Methotrexate (MTX) is a widely used chemotherapeutic agent that can cause acute, subacute, and chronic neurological complications. Subacute MTX neurotoxicity is manifest by abrupt onset of focal cerebral dysfunction occurring days to weeks after MTX administration, usually in children. We describe the neuroimaging features of an adult patient with primary CNS lymphoma who presented with transient aphasia and right hemiparesis 12 days after receiving intravenous high-dose MTX (8 g/m²) chemotherapy. Imaging within 1 h of symptom onset showed bilateral symmetrical restricted diffusion involving white matter of the cerebral hemispheres. CT angiogram and dynamic susceptibility MRI showed no evidence of vasospasm or perfusion defect. MRI five days later showed near-complete resolution of the abnormalities. MRI 3½ months later showed normal diffusion but new hyperintense T2-weighted signal changes in the subcortical white matter corresponding to previous areas of restricted diffusion. The absence of vascular or perfusion abnormalities suggests that transient cytotoxic edema in white matter may explain the syndrome of subacute MTX neurotoxicity.

**Case Study**

A 28-year-old right-handed man with idiopathic thrombocytopenic purpura and chronic variable immunodeficiency developed occipital headache, vomiting, and gait imbalance in January 2005. Gadolinium-enhanced MRI revealed enhancing masses in the right occipital lobe and the right frontal lobe. The results of CT scans of the chest, abdomen, and pelvis; whole-body ¹⁸F-fluorodeoxyglucose PET; and cerebrospinal fluid examination were normal. Resection of the right cerebellar mass revealed a mixed lymphohistiocytic infiltrate with...
prominent kappa light-chain plasma-cell component. Immunoglobulin-H gene rearrangement testing confirmed a monoclonal B-cell population consistent with a diagnosis of low-grade primary CNS lymphoma. He began treatment with i.v. high-dose MTX (8 g/m²) in March 2005, receiving four doses at two-week intervals. A complete radiographic response was documented after two cycles. Six additional treatments were administered at monthly intervals.

Twelve days after the 10th MTX infusion, he had abrupt onset of right-sided paresthesias involving the face and arm and speech difficulty while working at his desk. Upon evaluation 1 h later, he was afebrile and his blood pressure was normal. There was a nonfluent aphasia with relatively preserved comprehension, a right facial droop, and a right pronator drift. CT angiogram of the head showed no evidence of vascular irregularity to suggest vasospasm. An MRI performed approximately 1 h after symptom onset showed symmetrical hyperintense diffusion-weighted imaging (DWI) signal and decreased apparent diffusion coefficient (ADC) in the frontal and parietal lobe white matter without a pattern of posterior dominance (Fig. 1). Cortical and deep gray matter structures were unaffected. There was no associated signal change on fluid-attenuated inversion recovery (FLAIR) images. Dynamic susceptibility perfusion images showed no evidence of abnormal mean transit time, cerebral blood flow, or cerebral blood volume. The distribution of the restricted diffusion was bilateral but more prominent on the left side compared with the right, possibly correlating with the focal nature of his symptoms. Comprehensive metabolic panel, complete blood count, and toxicology screens were unremarkable. Plasma homocysteine was 8.1 μmol/liter (normal, 0–12 μmol/liter), and serum magnesium was 1.6 mEq/liter (normal, 1.4–2.0 mEq/liter). Results of tests for lupus anticoagulant, antithrombin III, activated protein C–resistance screen, protein C, and protein S were normal. Phenytoin was administered.

The symptoms gradually resolved over the next 12 h. The results of electroencephalography performed 8 h after symptom onset, as the neurological abnormali-
images showed new abnormal hyperintense signal involving areas of previously seen diffusion restriction (Fig. 4), likely indicating the presence of gliosis. There was no abnormal enhancement. Nine months later, the patient continued to be asymptomatic. MRI showed no evidence of recurrent lymphoma. FLAIR images showed stable mild abnormal hyperintense signal in the white matter, but no new areas of abnormality.

Discussion

The neurological syndrome experienced by this patient is consistent with subacute MTX neurotoxicity. This has been previously described in children receiving i.v. high-dose MTX and rarely in adults receiving i.t. MTX or combined i.t. and i.v. high-dose MTX. The imaging abnormalities associated with this syndrome after i.v. high-dose MTX in adults have not been well characterized and in our patient revealed transient restricted diffusion in the cerebral white matter without posterior predominance and without associated changes on FLAIR images 1 h after symptom onset. There was no evidence of a perfusion defect on dynamic susceptibility imaging, and CT angiogram demonstrated no evidence of vasospasm. Diffusion abnormalities had largely resolved five days after onset of symptoms. An MRI scan obtained 3½ months later revealed hyperintense FLAIR signal in the subcortical white matter in a similar distribution to diffusion studies at the time of symptom onset, suggesting the presence of gliosis.

Allen and Rosen first described the abrupt onset of focal neurological deficits occurring approximately 10 days after chemotherapy with vincristine and i.v. high-dose MTX in children being treated for osteogenic sarcoma. Symptoms were short-lived in two patients, but prolonged in two others. Since that initial report, series have been published documenting delayed-onset neurological symptoms following i.t. MTX infusion, either alone or in combination with i.v. MTX. Allen and Rosen first described the abrupt onset of focal neurological deficits occurring approximately 10 days after chemotherapy with vincristine and i.v. high-dose MTX in children being treated for osteogenic sarcoma. Symptoms were short-lived in two patients, but prolonged in two others. Since that initial report, series have been published documenting delayed-onset neurological symptoms following i.t. MTX infusion, either alone or in combination with i.v. MTX. Allen and Rosen first described the abrupt onset of focal neurological deficits occurring approximately 10 days after chemotherapy with vincristine and i.v. high-dose MTX in children being treated for osteogenic sarcoma. Symptoms were short-lived in two patients, but prolonged in two others. Since that initial report, series have been published documenting delayed-onset neurological symptoms following i.t. MTX infusion, either alone or in combination with i.v. MTX.
The earliest report of imaging abnormalities associated with subacute MTX neurotoxicity described a child with osteogenic sarcoma who developed left-sided tonic-clonic seizure activity and hemiparesis six days after i.v. high-dose MTX. A CT scan showed right posterior frontal cerebral hypodensity that was no longer present on a repeat study scan 10 days later. MRI abnormalities in children with subacute MTX neurotoxicity after i.t. or combined i.t. and i.v. therapy comprise transient symmetrical T2-weighted signal hyperintensity in the subcortical and periventricular white matter.

In our patient, imaging was performed within 1 h of symptom onset and showed transient symmetrical restricted diffusion in the cerebral white matter and no evidence of vasospasm or perfusion deficit. Five days later, the only residual abnormality was a small area of restricted diffusion in the white matter under the left precentral gyrus, and the FLAIR images remained normal. Similar findings of reversible DWI abnormalities have been described after i.t. or combined i.t. and i.v. MTX therapy in patients with subacute MTX neurotoxicity.

In our patient, FLAIR images 3½ months later showed abnormal hyperintense signal involving bilateral subcortical white matter in a similar distribution to the original diffusion abnormalities. Chu et al. have described asymptomatic bilateral white matter FLAIR abnormalities in 23% of children (five of 22) after combined i.t.-i.v. MTX therapy for acute lymphoblastic leukemia, peaking at 20 weeks after treatment and partially resolving after one to three years. MR spectroscopy in the subcortical white matter at 20 weeks after treatment showed decreased N-acetyl aspartate–choline and increased choline-creatine ratios, suggesting either demyelination or gliosis as a cause of the subacute FLAIR changes.

The mechanism of subacute MTX neurotoxicity is poorly understood. The radiographic findings of transient restricted diffusion without vascular or perfusion changes are consistent with reversible cytotoxic edema involving the white matter of both hemispheres. MTX is a cell cycle–specific folate analogue that inhibits dihydrofolate reductase, preventing the conversion of folic acid to tetrahydrofolate acid and thereby inhibiting cell replication through depletion of the DNA precursors purine and thymidylate. Multiple biochemical alterations are known to arise with MTX administration, including increased homocysteine, S-adenosylhomocysteine, and sulfur-containing amino acids; increased methionine and adenine levels; and decreased S-adenosylmethionine and tetrahydrobipterin levels. The possible relationship between individual biochemical changes and the clinical and radiographic findings in MTX neurotoxicity has yet to be defined.

Conclusions

Subacute MTX neurotoxicity is a rare syndrome with a neurological presentation and findings on DWI that permit a confident diagnosis to be made. Early normalization of both symptoms and ADC values without vascular or perfusion changes may be explained by transient cytotoxic edema due to MTX-related biochemical alterations.

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References