



Hyperpigmentation, severe alopecia, and six days of instability in a case of severe methotrexate hypersensitivity reaction

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Received: 28 June 2020 / Accepted: 27 November 2020 / Published online: 6 January 2021
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Abstract

Introduction Ectopic pregnancy (EP) is an emergency condition in the gynecologic field. Methotrexate (MTX) is a drug of choice for the medical treatment of EP. Severe adverse events are rare among patients treated with MTX for this condition.

Reason for report We describe a woman with severe multi-organ involvement experiencing about six days of instability after treatment with just a single-dose MTX for EP. This life-threatening condition is not common with a single dose of MTX.

Case summary A 30-year-old healthy woman was treated medically with MTX for an EP. Three days later the patient was admitted to the emergency department of our hospital with generalized pustular rashes, alopecia, hyperpigmentation, nausea and vomiting, oral ulcers, and raised Creatinine level. Four days later due to pancytopenia, fever, and loss of consciousness, she was transferred to the intensive care unit and was intubated.

Outcome After 38 days of hospitalization, treatment was successful with leucovorin and supportive care and the patient's symptoms and clinical manifestations were regressed.

Keywords Methotrexate · ectopic pregnancy · toxicity · Side effects

Introduction

Ectopic pregnancy (EP) is an emergency condition in the gynecologic field and single or multiple doses of methotrexate (MTX) is the preferred approach in most cases (1). Adverse reactions to MTX are usually mild and self-limited and occur in about 30% of patients who receive single-dose protocol while severe toxicity is a rare condition only seen with high doses (2). In this case report, we describe a woman with severe multi-organ involvement, about 6 days of unstable conditions, severe hyperpigmentation, and alopecia after treatment with just a single-dose MTX for EP.

Reason for report

We describe a woman with severe multi-organ involvement and about 6 days of unstable conditions after treatment with just one single-dose MTX for EP. This life-threatening condition is not common with a single dose of MTX.

Case presentation

A 30-year-old woman, Gestation1 EP1, with a history of Metronidazole allergy, had developed spotting, lower abdominal pain, and a positive pregnancy test. Serum Beta-hCG level did not have the expected surge and the doubling rate was slower than a normal pregnancy. Transabdominal and transvaginal ultrasound revealed no evidence of an intrauterine pregnancy and were suggestive of EP. Therefore, treatment was started with a single 80 mg (50 mg/m²) dose of intramuscular MTX considering normal Creatinine level and GFR. Three days later the patient was admitted to the emergency department of our hospital with 2 days history of generalized pustular rashes, alopecia, hyperpigmentation, nausea and vomiting, oral ulcers, and raised Creatinine level up to 4.5 mg/dl. On the initial examination, she had a high

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temperature (39.4). She admitted to the hospital and fluid therapy was started immediately due to dehydration. Besides, Leucovorin (20 mg every 6 h) was initiated for the patient on the first day due to clinical suspicion of MTX toxicity. Within the first few days of hospitalization, the Creatinine level decreased without hemodialysis. After 4 days in the hospital due to pancytopenia and continuous fever, the patient was transferred to the intensive care unit (ICU). Despite all supportive care, the patient's condition was deteriorated, pancytopenia was exacerbated (WBC = 100, Hb = 7.3, Platelet = 10,000), the level of consciousness was decreased, and eventually, the patient was intubated. Skin lesions, hyperpigmentation, and alopecia were intensified during ICU hospitalization. Also, the patient experienced severe hair loss and skin hyperpigmentation, particularly in the exposed areas. Comprehensive paraclinical tests were conducted investigating the source of infection. Blood and urine cultures were negative. A chest CT scan was performed due to the simultaneous COVID-19 (coronavirus disease) pandemic. Abdominopelvic sonography was requested to examine the fetal remains and other potential sources of infection. Meanwhile, broad-spectrum antibiotics (starting with Vancomycin and Piperacillin-Tazobactam and proceeding to Linezolid, Meropenem, and Ciprofloxacin after 3 days) were initiated for the patient. Eventually, no source of infection was found. After 2 days, antifungal (initiating with fluconazole and substituting to amphotericin B after 3 days) and antiviral (acyclovir) drugs were prescribed. Moreover, she received a transfusion of platelets and packed RBC because of pancytopenia and bleeding. Due to symptomatic anemia, we added erythropoietin, granulocyte colony-stimulating factor (G-CSF) to the patient's regimen. Despite all supportive care, the patient's condition did not show any improvement. For about 6 days patient had persistent high fever and symptoms of septic shock (systolic blood pressure was hardly maintained above 90 mmHg with vasopressor and intensive hydration). Cultures were examined again and on the 8th day of admission, *Pseudomonas aeruginosa* grew in the blood sample which was sensitive to Meropenem. Therefore, antibiotics were continued for the patient. Echocardiography was done and no evidence of endocarditis was found. Despite intensive hydration, the patient showed refractory hypernatremia that was successfully controlled. Methotrexate level was 0.36 $\mu\text{M/L}$ on the first day of admission, which slightly decreased to 0.07 $\mu\text{M/L}$ and 0.03 $\mu\text{M/L}$ after 3 and 7 days, respectively (Table 1). Collectively, a NARANJO score of 8 would suggest that MTX toxicity can probably justify the mentioned signs and symptoms in this patient. (Figures 1, 2 and 3).

Discussion

MTX has been accepted for medical treatment of EP and it is used in single, double, or multiple doses (3). The adverse effect can be seen more frequently in multi-dose protocol than in a single dose (4). A prospective randomized controlled trial in 2010 in Turkey comparing these protocols concluded that multi-dose therapy is associated with more side effects and even though is not significantly more effective (5). Overall, the single-dose protocol is suggested for initial treatment and multi-dose protocol is used for higher hCG levels (>3000 IU/L), bigger masses (>2 cm), and interstitial or cervical pregnancies (1).

MTX is a folic acid antagonist and the adverse effects of MTX are caused by the inhibition of the enzyme dihydrofolate reductase in purine synthesis and cell division. Therefore, rapidly dividing tissues such as skin, oral and gastrointestinal mucosa, and bone marrow are affected earlier and more often. Hence, adverse effects including stomatitis, leukopenia, nausea, abdominal distress, malaise, fatigue, chills and fever, and dizziness were reported more frequently. The potential severe adverse effects of MTX treatment that occur rarely are myelosuppression, risk of severe infections, septicemia, and neurotoxicity (6, 7). MTX toxicity can be accompanied by many dermatologic complications. A nonspecific drug rash can be seen in patients which is usually erythematous, macular, pruritic, and often seen on the neck and trunk. In severe cases, it can progress to bullous formation or desquamation. Photoreactivation in which drug administration in the absence of light causes a sunburn-like reaction in the same distribution, photo enhancement in which drug administration about two to 5 days after exposure to Sunlight can cause severe rashes in exposed areas and skin hyperpigmentation are other side effects (8, 9). The pigmentary changes can be temporary or persistent but usually resolve within weeks to months after drug discontinuation. Partial alopecia is another rare symptom (10, 11).

Gais et al. (12) reported a fatal MTX toxicity in a patient treated for EP that received 50 mg/m² MTX intramuscularly, same as our patient, and after 24 h developed mucositis, skin lesions, and fever. Unlike our patient, however, although neurotoxicity did not occur, she was expired due to bone marrow aplasia and severe septic shock. Their patient presented the highest MTX level (0.05 μM) on day 11 after administration and leucovorin and hydration therapy were started on this day. Our case, however, had an MTX level of 0.36 on the first day of admission and supportive therapy was immediately initiated. This might justify the fatal toxicity in the prior case compared to ours. It is also noteworthy that both patients reported a history of antibiotic allergy (penicillin allergy in the former case and metronidazole allergic history in this case).

MTX intracellular poly-glutamate is a more sensitive marker for MTX toxicity than MTX serum level but in this case,

Table 1 Patient’s Lab data during hospitalization

Time	Hemoglobin (%)	WBC (count)	Platelet (count)	Serum Creatinine (mg/dl)	Na (meq/l)	K (meq/l)	AST (mg/dl)	ALT (mg/dl)	ALP (mg/dl)	Bill T-D (mg/dl)	MTX level (μM)	ESR (mm/h)	CRP (mg/dl)	others
On Admission	11.2	1500	243,000	4.5	137	4.9	13	14	170	0.6–0.4	0.36	120	247	hCG = 189 (IU/L)
Day 2	11.2	600	187,000	4.6	149	4	–	–	–	–	–	–	–	–
Day 4	9.1	300	109,000	3.6	158	3.2	–	–	–	–	0.07	–	–	Folate>40 (μg/L) Urine analysis: NL
Day 6	7.3	100	10,000	2.1	167	2.2	31	60	105	3–2.3	–	–	–	LDH = 462 (mg/dl)
Day 9	7.2	200	12,000	1.7	164	3.7	–	–	–	–	0.03	–	–	hCG = 20.2
Day 10	6.6	200	22,000	1.6	160	3.7	–	–	–	–	–	130	180	–
Day 11	7.2	500	40,000	1.4	160	3.1	–	–	–	–	–	–	–	–
Day 12	7.5	700	39,000	1.4	162	3.4	163	185	540	2.9–2.1	–	–	–	–
Day 13	7.6	2400	35,000	1.2	159	3.2	–	–	–	–	–	–	–	–
Day 14	7.8	6000	23,000	0.9	153	3.1	119	133	584	2.2–1.8	–	–	–	hCG = 5.82
Day 17	8.3	6800	58,000	0.8	149	3.7	85	102	560	2–1.5	–	–	–	–
Day 20	9.6	5700	124,000	0.6	145	4.4	71	106	526	1.3–0.6	–	52	20	–
Day 38	11.6	5400	180,000	0.7	139	4.3	17	21	320	0.7–0.3	–	35	8	–

MTX, Methotrexate; WBC, White blood cell; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; hCG, Human chorionic gonadotropin; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; ALP, Alkaline phosphatase; Bill T-D, Bilirubin Total – Direct; LDH, Lactate dehydrogenase



Fig. 1 severe stomatitis

MTX serum level was high and clinical signs and symptoms suggested MTX toxicity (13). Although our patient's symptoms with MTX serum level of $0.36 \mu\text{M} / \text{L}$ indicated drug toxicity, this intensity of symptoms including severe myelosuppression ($\text{WBC} < 500$), septic shock, intubation due to neurotoxicity, and loss of consciousness is not common with only 80 mg of MTX. Despite the high serum level of MTX and toxicity, it is better to consider the hypersensitivity considerations for receiving the next dose of the drug in the future. Thus, MTX use for further medical conditions should be treated cautiously and it is important to alert the patient to inform her physician in case of any rheumatologic diseases or re-abortion in the future. Alternative treatment desensitization protocols could be utilized in those conditions. Also, it is



Fig. 2 skin hyperpigmentation



Fig. 3 severe alopecia

recommended to initiate leucovorin alongside MTX in case of any MTX use in the future if necessary.

Outcome

Finally, 6 days after intubation and continuing medications, pancytopenia began to relieve. One day later, fever relieved and after 12 days she regained consciousness. The patient's symptoms and clinical findings regressed. After 38 days of hospitalization (30 ICU days), she was discharged from the hospital with normal CBC, electrolytes, and stable vital signs. A repeat hCG titer 10 days after discharge was less than 5 mIU/mL. The patient began taking oral contraceptives.

Conclusion

Severe toxicity in a healthy woman is a very rare condition but adverse effects and complications of MTX therapy can occur at any dose. Unexpected severe toxicity with MTX should be kept in mind during the use of this simple treatment and careful follow-up and evaluation and early treatment in case of probable toxicity will be beneficial. MTX blood level can be affected by many factors, and therefore even a small dose injection should be given with caution.

Acknowledgments Written informed consent was obtained from the patient. This study was approved by the research and ethics committee of Tehran University of Medical Sciences.

Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

Funding None.

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