OLGU SUNUMU CASE REPORT

DOI: 10.24074/tjrms.2020-80598

Caution: Even in A Single-Low Dose Methotrexate for Treatment of Ectopic Pregnancy Could Have Severe Adverse Effects in Women with Chronic Renal Insufficiency: A Case Report

Dikkat: Kronik Renal Yetmezliği Olan Kadınlarda Ektopik Gebelik Tedavisinde Tek, Düşük Doz Metotreksat Bile Ciddi Yan Etkiler Yapabilir: Bir Olgu Sunumu

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ÖZET

Bu olgu sunumunda, kronik renal yetmezlik nedeniyle hemodiyaliz olan ve ektopik gebelik için tek, düşük doz metotreksat (Mtx) uygulaması sonrası şiddetli oral mukozit, cilt döküntüsü ve kemik iliği supresyonu geliştiren bir hasta bildirilmiştir. Böbrek yetmezliği olan hastalarda düşük dozda bile olsa Mtx'den kaçınılmalıdır

Anahtar Kelimeler: Ektopik gebelik, metotreksat, böbrek yetmezliği, kemik iliği depresyonu

ABSTRACT

In this case report, a patient on hemodialysis due to chronic renal insufficiency and developed severe oral mucositis, skin rash and bone marrow suppression after being treated with single low-dose methotrexate (Mtx) for ectopic pregnancy was reported. Mtx even in low dose should be avoided in patients with renal insufficiency.

Keywords: Ectopic pregnancy, methotrexate, renal insufficiency, bone marrow suppression

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Peer review under responsibility of Turkish Journal of Reproductive Medicine and Surgery.

Received: 14 Dec 2020 ***Received in revised form:*** 4 Jan 2021 ***Accepted:*** 6 Jan 2021 ***Available online:*** 25 Aug 2021

OBJECTIVE

Methotrexate (Mtx) is a folic-acid antagonist which inactivates synthesis of cellular DNA.[1] This cytotoxic agent has been used for the treatment of ectopic pregnancy (EP) since 1982. Side effects of this drug include pancytopenia, liver toxicity, stomatitis, mucositis, rash and pulmonary toxicity.

Mtx is excreted through the urine. Extreme attention should be paid for patients with renal insufficiency since severe even fatal pancytopenia has been reported for those patients on dialysis.[2]

Human chorionic gonadotropin (hCG) is degraded and excreted by the kidneys and pathologically elevated levels can be caused due to poor renal clearance.[3]

In this case report, a patient on hemodialysis due to chronic renal insufficiency developed severe oral mucositis, skin rash and bone marrow suppression after being treated with single low-dose Mtx for EP was reported.

CASE REPORT

28-year-old patient, who was dialysis dependent for 12 years, admitted to our clinic because of infertility. Medical history revealed she had been dependent for dialysis due to chronic renal failure and kidney transplantation was performed 12 years ago which was rejected. Her obstetric history revealed a termination of 26 weeks pregnancy due to severe preeclampsia and laparoscopic right salpingectomy for ruptured EP.

After detailed discussion with couple, and agreement and permission from the nephrology unit the IVF/ICSI treatment was planned. In her first IVF attempt, pregnancy was not achieved. After 5 months, frozen-thawed embryo transfer (ET) cycle was performed. On the 14th day of ET, level of serum β HCG was 20.1 mIU/ml and progesterone was 10.7 ng/ml. βHCG values are shown in Figure 1. Initial βhCG-levels were low, following levels steadily increased. At the 7th weeks of pregnancy transvaginal ultrasound demonstrated endometrial thickness of 10 mm, minimal fluid in the douglas and the absence of gestational sac in the cavity with βhCG-level of 4367 mIU/ml and progesterone of 1.45 ng/ml. Histopathological confirmation of EP was done by the endometrial curettage. A single-dose methotrexate treatment was planned considering intraabdominal adhesions due to previous surgeries. After the nephrology consultation, a single-half dose methotrexate (50% of planned dosage; 25 mg/m^2, 45 mg, intramuscular) was administered.

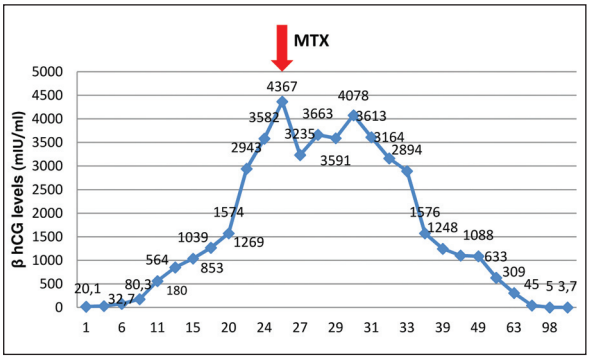
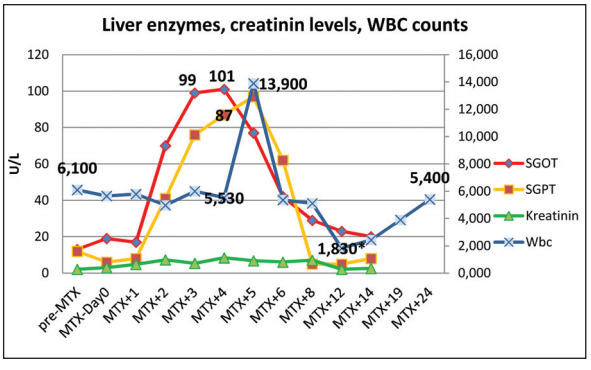


FIGURE 1: Serum βhCG levels

On the day of the treatment, glomerular-filtration-rate was 20.59 ml/ min, serum creatine level was 2.99 mg/dl and the other biochemical parameters were in normal range. Two days after creatine level increased to 7.38 and the patient was dialyzed. On the 4th day of treatment ulcerative lesions on oral mucosa developed. She had dysphagia and throat ache. Ulcerative lesions of the buccal mucosa, oropharyngeal hyperemia and papilla atrophy were consistent with oral mucositis. Same day serum SGOT/SGPT levels were; 101 IU/L and 87 IU/L (Figure 2). Diagnostic findings were consistent with methotrexate toxicity. Following next two days, pruritis and maculopapular rash on the neck and chest has developed. Mtx-level on the 5th day of treatment was 1.05 µmol/L. The hemodialysis was carried out four times during hospi-



Biochemical parameters during follow-up.

talization. Daily medication consisted of folic acid, nystatin oral suspension, flurbiprofen + chlorhexidine gluconate spray, parenteral rehydration and nutrition were initiated. Oral lesions began to regress following days and βhCG levels began to decrease. On the advice of oncology consultation, granulocyte colony stimulating factor (GCSF) (300 μg/day) administered for three days. The patient was discharged on her own insistence, at 9th day of hospitalization with recovering oral and cutaneous lesions and improved general health. Although GCSF was given, signs of bone marrow suppression was seen on the follow-up period (12th day of Mtx treatment) (WBC; 1830, Plt; 98,000) which was resolved a week later. Patient consent was obtained for the publication as a case report.

DISCUSSION

Two purposes have made us present this case; 1: Methotrexate serum levels do not reflect and correlate with clinical toxicity and clinicians see adverse effects even with low dose therapy, 2: The βhCG values may be misleading for patients with renal failure due to limited extraction.

After detailed search of the literature, we found only two other case reports related to Mtx toxicity after given for EP in a dialysis dependent patient. Willner et al. reported a patient on hemodialysis and presented pancytopenia, diffuse skin desquamation and severe mucositis after treatment with 100 mg Mtx for EP.[4] In another case unfortunately fatal methotrexate toxicity was reported.[5] Standard Mtx therapy (50 mg/m^2) intravenously was given in a woman on peritoneal dialysis and pancytopenia, adult respiratory syndrome, toxic epidermal necrolysis, necrosis of the distal gastrointestinal tract and unfortunately death was reported.[5] In our case, we used adjusted dose as a half dose of standard Mtx treatment (25 mg/m^2). Even in this low dose, our case also demonstrated skin desquamation, severe mucositis and early signs of bone marrow suppression. After supportive care and treatment, the patient was discharged at the 9th day of hospitalization without any complaints. It is evident that Mtx even in a half dose should be avoided in the management of EP in patients with renal insufficiency.

Mtx therapy could bring about fatal adverse effect in dialysis patients, even in low dose. Cheung et al. reported 14 patients with renal failure, recognized with severe pancytopenia even after low dose Mtx therapy (2.5 mg) mostly used for rheumatological diseases.[2] Higher plasma levels and prolonged half-life due to ineffective renal clearance of the drug has been stated.[2] The authors concluded strongly to discourage administrating Mtx to end stage renal disease patients. It has been suggested that only high-flux hemodialysis are potential options for effective removal of Mtx.[6]

Similarity in molecular weight for hCG, β2 microglobulin and α1 microglobulin favors the hypothesis of a lower hCG clearance in women with renal disease.[7] This knowledge should guide practitioners caring for women with renal disease to evaluate serum hCG tests carefully for diagnosis of EP or other complications.

In conclusion; even though dose adjustments for Mtx have been made, there still a possibility of serious adverse effects in dialysis dependent patients. Therefore, Mtx treatment even in low dose should not be given for treatment of EP in patients with renal insufficiency. In addition, because of the decreased renal clearance of hCG, clinicians must be careful when diagnosing EP and other pregnancy related problems.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Gülnaz Şahin, Ferruh Acet;* ***Design:*** *Gülnaz Şahin, Ferruh Acet;* ***Control/Supervision:*** *Erol Tavmergen;* ***Data Collection and/or Processing:*** *Ferruh Acet, Gülnaz Şahin;* ***Analysis and/or Interpretation:*** *Ege Nazan Tavmergen Göker;* ***Literature Review:*** *Gülnaz Şahin, Ferruh Acet;* ***Writing the Article:*** *Gülnaz Şahin, Ferruh Acet;* ***Critical Review:*** *Ege Nazan Tavmergen Göker, Erol Tavmergen.*

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