EKTOPİK GEBELİK TEDAVİSİNDE DÜŞÜK TEK DOZ METHOTREXATE SONRASI GELİŞEN PANSİTOPENİ VE STEVENS-JOHNSON SENDROMU; OLGU SUNUMU VE LİTERATÜR DERLEMESİ

Pancytopenia and Stevens-Johnson Syndrome After Single Low Dose Methotrexate for Treatment of Ectopic Pregnancy; Case Report and Review of the Literature

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ÖZET

Ektopik gebelik genellikle poliklinik şartlarında tanısı konulan ve tedavisi yapılan bir durumdur. Hemodinamik olarak stabil ve yandaş sorunu olmayan hastalarda düşük tek doz methotrexate sıklıkla tercih edilen tedavidir. Methotrexate'ye karşı gelişen mukozit, abdominal kramplar ve yorgunluk gibi yan etkiler sıklıkla öngörülebilir ve doz bağımlıdır. Her ne kadar ektopik gebeliklerde kullanılan düşük dozlar ile beklenmese de, pansitopeni benzeri ciddi ve öngörülemeyen yan etkiler de mümkündür. Sunduğumuz vakada düşük tek doz (50mg/m2 vücut yüzey alanı) methotrexate sonrası ciddi pansitopeni gelişimi anlatılmıştır. 30 yaşında, gravida 2, para 1 kadın hasta son adet tarihine göre 7 haftalık ektopik gebelik tanısı aldı. Düşük tek doz methotrexate uygulaması sonrasında ciddi pansitopeni ve yaygın deri döküntüleri izlendi.Bu vaka İngilizce literatürde böbrek fonksiyonları normal olan bir ektopik gebelik vakasında düşük tek doz methotrexate uygulaması sonrası gelişen ilk ciddi pansitopeni vakasıdır.

Anahtar kelimeler: *Ektopik gebelik; Methotrexate; Pansitopeni; Stevens-Johnson sendromu.*

ABSTRACT

Ectopic pregnancies are usually diagnosed and treated in outpatient setting. Single low dose methotrexate is often the choice of treatment in otherwise normal and hemodynamically stable patient. Adverse reactions to methotrexate are mostly predictable and dose dependent such as mucositis, abdominal crampings and malaise. Although it is safe with low doses used in ectopic pregnancy, serious adverse and unpredictable reaction such as pancytopenia is possible. We report here a case with a rare but serious drug reaction after a single low dose (50mg/m2 body surface area) methotrexate. A 30-year-old woman with gravida 2, para 1 was diagnosed as ectopic pregnancy at 7 weeks of pregnancy due to her last menstrual period. Severe pancytopenia and diffuse skin eruptions developed after single, low dose (50mg/m2) methotrexate application. This is the first reported case in English literature of pancytopenia caused by low dose methotrexate in a patient with normal kidney function.

Key words: *Ectopic pregnancy; Methotrexate; Pancytopenia; Stevens-Johnson syndrome.*

INTRODUCTION

Methotrexate is being used liberally and frequently in the treatment of ectopic pregnancies. Because of its availability, cost effectivity, safety measures, succesfull clinical outcomes and causing a decline in need for surgery, methotrexate recently became the choice of treatment in suitable cases of ectopic pregnancy. Although most of the side effects are predictable, clearly defined and easily diagnosed by most of the clinicians; rare but fatal and unpredictable side effects such as anaphylactoid reactions and pancytopenia are possible.

This is the first reported case of pancytopenia related to low dose methotrexate in a patient with normal kidney function in English literature. Although the adverse reaction we described here is extremely rare and should not be expected to change clinical management, the clinicians should be aware of this possibility even with low doses of methotrexate.

CASE REPORT

A 30-year-old woman with gravida 2, para 1 was diagnosed as ectopic pregnancy at 7 weeks of pregnancy due to her last menstrual period. Her first pregnancy was normal and ended up at term 9 months ago by C-section. She had an unremarkable past medical history, with no history of systemic illness, pelvic inflammatory disease, intrauterine device (IUD) use, ovulatory induction or drug sensivity. While she was still lactating, she admitted to the emergency service with complaints of mild vaginal bleeding and lower abdominal pain. On physical examination she had mild, nonfocal, lower abdominal tenderness. Pelvic examination revealed no active bleeding from cervical os, a uterus of normal size and slight fullness of left adnexa without adnexial tenderness. Pelvic sonography was performed and revealed a left adnexial mass of 32mmx43mm with no free fluid in the pelvis and no gestational sac within uterine cavity. The blood B-hCG level was 1,712 mIU/ml on admission. Based on these clinical findings, she was diagnosed as ectopic pregnancy. The blood tests for complete blood count and liver enzymes were all within normal ranges. After administration of low dose, 80mg methotrexate, (50mg/m2 body surface area) the patient had a profound desquamating skin eruption at the fifth day and pancytopenia at the seventh day of treatment.

The first dose of Methotrexate was applied via intramuscular route when blood B-hCG level was 1,712 mIU/ml. The 2-day interval follow-up of blood B-hCG measurements beginning at the fourth day of Methotrexate, yielded following results; 1,417mIU/ml, 1,110mIU/ml, 978mIU/ml, and 400mIU/ml respectively. On the fifth day of treatment, the patient presented with stomatitis, diffuse erythematous skin lesions and subclinical fever (37.8 C) and was hospitalized. The patient was haemodynamically stable with a blood pressure of 110/70mmHg, pulse 68/min and no abdominal tenderness or rebound on admission. Blood tests for BUN, Creatinine, ALT, AST and complete blood count were within normal limits.The transvaginal sonography revealed a heterogenous mass of 48x40mm in the left adnexial area compatible with haematosalpinx and 65x60mm of free fluid thought to be haemorrhage at the left paraovarian area extending to the pouche of Douglas. However on the seventh day of treatment, white blood cell count began to decrease. The graphical change in amounts of blood white cells, red cells and platelets with time is shown in Figure 1.

Serial sonographic examinations revealed a decrease in the size of free fluid (haemorrhage) area and haematosalpinx. At the end of the 31st day of methotrexate treatment, the patient recovered, totally free of the skin lesions, normal pelvic sonographic findings and discharged from the hospital.

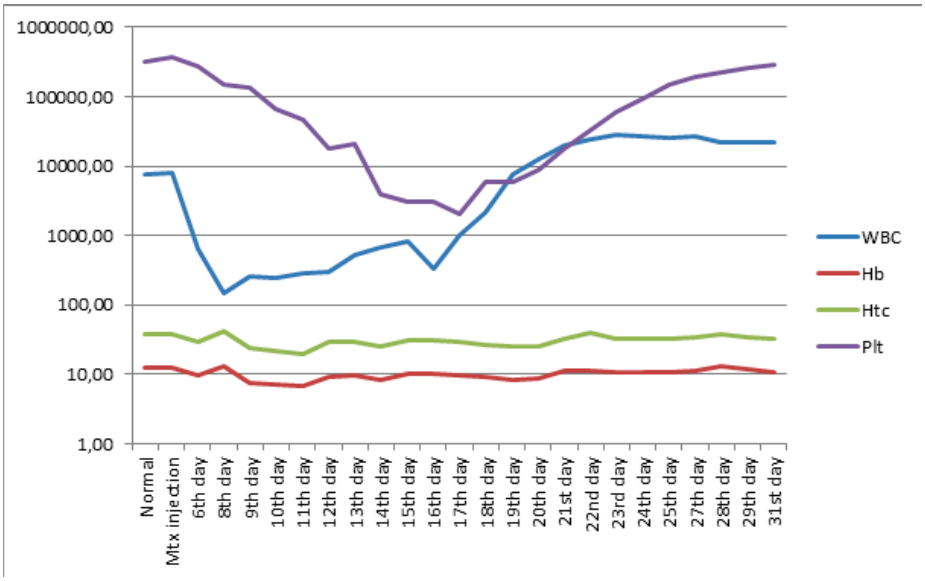

Figure 1. The change in amount of blood cell lines with time, starting with normal complete blood count before Methotrexate treatment.

DISCUSSION

The prevalence of ectopic pregnancy is about 1.5-2.0% of all pregnancies (1). Although the incidence has increased, the mortality rates has decreased over time, primarily due to earlier diagnosis and treatment options before rupture (2). Treatment options in developed world has shifted from primary surgery to either minimal invasive surgery or medical management with methotrexate. Medical management with methotrexate seems more cost effective over surgical management, either traditional or minimal invasive surgery, especially when B-hCG level is greater than 1,500 mIU/mL. Both outcomes of tubal patency and recurrence rates are comparable (3).

The first clinical usage of systemic methotrexate for gynecologic purposes is more than 40 years after it had been started to be used by haematologists for haematological malignancies. The first use of methotrexate by the gyaecologists ıs the fixed multiple dose regimen described by Goldstein and Bagshawe for treatment of gestational trophoblastic disease (4, 5). This regimen is combined with folinic acid (citrovorum/leucovorin rescue) to reduce toxicity. The first pioneer of single dose methotrexate for ectopic pregnancy in English literature was Stovall in 1985, whose ultimate dosage regimen led to a single dose 50mg/m2 body surface area given via i.m. route without any folinic acid (6). Today this is the preferred regimen for treatment of ectopic pregnancies. Methotrexate is an antagonist of folic acid which causes interference with DNA synthesis and cell proliferation by inhibiting de novo synthesis of purines and pyrimidines. Side effects are usually related to systems with high proliferation rates. The most common side effects include stomatitis, conjuctivitis, gastritis/enteritis, impaired liver function tests, bone marrow depression and photosensitivity. The mechanism of action, distribution and elimination dynamics of methotrexate are usually well known by the clinicians. Methotrexate and its metabolites are excreted predominantly via the kidneys with nonlinear kinetics due to the tubular secretion/reabsorption cycle (7). This can be altered in renal insufficiency and certain conditions such as ingestion of high dose aspirin. When needed to be used in a patient with impaired kidney function, dosage should be adjusted and closely monitored in order to minimize the potential harm. Kelly et al.

We reported a case of pancytopenia after single low dose methotrexate injection for ectopic pregnancy in a young, haemodialysis-dependent woman (8). However, as seen in our case presentation, a severe adverse reaction such as pancytopenia is possible and unpredictable even if kidney functions are normal.

In our case, we were lucky in such a devastating position that the single dose of methotrexate was enough for the termination of ectopic pregnancy and the internal haemorrhage caused by tubal abortion cessated spontaneously. But what should we do if not?

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