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# Methotrexate-induced peritonitis: Case report

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ABSTRACT

Peritonitis was observed during the second and third courses of chemotherapy of a patient with low-risk gestational trophoblastic neoplasia treated with sequential methotrexate and folinic acid. However, methotrexate - folinic acid therapy was continued and the peritonitis didn't relapse. Complete clinical response was achieved after nine courses of chemotherapy.

## 1. Introduction

Gestational trophoblastic neoplasia (GTN) is diagnosed when four values or more of plateaued β-hCG (±10%) persist for at least 3 weeks, or when there is a rise of β-hCG of 10% or greater for 3 values or more for at least 2 weeks after molar evacuation, or if there is histological diagnosis of choriocarcinoma - invasive mole and placental site trophoblastic tumor, or if persistence of β-hCG beyond 6 months is observed, or if β-hCG level of a woman with metastatic disease of an unknown origin is high and this woman is not pregnant [1]. Treatment of GTN is determined by the modified WHO prognostic index score and anatomic FIGO (International Federation of Gynecology and Obstetrics) staging system [2].

GTN is divided into two groups according to the modified WHO scoring system. One of these is low-risk group with a score of 6 or less and the other one is high-risk group with a score of 7 or greater. Clinical response is achieved at a rate of 85% by using single-agent methotrexate (MTX) in the treatment of low-risk GTN [3,4]. MTX is also used as a component of multi-agent chemotherapy in the treatment of high risk GTN. Acute toxicity such as nausea, vomiting, diarrhea, mucositis, bone marrow suppression and chronic toxicity such as liver atrophy, liver cirrhosis, nephropathy, defects in oogenesis and spermatogenesis and osteoporosis are seen in patients receiving methotrexate treatment [5]. Also serositis is one of the acute toxicities of MTX treatment and usually presents as pneumonia and pleural effusion. In rare cases it can be seen as peritonitis and pericarditis.

The aim of this article is to present a case of peritonitis induced by sequential methotrexate-folinic acid (MTX-FA) treatment in a patient with low risk GTN.

## 2. Case report

A 34-year-old patient who underwent dilatation and curettage with a pre-diagnosis of molar pregnancy in another center applied the same center with a complaint of abdominal pain after two days from the operation. Pelvic abscess was diagnosed as a result of the evaluation and antibiotic treatment was initiated.

Since β-hCG value of this patient whose pathological examination of the curettage specimen was reported as partial mole increased during follow-up, she was

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referred to our hospital with a pre-diagnosis of GTN. The uterus of the patient who had vaginal bleeding in the gynecological examination was 6-week sized. In transvaginal ultrasonograhy, a sonographic appearance consistent with GTN that was (59×42) mm in size and that had extensive vascularization in Doppler evaluation and invaded myometrial boundary was detected. Diagnosis of GTN was confirmed for this patient who had β-hCG value of 35 102 mIU/mL. The age of tumor was 1 month, tumor was limited to uterus and size of it was (59×42) mm. Brain magnetic resonance imaging, chest X-ray and abdominal computed tomography were normal. Sequential MTX (days 1-3-5-7, 1 mg/kg) - FA (days 2-4-6-8, 0.1 mg/kg) chemotherapy was planned for the patient whose modified WHO scoring system score was 3 and whose FIGO stage was 1. Severe abdominal pain developed in the patient at the beginning of the second course of treatment with MTX-FA, after the second dose of MTX of the second course was applied. Her β-hCG value was 882 mIU/mL. Bowel sounds of the patient who had gas and stool output were normal at the physical examination of the abdomen. On the other hand, tenderness, rebound and defense were observed at right lower quadrant of the abdomen. Considering the clinical features, three possible diagnoses were thought. These were secondary peritonitis related to former pelvic abscess, serositis induced by MTX, and appendicitis. The patient whose other biochemical values and urinalysis were normal, had a leukocyte count of 5 330/μL, sedimentation value of 74 mm/hour. Air-fluid level was not observed in abdominal radiography and intrauterine mass was found to be (42×34) mm in size in whole abdominal ultrasonography. Intraabdominal free fluid was absent. Acute appendicitis was excluded as a result of clinical examination and imaging studies. Masses with dimensions of (17×15×9) mm and (13×10×7) mm were defined at lower abdominal computed tomography. During follow-up, the patient did not have high fever. Antibiotic therapy was used considering the diagnosis of secondary peritonitis related to the former pelvic abscess. The symptoms of the patient whose leukocyte count was 4 480/μL, sedimentation was 40 mm/hour, C-reactive protein was 6 mg/dL, diminished on the sixth day of treatment. During evaluation of her symptoms, MTX therapy was continued and a second course was finished.

The third course of chemotherapy with MTX-FA was given to the patient who had β-hCG value of 165 mIU/mL. After the second dose of third course of MTX chemotherapy, the patient's abdominal pain repeated. In the abdominal examination of patient, bowel sounds were normal and abdominal tenderness was detected but rebound and defense did not exist. Abdominal radiograph was normal. The patient's leucocyte count was 6 010/μL and other biochemical values were normal. Serositis induced by MTX was diagnosed when considering the whole clinical presentation from the beginning. β-hCG values decreased to 129.5 mIU/mL after the second dose. When the patient was evaluated from the beginning, the response to treatment was accepted as well and serositis presentation was mild. Therefore it was decided to continue the treatment with MTX-FA without skipping doses and dose reduction. The third course of chemotherapy was completed without any problem. The patient was considered to have complete response clinically after eight courses and then one more course of MTX-FA was given. After this treatment, the patient was followed up regularly. After the third course of chemotherapy, serositis did not recur. In the following 3 months, the patient was considered to be in remission and abdominal pain or oncological problems didn't develop.

## 3. Discussion

MTX that is used for the treatment of neoplastic and non-neoplastic conditions is a folic acid analogue. It causes deficiency of folate coenzymes and interrupts DNA synthesis. Acute toxicity such as nausea, vomiting, diarrhea, mucositis, bone marrow suppression and chronic toxicity such as liver atrophy, liver cirrhosis, nephropathy, defects in oogenesis and spermatogenesis and osteoporosis are seen in patients receiving methotrexate treatment. Serositis, whose etiology and pathophysiology is unknown, is one of the acute toxicities of MTX treatment. It can be accepted that serositis is a cellular immune response developed against MTX treatment [6,7]. As a result, it is not accepted as a direct toxic effect of the drug. Serositis induced by MTX is reported to occur in 5-12 % of the treated patients [8]. Its frequency can reach to 20-25% for persistent cases where repeated doses are given [9].

Serositis usually presents as pneumonia and pleural effusion. In rare cases, it can be seen as peritonitis and pericarditis. The pleural toxicity induced by MTX is usually seen as mild pleuritic chest pain. These patients usually had normal chest X-ray and ventilation perfusion scan. It usually responds to hydration and simple analgesia [9]. Pneumonitis, whose prevalence is reported to be 0.3%-7.5%, is a serious and unpredictable side-effect of MTX [10]. This side-effect is not related to dose or duration of the treatment [10,11]. Because of the unspecificity of clinical and pathological findings, the diagnosis of pneumonitis induced by MTX is difficult. Dyspnea, cough and fever are the most frequent presenting symptoms. Infections and other pulmonary diseases should be excluded. The prognosis of pneumonitis induced by MTX is thought as benign. However, patients died of pneumonitis were reported. If it is suspected, the treatment should be discontinued [12].

Pericarditis induced by MTX was first defined by Forbat *et al* in 1994 for a patient with a diagnosis of GTN [5]. This 22 year-old patient who received nine courses of MTX chemotherapy had pleuritic chest pain after the seventh course and as a result of the evaluation; pneumonitis and pleurisy induced by MTX were diagnosed. The symptoms

were treated with hydration and simple analgesia. Two months from the end of the treatment, pleuritic chest pain of the patient repeated and dyspnea was observed. Pericardial effusion was found in examinations and diagnosis was accepted as pericarditis induced by MTX by excluding the other possible causes. The symptoms of the patient decreased after pericardial aspiration. There was not recurrence in the following 18 months. In addition, Dündar *et al* reported pericarditis induced by MTX, too. At the case where a 33 year-old patient diagnosed with low risk GTN was given MTX-FA chemotherapy, pericarditis was induced by MTX before the second course. Because of this, the treatment was ceased and after the healing of pericarditis, it was restarted [13]. At the following courses, it didn't recur.

MTX-induced peritonitis was first reported in 1999 by Sharma *et al*. MTX treatment was given to a 27 year-old patient who had GTN diagnosis [9]. Abdominal pain developed during the first course of treatment. The physical examination was normal and repeated ultrasound scans of abdomen and pelvis didn't change. The patient was treated with analgesia. And then the symptoms reduced. However, at the second course, repeated abdominal pain was observed and according to the physical examination and ultrasound findings, there was no difference and the patient was managed conservatively. When the whole clinical presentation was considered, peritonitis caused by MTX was thought and therefore the patient's treatment was changed. There were no further abdominal symptoms. In the current case reported here, due to the mild clinical symptoms and maintained response to the treatment, MTX treatment was continued. Serositis did not recur, despite 6 more courses were given after the peritonitis. Remission was obtained and any problems did not develop in the follow up period.

As a result, serositis is a complication of the MTX treatment and peritonitis is an infrequent type. In the case presented here, although the peritonitis developed, MTX treatment was not ceased and continued until providing remission. In the following courses, peritonitis didn't recur. However, there is no enough data regarding the use of MTX after serositis. Other management options may be considered for these cases.

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