International Journal of Medical and Health Research
ISSN: 2454-9142
www.medicalsciencejournal.com
Volume 4; Issue 4; April 2018; Page No. 32-34

Methotrexate induced neurotoxicity: A stroke mimic

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Abstract
High Acute Lymphoblastic Leukemia is one of the most common childhood malignancy, which is treated with high dose of intra thecal methotrexate. The drug has a poor oral bioavailability but has the ability to cross the blood brain barrier. This property is utilized in cases where disease has spread to involve CNS and specifically targets the leukemic cells. In addition, high doses of MTX not only thwart CNS recurrence but also hematologic relapses. MTX is usually associated with neurotoxicity manifesting as acute, sub-acute or chronic presentation and involves periventricular deep white matter region. Diffusion weighted magnetic resonance imaging (DW-MRI) is habitually used in clinical practice to recognize acute stroke and also to differentiate acute stroke from non-stroke like conditions.

Keywords: acute toxic leukoencephalopathy, diffusion weighted magnetic resonance imaging, methotrexate

Introduction
Acute lymphoblastic leukemia (ALL) is the most common form of childhood leukemia. Consequently, treatment of ALL is one of the main causes of cancer-related mortality in children [1]. The management of ALL involves multimodality therapy, and methotrexate (MTX) remains a mainstay of treatment with its ability to cross the blood-brain barrier and eradicate leukemic cells from the central nervous system. A frequent side effect of MTX therapy is acute, sub-acute, or delayed neurotoxicity [2, 3]. While delayed neurotoxicity may take months to years after treatment to manifest as leukoencephalopathy, acute to sub-acute neurotoxicity usually manifests within hours to weeks after administration. Acute or sub-acute symptoms include headaches, dizziness, mood disorders, seizures, stroke-like symptoms, or other neurologic deficits [4, 5]. We present a case of acute MTX neurotoxicity with a psuedostroke presentation.

Case Report
A 23 year old male patient with no additional comorbities presented on as a suspected case of acute leukemia with cervical lymphadenopathy for one month, weakness and back pain for 10 days and mild fever. He had history of seizure disorder and took Valporate for an interim 4 years in past and was now off therapy. Initial workup showed raised TLC (159200) with blasts. Flow cytometry, Bone marrow aspiration and biopsy revealed Precursor T – Lymphoblastic leukemia.

The management in induction phase consisted of Daunorubicin and Cytocristine. During the Consolidation phase Patient was admitted for prolonged cytopenia. Patient had an episode of seizure and was evaluated for Juvenile myoclonic epilepsy. CT head done was normal. Patient was admitted for Interim maintainence chemotherapy with high dose Methotrexate and Inj. Vincristine with Leucovorin rescue. He tolerated the chemotherapy well and had no transfusion reaction.

Patient presented with complains of Limb weakness and dysarthria. Acute infract was suspected clinically, supported by imaging evidence of MRI done outside that showed acute infract in right frontal lobe, left external capsule, adjacent insular cortex and left periventricular white matter. Patient was given supportive treatment and Aspirin and recovered uneventfully without any neurological deficit. MRI done at our hospital (7 days after outside MRI) showed previous seen areas of diffusion restriction have resolved into altered signal intensity ischaemic foci with no other significant interval change. Patient further received 3rd dose of High dose methotrexate followed by Inj Vincristine with Leucovorin rescue. Patient was discharged in stable condition.

Patient again presented (12 days after last High dose methotrexate injection) with complains of sudden onset left sided weakness and deviation of angle of mouth. MRI Brain showed focal areas of signal alteration in bilateral sub cortical white matter and left perisylvian cortex with focal area of restricted diffusion around the right frontal sub cortical lesion. Compared to previous MRI Brain, there is new finding of focal area of restricted diffusion around the right sub cortical lesion, with persistent area of signal alteration without restriction of diffusion in left cerebral hemisphere. Findings

were consistent with Methotrexate induced leukoencephalopathy.

Patient received supportive care at the referred tertiary care center and recovered spontaneously. Presently the patient is clinically the patient is normal without any residual neurological deficit. We have been following up with the patients family and are looking forward to do a repeat scan.

Discussion

Leukoencephalopathy is a structural alteration of cerebral white matter in which myelin endures the most harm [6]. The term 'toxic leukoencephalopathy' may be due to toxins secondary to chemotherapy or immunosuppressive therapy, or environmental or infectious in origin or may be due to cranial irradiation. Acute toxic leukoencephalopathy should be considered in the differential diagnosis of a patient who presents with recent onset of neurologic deficit and known exposure to a toxin that has been described as injuring the white matter. Various medications can cause toxic leukoencephalopathy with variable clinical severity, and usually a mild reversible form occurs [7].

The basic path physiologic mechanisms leading to MTX-leukoencephalopathy are unfamiliar but are most probable multifactorial. MTX is a folic acid antagonist that acts by inhibiting dihyro-folate reductase (DHFR), hence blocking conversion of folic acid to tertahydrofolic acid. The raised levels of homocysteine in both blood and CSF is due to DHFR inhibition which is required for remethylation of homocysteine to methionine. Homocysteine has notorious effect on vascular endothelium and its metabolites have excitatory effect on n-methyl-D aspartate (NMDA) receptor that in turn manifests as neurological findings [8, 9].

Apart from this case report of acute leukoencephalopathy that can present with restricted diffusion in periventricular white matter, a variety of other toxic and nontoxic metabolic causes can present with overlapping scenario and that can be reversible clinically and on MRI (with sub-acute leukodystrophies as mimic).

Notable among the nontoxic causes include venous ischemia, neoplasm, prolonged seizures, periventricular white matter infarcts, infections, mitochondrial diseases, and other congenital metabolic or demyelinating diseases [10].

Note is made of this reversible entity which should not be confused with posterior reversible encephalopathy syndrome, another reversible syndrome that can arise from a diversity of causes similar to those listed here (e.g., chemotherapy, Immunosuppressive, and hypertension) [11]. Posterior reversible encephalopathy syndrome (PRES) typically affects the cortex or sub cortical white matter on FLAIR; the periventricular white matter immediately around the ventricle is not involved except in severe cases in which the sub cortical white matter is already involved. In addition, posterior reversible encephalopathy syndrome only uncommonly involves reduced diffusion [11].

This case is reported to spread the awareness of a documented notorious effect of MTX treatment that manifest as acute neurological presentation. Keeping in mind the golden salvageable period for neurons this is an important diagnosis for the clinicians to keep in mind while dealing with a stroke like presentation. Being aware of this side effect of MTX can not only help in accurate diagnosis and timely intervention but avoid unnecessary administration of thrombolytic.

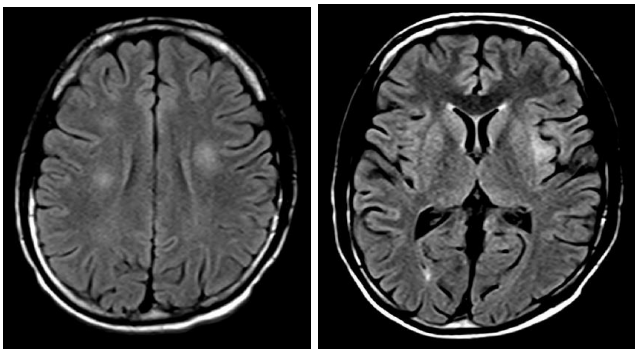

Fig 1 & 2: Axial FLAIR images show focal oval shaped areas of signal alteration are seen in bilateral frontal subcortical white matter and left perisylvian cortex.

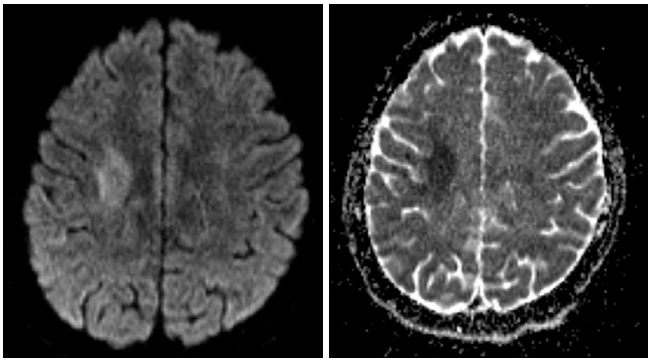

Fig 3 & 4: Focal area of restricted diffusion (showing hypo intense signal on ADC) is seen around the initial lesion in right frontal subcortical white matter.

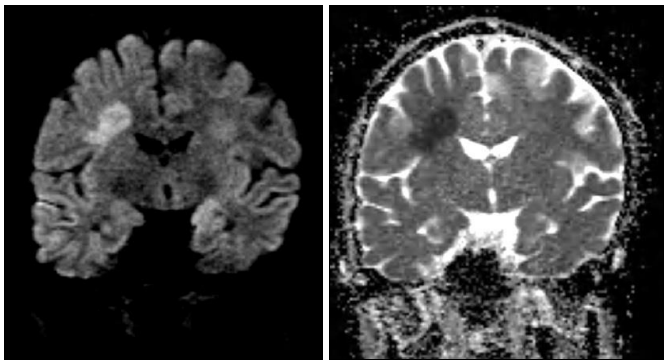

Fig 5 and 6: Coronal images of FLAIR sequence shows focal oval shaped areas of signal alteration with corresponding ADC images showing low (hypo intense) ADC values.

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