism is on MTX treatment, these polymorphisms may modulate and exaggerate the cytotoxic effect of MTX. Herein we represent successful treatment with single dose MTX in MTHFR mutant ectopic pregnant woman with extremely high serum β-hCG levels.

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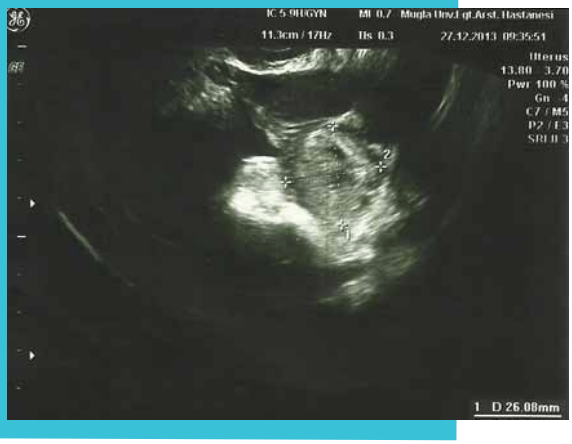
Case presentation

Thirty two-years-old primary infertile patient was admitted to our outpatient clinic and complaining with spotting 10 days after menstrual bleeding. Her first and second pregnancies were terminated due to loss of fetal cardiac activity at 6th and 8th gestational weeks. She could not get pregnant for the last four years. The patient was searched for infertility investigation results and we realized that her thrombophilia examinations revealed a homozygote MTHFR A1298C mutation and heterozygote MTHFR C677T mutation which was performed in another tertiary referral center.

In pelvic examination she had spotty bleeding. A 32x24 mm heterogeneous adnexal mass with peripheral blood circulation and an empty uterus were detected via transvaginal ultrasonography (TVUSG) examination (Figure 1, 2). There was free-fluid in the periphery of the mass and also in the pouch of Douglas. She was hemodynamically stable but her serum β-hCG level was 18598 mIU/ml which might have been regarded as high for MTX treatment. The patient was offered MTX treatment

and she gave written consent. In our gynecology department we use the single-dose MTX protocol which was first described by Stovall et al. [5]. Liver enzymes were checked before methotrexate injection and were all in normal limits. According to this protocol MTX at a dose of 50 mg/m2 was injected intramuscularly to the patient. The day of injection was regarded as the first day of MTX protocol. Her plasma β-hCG level was 15119 mIU/ml on day 4 and 8597 mIU/ml on day 7. Since such a decrease met the follow-up criteria, the patient was discharged for weekly β-hCG measurements. The patient's β-hCG level decreased to 22.24 mIU/ml on the 7th week after MTX injection (Graph 1).

Figure 1.



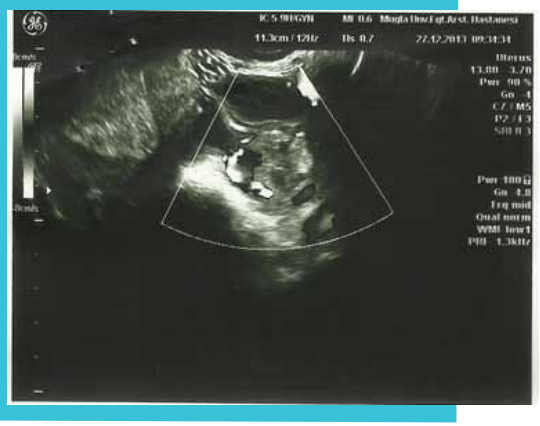
Ectopic pregnancy mass

Discussion

EP treatment could be individualized according to symptoms and findings of the patient. MTX is being used for several years in the medical treatment of EP. According to literature, there are several indications for MTX treatment such as, absent embryonic cardiac activity and < 4 cm size of EP in TVUSG, plasma β-hCG level <5000 mIU/mL, and the cooperability of the patient in the follow-up visits [6]. Contraindications for MTX in EP treatment such as hepatic or renal failure, thrombocytopenia, anemia, or clinical and imaging suspicion of tubal rupture. Besides these contraindications there are also several relative contraindications for MTX treatment in EP such as high β-hCG concentration, presence of fetal cardiac activity, large ectopic size (≥3.5 cm) and presence of peritoneal fluid [7,8]. If the patient is hemodynamically stable, the presence of hemoperitoneum is not a contraindication to medical treatment with MTX [9].

The most important parameter for prediction success of MTX therapy is the serum beta-hCG level in patients with ectopic pregnancy [10]. In the present case, β-hCG level was 18598 mIU/ml. In a review conducted by Cecchino et al., for every 10 treatments of patients with β-hCG levels exceeding 5000 mIU/mL, there was at least one more treatment failure [11]. According to long non-randomized clinical trial results of Sagiv et al. levels of β-hCG greater than 2,000 mIU/mL increased the odds of failure by about 4.5 times [12]. In the present case, despite the high levels of serum β-hCG levels, MTX treatment was uneventfully successful. This interesting result led us to reevalute the mechanism of action of MTX.

Figure 2.



Doppler flow scan of ectopic pregnancy mass.

MTX is a chemotherapeutic agent that interrupts folic acid cycle. An important enzyme in the folate/MTX metabolism pathway is MTHFR. Because folate and homocysteine homeostasis are affected by MTX action, it is possible that MTHFR polymorphisms may also modulate the outcome in patients treated with this drug and may lead to the toxicity of MTX.

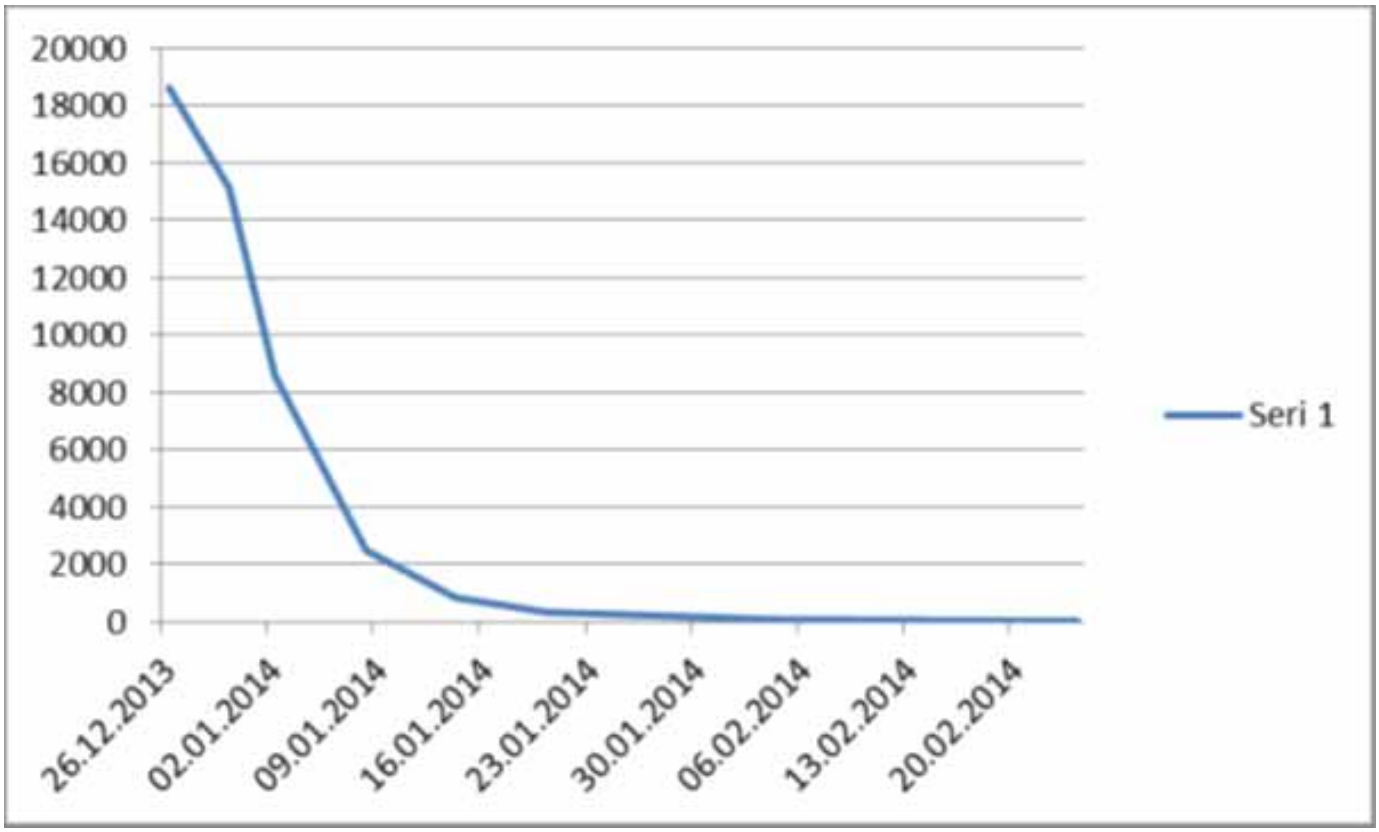
In the literature investigations are going on about MTHFR mutations and MTX toxicity especially on hematological malignancies and rheumatology. In a metaanalysis conducted by Song et al., the MTHFR C677T and A1298C polymorphisms are associated with MTX toxicity in patients with rheumatoid arthritis (RA) [13]. In contrast to these findings, Morgan et al. conducted a meta-analysis of comparable studies and found that A1298C (rs1801131) and C677T (rs1801133) polymorphisms were not associated with MTX treatment response and are unlikely to have a clinically meaningful effect on the first 6 months of MTX treatment in early RA [14]. Ayad et al. demonstrated a statistically significant increase in hepatic toxicity with MTX in lymphoma patients with MTHFR C677T than the other wild type polymorphisms [15].

According to our knowledge, this is the first ectopic preg-

nancy case presented with MTHFR homozygote mutancy and a deal with MTX treatment. We conclude that MTX treatment is more effective in ectopic pregnant woman with MTHFR A1298C and C677T genetic polymorphism even in extremely elevated serum β-hCG level. This case report might lead to further studies about MTX dose adjustment in MTHFR mutant patients with EP.

Conflict of interest statement

The authors declare no conflict of interest.



Graph 1 *Serum β-hCG levels in mIU/ml after injection of MTX*

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