Intensive care management of multiorgan failure following single low dose methotrexate for ectopic pregnancy: An intriguing case report

Sir,

Methotrexate (MTX), a dihydrofolate reductase inhibitor and a first line drug for medical management of ectopic pregnancy, has an overall success rate of 88.1% with single-dose protocol. Approximately 10%–30% patients have mild self-limiting adverse effects, whereas very few cases of severe unexpected idiosyncratic reactions including nephrotoxicity, neurotoxicity, interstitial pneumonitis, alopecia dermatitis and myelosuppression may arise.[1]

A 38-year-old female who came with left adnexal ectopic pregnancy was managed with injection (inj.) MTX 80 mg intramuscularly after ruling out its contraindications. After 6–8 h, patient became restless with difficulty in breathing, with SpO2 of 88% on room air, and had epigastric pain with 3–4 episodes of vomiting. On arrival in ICU, she had fever (100°F), tachycardia (hear rate 110/min), tachypnoea (respiratory rate 32 breath/min) along with basal crepitation in chest. Chest X-ray showed bilateral basal and mediastinal infiltrates [Figure 1]. Arterial blood gas analysis revealed mild hypoxaemia with respiratory alkalosis. Oxygen supplementation, inj. ondansetron, inj. pheniramine maleate and inj. hydrocortisone 100 mg were given intravenously (IV) considering it a drug reaction. Empirically, inj. leucovorin 20 mg IV every 6 h was started. Due to lack of facility, serum MTX levels could not be done. Patient received generous IV fluids to maintain hydration, was given antibiotics and inj. Sodium bicarbonate to maintain urinary pH above 7, as on analysis it was found to be 6.

The next day, patient developed icterus, yellow discolouration of urine and melaena along with elevated hepatic transaminases levels. Petechiae appeared over the lower limbs, neck and chest. Sepsis, disseminated intravascular coagulopathy, viral hepatitis and viral haemorrhagic fever were ruled out. Dermatology opinion suggested maculopapular rash probably due to drug toxicity or liver enzyme derangement [Figure 2]. Later that day, she developed anasarca and urine output started decreasing along with deteriorating kidney function test (KFT) [Table 1]. Echocardiography was normal. As the patient became anuric, intermittent haemodialysis was started. On day 3, platelet count fell to 19,000 with INR 2.06 [Table 1]. On day 4, beta HCG dropped to 776, oxygen support tapered and patient received multiple transfusions (2 units packed red blood cells, 11 units fresh frozen plasma, 9 units random donor platelets). As all the three-cell lineage showed continuous fall despite multiple transfusions by day 6 too, inj. Filgrastim 5 μg/kg/day IV and inj. fluconazole 400 mg IV were given. Haemodialysis continued on daily basis. By day 7, beta HCG dropped to 227 and day 8 onwards, patient's platelet count and haemoglobin started improving. Patient continued to undergo maintenance haemodialysis thrice weekly for another week after which the KFT

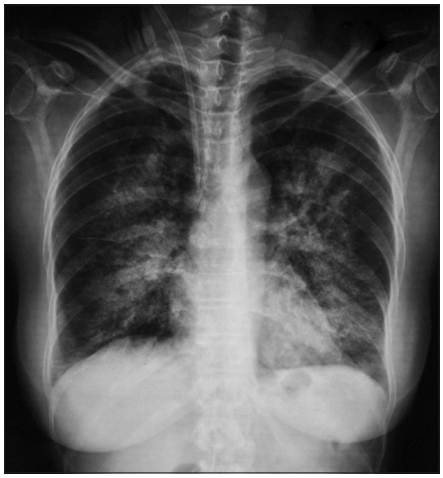

Figure 1: X-ray showing bilateral infiltrates

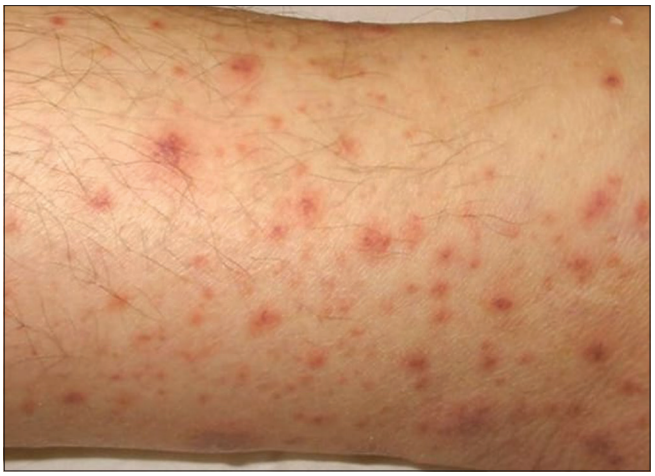

Figure 2: Showing maculopapular rash on extremities

Table 1: Table showing biochemical parameters during ICU stay

	Pre MTX	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 10	Day 12	Day14
Hb (gm/dl)	13.4	10.9	13.5	10.1	10.3	9	6.0	6.3	7	7.6	8.4	8.6
TLC (per cubic mm)	6580	6960	7200	12200	9400	5400	2650	3500	5830	6600	6100	7000
Platelet count (per cubic mm)	2.32L	2.3L	2.02L	1.01L	48K	25K	15K	20K	20K	24K	44K	62K
Haematocrit (%)	37	36	36.6	29.8	27	27	18.6	19.2	20.8	22.8	25.6	18
Total serum bilirubin (mg/dL)	0.4	0.4	3.8	3.9		8.2	6.8	5.4	3.2	1.7	1.6	1.42
Direct bilirubin (mg/dL)			2	3		4.8	4.3	3.2	1.6	0.6	0.6	0.5
S. ALT (IU/L)	18	16	38	434	700	225	198	122	48		57	54
S. AST (IU/L)	15	13	135	138		764	687	345	48		40	42
S. ALP (IU/L)	56		63		67	84	65	55	61			71
Blood urea (mg/dL)	32	75	36	103	126	125	121	175	167	159	128	95
Serum creatinine (mg/dL)	0.7	0.7	1.7	3.9	4.6	4.6	4.8	5	4.7	4.6	4	3.2
Serum sodium (mmol/L)	137	136	130	138	138	140	128	132			140	142
Serum potassium (mmol/L)	3.9	3.7	3.6	4	4.6	3.8	3.6	3.8			4.1	3.8
β- HCG (mIU/mL)	1998				776			227				
INR				1.417	2.917	2.5		2.6		2.2		1.15
APTT						>3 min	>2 min		98 sec			32 sec
D-dimer						>5000						4245

ICU: Intensive Care Unit, Hb: Haemoglobin, TLC: Total leucocyte count, DLC: Differential leucocyte count, L: 105, K: 103, S. ALT: Serum alanine aminotranferase, S. ALT: S. serum aspartate aminotransferase, S. ALP: Serum alkaline phosphatase, HCG: Human chorionic gonadotropin, INR: International normalised ratio, APTT: Activated partial thromboplastin time

started improving. Finally, dialysis was tapered to twice weekly and patient was shifted to ward.

Patient presented with signs of stomatitis, melena and petechiae in the beginning as MTX acts on sites with rapid cell turnover. As MTX crystallises in tubules, it decreases tubular secretion and increases likelihood of toxicity, more so in acidic urine.[2] As 90% of IV MTX is excreted via renal route, its accumulation leads to myelosuppression and pancytopenia. Patients with already deranged KFT have 55% incidence of myelosuppression as against only 3% with normal KFT. Moreover, occurrence of myelosuppression after single low dose has hardly been reported.

Serious pancytopenia has been reported in around 1.4% of the cases. One reported case of ectopic pregnancy that had developed severe stomatitis, myelosuppression and pancytopenia and required one week of ICU treatment.[3] Severe multiorgan involvement, though rare, can occur even with single dose, in patients with prior renal insufficiency. Extremes of age, malnutrition, folate deficiency and blood dyscrasias are among few other risk factors. Single-dose MTX toxicity in previously healthy females is a rare occurrence. Till date, only a single case of multiorgan involvement with early involvement of lungs has been reported in which pneumonitis developed on day 4 and multiorgan failure was noticed by a week. The probable reason for such fast involvement of organs was uncontrolled cytokine production following exaggerated cell-mediated reaction.[4] Our patient had an unprecedented fulminant course, with a single day history of respiratory involvement and multiorgan involvement within two days. However high index of vigilance and aggressive ICU management prevented the disastrous consequences.

The standard-of-care regimen includes leucovorin along with continuous urinary alkalinisation (with sodium bicarbonate) and rigorous hydration. G-CSF, blood products and haemodialysis are other supportive measures.[5,6] Leucovorin, a rescue agent, exerts its effects via competitive cellular uptake though it does not sufficiently reduce MTX toxic levels. Glucarpidase, a carboxypeptidase, is needed in 2%–10% patients where nephrotoxicity may not reverse in normal pretreatment kidney.[7] Although FDA approved for reversing MTX toxicity in patients with delayed MTX clearance, it is unavailable in India.[8] Thymidine, rescues cells from the cytotoxic effects of MTX but its use is under investigation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Divya Gupta, Sukhyanti Kerai

Department of Anaesthesiology and Critical Care, Maulana Azad Medical College, Delhi, India

Address for correspondence:
Dr. Divya Gupta,
Flat No. 4 5/7 Roopnagar, Delhi - 110 007, India.
E-mail: darydivs@yahoo.com

Received: 10th May, 2019
Revision: 04th August, 2019
Accepted: 09th August, 2019
Publication: 10th October, 2019

REFERENCES

1. Bachman EA, Barnhart K, Medical management of ectopic pregnancy: A comparison of regimens. Clin Obstet Gynecol. 2012;55:440-7.
2. Canestra J. Methotrexate poisoning. Emerg Med 1996;8:89-92.
3. Soysal S, Anık İlhan G, Vural M, Yıldızhan B. Severe methotrexate toxicity after treatment for ectopic pregnancy: A case report. Turk J Obstet Gynecol 2016;13:221-3.
4. Saigal S, Singh RK, Poddar B. Acute methotrexate toxicity presenting as multiorgan failure and acute pneumonitis: A rare case report. Indian J Crit Care Med 2012;16:225-7.
5. Tan KW, Tay YK. A case of acute methotrexate toxicity. Ann Acad Med Singapore 2011;40:97-9.
6. Fleisher M. Antifolate analogs: Mechanism of action, analytical methodology, and clinical efficacy. Ther Drug Monit 1993;15:521-6.
7. Holmboe L, Andersen AM, Mørkrid L, Slørdal L, Hall KS. High dose methotrexate chemotherapy: Pharmacokinetics, folate, and toxicity in osteosarcoma patients. Br J Clin Pharmacol 2012;73:106-14.
8. Schwartz S, Borner K, Muller K, Martus P, Fischer L, Korfel A, *et al.* Glucarpidase (carboxypeptidase g2) intervention in adult and elderly cancer patients with renal dysfunction and delayed methotrexate elimination after high-dose methotrexate therapy. Oncologist 2007;12:1299-308.

Access this article online	
Quick response code	Website: www.ijaweb.org
	DOI: 10.4103/ija.IJA_366_19

How to cite this article: Gupta D, Kerai S. Intensive care management of multiorgan failure following single low dose methotrexate for ectopic pregnancy: An intriguing case report. Indian J Anaesth 2019;63:870-2.