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Methotrexate-induced myelopathy responsive to substitution of multiple folate metabolites: A case report

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Methotrexate (MTX)-associated myelopathy is a rare but serious complication of MTX-based chemotherapy.

**Case report:** A 54-year-old woman with leptomeningeal metastasis from breast cancer was admitted to our hospital with progressive paraparesis. Three months earlier, ventriculoperitoneal shunting for malresorptive hydrocephalus had been performed, followed by whole brain radiation with 10 x 3 Gy. Because of recurrent leptomeningeal metastasis, 4 cycles of intrathecal chemotherapy with 15 mg MTX and 4 mg dexamethasone every 5 days were administered without folinate rescue. Five days after the last cycle, she developed bloody diarrhea, emesis and pancytopenia. Filgrastim, platelet transfusions and antibiotics were initiated. While the patient recovered from hematological and gastrointestinal toxicity, progressive neurological deficits emerged, and the patient was transferred to the neurooncology service. Upon admission, 16 days after the last intrathecal injection, a high-grade spastic paraparesis (MRC grade 1-2) with urinary retention and anal incontinence was present. Sensory deficits were absent. No malignant cells were found in the CSF. Protein was 2828 mg/l (normal: 0-550 mg/l), lactate was 4.2 mmol/l (normal: 1.2-2.1 mmol/l). The concentration of MTX in the CSF was below the limit of detection. Cultures from blood and CSF remained sterile. Magnetic resonance (MR) imaging of the spinal cord demonstrated hyperintense intramedullary lesions throughout the cervical and thoracic segments suggestive of subacute MTX-induced myelopathy (fig. 1), without contrast enhancement.

Although plasma levels of folate, vitamin B12 and homocysteine were normal, we substituted high doses of the key metabolites of the methyl-transfer pathway: S-adenosylmethionine (SAM), 200 mg three times daily i.v., folinate 80 mg once daily i.v., cyanocobalamine, 100 µg once daily i.v. and methionine, 5 g once daily per os. Three days later, marked improvement with resolution of paraparesis from MRC grade 1-2 to MRC grade 3 was noted. After one week, all therapy was continued orally. There was some further improvement, and the patient was referred to a rehabilitative program. Upon reevaluation one month later, there was residual paraparesis (MRC 3-4) and persisting urinary incontinence. MR imaging showed resolution of the intramedullary lesions (fig. 1). Genetic analyses revealed homozygosity for the A allele of methylenetetrahydrofolate reductase (MTHFR).
c.1298A>C (p.E429A), whereas other genetic variants of folate/methionine metabolism associated with MTX neurotoxicity were not present (details not shown; Linnebank et al., 2009).

**Discussion:**

Acute and chronic encephalopathies are the most common types of MTX-induced neurotoxicity. In contrast, subacute myelopathy is rare [Vezmar, 2003] (2). While it is notable that folinate rescue was not administered in our patient, this is often viewed as dispensable for low-dose MTX regimens including intrathecal therapy. The severe MTX-induced toxicity in our patient - both systemic and in the CNS - is therefore indicative of hypersensitivity towards MTX. Systemic and intrathecal therapy with MTX interferes with folate/methionine metabolism, increasing both plasma and CSF concentrations of homocysteine and decreasing SAM, methionine and 5-methyltetrahydrofolate concentrations [Quinn, 2004] (3). MTX neurotoxicity is associated with polymorphic mutations of folate/methionine metabolism that may influence nucleic acid and SAM synthesis as well as homocysteine metabolism. MTHFR is necessary to synthesize a cofactor for methionine synthesis, 5-methyltetrahydrofolate, from 5,10-methylenetetrahydrofolate. Homozygosity for the wildtype A-allele of the MTHFR variant c.1298A>C, as observed here, has been reported in association with a higher risk of MTX-neurotoxicity. However, the effect of this variant on SAM synthesis has not yet been investigated, and homozygosity for the A-allele is common in the normal Caucasian population Linnebank, 2009] (5). Thus, the relevance of this genotype for the neurotoxicity of the patient reported here remains speculative. Nevertheless, substitution with SAM, 5-methyltetrahydrofolate or methionine normalizes CSF levels of folate/methionine metabolites and promotes remyelination in children affected by inborn errors of folate/methionine metabolism [Surtees, 1991] (6). We therefore considered substitution of high doses of different folate metabolites acting at multiple levels of the methionine synthesis pathway a promising strategy in to achieve the best functional MTX rescue in the affected neural tissue. To our knowledge, this is the first report of substitution of multiple metabolites of folate/methionine metabolism for acute/subacute MTX-induced neurotoxicity. The patient’s rapid improvement following initiation of therapy may indicate a benefit derived from this regimen given the relentless progression of symptoms before, although spontaneous recovery from MTX-induced myelopathy can not fully be
excluded as alternative explanation. In summary, substitution with SAM itself accompanied by components necessary for endogenous SAM synthesis, like methionine, folate/ribofoline and vitamin B12, may be a safe and promising strategy for the treatment of MTX-induced neurotoxicity. Considering folinate rescue for intrathecal MTX therapy may help to avoid systemic toxicity.

Reference List


Figure legends

Figure 1

MRI of the cervical and thoracic spinal cord at presentation (A) and after four weeks of substitution with multiple folate metabolites (B). T2-weighted sagittal and transversal images at the level of the cervical spinal cord without administration of gadolinium.