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Case report

Subacute encephalopathy after combination chemotherapy including moderate-dose methotrexate in a patient with gastric cancer

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An episode of subacute encephalopathy after the infusion of a moderate dose of methotrexate (1500 mg/m^2) (MTX) is reported in a young adult with metastastic gastric cancer. Weakness of the right arm, focal seizures, lethargy and confusion appeared on day 10. High signal intensity in periventricular white matter was observed on T_2-weighted magnetic resonance imaging. Symptoms resolved spontaneously and completely after 48 h. We believe that this represents an unusual case of moderate-dose MTX-induced neurotoxicity in a patient with gastric cancer, which has not previously been reported. [© 1999 Lippincott Williams & Wilkins.]

Key words: Gastric cancer, methotrexate, subacute encephalopathy.

Introduction

Neurotoxic effects of methotrexate (MTX) include acute arachnoiditis, subacute encephalopathy and delayed leukoencephalopathy. Acute arachnoiditis typically appears within hours after intrathecal (i.t.) MTX, while subacute encephalopathy occurs after high doses of intravenous (i.v.) MTX (above 3 g/m^2) or after combination of i.v. and i.t. MTX. We describe a case of subacute encephalopathy that occurred after systemic chemotherapy with moderate-dose MTX administered in a patient with metastatic gastric cancer.

Case report

A 30-year-old man was diagnosed as having gastric cancer with hepatic and pulmonary metastases. He was treated with FAMTX, an accepted regimen in advanced gastric cancer consisting of 5-fluorouracil (5-FU), doxorubicin and MTX. On day 1 he received a MTX infusion of 1500 mg/m^2 over 1 h, followed by 5-FU 1500 mg/m^2. The MTX infusion was preceded by optimal hydration and started after alkalinization of the urine was achieved. The creatinine clearance was normal. Ranitidine, noramidopyrine and ondansetron were the only medications used concurrently. Folinic acid rescue was 30 mg/m^2 i.v. given 24 h after the start of MTX and every 6 h thereafter for 24 h. The MTX plasma concentrations were: 178.8, 7.6 and 0.2 μmol/l at 24, 34 and 48 h, respectively, after the start of MTX. The patient was discharged on day 4 but had to be readmitted to the hospital on day 7 because of nausea, vomiting and headache. On day 10, he developed weakness of the right arm, focal seizures, lethargy, confusion and ataxia. An electro-encephalogram showed no focal abnormalities. T_2-weighted magnetic resonance imaging (MRI) revealed hyperintense areas within the cerebellum, the left temporo-occipital region and both frontal lobes (Figure 1). The symptoms disappeared spontaneously within 2 days, with full neurologic recovery.

Discussion

Subacute encephalopathy is a well-known adverse event after repeated courses of high-dose i.v. MTX that are used in the treatment of osteosarcoma, acute lymphoblastic leukemia (ALL) and high-grade lymphoma.[1,2] In some of the reported cases the causal role of the i.t. MTX application alone was strongly suspected, because all patients received i.v. MTX at least 38 days before the neurologic complications.[3] Following MTX i.v. treatment, MTX plasma concentrations greater

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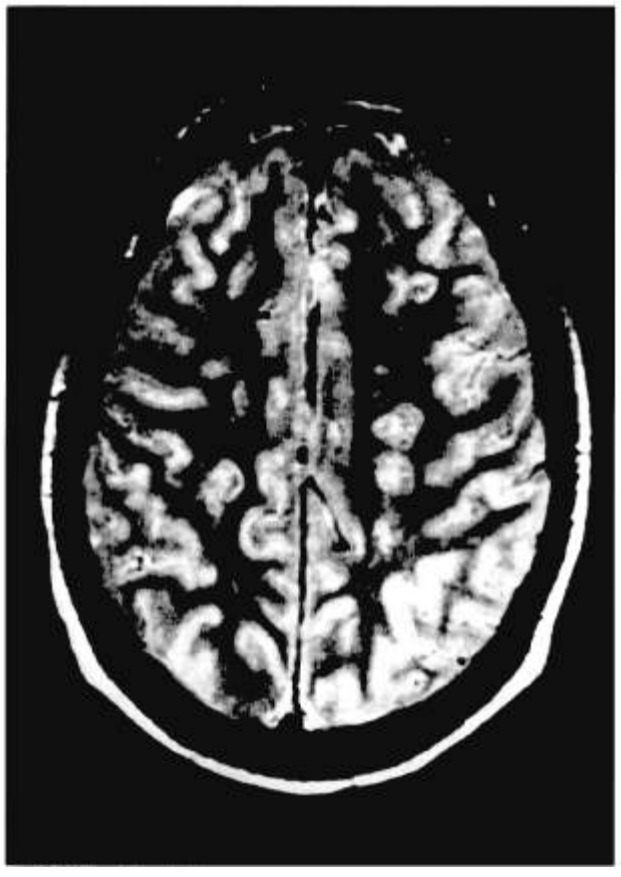

Figure 1. T_2-weighted MRI scan of the brain. Frontal and temporo-occipital hyperintense lesions in the periventricular

than 1 μmol/l 42 h after the start of MTX have been associated with an increased risk for toxicity. Moreover, higher MTX area-under-the-concentration-time curve, low urine pH and emesis were identified as the strongest predictors of high-risk MTX concentrations.[4]

Meningeal MTX diffusion represents 3% of the plasmatic concentration. Therefore high MTX plasma concentrations and/or disruption of the blood-brain barrier may predispose to central nervous system toxicity. Since MTX is known to promote adenosine release[5] and because this substance dilates cerebral blood vessels, neurotoxicity of MTX may be in part mediated by adenosine. Strengthening this hypothesis, adenosine concentrations in cerebrospinal fluid of patients with MTX-induced neurotoxicity were significantly higher.[6]

An interesting fact is that MTX encephalopathy is mostly reported in children or adolescents, and rarely reported among adults with ALL who received high-dose MTX.

Typically, as in our patient, the subacute encephalopathy occurs within a few days after MTX, and resolves spontaneously and completely. It is characterized by seizures, paraparesis or cerebellar abnormalities. Subacute encephalopathy shows hyperintense areas on T_2-weighted MRI typically affecting the periventricular white matter. Our case is unusual in that subacute encephalopathy occurred after a moderate dose of MTX without i.t. treatment. Moreover, such a neurotoxicity has not been reported so far after chemotherapy with the FAMTX regimen in patients with gastric cancer, even in large cohorts.[7,8]

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