Severe Peritonitis Induced by Methotrexate During Treatment of Persistent Gestational Trophoblastic Disease

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A 47-year-old woman with three children, without previous endometriosis or abnormal menstrual history, was referred to our department following a diagnosis of International Federation of Gynecology and Obstetrics stage III (lung metastasis) gestational trophoblastic neoplasia [1]. The patient had been treated by suction curettage for an invasive complete mole. Serial monitoring of serum β -human chorionic gonadotrophin (hCG) showed increasing concentrations after a nadir of 240 IU/L 6 weeks after curettage. Staging chest computed tomography (CT) scan showed a 6-mm pulmonary nodule in the left lower lobe. Abdominal and pelvic CT scan and brain magnetic resonance imaging were normal.

The patient presented a low risk of resistance to monotherapy (score <7) classification. Therefore, single-agent intramuscular methotrexate (MTX) was started at a dose of 1 mg/kg body weight on days 1, 3, 5 and 7, alternating with oral folinic acid rescue on days 2, 4, 6, and 8 every 14 days [2]. The first cycle was well tolerated except for grade I stomatitis.

On day 7 of cycle 2, the patient developed fever and severe left-sided abdominal pain, exacerbated by movement and deep breathing, without associated nausea, vomiting, or diarrhea. Physical examination showed rebound tenderness but no guarding or rigidity of the abdominal wall. Blood leukocyte count was normal. C-reactive protein (CRP) was markedly elevated at 217 mg/L.

An abdominal CT scan showed a colonic wall thickening at the splenic flexure with pericolic fat edema, consistent with colitis, without intra-abdominal or pelvic fluid collection. Colonoscopy was macroscopically normal and pathological examination of mucosal biopsies as well as polymerase chain reaction for cytomegalovirus detection did not reveal any anomalies. Empirical antimicrobial therapy (ciprofloxacin and

metronidazole) was administered for a total duration of 7 days. Symptoms resolved entirely within 2 days. Multiple blood cultures remained negative, and stool cultures showed no intestinal pathogen.

Cycle 3 started according to schedule. The patient was readmitted on day 6 with identical clinical symptoms. Blood leukocyte count was elevated at 16 G/L and CRP was markedly elevated at 287 mg/L. CT scan showed left colonic flexure wall thickening, pericolic fat edema, and a small amount of ascites (Fig. 1). The pretherapeutic CT scan was normal (Fig. 2), without signs of peritoneal implants. Empirical antimicrobial therapy (ciprofloxacin and metronidazole) was initiated; symptoms subsided within 2 days. Once more, multiple blood cultures and stool cultures were normal.

Cycle 4 started with a 1-week delay. The patient was readmitted on day 6 with the same clinical-biological presentation. Colonoscopy remained normal. Considering the history of the previous events with quick resolution and no infectious complications, MTX-induced peritonitis was suspected and no antimicrobial therapy was given. Symptoms spontaneously resolved within 2 days. By that time, the patient had completed the planned two cycles of chemotherapy beyond normalization of hCG concentration and treatment was discontinued.

Putative differential diagnoses include surgical visceral emergencies, familial Mediterranean fever (this patient had Balkan ancestry), acute intermittent porphyria, and systemic lupus erythematosus. However, these entities seem highly unlikely in view of the cyclical symptomatology related to drug administration, the spontaneous resolution of symptoms, the age at first onset, and the absence of new episodes following MTX discontinuation.

Serosal complications of MTX treatment have been previ-

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Figure 1. Abdominal computed tomography scan on day 6 of cycle 3: left colonic flexure wall thickening with pericolic fat edema.

Figure 2. Normal pretreatment baseline abdominal computed tomography scan.

ously described. First reports can be traced back to the 1970s [3], although these complications were nearly exclusively reported to occur in the pleura and pericardium. One case series reported that 25% of patients treated with low-dose methotrexate for persistent gestational trophoblastic disease developed serosal symptoms [4]. The majority experienced mild to moderate pleurisy symptoms, sometimes associated with clinical and ultrasound signs of pericarditis. To our knowledge, only two cases of acute serositis occurring in the peritoneum have been reported to date [4, 5], with one additional case of MTX-associated sclerosing encapsulating peritonitis [6].

The clinical presentation of serosal side effects of MTX is

characterized by a temporal relationship between MTX administration and patient's symptoms—a feature shared by previously reported cases and our own experience [4]. The clinical presentation of MTX-induced peritonitis—with associated abdominal signs evocative of a surgical emergency together with a biological inflammatory syndrome (elevated CRP) and abnormal CT scan findings—could lead to unnecessary aggressive surgical exploration. It is therefore important to consider this diagnosis in patients receiving low-dose MTX during persistent gestational trophoblastic disease treatment. The pathophysiological mechanism of this serous inflammation remains unclear, but it may be immune mediated [4].

In conclusion, MTX-induced peritonitis is a rare event, but it must be considered to avoid unnecessary surgical exploration or antibiotic treatment.

AUTHOR CONTRIBUTIONS

Conception/Design: Stefan Zimmermann, William Jacot

Provision of study material or patients: Stefan Zimmermann, Khalil Zaman, Anita Wolfer, William Jacot

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