

Interesting Presentation of Acute Intravenous Methotrexate Leukoencephalopathy

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Abstract

Acute toxic leukoencephalopathy should be considered in a patient presenting with new onset neurologic deficit with known exposure to a toxin that has been described to injure the white matter. Methotrexate and 5-Fluorouracil are the most commonly reported offenders chemotherapeutic drugs. The below reported case is interesting as it is the first reported case of acute focal neurological deficit, followed by improvement few hours later; with minimal residual deficits on neurologic exam, along with acute changes on MRI, being diffuse white matter lesions without any restriction or enhancement, in a patient without exposure to intrathecal methotrexate. It confirms that Methotrexate induced leukoencephalopathy should be high on our differential, even when only administered intravenously

Keywords: Chemotherapy; Acute toxic leukoencephalopathy; Intravenous methotrexate

Introduction

Toxic leukoencephalopathy is important to identify early on as it is potentially reversible if the offending agent is withdrawn before the onset of irreversible damage [1]. Although multiple chemotherapy drugs are used in addition to methotrexate, the acute neurotoxicity reported in cancer patients are mostly attributed to methotrexate. Its incidence ranges from 3% to 10%, and varies with the dosage, route of administration and frequency of methotrexate given. Risk factors being high dose treatment, intrathecal route, young age and association with cranial irradiation [2]. This can be explained based on the metabolic derangement from folate deficiency and homocysteine elevation induced by cumulative effects of repeated administration of methotrexate, both intravenously and intrathecally, which might result in small vessel vasculopathy or indirect excitotoxic effects [2]. The clinical presentation can vary from headache, dizziness and depression when the toxic agent is taken in low doses to more severe symptoms like confusion, seizures, ischemic attacks, posterior reversible encephalopathy syndrome, cerebellar dysfunction and myopathy [1].

Brain Magnetic Resonance Imaging (MRI) plays a crucial role in diagnosis, as it excludes the main differential diagnosis including ischemic events, malignancies, and infections. The typical findings in methotrexate induced leukoencephalopathy include nonspecific diffuse white matter T2/ Fluid-attenuated inversion recovery (FLAIR) changes [3]. However, it can also present as focal area of restricted diffusion in deep periventricular white matter which is reversible radiologically on Diffusion Weighted (DW) MRI and corresponding Apparent Diffusion Coefficient (ADC) map, in parallel with clinical outcome [3].

Case Report

A 27-year-old right handed lady, known to have osteosarcoma involving the Right ulna diagnosed 8 months prior to presentation s/p resection and systemic chemotherapy (cisplatin, methotrexate 12 grams, doxorubicin), with the last session being few days prior to her presentation; where the patient experienced acute right lower extremity weakness upon awakening, not being able to move her leg against gravity. This lasted more than 4 hours, after which improvement was noted, but was still not back to her baseline. Review of system was negative for other focal deficits, seizure-like activity, altered level of consciousness, palpitations, or chest pain.

On physical examination, patient was afebrile, with a blood pressure of 140/80 mmHg and a heart rate of 70 b/min. Neurologic examination revealed no evidence of cranial nerve abnormalities, her right upper extremity testing was limited by the previous surgery involving the right ulna but there was no difference in the arm from her baseline. Her right lower extremity had a 4/5 motor power, mainly involving hip flexion. Rest of muscles had a 5/5 power. No peripheral or cortical sensory deficits. Deep tendon reflexes were symmetric 1+ in both arms, no reflexes elicited in both lower extremities and absent Babinski sign bilaterally. There were no abnormal cerebellar signs.

Patient underwent Brain MRI that compared to a previous image done few months prior showed new bilateral and asymmetric (left more severe than right), confluent periventricular white matter, centrum semi-ovale high T2 signal abnormalities, sparing the U-fibers (Figure 1). They were not typical of multiple sclerosis, infectious process, or cancer.

Lumbar puncture was performed, and cerebrospinal fluid studies showed 2 white blood cells with a protein of 0.35 g/L. Cytology was negative for malignant cells, and infectious profile for viruses, bacteria and fungi, was completely negative. John Cunningham (JC) virus titers were negative as well.

Discussion

Acute toxic leukoencephalopathy should be considered in a patient presenting with new onset neurologic deficit with known exposure to a toxin that has been described to injure the white matter [2]. Methotrexate and 5-Fluorouracil are the most commonly reported offenders chemotherapeutic drugs [2]. The patient reported in this case was on methotrexate IV, which was believed to be the cause of her symptoms. Previous reports of methotrexate-induced leukoencephalopathy

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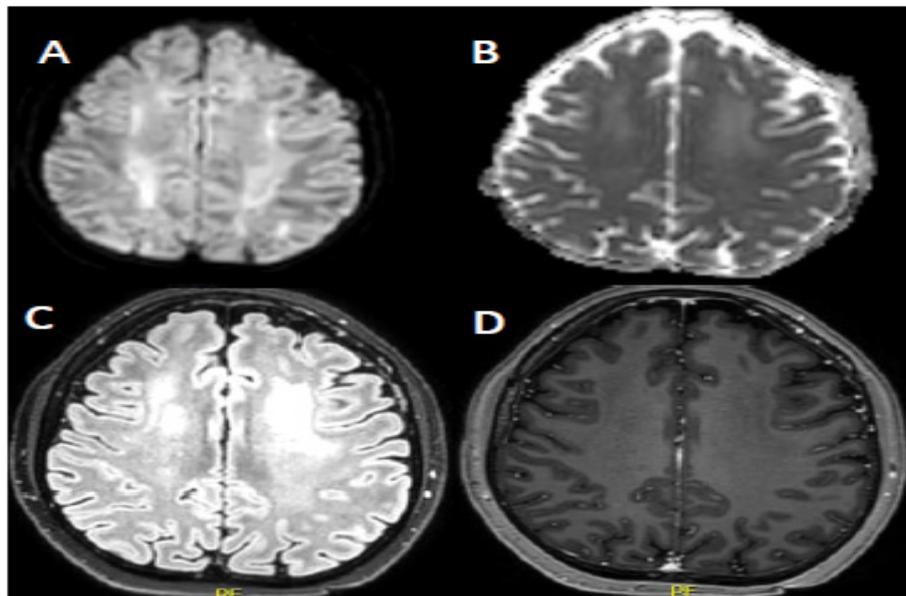


Figure 1: A) DW-MRI B) ADC C) FLAIR D) T1 with Gadolinium.

emphasize the importance of recognizing the neurological side effects of intravenous and intrathecal methotrexate, which can be managed easily and are reversible. Although they symptomatically can resemble a stroke, mistaking a case of methotrexate-induced leukoencephalopathy as such can be detrimental if managed as a cerebrovascular accident [3].

Imaging findings on brain MRI assist in ruling out stroke and aid in the diagnosis. Toxic leukoencephalopathy commonly appears as diffuse T2 and FLAIR hyperintense signal in deep periventricular white matter and corpus callosum, with sparing of basal ganglia, thalamus, and subcortical U-fibers. Post gadolinium images may or may not show any abnormal contrast enhancement [1]. On DWI focal or diffuse areas of reversible restricted diffusion with low ADC can be observed in acute cases, which may show improvement over a period if the drug is stopped. However, the corresponding changes in conventional MRI such as T2 and FLAIR hyperintensities may show a larger transitional period for improvement.

Conclusion

This case is interesting as it is the first reported case of acute focal neurological deficit, followed by improvement few hours later; with minimal residual deficits on neurologic exam, along with acute changes on MRI, being diffuse white matter lesions without any restriction or enhancement, in a patient without exposure to intrathecal methotrexate. It confirms that Methotrexate induced leukoencephalopathy should be high on our differential, even when only administered intravenously.

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