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Acute Methotrexate Neurotoxicity with Choreiform Movements and Focal Neurological Deficits: A Case Report

Daniela A. Bota, MD, PhD, and Rima M. Dafer, MD

Abstract: Methotrexate (MTX) is an effective antimetabolite treatment for various oncological disorders including the central nervous system involvement (CNS) in widespread leukemia and CNS lymphoma. This form of treatment has a notable toxic effect on the nervous system, and the pediatric population seems to be more vulnerable to the neurologic toxicity of this drug. Though chronic leukoencephalopathy from an MTX regimen, especially when administered in conjunction with whole brain radiation, is well described, the acute manifestations are rare and not well understood. The diagnosis of acute focal symptoms from MTX treatment is especially difficult in patients who receive chemotherapy for neoplastic disorders and who may have many reasons for CNS involvement in general and parenchymal involvement in particular. We report the unusual clinical and neuro-imaging findings in a teenager with acute focal symptoms after MTX treatment for acute lymphoblastic leukemia.

Key Words: acute lymphoblastic leukemia, methotrexate, neurologic complications

Acute lymphoblastic leukemia (ALL) is the most common form of childhood leukemia and one of the main causes of cancer-related mortality in children.¹ Improved outcomes have been reached recently by the use of methotrexate (MTX) therapy for the consolidation and prevention of relapse at sanctuary sites such as the central nervous system (CNS). However, this treatment is not without risks, the most severe being neurotoxicity.^{2,3} In the acute phase, the patients present with confusion,⁴ seizures,⁵ and focal neurologic deficits,⁶ which are sometimes followed by cognitive and developmental impairments secondary to persistent white matter lesions in the chronic state.^{7,8}

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We describe the case of an adolescent patient with ALL and neurotoxicity following intrathecal methotrexate and review the current published literature.

Case Report

A 17-year-old male was diagnosed with ALL after presenting with a 3-week history of fever, fatigue, decreased appetite, and weight loss. Immunophenotypic analysis of the bone marrow showed a majority of immature B-cells, which were diagnostic of precursor B-cell acute lymphoblastic leukemia. The cerebrospinal fluid (CSF) was negative for neoplastic cells. The patient received a 6-week induction therapy with oral prednisone, vincristine, daunomycin, and asparaginase and 4 doses of intrathecal MTX. The last dose of asparaginase and daunomycin were held after he developed pancreatitis. He then received consolidation therapy with intrathecal MTX, cytosine arabinoside, and oral 6-mercaptopurine.

Eight weeks into the beginning of treatment and after 5 doses of intrathecal MTX, he presented with confusion, nausea, headache, unilateral choreiform movements, and right side weakness. Examination revealed

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Key Points

- Acute lymphoblastic leukemia (ALL) is the most common form of childhood leukemia and one of the main causes of cancer-related mortality in children.
- Methotrexate (MTX) is a folate antagonist widely used in the treatment of ALL. It inhibits methionine synthesis, an important metabolite necessary for central nervous system myelination.
- Acute MTX neurotoxicity may have a wide spectrum of clinical presentations and should be included in the differential diagnosis of acute neurologic symptoms for all patients treated with this drug.

(Case Report continued from previous page)

altered mental status, right facial droop, right arm and leg weakness, right side ataxia out of proportion to the weakness, ankle areflexia, and bilateral plantar extensor responses. Diffusion-weighted magnetic resonance imaging (DW-MRI) showed areas of high signal intensity within the centrum semi-ovale bilaterally (Fig. 1, C) with normal T₂ sequential imaging, fluid-attenuated inversion-recovery (FLAIR), and T₁ post-contrast imaging (Figs. 1, A, B, and D). CSF analysis showed normal protein and cellularity, no blasts, and negative cultures. CNS levels of MTX were not measured. Electroencephalography (EEG) was normal. And, a spectroscopy study was suggested but not performed.

The patient received dexamethasone with rapid clinical improvement. On his tenth hospitalization day, he received leucovorin 11 mg pre- and post-treatment with intrathecal MTX. He tolerated his chemotherapy well without recurrence of any neurologic symptoms. He was discharged home 2 weeks later.

Neurological examination 2 months later revealed normal cognitive functions, a subtle right hemiparesis with disappearance of ataxia and chorea. Follow-up brain MRI showed chronic white matter changes with abnormal T₂ and FLAIR imaging (Figs. 2, A and B) suggestive of residual gliosis and resolution of the diffusion abnormalities with no contrast enhancement (Figs. 2, C and D).

Discussion

Cytotoxic agents such as methotrexate, carmustine, cisplatin, cytarabine, fluorouracil, levamisole, fludarabine, thiotepa, interleukin-2, and interferon alfa^{9,10} are potent neurotoxins reported to cause widespread cortical, subcortical, hippocampal, and white matter pathologies.¹¹

MTX is a folate antagonist widely used in the treatment of ALL. It inhibits methionine synthesis, an important metabolite necessary for CNS myelination.^{12,13} Neurotoxicity has been reported after acute, subacute, or chronic treatment with MTX. Acute MTX neurotoxicity ranges from 3–10% and varies with the dose and route of administration.³ The time from induction to the onset of acute neurotoxicity varies from 2–127 weeks and is more often seen 10–11 days after intrathecal MTX induction therapy.

Neurological symptoms associated with MTX include headaches, nausea, emesis, lethargy, mental status change, cognitive impairments, Klüver-Bucy syndrome, blurred vision, aphasia, transient or persistent hemiparesis, seizures, choreiform movements, arachnoiditis, encephalomyelitis, and death.^{2,5,14–16} Leukoencephalopathy has been observed in less than 10% of patients after intravenous MTX administration and up to 40% following intrathecal infusion.^{2,3,16,17}

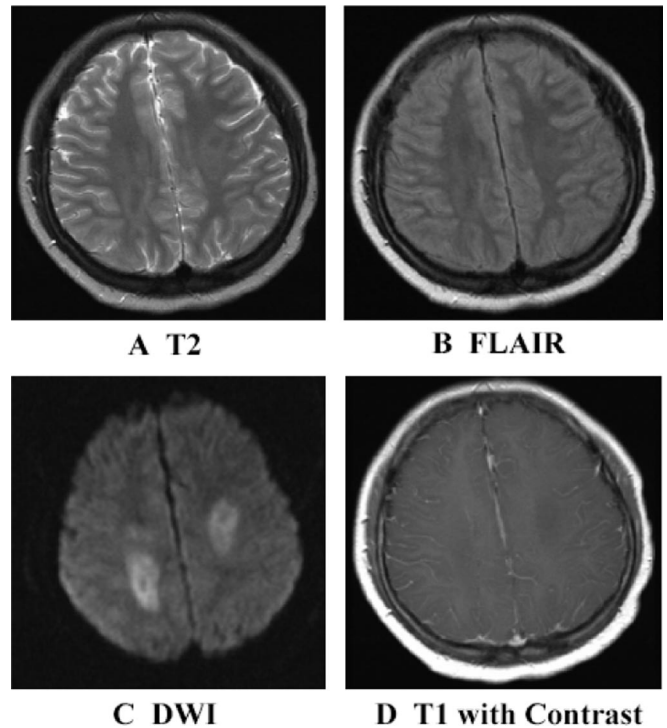


Fig. 1 Brain magnetic resonance imaging (MRI) at the initial presentation with methotrexate (MTX) toxicity. (A) T₂ sequence imaging, (B) fluid-attenuated inversion-recovery (FLAIR), (C) diffusion weighted (DW), (D) T₁ postcontrast. Hyperdense lesions are noted bilaterally on DW in the centrum semiovale.

The mechanism for MTX-induced neurotoxicity remains unclear. Various multifactorial mechanisms have been suggested for the effects of MTX such as: the direct toxic effect on myelin, inhibition of glucose metabolism,^{18,19} injury to oligodendrocytes with disruption of myelin synthesis, disruption of mitochondrial energy metabolism resulting in oxidative stress and increased vulnerability of neurons to physiological glutamate concentrations,¹¹ breakdown of the blood–brain barrier,¹⁷ and inhibition of the enzyme dihydrofolate reductase, which prevents the conversion of folic acid to tetrahydrofolic acid and thereby increases the levels of homocysteine and excitotoxic neurotransmitters and inhibits cell replication.^{18,19}

MTX neurotoxicity should be suspected in all patients with acute neurologic findings receiving treatment for oncological conditions. In this population, CSF analysis is usually unremarkable. Electroencephalographic findings are usually non-specific. Acutely, DW-MRI studies show white matter changes probably due to demyelination.^{6,20,21} Magnetic resonance spectroscopy may demonstrate metabolite changes in the absence of structural white matter abnormalities.²²

The treatment of acute MTX toxicity is still open for debate.

MTX neurotoxicity was reported to be reversible with administration of dexamethasone and leucovorin.^{7,23} Leuco-

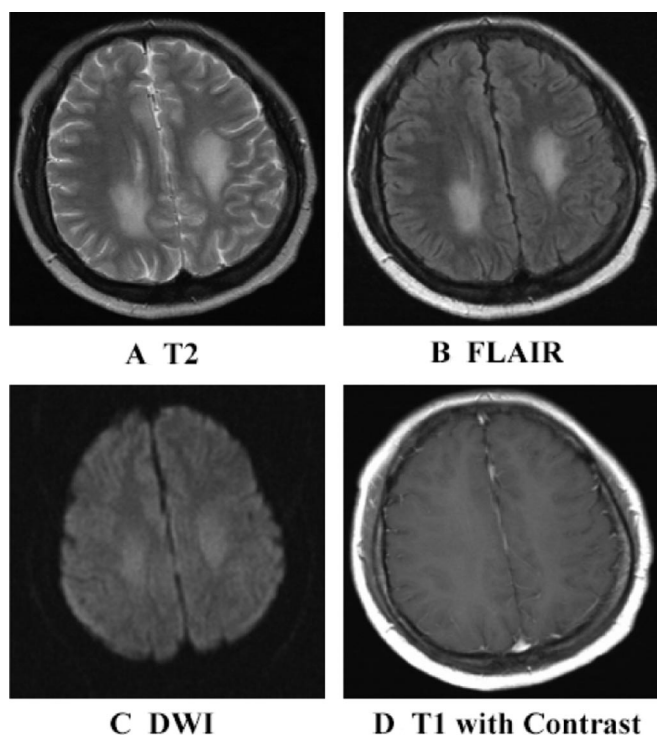


Fig. 2 Two-month follow-up brain magnetic resonance imaging (MRI). (A) T₂ imaging, (B) fluid attenuated inversion recovery (FLAIR), (C) diffusion weighted (DW), (D) T₁ post-contrast. In the chronic stage, bilateral white matter lesions are on T₂ and FLAIR, with resolution of the lesions on DW. The lesions are not enhancing. At this stage, the clinical symptoms are markedly improved.

vorin could antagonize the effects of MTX on purine metabolism through maintenance of DNA/RNA synthesis, despite the blockade of dihydrofolate reductase. Significant improvement of neurological symptoms has also been achieved with combined administration of aminophylline—an adenosine antagonist—and high dose folinic acid.²⁴ Whether glutamate antagonists could prevent neurotoxicity of MTX when given with cancer chemotherapy remains to be determined.²⁵

Conclusion

Neurological complications of MTX are increasingly recognized with the advances of neuroimaging. Acute MTX neurotoxicity may have a wide spectrum of clinical presentations and should be included in the differential diagnosis of acute neurologic symptoms for all the patients treated with this drug. These symptoms and the MRI findings are usually reversible.

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