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Fatal Neutropenic Enterocolitis Following Methotrexate Overdose: A Case Report

Yüksek Doz Metotreksat Alımı Sonrası Gelişen Fatal Nötropenik Enterokolit: Olgu Sunumu

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ABSTRACT

Methotrexate, a folic acid antagonist, is widely used in the treatment of neoplasms in addition to diseases such as psoriasis and rheumatoid arthritis. Although well tolerated under normal conditions, the use of more than the recommended doses may cause life-threatening toxicities. Toxicity due to high doses of methotrexate is manifested by bone marrow inhibition, gastrointestinal mucosal damage and pancytopenia. Most cases result from overdose. However, serious adverse events that result in mortality, in particular those of mixing medication in elderly patients, are rare. Herein, we present the case of a 72-year-old man who admitted to the emergency department with painful oral ulcers, inability to swallow and a general impaired condition, and died of sepsis after developing neutropenic enterocolitis following a fever and neutropenia.
Keywords: Methotrexate; overdose; pancytopenia; neutropenic enterocolitis.

ÖZ

Bir folik asit antagonisti olan metotreksat, psoriazis ve romatoid artrit gibi hastalıklara ek olarak, neoplazmaların tedavisinde yaygın olarak kullanılır. Normal koşullarda iyi tolere edilse de önerilen dozlardan fazla kullanılması hayatı tehdit eden toksikasyonlara neden olabilir. Yüksek doz metotreksat'a bağlı toksisite, kemik iliği inhibisyonu, gastrointestinal mukozal hasar ve pansitopeni ortaya çıkabilir. Çoğu durumda doz aşımı sonucu ortaya çıkar. Bununla birlikte, özellikle yaşlı hastalardaki ilaçları karıştırmak gibi, ölümcül sonuçlanan ciddi yan etkiler daha nadirdir. Burada, acil servise ağrılı oral ülser, yutkunma bozukluğu ve genel durum bozukluğu ile başvuran, ateş ve nötropeninin ardından nötropenik enterokolit geliştikten sonra sepsisten ölen 72 yaşında bir erkek olguyu sunuyoruz.
Anahtar kelimeler: Metotreksat; aşırı doz; pansitopeni; nötropenik enterokolit.

INTRODUCTION

Methotrexate (MTX) is a folic acid antagonist with antiproliferative effect used in high doses in the treatment of malignancies and in low doses in the treatment of chronic inflammatory diseases such as psoriasis and rheumatoid arthritis (RA) (1). Methotrexate particularly affects rapidly proliferating cells, such as bone marrow and mucosa. As a result, its side effects include myelosuppression, mucositis and hepatic and tubular necrosis (2,3). One of the most common causes of MTX intoxication stems from incorrect application in the amount and range of doses (4). Some errors may occur in the use of MTX, especially in the elderly and in patients with multiple drug intake. One of the dreaded complications following neutropenia is neutropenic enterocolitis with its high mortality. Here, we present a case of neutropenia and neutropenic enterocolitis admitted with a generally impaired condition, difficulty in swallowing, widespread oral mucositis and a maculopapular rash on the trunk which, according to a detailed drug interrogation, had developed as a result of mistakenly using a high dose of methotrexate.

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CASE REPORT

A 72-year-old male patient was admitted to the emergency department having complaints of fatigue, malaise, burning in the mouth and sore throat for approximately five days. Upon physical examination, his general condition was moderate and he was conscious and alert, orientated and cooperative. His temperature was 36.9 °C, pulse 130/min, blood pressure 130/100 mmHg, respiratory rate 20/min, and oxygen saturation 94%. The patient had signs of dehydration due to lack of oral intake and white plaques compatible with candida infection were seen on the tongue and hard palate mucosa. The oropharynx was hyperemic and he was unable to swallow because of oral mucosal pain. The patient had a diffuse maculopapular rash on his back, neck and extremities, with no other findings upon pathological examination. His history showed no chronic disease other than RA. Laboratory tests revealed white cell count 800/uL, neutrophil 360/uL, hemoglobin 12.5 g/dL, hematocrit 35.9%, platelet 108000/uL, C-reactive protein 44.8 mg/dL, urea 71 mg/dL, creatinine 0.93 mg/dL and albumin 3.21 g/dL. He was admitted to the Infectious Diseases Department with preliminary diagnosis of neutropenic rash etiology and candida mucositis. The patient had a fever of 38.5 °C on the first day of hospitalization and after cultures were taken, fluconazole 400 mg / day was started intravenously. On the second day of hospitalization, the patient complained of severe abdominal pain and black stools; air-fluid levels were seen in the patient's erect radiography of the abdomen. Abdominal ultrasonography was performed and no pathology was detected except for a hydropic sac and intestinal wall thickness. Upon calculating the glomerular filtration rate, meropenem, teicoplanin and metronidazole were added to the treatment plan for neutropenic enterocolitis with a preliminary diagnosis of neutropenia. Stool microscopy showed multiple leukocytes and erythrocytes, no signs of parasites, and was negative for clostridium toxin A-B. Hematological consultation was made concerning the white cell count of 300/uL, neutrophil count of 80/uL and platelet count of 19000/uL. When the patient and his medications were examined in detail to discover the cause of the neutropenia, it was learned that the MTX report was prepared seven months previously and that the patient had been taking this medication intermittently. Finally, when the joint pain did not pass, he was mistakenly administered MTX at 15 mg/day IM for 7-10 days. When it was understood that the cause of neutropenia was MTX, irradiated-platelet replacement and granulocyte-colony stimulating factor were started. On the fourth day of treatment, the patient's general condition deteriorated and consciousness was impaired. The patient was taken to intensive care and colistin (2 × 150 mg IV) was added to his current treatment because a multi-drug resistant *Acinetobacter* spp was detected in his blood cultures. On the seventh day of hospitalization, he died due to sepsis-associated DIC. Consent was obtained from the patient's relatives for the case report.

DISCUSSION

Methotrexate is one of the first drugs of choice for the treatment of rheumatoid arthritis, an autoimmune systemic disease. Even in low dose therapy, hematologic toxicity, gastrointestinal mucositis, pulmonary symptoms, hepatotoxicity, acute renal failure and skin erythema can be seen (3). Skin ulcers are considered as early signs of systemic toxicity. Mucositis is usually occurs within 3-7 days, and a few days later there is a decrease in the number of granulocytes and platelets. More severe toxicity findings such as deep neutropenia, neutropenic enterocolitis and sepsis similar to the example of our patient carry high morbidity and mortality. In a review by Gutierrez-Urena et al. (5), 1-2% of RA patients receiving MTX therapy had clinically significant pancytopenia.

Neutropenic enterocolitis is a complication of immunosuppressive drugs. This clinical syndrome is characterized by transmural inflammation of the small and large intestines, mainly the cecum (6). Ultrasonography reveals intestinal wall thickness, a dilated cecum, an inflammatory mass in the right lower quadrant and pericaecal fluid. Although computed tomography (CT) is the most commonly used method, in our patient, CT could not be performed because of his high creatinine level and generally deteriorated condition, and thus, neutropenic enterocolitis was diagnosed clinically. On the fourth day of hospitalization the patient was admitted to the intensive care unit due to development of impaired consciousness and renal failure and he died on the seventh day.

In the literature, there are numerous case studies and publications on MTX toxicity. In some publications, gastrointestinal toxicity has been found to develop from low doses of MTX. Tsukada et al. (7) reported pancytopenia and gastrointestinal mucosal necrosis in a patient receiving 8 mg / week of MTX. Misuse of the dosage range was reported by Peker et al. (8) with a case of GI bleeding and pancytopenia in a patient using MTX daily instead of weekly. The use of the wrong drug is one of the rarer causes of overdose side effects. Bidaki et al. (9) published a report of two geriatric patients mistakenly given MTX instead of digoxin at the pharmacy, in which one patient died due to development of toxicity. Publications on MTX toxicity are often case reports of oral overdose or mistaken use in place of another drug (10). Cases like ours, where daily parenteral administration of MTX as a presumed analgesic and development of severe neutropenia and neutropenic enterocolitis ending in patient death, are less frequently reported.

In conclusion, although it is well tolerated under normal conditions, the use of more than the recommended doses may cause life-threatening toxicities. In patients with RA, MTX toxicity should be kept in mind when symptoms such as pancytopenia, oral ulcers and GI problems occur. When considering starting MTX treatment in the geriatric patient group in particular, it is important that all healthcare workers be extremely careful about drug compliance and follow-up.

REFERENCES

1. Altındağ Ö, Küçükoğlu B. Intoxication due to high dose methotrexate in a patient with arthritis: A case report. Turk J Rheumatol. 2011;26(1):58-60.
2. Cheng KK. Association of plasma methotrexate, neutropenia, hepatic dysfunction, nausea/vomiting and oral mucositis in children with cancer. Eur J Cancer Care (Engl). 2008;17(3):306-11.

3. Romão VC, Lima A, Bernardes M, Canhão H, Fonseca JE. Three decades of low-dose methotrexate in rheumatoid arthritis: Can we predict toxicity? Immunol Res. 2014;60(2-3):289-310.
4. Madke B, Singh AL. Acute methotrexate toxicity. Indian J Drugs Dermatol. 2015;1(1):46-9.
5. Gutierrez-Ureña S, Molina JF, García CO, Cuéllar ML, Espinoza LR. Pancytopenia secondary to MTX therapy in rheumatoid arthritis. Arthritis Rheum. 1996;39(2):272-6.
6. Schlatter M, Snyder K, Freyer D. Successful non operative management of typhlitis in pediatric oncology patients. J Pediatr Surg. 2002;37(8):1151-5.
7. Tsukada T, Nakano T, Miyata T, Sasaki S. Life-threatening gastrointestinal mucosal necrosis during methotrexate treatment for rheumatoid arthritis. Case Rep Gastroenterol. 2013;7(3):470-5.
8. Peker A, Yarkıcı H, Akar H. Gastrointestinal bleeding secondary to use of high-dose methotrexate: A case report. J Surg Med. 2018;2(2):151-3.
9. Bidaki R, Kian M, Owliaey H, Babaei Zarch M, Feysal M. Accidental chronic poisoning with methotrexate: Report of two cases. Emerg (Tehran). 2017;5(1):e67.
10. Isoardi KZ, Harris K, Carmichael KE, Dimeski G, Chan BSH, Page CB. Acute bone marrow suppression and gastrointestinal toxicity following acute oral methotrexate overdose. Clin Toxicol (Phila). 2018;56(12):1204-6.