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A Case of Pancytopenia Secondary to Low-Dose Pulse Methotrexate Therapy in a Patient with Rheumatoid Arthritis and Renal Insufficiency

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Most reports on serious MTX toxicity have focused on hepatic abnormalities, while other effects, including hematologic reactions, have not been emphasized. We experienced a case of pancytopenia secondary to MTX therapy in a patient with RA and renal insufficiency. A 67-year-old woman with a 12-year history of active seropositive RA that was a response to non-steroidal anti-inflammatory drugs, hydroxychloroquinine and intra-articular steroid injections, had been followed up and was diagnosed as early chronic renal failure in October, 1993. Recently, because of significant morning stiffness and polyarthralgia, the decision was made to institute MTX treatment. This was begun as a single oral dose of 5mg/week. After 2 doses, the patient was admitted to the hospital with general weakness. Laboratory tests showed a hemoglobin level of 7.9 g/dl, WBC count 1800/mm^3 and platelet count of 64000/mm^3. The serum creatinine level was 6.1 mEq/dl and the BUN level was 82 mEq/dl. Liver function test results were normal, but the serum albumin level was 2.7 g/dl. The patient subsequently developed fever and blood transfusions, granulocyte colony stimulating factor(G-CSF) and intravenous prophylactic antibiotic therapy were required. Her condition was improved.

In summary, Low-dose MTX-related adverse hematologic side effects, including fatal pancytopenia, are rare but are a cause of increasing concern in patients with RA and renal insufficiency. Close monitoring of associated risk factors, particulary impaired renal function, should be mandatory for all patients who are receiving MTX therapy.

Key Words : *MTX, RA, Renal Insufficiency, Pancytopenia*

INTRODUCTION

Low-dose Methotrexate (MTX) (5.0-20.0 mg/week), initially widely used to treat severe psoriasis and psoriatic arthritis, is one of the effective therapies for rheumatoid arthritis (RA)[1]. Its tolerability, prompt clinical response and relatively lack of serious side effects have all contributed to its widespread use in RA and other arthritides.

Most reports on serious MTX toxicity have focused on hepatic abnormalities, while other effects, including hematologic reactions, have not been emphasized. The latter, however, are not an uncommon finding in RA patients receiving low-dose pulse MTX. The prevalence of hematologic toxicity, including leukopenia, thrombocytopenia, megaloblastic anemia and pancytopenia, is estimated to be 3% in MTX-treated RA patients[2]. There is an increasing number of reports of severe, and at times fatal, pancytopenia, reported to occur in these

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patients[3-7].

We experienced a case of pancytopenia secondary to MTX therapy in a patient with RA and renal insufficiency, and also reviewed the literature related to MTX-induced pancytopenia in RA patients, with clinical significance and associated risk factors, in this report.

CASE HISTORY

A 67-year-old woman with a 12-year history of active seropositive RA, that was a response to non-steroidal anti-inflammatory drugs(NSAIDs), hydroxychloroquinine and intra-articular steroid injections, had been followed up in our department since June 1993. Initial laboratory tests showed a hemoglobin level of 7.6 g/dl [mean corpscular volume(MCV) 77.3 fl mean corpscular hemoglobin(MCH) 24.2 pg mean corpscular hemoglobin concentration (MCHC) 31.3 g/dl], WBC count 6300/mm^3 and platelet count of 463000/mm^3. The erythrocyte sedimentation (ESR) was 61 mm/hour. The serum creatinine level was 2.3 mEq/dl and the BUN level was 38 mEq/dl. Liver function profiles were normal. Recently, because of significant morning stiffness and polyarthralgia, the decision was made to institute MTX treatment. This was begun as a single oral dose of 5 mg/week in June 1997. After 2 doses, the patient was admitted to the hospital with general weakness. Physical examination revealed a mild-dehydrated and poor nourished woman. The blood pressure was 150/100mmHg and the temperature was 36.7℃. Laboratory tests showed a hemoglobin level of 7.9 g/dl (MCV 86.8 fl MCH 28.3 pg MCHC 32.5 g/dl), WBC count 1800/mm^3 and platelet count of 64000/mm^3. The serum creatinine level was 6.1 mEq/dl and the BUN level was 82 mEq/dl. Liver function tests were normal, but the serum albumin level was 2.7 g/dl. Over 3 days, the patient developed fever. Laboratory data were as follows: hemoglobin 6.5 g/dl, WBC count 800/mm^3 (10% polymorphonuclear cells, 77% lymphocytes and 7% eosinophils), platelet count 90000/mm^3. MTX and Sulindac were discontinued, and granulocyte colony stimulating factor and intravenous prophylactic antibiotic therapies were required. Because of weakness and easy fatiguability, she received 1 unit of packed red blood cells. On the twelfth hospital day, laboratory testing revealed the following values: hemoglobin 7.6 g/dl, WBC count 15400/mm^3, platlet 126000/mm^3. The BUN level was 84 mEq/dl, and the serum creatinine value was 6.6 mEq/dl. Her condition was improved.

DISCUSSION

Adverse drug reactions can lead to significnat morbidity and mortality. It is estimated that between 3% and 11% of hospital admissions can be attributed to drug side effects. Any drug can conceivably have a toxic or undesirable drug reaction which may be preventable[8].

Since 1980, pancytopenia due to MTX therapy in RA has been reported in 70 patients. Sergio et al[9] reported that an estimate of the frequency was derived using data from long-term prospective studies, in which 7 of 511 patients(1.4%) exposed to MTX developed pancytopenia. In most cases, pancytopenia is transient and recovery occurs after discontinuation of MTX and treatment of the disorder. Seventeen percent of these patients, however, have died despite medical intervention.

Poor renal function[10-12], or concomitant trimethoprim-sulfamethosazole(TMP/SMX) therapy[13,14] or a rising MCV[15,16] or increasing age[10,11] are all associated with an increased risk of pancytopenia. The excretion of MTX is primarily renal, through glomerular filtration and proximal tubular secretion, and it may be affected by changes in the glomerular filtration. Therefore, in the presence of renal impairment, precaution is needed in patients with RA receiving low-dose MTX therapy. As reported, several patients have developed severe hematologic reactions to small amounts of MTX (total cumulative dose as low as 10mg). This has led to the recommendation of a test dose of 5mg, which probably should be mandatory in patients with significant risk factors.

Advanced age and perhaps NSAID therapy might be indirectly related to increased risk through their association with declining renal clearance. Even concurrent penicillin therapy may interfere with renal excretion of MTX, leading to severe pancytopenia[17].

The usefulness of the RBC MCV as a harbinger of pancytopenia has been suggested by Weinblatt and others[16] using smaller numbers of cases. An elevation of MCV coincided with the development of pancytopenia in most patients, but the exact mechanism for the development of pancytopenia remains unknown. In this case , the level of MCV was normal.

As reported by others, the concurrent use of TMP/SMX appears to be an independent risk factor, presumably due to the antifolate effect of trimethoprim, although sulfamethosazole may be the offending component, as sulfamethosazole and other sulfa drugs

are known to cause pancytopenia as single agents. Therefore, folinic acid therapy is the recommended therapy for MTX induced pancytopenia[18].

Other risk factors, such as infections, obesity, increased alcohol ingestion, diabetes mellitus, peptic ulcer disease and hypoalbuminemia may also contribute to the frequency and severity of bone marrow toxicity.

The most important point is to avoid the use of MTX therapy in a case where there are risk factors directly implicated in the development of pancytopenia, such as renal dysfunction, drug interaction and advanced age. In addition to the standard CBC with differential and platelet counts and liver function tests, monitoring of the renal function before and 2 weeks after initiation of MTX and monthly thereafter is strongly recommended. The role of serum levels of MTX in RA patients with or without renal insufficiency has not yet been well defined. Also, a recent report suggests granulocyte colony stimulating factor may be a useful adjunctive treatment for MTX induced pancytopenia.

In summary, MTX-related adverse hematologic side effects, including fatal pancytopenia, are relatively common, and a cause of increasing concern in patients with RA and renal insufficiency. Close monitoring of associated risk factors, particulary impaired renal function, should be mandatory for all patients who are receiving MTX therapy.

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