

Methotrexate-induced pancytopenia in a patient with ectopic pregnancy

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Methotrexate (MTX) has been used as the primary treatment for ectopic pregnancies; however, it raises the risk of a life-threatening adverse drug reaction such as pancytopenia [1]. We present a case of MTX-induced pancytopenia in a patient with ectopic pregnancy, which may be idiosyncratic and perhaps unavoidable, and we identify a few early signs of MTX toxicity that might assist in monitoring in order to minimize unintended consequences in patients.

A 27-year-old woman (gravida 2 and para 1), whose body surface area was 1.46 kg/m², presented without contributory medical history. She was diagnosed with ectopic pregnancy based on the findings of an ultrasound scan (ectopic mass: 1.9 cm) and hCG titer (1774.8 mIU/ml). In pre-treatment evaluations, hemoglobin (Hb: 13.1 g/dl), white blood cells (WBC: $7.72 \times 10^9/l$), platelet count ($262 \times 10^9/l$), blood urea nitrogen (8 mg/dl), serum creatinine (0.51 mg/dl), aspartate aminotransferase (11 U/l), and alanine aminotransferase (11 U/l) were in the normal range. She was subsequently administered a single dose of 50 mg MTX intramuscularly; however, on day 4 after MTX initiation she presented with severe vomiting and mucositis, which limited her daily dietary intake. On day 6, she went to the emergency service due to fever (39.3°C). Although her vital signs were stable (blood pressure: 103/66 mm Hg, pulse rate: 91 beats/min, respiratory rate: 20 breaths/min), hematological assessment revealed febrile neutropenia (WBC: $0.7 \times 10^9/l$, neutrophils: 27.0%, Hb: 11.5 g/dl; platelet count: $174 \times 10^9/l$). She received a granulocyte colony-stimulating factor agent (filgrastim 300 µg/day) and an empiric broad-spectrum antibiotic for febrile neutropenia. Because her prior complete blood counts were normal, we suspected MTX as the likely cause of neutropenia. She started leucovorin 120 mg/day as a rescue therapy on day 7, but anemia (nadir of Hb was 8 g/dl on day 10; hematocrit: 23.5%; mean cell volume: 92.2 fl) and thrombocytopenia (nadir of platelet count was $11 \times 10^9/l$ on day 12) were found on the following days. Although bone marrow evaluations were indicated to rule out malignancy and myelodysplasia, the patient did not accept a biopsy. She was transfused with blood products including packed red blood cells and platelets. Her hematologic parameters returned to the normal range and her condition improved gradually after 3 weeks from admission.

Pancytopenia has been reported in 3% of patients with rheumatoid arthritis receiving MTX, and the risk has been found to be associated with cumulative exposure [2]; however, the occurrence of pancytopenia

Table 1. Comparisons of methotrexate-induced pancytopenia in ectopic pregnancies among case reports

Reference	Age of patient	Past history	Methotrexate dosage	Onset of blood toxicity	Initial symptoms	Nadir of blood counts	Blood level of MTX	Outcome after treatment**
Isaacs Jr et al. [4]	23	Previous ectopic pregnancy with left salpingectomy	50 mg/m ² i.m.	4 days	Nausea, vomiting, mucositis, fever and pruritic rash	ANC*: 0.3 × 10 ⁹ /l on day 11 Hb: 6.7 g/dl on day 11 PLT: 17 × 10 ⁹ /l on day 11	No report	Recovery began on day 14
Kelly et al. [5]	Young woman (no exact age)	Hemodialysis-dependent	50 mg/m ² i.v.	3 days	Nausea, vomiting, severe mouth pain and fever	WBC: 0.4 × 10 ⁹ /l on day 9 Hb: 7.7 g/dl on day 5 PLT: 10 × 10 ⁹ /l on day 20	0.11 μmol/l on day 3	Died with pancytopenia, desquamation, acute respiratory distress syndrome, and profound bowel ischemia
Willner et al. [6]	21	Hemodialysis-dependent	100 mg i.v.	10 days	Sore throat and mouth, pruritus, fever and rash	WBC: 0.73 × 10 ⁹ /l on day 13 Hb: 7.99 g/dl on day 10 PLT: 9.9 × 10 ⁹ /l on day 15	0.02 μmol/l on day 10	Recovery began on day 15
Present case	27	No special medical history	50 mg i.m.	6 days	Nausea, vomiting, mucositis, fever and rash	WBC: 0.7 × 10 ⁹ /l on day 6 Hb: 8 g/dl on day 10 PLT: 11 × 10 ⁹ /l on day 12	Less than 0.02 μmol/l on day 7	Recovery began on day 16

MTX – methotrexate, ANC – absolute neutrophils count, WBC – white blood cell, Hb – hemoglobin, PLT – platelet, i.v. – intravenously, i.m. – intramuscularly. *No report on WBC data. **Treatment including leucovorin rescue therapy, the use of granulocyte colony-stimulating factor such as filgrastim, antibiotics and blood transfusion.

in the early stage with a single MTX injection is rare [3]. So far, only 4 cases, including the present one, of single-dose MTX-induced pancytopenia in patients with ectopic pregnancies have been reported [4–6] (Table 1).

We found that the blood counts reached a nadir 10 days after MTX initiation and in most cases recovered by 14 days; furthermore, we found that in most cases initial symptoms were gastrointestinal upsets and oral ulcerations, which could be considered early signs of MTX-induced pancytopenia because cells with a high turnover rate such as in the gastrointestinal tract or oral mucosa are more susceptible to the cytotoxic effects of MTX [2]. All the similarities to previous reports support the association between MTX and pancytopenia in the present case, including the onset of blood toxicity, initial symptoms, time to nadir of blood counts and time to recovery. However, it is noteworthy that the patient did not have concurrent predisposing factors such as renal dysfunction or concomitant use of other medications associated with pancytopenia or potential drug interactions with MTX [7].

Although MTX-induced pancytopenia is rare, physicians should be aware of such life-threatening adverse drug reactions from a single-dose MTX regimen in ectopic pregnancies. We suggest that health care providers and patients should monitor early signs and symptoms of MTX toxicity such as oral and gastrointestinal side effects to minimize unintended life-threatening events and consequences.

Conflicts of interest

The authors declare no conflict of interest.

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