Learning from errors

Life-threatening complications following multidose methotrexate for medical management of ectopic pregnancy

Papa Dasari, Haritha Sagili

Department of Obstetrics and Gynaecology, JIPMER, Puducherry, India

Correspondence to Professor Papa Dasari, dasaripapa@gmail.com

Summary

A 25-year-old primigravida was diagnosed to be suffering from unruptured ectopic pregnancy. The serum β -human chorionic gonadotropin levels were 2851 mIU/l and the ectopic gestational sac was 2.7×2.7 cm without any fetal pole. It was decided to manage her by expectant therapy. But she received medical therapy with multidose methotrexate because of misinterpretation of expectant therapy as medical therapy. She suffered from methotrexate toxicity, which manifested as high-grade fever, vomiting, melena, oral ulcerations, pneumonitis, subconjunctival haemorrhages and skin pigmentation. She developed severe third space fluid collection and shock, which was mistaken for rupture ectopic gestation. Her haematological picture showed severe neutropaenia and thrombocytopenia which confirmed the clinical picture to be due to methotrexate toxicity. She also developed septicaemia and candidal infection secondary to immunosuppression. She was managed in intensive care unit with ventilatory support, high-dose leucovorin and injection filgastrim. She responded well to the therapy with dramatic recovery in 4 days.

BACKGROUND

Systemic methotrexate treatment for unruptured ectopic pregnancy is being increasingly employed to avoid surgical therapy and to preserve the integrity of fallopian tube.

But the side effects of this potentially toxic drug have to be kept in mind and careful consideration to be given for the same because it can be life-threatening at times as in this case.

Giving correct dosage according to the body weight and body surface area is important to avoid the complications.

It is essential to suspect methotrexate toxicity when the minor side effects appear itself. Adding injection filgastrim to leucovorin rescue can enhance the recovery.

CASE PRESENTATION

A 25-year-old primigravida presented to our emergency services with a history of 2 months of amenorrhoea and lower abdominal pain associated with spotting per vaginum for 2 days. There was no history of shoulder pain or syncope. She did not give any history of significant medical or surgical illness. She has been married for the past 2 years and did not take any drugs for conception. On examination, her pulse rate was 80/min and blood pressure (BP) was 110/70 mm Hg. Abdominal examination revealed minimal tenderness in suprapubic area and there were no other positive findings. Per speculum examination revealed posteriorly placed cervix with minimal bleeding through os. On per vaginal examination, there was cervix motion tenderness and forniceal tenderness. Ectopic pregnancy was suspected and she was investigated for the same. Urine pregnancy test was positive and transvaginal ultrasound performed the next day showed empty uterine cavity and a 2.7×2.7 cm sac-like structure without any fetal pole. β -Human chorionic gonadotropin (HCG) on the next day (day 3 of admission) was 2851 mIU/l. Conservative management was advised by the consultant. But she was treated with

variable-dose (multidose) methotrexate¹ by misinterpretation of conservative treatment as medical management. Her complete haemogram, liver function tests and renal function tests were within normal limits but cardiac evaluation was not done.

The dose of methotrexate given was 50 mg intramuscularly on days 1, 3, 5 and 7. Injection leucovorin 5 mg was given intramuscularly on days 2, 4, 6 and 8. After 48 h β -HCG reduced to 567 mIU/ml and it was 155 mIU/ml on the last day of methotrexate (day 7). The patient developed fever of 101.6°F on day 7 and had vomiting and was symptomatically managed. It was commented by the consultant during the ward rounds that the dose of methotrexate may be high as she looked small built not more than 40 kg. But it was told that the dose of methotrexate was calculated as 1 mg/kg body weight prior to administration. Her actual weight measured 35 kg.

On day 8, she had oral ulcers and complained of melena. She was treated with intravenous fluids. It was advised to administer injection folic acid double dose (0.2 mg/kg) daily for 4–5 days by the consultant because of the obvious side effects and to repeat the complete haemogram. But she did not receive injection folic acid as it was not prescribed by the attending doctor and was treated symptomatically with B complex tablets and vitamin C and mucaine gel and antipyretics for 4 days. She had persistent fever and melena and complained of breathlessness on day 12 (ie, after 4 days of completion of methotrexate therapy) (table 1). She had pigmentation of the face and subconjunctival haemorrhages (figure 1). The respiratory system was found to be clear and she was given symptomatic treatment that day. Her symptoms worsened by 22:00 in the night and she was found to have distension of abdomen and subconjunctival haemorrhages. Her pulse was 120/min, respiratory rate was 32/min and BP was 80/60 mm Hg. Auscultation of the chest revealed crepitations on right side. Her oxygen saturation

Table 1 Premethotrexate therapy

Parameter	Result
28 November11	
Haemoglobin	12.5 gm%
Total WBC count	6100/mm ³
Differential count	
Neutrophils	45%
Lymphocytes	41%
Eosinophils	14%
Absolute eosinophil count	840/mm ³
Platelets	2 84 000/mm ³
Random blood glucose	71 mg/dl
Blood urea	14 mg/dl
Serum creatinine	0.6 mg/dl
Total bilirubin	0.7 mg/dl
Albumin	3.9 gm/dl
Serum electrolytes	
Sodium	137 meq/l
Potassium	4 meq/l
Blood group Rh	O +ve
Urine	Nil
Albumin and sugar	
Serum β-HCG	2581 mIU/l
TVS	Uterus—normal size Right adnexa—2.7×2.7 cm cystic structure Gestational sac No fetal pole

HCG, human chorionic gonadotropin; TVS, transvaginal ultrasonogram; WBC, white blood cell.

was 94%. Abdominal examination showed distension, guarding and rigidity with free fluid. Ultrasound-guided aspiration revealed serous fluid. Rupture ectopic pregnancy suspected and planned for laparotomy. The investigation reports were reviewed and it was found that the haemogram performed on the same day morning revealed severe neutropaenia and thrombocytopenia. Chest x-ray showed bilateral pneumonitis. Methotrexate toxicity was diagnosed and she was shifted to intensive care unit (ICU) after intubation (table 2).

DIFFERENTIAL DIAGNOSIS

Rupture ectopic pregnancy.

Subconjunctival
haemorrhages Pigmentation

Figure 1 Facial appearance - methotrexate toxicity.

Table 2 Postmethotrexate therapy (methotrexate toxicity)

Parameter	Value
10 December2011	
Haemoglobin	9.1 gm%
Total WBC count	<100/cmm ³
Platelets	16 000/cmm ³
Parasites	Nil
Blood urea	55 mg/dl
Serum creatinine	2.1 mg/dl
Serum electrolytes	
Sodium	130 meq/l
Potassium	3.5 meq/l
Peritoneal fluid	
Protein	3.3 gm%
Albumin	2.8 gm%
Sugar	120 mg%
Sodium	130 meq/l
Potassium	3.1 meq/l
Prothrombin time	22.5''
INR	1.63
Chest x-ray P/A	Features of pneumonitis

INR, international normalised ratio; P/A, per abdominal examination; WBC, white blood cell.

TREATMENT

She was supported with SIMV (Synchronise Intermittent Mandatory Ventilation) mode, inotropes, higher antibiotics viz., injection ceftriaxone and amikacin, 8 units of platelet and 4 units of fresh frozen plasma transfusion, injection filgastrim 200 µg subcutaneously for 3 days and injection leucovorin 4 mg intravenous every eighth hour. Repeat counts after 2 days revealed white blood cell (WBC) count of 2000 and platelets were 13 000. On day 3 of treatment the peripheral smear showed metamyelocytes giant forms of platelets and nucleated red blood cells (table 3) and her platelet count was 45 000/mm³ and WBC rose to 9100/mm³. She gradually improved and she was weaned-off the inotropic support on day 3 and extubated on day 4 after admission to ICU. Blood culture grew *Klebsiella pneumoniae* sensitive to gentamicin, amikacin and meropenem. She was treated with amikacin and meropenem. She continued to have high spiking fever despite 8 days of antibiotic therapy. Repeat blood culture showed *Acinetobacter baumannii* not sensitive to any antibiotics. Urine culture showed *Candida* sensitive to fluconazole which was prescribed. Echocardiography was done which showed rheumatic heart disease with mitral stenosis and aortic regurgitation. There was no thrombus or vegetation. Infective endocarditis prophylaxis was started with injection ampicillin and gentamicin. Fever spikes started to settle down and she became afebrile by day 13 after ICU admission and was discharged 3 days later with serum β-HCG <1 mIU/ml. Subconjunctival haemorrhages and pigmentation of skin still persisting (figure 1).

OUTCOME AND FOLLOW-UP

Methotrexate toxicity is the outcome of multidose therapy for unruptured ectopic pregnancy with serum β-HCG level <3000 mIU/l.

The clinical evidence of toxicity was fever, vomiting, melena, diarrhoea, subconjunctival haemorrhages, pigmentation of skin involving face and abdomen, pneumonitis, third space fluid collection and septicemia. The haematological

Table 3 Investigations after shifting to intensive care unit-recovery phase of methotrexate toxicity

Date (day)	Haemoglobin %	Total count	Platelet count	Blood sugar	Blood urea	Serum creatinine	Na ⁺	K ⁺	TP	Albumin	Serum bilirubin	Others
11 December 2011 (day 1)	6.8; 11	<1000	<20 000	80	41; 49	1; 0.9	142; 141	6.4; 2.8	5.8		4.1	FDP-negative
Day 2	8.7	2000	13 000	122	69	1.2	135	2.7	5.5	3.2	4.9	
Day 3	8.7	9100; N-34; E-5; L- 52	45 000 Giant forms+	62	35	0.8	121	3.0	6.8	3.4	0.9	MC-5; MMC-4; NRBC; -2/100
Day 4	10.1	33 000	88 000	62	50	0.3	133	3.6	—	—		PT-18 INR-1.28

Blood culture (11 December 2011)—*Klebsiella pneumoniae* sensitive to amikacin, gentamicin and meropenem.

Repeat blood culture—14 December 2011—*Acinetobacter baumani* resistant to all.

Urine culture—12 December 2011—candida sensitive to fluconazole.

Echo cardiogram—20 December 2011 mitral stenosis and aortic regurgitation.

E, eosinophils; FDP, fibrin degradation products; INR, international normalised ratio; L, lymphocytes; MC, megakaryocytes; MMC, metamyelocytes; NRBC, nucleated red blood cells; N, neutrophils; PT, prothrombin time; TP, total protein.

evidence was severe bone marrow depression involving all the three blood components viz., anaemia, severe neutropaenia and thrombocytopenia.

The outcome of methotrexate toxicity was life-threatening leading to septicaemia secondary to bone marrow suppression and immunosuppression requiring ICU care and the recovery in this case was enhanced with prompt treatment of pneumonitis with steroids and assisted ventilation and high-dose leucovorin along with injection Filgastrin. Septicaemia could be treated successfully with combination of two sensitive drugs in the presence of severe bone marrow suppression.

Subconjunctival haemorrhages and pigmentation persisted even after 2 weeks of recovery though the third space collection resolved completely.

DISCUSSION

The various modalities of therapy used for treatment of unruptured ectopic pregnancy include conservative/expectant, medical, surgically administered medical and surgical. The selection criteria for these modalities vary. Methotrexate therapy has been widely accepted for medical management of ectopic pregnancy and it is employed as a single-dose, double-dose or multidose therapy. Initial reports of methotrexate therapy reported few minor side effects.² Life-threatening complications following methotrexate therapy are reported rarely.

When instituting medical therapy, it is essential to decide on the strategy whether the single-dose therapy results in success or multidose therapy is required. There are many strategies that were employed viz., single-dose therapy alone,^{3 4} starting initially with a single dose of 50 mg intramuscularly and monitoring the β -HCG level and giving another dose if the expected decline does not occur.⁵ A randomised prospective trial of 120 women comparing the single dose with multidose therapy for unruptured ectopic pregnancy concluded that multidose therapy to be associated with more side effects and its success was not higher than a single-dose therapy though the time for the fall of β -HCG was shorter than single-dose therapy.⁶ However, a meta-analysis comparing both the regimens concluded multidose therapy to be more effective than single-dose therapy.⁷ These studies were basically undertaken to find out the efficacy and safety of determining the

optimum dose of methotrexate to completely resolve the unruptured ectopic pregnancy.

The success rate with single-dose methotrexate was highly dependent on the pretreatment β -HCG levels. Treatment failure more often occurred when β -HCG levels were >3000 IU requiring multidose therapy or surgical treatment.⁵ The risk of treatment failure with single-dose therapy increased significantly when the β -HCG levels were >1300 IU/l.⁴ The presence of subchorionic tubal haematoma in the ectopic gestation, the presence of an embryo and day 1 serum β -HCG level ≥ 3000 mIU/ml were found to be the main predictors of treatment failure. Transvaginal ultrasound findings were found to be as important as pretreatment β -HCG levels.⁸ Keeping the absence of embryo and irregularity of the sac and low β -HCG levels expectant/conservative treatment was planned initially for the present case. Single-dose methotrexate therapy would have been adequate for the present case to achieve resolution. Although one may not be successful in achieving complete resolution, 62% success rate may be obtained with single-dose therapy even if rupture occurs when the patient is haemodynamically stable.³

Methotrexate is a folic acid antagonist which acts on the rapidly dividing cells such as cytotrophoblasts and prevents their proliferation, reduces cell viability and β -HCG secretion and progesterone support thus facilitating resolution of ectopic pregnancy and tissue remodeling.⁹ As it specifically inhibits the synthesis of RNA and DNA its toxicity is greater on rapidly dividing cells such as malignant cells, myeloid cells and oral and gastrointestinal mucosa. The adverse effects of methotrexate therapy include cardiovascular, neurological, dermatological, haematological, hepatic and gastrointestinal symptoms. The most frequently reported adverse reactions include ulcerative stomatitis, leukopaenia, nausea and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection. Adverse reactions depend on the dose and the duration of therapy and the common side effects were observed in less than 10% of the cases. Haematological complications are reported in less than 2% of the cases.¹⁰ The present case suffered from toxicity which includes agranulocytosis, immunosuppression and resultant septicaemia and pneumonitis. The side effects following methotrexate therapy for ectopic pregnancy were rarely reported. We could not find any case report

with third space accumulation of fluid (ascites) when it was used for treatment of ectopic pregnancy though it was described as one of the effects due to toxicity.¹⁰

Two cases of life-threatening neutropaenia and febrile morbidity requiring hospitalisation have been reported following methotrexate treatment of ectopic pregnancy, one patient had received a single dose and the other received three doses intramuscularly.² In order to prevent the toxicity giving leucovorin rescue has been the practice even for malignant patients. The present case developed toxicity despite the rescue, the probable factors to be considered are high dosage with respect to her body weight, not recognising the minor side effects initially and not advocating the double dose of leucovorin in spite of the advice and may be due to hypersensitivity to methotrexate because of MTHFR 2 mutations.¹¹ The other reasons for methotrexate toxicity reported in the literature include genetic polymorphism in the folate metabolic pathway delaying the clearance of methotrexate,¹² delay in renal excretion due to consumption of cola beverages,¹³ the state of hydration, concomitant drugs taken such as trimethoprim and sulphamethoxazole, and proton pump inhibitor like dilantin.¹⁴ Methotrexate clearance was moderately reduced in patients with the MTHFR 677TT. An association between the 677T and 1298C carriers and global toxicity was found when high-dose methotrexate was employed.¹⁵ Availability of pharmacogenomics evaluation would help to establish such cause. Treatment of methotrexate toxicity includes high-dose leucovorin alone or carboxypeptidase and thymidine therapy.¹⁶ In the present case, high-dose leucovorin and injection Filgastrin were used and the response to therapy was dramatic and the patient could recover in 72 h though her fever did not subside early in spite of targeting the septicaemia with appropriate antibiotics (table 4). This may be due to endocarditis secondary to septicaemia which responded to a course of penicillins and aminoglycosides.

Preventing toxicity is of utmost importance especially when it is used for non-malignant indications where alternate therapies can achieve similar results. Strategies to reduce the side effects and their early recognition include a safety checking procedure like SMART (safety of methotrexate therapy by assessing risks and toxicity)¹⁷ and determining plasma methotrexate concentrations.¹⁸ Safety

checking procedure is easy and can be adopted at any hospital setting. Methotrexate blood level can be affected by many factors, and therefore even a small dose of this drug should be given with caution, fully prepared to deal with life-threatening toxicity.

Learning points

- ▶ It is essential to choose the appropriate protocol of medical therapy with methotrexate for unruptured ectopic pregnancy depending on ultrasonogram findings and β -human chorionic gonadotropin (HCG) levels.
- ▶ The terms conservative treatment and medical therapy should not be used interchangeably.
- ▶ Single-dose therapy is safer in most of the circumstances and need for further doses to be assessed by ultrasound findings as well as the rate of fall of β -HCG as late as 7 days of administration.
- ▶ It is important to write down the protocol by the treating or in charge obstetrician rather than mentioning the name of the protocol so as to avoid confusion.
- ▶ Direct supervision of a junior doctor is mandatory when potentially toxic drugs are being administered to any patient.
- ▶ It is necessary to check the details personally by the responsible obstetrician at least the next day whether the treatment was carried out as per the instructions.
- ▶ Methotrexate toxicity should be screened and prevented by close monitoring when minor side effects develop.
- ▶ Third space collection in the peritoneal cavity with methotrexate therapy should not be mistaken for the rupture of ectopic pregnancy.
- ▶ High-dose leucovorin along with filgastrin can enhance the recovery of bone marrow.

Competing interests None.

Patient consent Obtained.

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Table 4 Response of ectopic gestation to multidose methotrexate

Date/day	β -HCG level	TVS	Side effects
28 November 2011 pretherapy	2851	Uterus—normal size Right adnexa-2.7×2.7 cystic structure- Gestational sac No fetal pole	—
2 December 2011 (day 3)	567	No extrauterine GS Minimal free fluid in pelvis-25 ml	—
4 December 2011 (day 6)	155	Free fluid-41 ml	Fever
6 December 2011 (day 8)	—	Free fluid in pelvis	Side effects Obvious
10 December 2011 (day 12)	17.04	Free fluid >200 ml	Toxicity diagnosed

HCG, human chorionic gonadotropin; TVS, transvaginal ultrasonogram.

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