

# Methotrexate-induced Leukoencephalopathy without Typical Restricted Diffusion on Diffusion-weighted Imaging and the Utility of Magnetic Resonance Spectroscopy to Support the Diagnosis

## Abstract

Methotrexate (MTX) is a common antimetabolite agent that is widely used today in treating leukemia, lymphoma, and osteosarcoma. Its use has been associated with leukoencephalopathy causing seizures, paralysis, and even coma. To achieve the best possible outcome, it is important to be able to make a prompt diagnosis. Studies reported restricted diffusion on diffusion-weighted imaging (DWI) which is a reliable early sign of acute MTX-induced leukoencephalopathy. However, we report here the first case of MTX-induced leukoencephalopathy without typical restricted diffusion on DWI and the utility magnetic resonance spectroscopy to support this diagnosis in the difficult case such as the one being presented here.

**Keywords:** *Leukoencephalopathy, magnetic resonance spectroscopy, methotrexate*

## Introduction

Methotrexate (MTX), which was first introduced around 70 years ago for the treatment of childhood leukemia, is a common antimetabolite agent that is widely used today in treating leukemia, lymphoma, and osteosarcoma.<sup>[1,2]</sup> Its use has not been limited in treatment regimen for oncological problems, but it is also commonly used in treating patients with rheumatoid arthritis and other autoimmune diseases.<sup>[1]</sup> Its side effects range from nephrotoxicity and hepatotoxicity to neurotoxicity such as leukoencephalopathy, causing seizures, paralysis, and even coma.<sup>[3-5]</sup> To accurately diagnose MTX-induced leukoencephalopathy, researchers had shown a specific pattern of restricted diffusion on diffusion-weighted imaging (DWI) magnetic resonance imaging (MRI) that often coincides with the fluid-attenuated inversion recovery (FLAIR) signal as a reliable early sign of MTX-induced leukoencephalopathy.<sup>[2,3]</sup>

However, we report here the first case of MTX-induced leukoencephalopathy without typical restricted diffusion on DWI and the utility magnetic resonance spectroscopy (MRS) to support this diagnosis in the difficult case such as the one being presented here.

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## Case Report

A 55-year-old male patient with medical history significant for tobacco abuse and hypertension presented in 2014 with a mass at the base of the tongue. After undergoing excision biopsy, the patient was diagnosed with stage IV-A mantle cell lymphoma. He was started on the cyclophosphamide-hydroxydaunorubicin-oxycortin-prednisone therapy and received radiation. He presented 1 year later with ptosis, diplopia, and oculomotor nerve palsy. Cerebrospinal fluid cytology at that time revealed lymphoma cells indicating the central nervous system (CNS) involvement. The patient underwent the right Ommaya reservoir placement to facilitate the intrathecal MTX chemotherapy. The therapy was switched to the hyper-cyclophosphamide-vincristine-doxorubicin-dexamethasone (hyper-CVAD) protocol, which includes the twice, weekly high-dose intrathecal MTX chemotherapy. The patient completed two cycles of hyper-CVAD without any issue and was admitted to the hospital during the cycle 3 of the treatment due to lethargy and mental status changes. To rule-out infection, the patient underwent a lumbar puncture, which was unremarkable and

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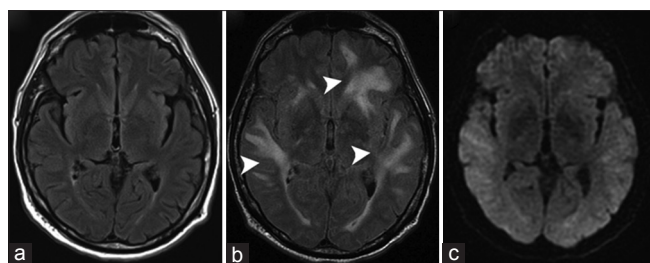
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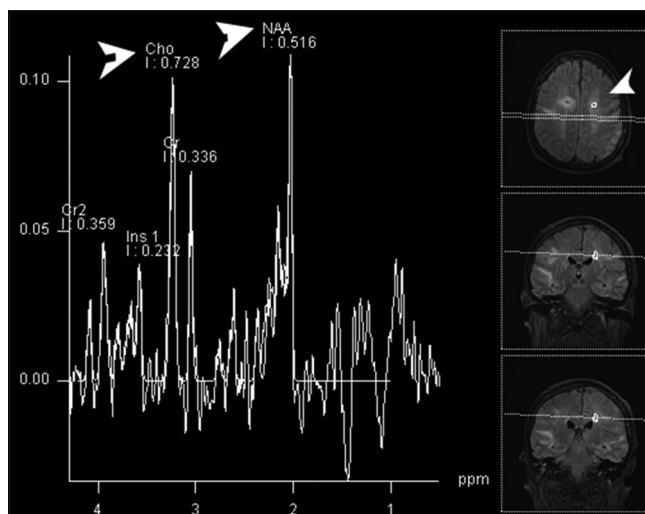


**Figure 1:** Magnetic resonance imaging of the brain, (a) fluid-attenuated inversion recovery sequence preintrathecal methotrexate treatment revealing the lack of hyperintense fluid-attenuated inversion recovery signals, (b) fluid-attenuated inversion recovery sequence postintrathecal methotrexate treatment showing widespread hyperintense fluid-attenuated inversion recovery signals, indicated by arrows, and (c) diffusion-weighted imaging sequence of the corresponding image of B failing to show restricted diffusion that is commonly present in patients with methotrexate-induced leukoencephalopathy

negative for lymphoma cells. Given the concern for either progressive CNS lymphoma or MTX side effects, electroencephalogram (EEG) and MRI of the brain were obtained. MRI of his brain showed widespread noncontrast-enhancing periventricular FLAIR signal changes without the copresentation of the typical pattern of restricted diffusion on DWI, which had been shown to commonly present in patients with MTX-induced leukoencephalopathy [Figure 1b and c]. EEG was significant for frequent triphasic waves consistent with encephalopathy. Due the lack of the typical DWI signal, MRS was performed and this showed a slight elevation of the choline peak with a normal choline-to-N-acetylaspartate ratio, indicating multifocal supratentorial neuronal losses suggestive of a demyelinating process, which was more consistent with leukoencephalopathy [Figure 2]. The patient was treated with dextromethorphan 1–2 mg/kg daily for the diagnosis of MTX-induced leukoencephalopathy.

## Discussion

MTX interferes with the DNA synthesis by inhibiting dihydrofolate reductase, an enzyme that plays a crucial role in reducing folate, which plays an important role in DNA synthesis.<sup>[2]</sup> The incidence of MTX-induced leukoencephalopathy ranges from 3% to 10%.<sup>[2]</sup> In their study, Kim *et al.* showed that the incidence of leukoencephalopathy was as high as 75% in their research group.<sup>[5]</sup> The mechanism of leukoencephalopathy was reported to involve the accumulation of homocysteine and excitatory amino acid neurotransmitters at the N-methyl-D-aspartate (NMDA) receptors in leading to neurodegeneration.<sup>[6]</sup> Vezmar *et al.* discussed various other possible etiologies for neurotoxicity, including adenosine and NMDA receptor excitation theory, to conclude that MTX affects various biochemical pathways in our body and directly destroys neurons and astrocytes.<sup>[1]</sup> In their study, Kim *et al.* reported several risk factors such as age <60 years, history of brain radiation treatment, dose of the radiation treatment as possible risk factors for



**Figure 2:** Magnetic resonance spectroscopy of the region with the hyperintense fluid-attenuated inversion recovery signal, denoted by the arrow, shows a high choline peak and an N-acetylaspartate peak indicated by arrows

MTX-related leukoencephalopathy.<sup>[5]</sup> In our case, the patient is 55 years of age and had a history of radiation therapy, predisposing him to MTX-induced leukoencephalopathy.

Multiple studies had demonstrated DWI signals as reliable markers to diagnose MTX-related leukoencephalopathy.<sup>[2,3,7]</sup> In our case, the patient was on MTX and his recent MRI before the start of MTX treatment did not reveal the restricted diffusion or hyperintense FLAIR signals [Figure 1a]. However, following the initiation of intrathecal MTX, the MRI of the brain showed widespread periventricular hyperintense FLAIR signal changes without the copresentation of the typical pattern of restricted diffusion on DWI and MRS suggested demyelination and further supported the diagnosis of MTX-induced leukoencephalopathy [Figures 1 and 2]. We report here the first case of MTX-induced leukoencephalopathy without typical restricted diffusion on DWI and the utility MRS to support this diagnosis in the difficult case such as the one being presented here.

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## Conflicts of interest

There are no conflicts of interest.

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