Low Dose Methotrexate Associated Pancytopenia in a Patient with Rheumatoid Arthritis

Düşük Doz Metotreksat Alan Romatoid Artritli Bir Hastada Pansitopeni Gelişimi

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Summary

Methotrexate (MTX) is one of the most widely used anti-rheumatoid drugs for Rheumatoid Arthritis (RA). Pancytopenia associated with low dose MTX therapy is a life threatening adverse effect often associated with known risk factors. In this article a 33-year-old woman taking low dose MTX for 6 years for RA referred to our clinic with pancytopenia is presented. This case highlights that low dose MTX is safe but the patient should be evaluated for dehydration, medication interactions and renal function. *Turk J Phys Med Rehab 2008;54:79-81*

Key Words: Low-dose methotrexate, pancytopenia, rheumatoid arthritis

Özet

Metotreksat (MTX), Romatoid Artrit (RA) tedavisinde yaygın olarak kullanılan bir antiromatizmal ilaçtır. Düşük doz MTX tedavisine bağlı pansitopeni yaşamı tehdit eden istenmeyen bir etkidir, bu da bilinen risk faktörleriyle birlikte görülebilir. Bu olgu sunumunda pansitopeni nedeniyle kliniğimize yönlendirilen 33 yaşında 6 yıldır düşük doz MTX kullanan RA'lı kadın hasta bildirilmiştir. Bu olguyla, düşük doz MTX tedavisinin güvenli olduğunu fakat diğer ilaçlarla birlikte verildiğinde ve dehidratasyon hallerinde dikkatli olunması gerektiğini vurgulamak istedik. *Türk Fiz Tıp Rehab Derg 2008;54:79-81*

Anahtar Kelimeler: Düşük doz metotreksat, pansitopeni, romatoid artrit

Introduction

Methotrexate (MTX) is an agent that is preferred in rheumatoid arthritis (RA) management because of its immunosuppressive effects (1). Low-dose MTX treatment is commonly employed. The most commonly encountered side effects of this treatment are gastrointestinal complications, whereas other side effects such as stomatitis, hepatotoxicity, skin rash, hair loss, pulmonary and hematological toxicity are encountered less frequently (2). The prevalence of hematologic toxicity including thrombocytopenia, megaloblastic anemia, leukopenia and pancytopenia is demonstrated with a percentage of 3% in MTX-treated RA patients (3). Pancytopenia is a rare complication of low-dose oral MTX treatment; however, the frequency of this complication may increase with co-administration of other drugs, low folate levels, hypoalbuminemia, concomitant infections, old age, dehydration and in the presence of renal dysfunction (3,4). Herein we present a case with pancytopenia secondary to dehydration following uncomplicated MTX treatment for 6 years.

Case Report

A 33-year-old woman with a seven year history of seropositive RA and being treated with MTX 7.5 mg/week for 6 years (cumulative dose 2340 mg) was referred to our clinic with pancytopenia. She had undergone hip prosthesis implantation surgery for congenital hip dislocation in the right hip three months prior to admission to our center. Carbamazepine 200 mg/day had been added to MTX treatment for sciatic neuralgia for one month postoperatively. The patient had had no

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hematological problems in this period. After resolution of neuralgia, she received only MTX for a one month period without carbamazepine. Two months after the first operation, the patient underwent a further hip prosthesis implantation surgery of her left hip. She received further carbamazepine treatment with MTX for one month for the same prior reason. While the hematological parameters at the time of initiation of carbamazepine treatment were normal, pancytopenia was found one month later.

On admission, physical examination of the patient revealed no remarkable findings other than restriction of movement in bilateral hip joints and wrists. Active synovitis was not recognized in any joints. Furthermore, pain was present in bilateral hip joints. Rheumatoid factor level was 38 IU/ml (0-15) and erythrocyte sedimentation rate 50 mm/h. At that time, abnormal hematologic parameters were as follows: Hemoglobin: 6 g/dl; leukocyte count: 2,400/mm^3; neutrophil count: 1,400/mm^3, mean corpuscular volume (MCV): 88 fl and platelet count: 32,000/mm^3.

MTX and carbamazepine were discontinued. Prior to the admission, the patient received 3 units of erythrocyte suspensions. We initiated ceftazidime treatment due to fever (38.5 Co). The other tests included; folic acid: 1.53 ng/ml (3-17); BUN: 17 mg/dl and creatinine: 2.4 mg/dl. Thyroid function tests and Vit-B12 level were within normal limits. Data on liver function were normal. Serological investigations for Salmonella typhi and Brucella, as well as, TORCH, anti-HIV, HBsAg and anti-HCV were negative. Hepatosplenomegaly or lymphadenopathy was not observed in abdominal ultrasound examination.

Bone-marrow aspiration was hypercellular and mild megaloblastic changes were observed. The cellularity was increased in the bone marrow biopsy. The patient was referred to the department of infectious diseases and imipenem treatment 2 g/day was initiated for fever and neutropenia. Following re-hydration, the creatinine level decreased to 0.7 mg/dl. Repeated blood cultures were all negative. Folinic acid was also prescribed as the patient also had folic acid deficiency, however the patient could not obtain this drug during hospitalization. The hematologic parameters were normal at the time of discharge without folinic acid and granulocyte colony stimulating factor (G-CSF) treatment as well (Table 1). She was discharged after two weeks hospitalization. Following discharge, the patient was recommended to receive folinic acid when the MTX treatment was reinitiated.

Discussion

Pathogenesis of MTX-induced pancytopenia is uncertain. Theoretically, pancytopenia observed with MTX may be acute or chronic. Acute pancytopenia with MTX is thought to be an allergy-like reaction with rapid onset, while the progression in chronic pancytopenia is thought to be insidious (5,6). Our patient had been receiving MTX for 6 years without complication, which makes a total dose of 2.4 g on admission to our clinic. The patient had a history of surgery of bilateral hip prosthesis. MTX was not stopped during the surgery, as reported in the literature that MTX does not need to be discontinued prior to elective orthopedic operations (7).

Several risk factors for MTX-induced pancytopenia have been documented. Nakazaki et al. (8) reported that hematological toxicity of MTX is more frequent in patients with high MCV (more than 94 fl); however, the toxicity can not be predicted in some patients. But according to a review of 70 patients with pancytopenia associated with low dose MTX therapy for RA, only two had increased MCV (9). Our patient did not have high MCV. She did not develop pancytopenia during combination of carbamazepine and MTX treatment following the first operation. Following the second operation, the patient again received carbamazepine plus MTX. The pancytopenia that developed in our case could also have been MTX induced, but not secondary to carbamazepine; however, the hypercellularity and megaloblastic alterations observed in the bone marrow indicate that the event was MTX-related. The bone marrow should be hypo-cellular in carbamazepine induced pancytopenia (10).

Although both drugs can affect the bone marrow pancytopenia did not develop during the first treatment period (9,10). However, the significant pancytopenia present in the second treatment period is attributed to increased creatinine levels of the patient. It reflects insufficient renal function. The most important risk factor for MTX toxicity is impaired renal function. It should be recognized that dehydration and high creatinine values could influence the renal elimination of the drug. The elimination rate of MTX by the kidneys is approximately 65-80% (2,5). Dehydration is also known to increase the hematological toxicity of MTX particularly in the elderly patients and in renal dysfunction (7,11). Non-steroidal anti-inflammatory drugs (NSAIDs) frequently administered to RA patients reduce the renal elimination rates of MTX by prevention of the secretion of the drug by tubules or by decreasing the glomerular filtration rate. Therefore, extreme attention should be paid to these interactions (12). The patient had not been using NSAIDs, trimetophrim or pyrimethamine, which are known to increase MTX toxicity (9,12).

Bone marrow aspiration specimen of the patient was also examined regarding the hemophagocytic syndrome, which is rarely encountered in RA (13). Blood parameters of the patient had returned to normal by the sixth day. She did not use G-CSF in that period. Prompt discontinuation of the drug constitutes the

Table 1. The alterations of the complete blood count in our patient.

Day	Hemoglobin (g/dl)	WBC (/mm^3)	Neutrophil count (/mm^3)	Platelet count (/mm^3)
Day 0*	6	2.400	1.400	32.000
4th day	8	3.000	1.400	130.000
6th day	8.6	5.200	2.500	79.000
8th day	8.5	6.200	3.200	126.000
9th day	9	7.200	3.500	152.000
10th day	9.5	7.400	3.600	154.000

*Discontinuation of the drugs

basis of therapy in MTX-induced pancytopenia. In the literature, the benefits of both G-CSF and methylprednisolone in the recovery of MTX-induced pancytopenia have also been showed (14).

We hypothesized that dehydration of patient resulted in renal insufficiency which effected the elimination of MTX. We did not feel that the cause of bone marrow inhibition was carbamazepine since carbamazepine can cause aplasia, but not megaloblastic changes. This case highlights that low dose MTX is safe but the clinician must be careful to avoid toxicity in obvious clinical situations such as dehydration and other medications.

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