Clinical Case Reports

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CASE REPORT

# Methotrexate-induced leukoencephalopathy presenting as stroke in the emergency department

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**Funding Information**
No sources of funding were declared for this study.

Received: 23 September 2016; Revised: 5 April 2017; Accepted: 11 April 2017

***Clinical Case Reports* 2017; 5(10): 1644–1648**

doi: 10.1002/ccr3.1110

### Key Clinical Message

Methotrexate-induced leukoencephalopathy is to be considered as a potential etiology in any patient presenting with stroke-like symptoms after receiving methotrexate. One of our cases suggests that the method of administration of the methotrexate can be IV or intrathecal and still results in leukoencephalopathy.

### Keywords

Acute lymphocytic leukemia, focal weakness, intrathecal methotrexate, methotrexate-induced leukoencephalopathy, neurotoxic side effects.

## Introduction

Methotrexate (MTX) is an antimetabolite that is used both intravenously and intrathecally for the treatment of many cancers. MTX is also commonly used for CNS prophylaxis which is important during therapy of childhood cancers. Unfortunately, MTX can generate neurotoxic side effects such as leukoencephalopathy (LE), which may present as focal weakness, seizures, headaches, and confusion. However, unlike a vascular stroke, the symptoms in MTX LE are transient and can resolve without intervention. It is important to be able to distinguish MTX-induced LE from a stroke in an emergency setting to aid appropriate triage and treatment. Herein, we report two cases of MTX neurotoxicity mimicking stroke-like symptoms and highlight salient features to enable timely and appropriate diagnosis in the emergency room.

## Case Reports

### Case 1

An 18-year-old man with a 2-month history of T-cell acute lymphocytic leukemia (ALL), for which he was receiving the augmented Berlin–Frankfurt–Münster chemotherapy regimen as part of a treatment protocol, presented to the emergency department (ED) with slurred speech and left-arm weakness witnessed by his mother of a few hours evolution. His most recent dose of intrathecal MTX (12 mg) had been given 12 days prior to the visit. He was given was given leucovorin (30 mg intravenously), methylprednisolone (40 mg intravenously), as well as dextromethorphan (DM; 65 mg intravenously), which improved his symptoms. An MRI of the brain revealed confluent nonenhancing fluid-attenuated inversion recovery (FLAIR) hyperintensity in the periventricular white matter, asymmetrically more on the right, and also involving the genu of the corpus callosum (Fig. 1). There was no evidence of restricted diffusion, midline shift, or mass effect. The transient LE findings were thought to be secondary to intrathecal MTX-induced LE, and symptoms resolved with leucovorin, methylprednisolone, and DM. The patient continued with the augmented Berlin–Frankfurt–Münster regimen, but intrathecal MTX was omitted from the regimen.

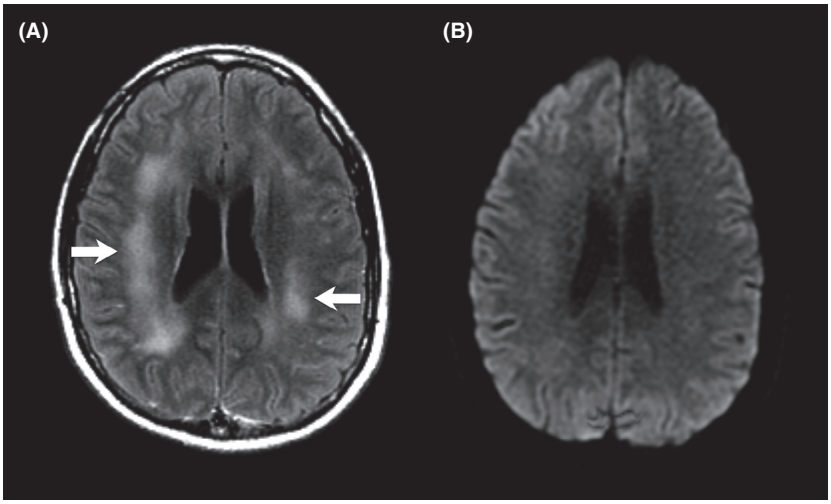


**Figure 1.** Axial T2-weighted FLAIR MR image (A) demonstrates diffuse hyperintensity within the right periventricular white matter (arrow) and to a lesser extent on the left, without any corresponding signal abnormality on diffusion-weighted imaging (B).

## Case 2

A 17-year-old girl with a history of high-grade osteosarcoma of the right distal femur, for which she had undergone extensive surgery and reconstruction with prosthesis, presented to our emergency center with the chief complaints of slurred speech, weakness, and numbness on the right side of the face and right arm after waking up from a nap. She was receiving doxorubicin, cisplatin, high-dose intravenous MTX (12 g/m$^2$), and leucovorin calcium 20 mg orally q 6 h started 30 h post-MTX as part of a clinical protocol. Her last dose of MTX had been administered about 5 days prior to her visit to the ED. She had flattening of the right nasolabial fold and an absent gag reflex. Her symptoms resolved within 4 h but recurred after an MRI was performed, with right facial paralysis being the most obvious symptom. MRI of the brain demonstrated an area of restricted diffusion in the left corona radiate and centrum semiovale without any associated FLAIR signal abnormality or enhancement (Fig. 2). These findings were attributed to the high-dose MTX. The patient was treated with aminophylline, DM (30 mg by mouth) and a course of leucovorin, recovering with no evidence of any symptoms after 2 days. Protocol therapy was discontinued and changed to doxorubicin, cisplatin, ifosfamide plus etoposide.

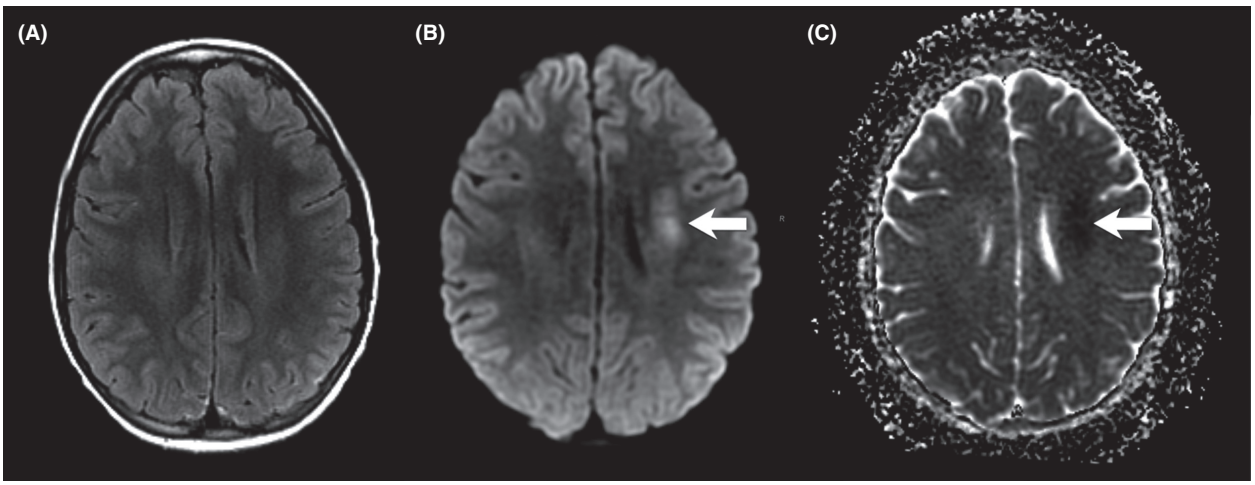


**Figure 2.** Axial T2-weighted FLAIR MR image (A) is unremarkable, but the diffusion image (B) demonstrates increased signal within the left corona radiata (arrow) with corresponding low signal on the apparent diffusion coefficient (ADC) map (B), reflective of restricted diffusion.

 

## Discussion

High-dose intrathecal methotrexate has shown to decrease central nervous system disease or metastasis in childhood acute lymphocytic leukemia and non-Hodgkin lymphoma [1]. Although MTX-related neurotoxicity is rare, acute and subacute neurological symptoms including seizures, sudden onset of transient paresis, blurred vision, aphasia, anarthria, pseudobulbar palsy, loss of consciousness, opisthotonus and confusion have been reported in the literature [2–5]. While these side effects can occur days or a few weeks after treatment with intrathecal MTX, a delayed form of MTX-induced neurotoxicity can manifest several months to years after treatment with intrathecal MTX [6–9]. Symptoms in acute–subacute MTX-induced LE are transient and can resolve within a few days with clinical recovery occurring 1–10 days after the onset of LE [10].

The etiology of acute neurological deficits in cancer patients receiving chemotherapy includes stroke, infection, neoplastic involvement of the central nervous system, drug-induced neurotoxicity, metabolic or electrolyte derangement. In stroke, restricted diffusion is a hallmark finding but corresponds to distinct vascular territories, and there is evolution of the imaging findings with development of enhancement and later on encephalomalacia. Additionally, there is either gradual improvement or lack thereof clinically, usually without any spontaneous resolution of symptoms and signs. Neoplastic or infectious pathologies of the brain generally demonstrate contrast enhancement and mass effect. MRI findings in MTX-associated LE vary based on whether the patient is symptomatic or not. In asymptomatic patients imaged during treatment deep white matter T2/FLAIR hyperintensity are identified. Patients presenting with acute symptoms in MTX-related LE have more atypical localization of changes on T2/FLAIR such as within the supratentorial cortex, subcortical white matter, thalamus, basal ganglia, cerebellum, and brainstem. Also, typically, acute to subacute LE demonstrates restricted diffusion, without initial FLAIR signal abnormality on MR imaging of the brain. One of our cases demonstrated the typical restricted diffusion findings in the left corona radiate and centrum semiovale accounting for her right sided weakness and numbness. The other patient demonstrated diffuse T2/FLAIR signal abnormality without any restricted diffusion, the latter not previously reported in acute symptomatic MTX-related LE. This case highlights that restricted diffusion may not always be present on the MRI acquired with ongoing symptoms and that nonspecific appearing diffuse white matter T2/FLAIR changes in a young person should raise suspicion for MTX-induced LE especially in the presence of stroke-like symptoms.

Methotrexate neurotoxicity can have a fluctuating course and occur more than once [11]. Bhojwani et al. have also shown that patients older than 10 years had a higher risk of MTX neurotoxic events than those between the ages of 1 and 10 years [12]. This is reflected in our two cases, as well as in the majority of the case reports in the literature, with most patients being older than 10 years. Additionally, the prevalence of LE associated with intravenous MTX is dose dependent as described in 45 children with ALL treated with seven courses of intravenous MTX without cranial irradiation. Importantly, the prevalence of LE decreased by half after the completion of intravenous MTX [13].

In addition to identifying patients most at risk, it is important to understand the mechanisms of MTX and how it affects the brain. Methotrexate is an antimetabolite that inhibits dihydrofolate reductase (DHFR) and hence the formation of tetrahydrofolate. The synthesis of macromolecules such as myelin is affected, and reversible LE has been suggested to be secondary to impairment of myelin turnover [1]. In addition, inhibition of DHFR decreases S-adenosylmethionine (SAM), which in turn plays a role in maintenance of the myelin sheath, and thus, SAM deficiency can lead to demyelination with intrathecal MTX [14, 15]. DHFR inhibition also leads to lack of folate and cobalamin, as well as an increase in homocysteine. Homocysteine which is toxic to vascular endothelium may cause seizures and vascular disease [16, 17]. It has also been reported to be present at elevated levels in the cerebrospinal fluid of patients experiencing neurotoxicity when compared to asymptomatic patients [18]. MTX has further been reported to lead to high levels of adenosine in the cerebrospinal fluid, interfering with neurotransmitter synthesis [19, 20].

Drugs such as leucovorin, DM, and aminophylline have been described to be useful in addressing the metabolic derangements mentioned above and ameliorating the side effects of MTX. Leucovorin (folinic acid) a reduced folic acid serves as a source of tetrahydrofolate which is inhibited by MTX. It has also shown to be useful for other MTX side effects such as nephrotoxicity [21], and nausea and vomiting [22]. Homocysteine metabolites are agonists of N-methyl-D-aspartate receptors; therefore, noncompetitive antagonists such as DM are recommended for the treatment of MTX neurotoxicity [12, 16, 23]. In a case series, five patients with progressive neurological symptoms such as dysarthria, cranial VII palsy, and hemiparesis 1–2 weeks after receiving a dose of MTX were given DM (1–2 mg/kg orally) and the symptoms resolved [18]. Aminophylline an antagonist of adenosine has been used in treatment of MTX side effects with four of six patients demonstrating resolution of neurotoxic symptoms [24]. Methylprednisolone, a steroid, has also been shown to

improve juvenile dermatomyositis when combined with MTX [25]. Some of these drugs may also work well when combined as reported in a case of a 20-year-old woman with rapid deterioration in a conscious state, including diminished verbal output and behavioral changes, who was given leucovorin (2500 mg) and intravenous aminophylline (145 mg) for 7 days. MRI a month later showed complete resolution of bilateral white matter T2 signal abnormality [26]. The efficacy of combination regimen was also seen in our two cases where administration of leucovorin, methylprednisolone, and DM in the 18-year-old man, and aminophylline, DM and course of Leucovorin in the 17-year-old girl, resulted in symptom resolution.

The two cases reported here, in addition to the previous publications of MTX-induced LE, emphasize the importance of recognizing the neurological side effects of intravenous and intrathecal MTX which can be managed easily and are reversible. Although they symptomatically can resemble a stroke, mistaking a case of MTX-induced LE as such can be detrimental if managed as a cerebrovascular accident. This was demonstrated in a recent case of a 16-year-old girl with ALL treated with intravenous and intrathecal MTX who presented with sudden onset of paresthesia on the left side of her face and body. She was misdiagnosed as having a stroke and was unnecessarily given antiplatelets treatment [27]. This could have been prevented if healthcare staff were cognizant of MTX-induced LE symptoms, and if even patients were informed of the stroke-like symptoms that accompany MTX neurotoxicity.

In summary, MTX-induced LE should be part of the differential diagnosis for all patients presenting with stroke-like symptoms after receiving MTX either intravenously or intrathecally. Imaging findings on MRI of the brain assist in ruling out stroke and aid in the diagnosis of LE. Healthcare professionals practicing emergency medicine in the community and outside an oncologic setting should be aware of MTX toxicity mimicking a stroke. This is imperative to enable appropriate triage for this reversible condition and more importantly to avoid activation of stroke treatment protocol and possible detrimental effects of stroke therapy.

## Authorship

MTCC, CG, PC: Department of Emergency Medicine, the University of Texas MD Anderson Cancer Center, Houston, Texas, involved in manuscript writing and development. AS: Department of Emergency Medicine, the University of Texas MD Anderson Cancer Center, Houston, Texas, involved in manuscript writing. NG-T: Department of Radiology, the University of Texas MD Anderson Cancer Center, Houston, Texas, involved in development and writing of figures and legends.

## Conflict of Interests

None declared.

### References

1. Abromowitch, M., J. Ochs, C. H. Pui, D. Kalwinsky, G. K. Rivera, D. Fairclough, et al. 1988. High-dose methotrexate improves clinical outcome in children with acute lymphoblastic leukemia: St. Jude Total Therapy Study X. Med. Pediatr. Oncol. 16:297–303.
2. Rogers, P., W. J. Pan, R. A. Drachtman, and C. Haines. 2017. A stroke Mimic: Methotrexate-induced Neurotoxicity in the Emergency Department. J. Emerg. Med. 52:559–561.
3. Pavlidou, E., E. Pavlou, A. Anastasiou, Z. Pana, V. Tsotoulidou, M. Kinali, et al. 2016. Posterior reversible encephalopathy syndrome after intrathecal methotrexate infusion: a case report and literature update. Quant. Imaging Med. Surg. 6:605–611.
4. Magge, R. S., and L. M. DeAngelis. 2015. The double-edged sword: neurotoxicity of chemotherapy. Blood Rev. 29:93–100.
5. Afshar, M., D. Birnbaum, and C. Golden. 2014. Review of dextromethorphan administration in 18 patients with subacute methotrexate central nervous system toxicity. Pediatr. Neurol. 50:625–629.
6. Keime-Guibert, F., M. Napolitano, and J. Y. Delattre. 1998. Neurological complications of radiotherapy and chemotherapy. J. Neurol. 245:695–708.
7. Borgna-Pignatti, C., L. Battisti, P. Marradi, R. Balter, and R. Caudana. 1992. Transient neurologic disturbances in a child treated with moderate-dose methotrexate. Br. J. Haematol. 81:448.
8. Sandoval, C., M. Kutscher, S. Jayabose, and M. Tenner. 2003. Neurotoxicity of intrathecal methotrexate: MR imaging findings. AJNR Am. J. Neuroradiol. 24:1887–1890.
9. Agarwal, A., K. Vijay, K. Thamburaj, and T. Ouyang. 2011. Transient leukoencephalopathy after intrathecal methotrexate mimicking stroke. Emerg. Radiol. 18: 345–347.
10. Ziereisen, F., B. Dan, N. Azzi, A. Ferster, N. Damry, and C. Christophe. 2006. Reversible acute methotrexate leukoencephalopathy: atypical brain MR imaging features. Pediatr. Radiol. 36:205–212.
11. Salkade, P. R., and T. A. Lim. 2012. Methotrexate-induced acute toxic leukoencephalopathy. J. Cancer. Res. Ther. 8:292–296.
12. Bhojwani, D., N. D. Sabin, D. Pei, J. J. Yang, R. B. Khan, J. C. Panetta, et al. 2014. Methotrexate-induced neurotoxicity and leukoencephalopathy in childhood acute lymphoblastic leukemia. J. Clin. Oncol. 32:949–959.

 

13. Reddick, W. E., J. O. Glass, K. J. Helton, J. W. Langston, X. Xiong, S. Wu, et al. 2005. Prevalence of leukoencephalopathy in children treated for acute lymphoblastic leukemia with high-dose methotrexate. AJNR Am. J. Neuroradiol. 26:1263–1269.
14. Clark, A. W., S. R. Cohen, M. J. Nissenblatt, and S. K. Wilson. 1982. Paraplegia following intrathecal chemotherapy: neuropathologic findings and elevation of myelin basic protein. Cancer 50:42–47.
15. Surtees, R., J. Clelland, and I. Hann. 1998. Demyelination and single-carbon transfer pathway metabolites during the treatment of acute lymphoblastic leukemia: CSF studies. J. Clin. Oncol. 16:1505–1511.
16. Quinn, C. T., J. C. Griener, T. Bottiglieri, K. Hyland, A. Farrow, and B. A. Kamen. 1997. Elevation of homocysteine and excitatory amino acid neurotransmitters in the CSF of children who receive methotrexate for the treatment of cancer. J. Clin. Oncol. 15:2800–2806.
17. Shuper, A., B. Stark, L. Kornreich, I. J. Cohen, S. Aviner, A. Steinmetz, et al. 2000. Methotrexate treatment protocols and the central nervous system: significant cure with significant neurotoxicity. J. Child Neurol. 15:573–580.
18. Drachtman, R. A., P. D. Cole, C. B. Golden, S. J. James, S. Melnyk, J. Aisner, et al. 2002. Dextromethorphan is effective in the treatment of subacute methotrexate neurotoxicity. Pediatr. Hematol. Oncol. 19:319–327.
19. Quinn, C. T., and B. A. Kamen. 1996. A biochemical perspective of methotrexate neurotoxicity with insight on nonfolate rescue modalities. J. Investig. Med. 44:522–530.
20. Wilson, D. A., R. Nitschke, M. E. Bowman, M. J. Chaffin, C. L. Sexauer, and J. R. Prince. 1991. Transient white matter changes on MR images in children undergoing chemotherapy for acute lymphocytic leukemia: correlation with neuropsychologic deficiencies. Radiology 180: 205–209.
21. Flombaum, C. D., and P. A. Meyers. 1999. High-dose leucovorin as sole therapy for methotrexate toxicity. J. Clin. Oncol. 17:1589–1594.
22. Tishler, M., D. Caspi, B. Fishel, and M. Yaron. 1988. The effects of leucovorin (folinic acid) on methotrexate therapy in rheumatoid arthritis patients. Arthritis Rheum. 31: 906–908.
23. Do, K. Q., P. L. Herrling, P. Streit, and M. Cuenod. 1988. Release of neuroactive substances: homocysteic acid as an endogenous agonist of the NMDA receptor. J. Neural. Transm. 72:185–190.
24. Bernini, J. C., D. W. Fort, J. C. Griener, B. J. Kane, W. B. Chappell, and B. A. Kamen. 1995. Aminophylline for methotrexate-induced neurotoxicity. Lancet 345:544–547.
25. Al-Mayouf, S., A. Al-Mazyed, and S. Bahabri. 2000. Efficacy of early treatment of severe juvenile dermatomyositis with intravenous methylprednisolone and methotrexate. Clin. Rheumatol. 19:138–141.
26. Jaksic, W., D. Veljkovic, C. Pozza, and I. Lewis. 2004. Methotrexate-induced leukoencephalopathy reversed by aminophylline and high-dose folinic acid. Acta Haematol. 111:230–232.
27. Gosavi, T. D., M. T. Ahmad, L. H. Lee, and S. H. Lim. 2013. Methotrexate induced leucoencephalopathy: a stroke mimic. Ann. Indian Acad. Neurol. 16:418–421.