Clinical Case Report

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Complete clinical and functional recovery following low-dose methotrexate related paraparesis in a patient with compound c.1298A>C AND c.677C>T MTHFR polymorphism

A case report

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Abstract

Rationale: The mechanisms of action of MTX (methotrexate) in the treatment of RA (rheumatoid arthritis) and PsA (psoriatic arthritis) is related to its antifolic activity, due to the high affinity for enzymes that require folate cofactors as dihydrofolate reductase and to the anti-inflammatory activity derivated from the inhibition of thymidylate synthetase that leads to the over-production of adenosine.

Patient concerns: Our patient was a 41-year-old female, affected by PsA in treatment since 2 years with low-dose methylprednisolone and low-dose subcutaneous MTX. The treatment was effective. The patient subacutely developed a severe paraparesis with impossibility of gait or standing without aid and was admitted to a Neurology Department where the cause of the paraparesis was not clear in spite of accurate radiological neurophysiologic and laboratory tests. Therefore, she was admitted in a rehabilitation unit.

Diagnosis and interventions: Paraparesis in PsA patient in treatment with methotrexate. MTX toxicity was hypothesized; therefore the drug was discontinued while i.m. folic acid and cyanocobalamin were administered for 20 days. The diagnosis was clinical, based on neurological examination (paraparesis) and on the chronic use of MTX (hypothesis of toxicity).

Outcomes: The patient obtained a complete resolution of paraparesis. Genetic analyses showed associated a compound heterozygosity for the c.1298A>C and c.677C>T variants of methylenetetrahydrofolate reductase (MTHFR) gene.

Lessons: Neurological side effects of MTX are uncommon. In literature no previous case of MTX induced paraparesis in patients treated with low-dose MTX for chronic arthritis has been described. The association between the gene polymorphisms of MTHFR (c.1298A>C and c.677C>T) and MTX toxicity in arthritis patients is confirmed. The case also confirms that folates are a precious antidote of MTX toxicity.

Abbreviations: MTX = methotrexate, RA = rheumatoid arthritis, PsA = psoriatic arthritis, MTHFR = methylenetetrahydrofolate reductase, MRC = Medical Research Council, DMARD = disease modifying antirheumatic drug.

Keywords: folic acid, methotrexate, paraparesis, psoriatic arthritis, rehabilitation

1. Introduction

Methotrexate (MTX) is a folic antagonist developed in1948 as an innovative antineoplastic drug for treating childhood leukemia. Side effects obviously depend on the dose and sometimes on the way of administration of the drug. Given that MTX acts on rapidly dividing cells, the earliest symptoms of toxicity are oral ulcerations and dyspepsia. However, the most common side effect is hepatotoxicity first described in patients taking a weekly dose of 25 to 50 mg. Acute and chronic encephalopathies are the most common types of MTX-induced neurotoxicity.[1,2]

The mechanisms of action of low-dose MTX in the treatment of arthritis may be more anti-inflammatory than antiproliferative. In particular, the cellular effects are related to its antifolic activity, due to the high affinity for enzymes that require folate cofactors as dihydrofolate reductase; the anti-inflammatory activity derives from the inhibition of thymidylate synthetase that in turn leads to the over-production of adenosine, a potent anti-inflammatory molecule.[3]

Neurological side effects of MTX are uncommon.[4] In our experience and in literature no previous case of MTX-induced paraparesis in patients treated with low-dose MTX for chronic arthritis has been described. However, in a previous case report, a 54-year-old woman with leptomeningeal metastasis from breast cancer treated with intrathecal MTX developed a high-grade

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spastic paraparesis with muscle power 1–2 on MRC scale. The patient was treated with: i.v. S-adenosylmetionine, folinate, cyanocobalamin, and oral methionine with a marked improvement. After 1 month, residual paraparesis was evaluated as Medical Research Council (MRC) grade 3–4. As highlighted, at genetic analyses the patient showed a homozygosity for the c.1298A>C variant of the methylenetetrahydrofolate reductase (MTHFR) gene.[5] Here we report about the case of a severe paraparesis in course of treatment with low dose MTX for PsA that obtained a complete resolution with discontinuation of the drug added to administration of folic acid and rehabilitation.

2. Case report

Our patient was a 41-year-old female, wedding photographer, affected by psoriatic arthritis (PsA) in treatment since 2 years with low-dose methylprednisolone (4 mg/day) and low-dose subcutaneous MTX (mean dose of 7.5 mg/week). The treatment was effective, the arthritis had reached a satisfying degree of remission and the patient could continue her job that requires a long-distance driving, to stand for some hours, and to move very quickly. In April 2016 blood count was tested twice, respectively, 1 months and 1 week before the admission to the hospital, because of a vague weakness. Blood count was completely normal, and no fever or any other sign of infection was present. In a few days, after an insidious onset of symptoms, the patient developed a severe paraparesis with impossibility of gait or standing without aid. Therefore, she was admitted to a Neurology Department. Neurological examination showed a severe hypotonic paraparesis with weakness (MRC grade 1) of all muscles and of the lower limbs. Upper limbs were not affected. No sensory abnormalities were found. Deambulation was severely paraparethic and impossible without bilateral aid. Plain-RX of thoracic and lumbar, brain and spine magnetic resonance with gadolinium were normal. A Guillen-Barre syndrome was excluded because: electromyography of the upper and lower limbs was negative, tendon reflexes were normal, lumbar puncture showed absence of cells and normal range of proteins (absence of typical albumin-cytological dissociation). Somatosensorial evocated potentials of lower limbs were normal; isoelectrofocusing for oligoclonal bands was negative. Blood examinations showed only a moderate and transient neutrophilic leukocytosis. After 2 months of rehabilitation, the paraparesis was still present but the patient could stand up with a little help and could walk for a short stretch with a medical walker or 2 walking sticks. At that time MTX toxicity was hypothesized, therefore the drug was discontinued. Daily i.m. folic acid (0.9 mg) and cyanocobalamin (2 mg) were administered for 20 days. This schedule, based on the administration of high doses of folate and vitamin B 12, was similar to the one used in the case reported in the introduction chapter.[5] After this brief treatment, the patient completely recovered being able to stand up and to walk without any help. At the same time, PsA worsened and needed to be treated with a new disease modifying antirheumatic drug (DMARD). Genetic analyses showed associated a compound heterozygosity for the c.1298A>C and c.677C>T variants of methylenetetrahydrofolate reductase (MTHFR) gene. After 2-year follow-up the patient does not show any neurological sign or symptom. Informed written consent was obtained from the patient for publication of this case report.

3. Discussion

This is the first reported case of paraparesis in a rheumatological patient in treatment with low-dose MTX for chronic arthritis. The complete resolution of paraparesis was obtained by MTX discontinuation followed by treatment with im folic acid and cyanocabalamin and rehabilitation. MTX acts as an inhibitor of folate pathway enzymes. MTHFR is an enzyme that catalyzes the conversion of omocysteine to methionine, a crucial step in the folate pathway. The association between the gene polymorphisms of MTHFR (c.1298A>C and c.677C>T) and MTX toxicity in RA patients has been demonstrated in a meta-analysis (respectively $P=.012$ and $P=.017$) and in previous other papers.[6,7,8] The associated compound heterozygosity for the c.1298A>C and c.677C>T variants of MTHFR gene can explain the risk of toxicity as well as the immediate and complete resolution of the paraparesis and the consequent flare of PsA, after using folic acid, thus confirming that folates are a precious antidote of MTX toxicity.[3,9] Folic acid supplementation is often used during treatment of chronic arthritis with MTX. van Ede and colleagues[10] in 2001 proposed to add folate to MTX to avoid the increase of liver enzymes, a common side effect of MTX. However, the addition of folic acid was shown to reduce the efficacy of the drug. Indeed, to obtain an effective amelioration of disease activity (following ACR criteria) the dosage of MTX must be increased by 20% to 25%.[10] In our case the patient was treated without folic supplementation because of the efficacy of low dosage of MTX (7.5 mg/week) and no sign of liver toxicity.

In the future, to personalize the treatment of chronic arthritis with MTX, also the detection of MTHFR polymorphism should be considered. Consequently, the use of folic acid supplementation in course of therapy with MTX should be decided case by case, to avoid the lack of efficacy and the risk of toxicity.[9,10] In paraparesis patients also the role of rehabilitation should be considered as a necessary and effective part of the treatment.

Author contributions

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