Acute renal failure due to low dose methotrexate administration for medical treatment in ectopic pregnancy

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Abstract

Methotrexate is an antimetabolite agent which inhibits folic acid metabolism competitively. Single dose or multiple doses is/are used for medical treatment of ectopic pregnancy. Serious side effects are not expected due to low dose methotrexate administration in the patients whose renal function is normal. It is known that serious side effects such as bone marrow toxicity, mucosal defect in gastrointestinal tract, liver failure may develop due to methotrexate administration. Serious renal failure is highly rare with low dose methotrexate administration. In our case, we report a 23-year-old female patient who developed acute renal failure as a result of administration of single dose of methotrexate due to ectopic pregnancy. Oral and intravenous hydration, calcium folinate, granulocyte colony-stimulating factor and sodium bicarbonate for urine alkalisation were used for treatment. This case did not need the haemodialysis. The patient responded well to the treatment. Her laboratory values and clinical conditions totally recovered.

Keywords: acute kidney injury, ectopic, methotrexate, pregnancy.

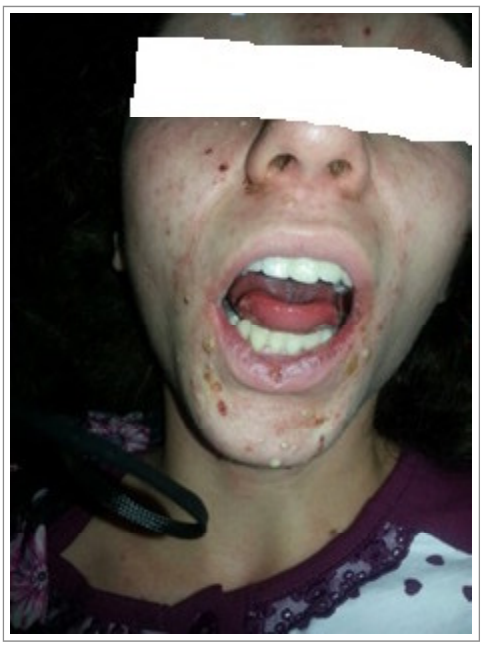
Introduction

Methotrexate is an antimetabolite agent that disrupts deoxyribonucleic acid (DNA) synthesis by inhibiting folic acid metabolism competitively. It is commonly used in treatment of rheumatoid arthritis, psoriasis, and various malignities (1). It is also prevalently used in ectopic pregnancy treatment due to its good efficiency and reliability profile. High dose use of methotrexate (1gr/m2) is known to lead to severe side effects such as renal failure, liver failure, bone marrow toxicity, and gastrointestinal system mucosal injury (2). Methotrexate may also acutely disrupt renal functions by leading to a toxic effect directly on tubular epithelial cells through metabolites and/or when methotrexate crystals cause intratubular obstruction (2-4). In this case report we present the diagnosis and treatment process of an acute renal failure (ARF) case developed due to the administration of single-dose 50 mg intravenous methotrexate owing to ectopic pregnancy.

Case

A 23-year-old female patient admitted to the emergency department with complaints of severe skin rash, itching, nausea, and vomiting. In patient's anamnesis, it was understood that the patient's complaints started 2 hours after receiving a single-dose intravenous 50 mg methotrexate due to ectopic pregnancy 3 days before applying to the emergency department and gradually became more severe. Renal function tests were normal in laboratory examinations conducted in the external centre. No characteristics were found in patient's medical background and family history. In the physical examination, TA was 110/70 mmHg, pulse was 78 pulses/min, height was 1.63 m, weight was 55 kg, VYA was 1.58 m^2; conjunctiva respiration, oral mucosa hyperaemic, and disseminated erythematous pustular lesions on face, chest, back and upper and lower extremities were identified (Figure 1). Respiration and cardiovascular system examinations were determined to be normal. No characteristics were found in abdominal examination. Having found the following results in the examinations (Urea: 58 mg/dL, Creatinine: 2.4 mg/dL, Uric acid: 4.8 mg/dL, Na: 139 mmol/L, K: 4.3 mmol/L, Cl: 100 mmol/L, P: 8.5 mg/dL, Ca: 8.1 mg/dL), the patient was admitted to the nephrology unit due to acute renal injury. It was found that both kidneys of the patient who underwent urinary ultrasonography were bigger than normal (right kidney 132x41 mm, left kidney 146x54), both kidneys' parenchymal thickness was 16 mm and parenchyma echogenicity grade 1 increased. Na and Creatinine levels in patient's spot urine examination were measured and fractional sodium excretion level was calculated as 2.82%. Renal parenchyma injury developed secondarily to methotrexate administration was considered. Calcium folinate was administered intravenously with a dose of 50 mg/day for 5 days. In order to ensure patient's urine alkalization hydrated with isotonic sodium chloride at a dose of 2.5 ml/kg/hour, treatment of 440 mEq/day sodium bicarbonate was started. Gradual recovery in renal function tests and recovery in skin lesions were observed in patient's follow-ups. She did not need the haemodialysis. On the 8th day after her admittance, Urea was 20 mg/dL, Creatinine: 0.9 mg/dL, Na: 141 mmol/L, K: .6 mmol/L, Wbc: 1.1, Hgb: 10.3 and Plt: 39.3. The patient was referred to Haematology clinic due to the ongoing pancytopenia on the 8th day after patient's renal functions returned to normal. 30 MIU filgrastim was administered on patient per day during her follow-ups in Haematology clinic. On the 14th day after admittance, filgrastim treatment was interrupted after the values Wbc: 5.4, Hgb: 10.7, Plt: 191 were determined in the complete blood count. On the 18th day after the admittance, the patient whose renal function tests were normal in follow-ups and no pancytopenia was observed, was discharged from hospital after Haematology and Nephrology policlinic examinations.

Figure 1. Oral mucositis and disseminated erythematous pustular lesions on skin



Discussion

Methotrexate, which is commonly used in treatment of various malignity and chronic inflammatory diseases, is an agent whose folic acid antagonist is antiproliferative (2,3). As it is excreted from kidneys at the rate of 80-90%, it may show toxic effects particularly in bone marrow by accumulating in cases with renal function failures (2,3). Additionally, it may disrupt renal functions acutely by leading to direct toxic effects in tubulo-epithelial cells through methotrexate metabolites and/or causing intratubular obstruction, or decreases excretion and increases toxicity by leading to decrease in glomerular filtration rate through vasoconstriction in afferent arterioles (5,6).

No serious side effects are expected in cases with healthy renal functions due to low dose of methotrexate administration. Despite not being very common, mucositis, hepatotoxicity and myelosupression may be observed (2,7). Serious renal failure has been detected with low dose of methotrexate administration, although rarely (7,8). In such cases, medications that are commonly administered, especially non-steroid anti-inflammatory drugs and salicylic acid have been accused (9). In our case, there was no anamnesis of additional medication and a low dose of methotrexate (50 mg/day single dose) was administered to our patient, whose renal functions were completely normal, due to ectopic pregnancy.

Methotrexate started to be used in ectopic pregnancy treatment method in early 1980s and became widespread in gynaecology obstetric practice later on (10,11). In early periods, methotrexate treatment in ectopic pregnancy was conducted in multiple doses and when the patient was hospitalised. However, later on, the treatment method was revised and single dose methotrexate administration and ambulatory follow-ups have been initiated (10). In an analysis conducted by Hoover et al., in the USA regarding ectopic pregnancy diagnosis and treatment tendencies, it has been reported that the use of methotrexate increased from 11.1% to 35.1% between 2002-2007 and surgical practices within this period of time decreased from 90% to 65% (12). The use of methotrexate in ectopic pregnancy treatment

reduces the rate of surgical practices and costs, and also ensures avoiding complications that may develop after surgical practice and anaesthesia.

In a treatment regimen that includes a single dose methotrexate use in ectopic pregnancy, methotrexate is administered intramuscularly as a dose of 50 mg/m^2 (10). Although rare, it has been reported that acute renal failure may develop with this practice. Although 2/3 of the recommended treatment dose was administered to our patient, the case displayed side effects such as disseminated erythematous pustular lesion, mucositis and acute renal failure 3 days after methotrexate administration. Patients are known to apply to hospital with dermatological and gastrointestinal side effects within 24-48 hours after low dose methotrexate administration (7,13,14). However, there is no precise information regarding the development period of acute renal failure. In our case, there was evidence of acute renal failure on the 3rd day after methotrexate administration.

Day et al. have recommended that secondary adverse drug reactions to low dose methotrexate use should be classified in 4 different dose-related categories and defined these categories as Type A-dose dependent, Type B-idiosyncratic, Type C-cumulative dose and Type-D-delayed effects after discontinuing the medication (15). When we classified the side effects occurring in our case due to the use of low dose methotrexate according to classification suggested by Day et al., we interpreted these side effects as Type B, in other words idiosyncratic side effects. Toxic effects of methotrexate are known to be associated with plasma concentration and the degree of renal function failure (2-4). Therefore, we tried to prevent accumulation of metabolites and crystallisation by hydrating the case. In our case, there was no need for haemodialysis (HD) due to renal failure. As it was known that methotrexate was attached to plasma proteins firmly and excretion through HD was insufficient, haemodialysis practice was not considered for the patient. After the hydration and urine alkalization conducted in line with literature, sufficient urination and recovery in renal function tests were ensured (2-6). Filgrastim was administered as 30 MIU per day for the developing pancytopenia. In addition to hydration and methotrexate excretion of the case, calcium folinate treatment was also conducted based on literature (2,3). Sucralfate and benzydamine combinations have also been used in treatment for oral mucositis. Nephrology policlinic follow-ups of the patient, whose existing side effects completely recovered, have continued and no permanent injury has been followed up in renal functions.

Consequently, we aimed to share this case that low dose methotrexate administration, which is considered very innocent and is commonly used in gynaecological obstetric practice, may lead to serious complications that threaten life including acute renal failure, although rarely. After conducting the treatment, renal function tests should also be followed up closely in the first days in the evaluation of cases. When deterioration is detected in renal function tests, the case's treatment should be initiated as soon as possible in order to prevent development of a permanent injury or increasing of side effect severity.

Conflicts of interest: None declared.

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