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An Unusual Mimic of Acute Ischemic Stroke - Methotrexate induced Subacute Leukoencephalopathy

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Abstract: With the increasing use of thrombolytic therapy for acute ischemic stroke within the 4.5 hour therapeutic golden hour window, timely and accurate diagnosis is crucial. As stroke mimics, though uncommon, may receive unnecessary thrombolysis and face risks such as hemorrhagic complications. Methotrexate, widely used in the treatment of malignant and autoimmune disorders can rarely cause neurotoxicity. Methotrexate-induced leukoencephalopathy is an important stroke mimic presenting with acute focal neurological deficits that can be mistaken for ischemic stroke creating diagnostic and therapeutic challenges. We report a 32-year-old male with B-cell acute lymphoblastic leukemia who developed sudden neurological deficits, 2 weeks after completing 4 weeks of methotrexate therapy. Initial clinical assessment suggested acute stroke. Brain MRI demonstrated bilateral white matter diffusion restriction not confined to a vascular territory. On contrast-enhanced imaging, no abnormal enhancement was seen suggesting white matter disease favouring methotrexate-induced leukoencephalopathy. This case highlights the potentially severe and fatal course of methotrexate neurotoxicity and underscores the need for high suspicion and recognition of characteristic clinical and imaging features to guide timely management and avoid inappropriate interventions.

Keywords: *Methotrexate, Leukoencephalopathy, Stroke Mimic, Neurotoxicity, MRI.*

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I. INTRODUCTION

Methotrexate (MTX) is a cornerstone in the treatment of hematological malignancies and various autoimmune disorders. While generally well tolerated, it can rarely cause acute neurotoxicity most commonly in the form of leukoencephalopathy (1-3).

MTX-induced neurotoxicity is a well-documented yet unpredictable complication with an incidence ranging from 3% to 15% depending on the dose, route of administration and patient age (4,7). The toxicity manifests as acute form occurring within hours of administration characterized by chemical arachnoiditis (headache, nausea, vomiting & nuchal rigidity) which is typically self-limiting. Subacute form occurs in days to weeks (typically 2–14 days) after exposure presenting as encephalopathy, seizures or the distinct "stroke-

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like" syndrome (1,4). Chronic form occurring months to years later often manifesting as a progressive, irreversible leukoencephalopathy with cognitive decline particularly in patients who received concomitant cranial irradiation (13).

The subacute "stroke-like" syndrome poses the most acute diagnostic dilemma for the neuroradiologist and treating physician. Patients present with sudden-onset neurological deficits indistinguishable on physical examination from a thromboembolic event (6,8). In the hyperacute setting, where the window for thrombolysis [tissue plasminogen activator (tPA)] or mechanical thrombectomy is narrow (typically <4.5 hours), the pressure to diagnose and treat is immense. However, administering anticoagulants or fibrinolytics to a leukemia patient with chemotherapy-induced thrombocytopenia and coagulopathy carries a devastating risk of intracranial hemorrhage (1,6). Therefore, the rapid and accurate identification of MTX induced neurotoxicity using advanced neuroimaging is a critical patient safety competency.

Although rare, early recognition of this condition and its characteristic imaging features is essential for clinicians and radiologists to differentiate it from true cerebrovascular events and enable timely management, given the potential for severe outcomes (1,10).

II. CASE REPORT

A 32-year-old male diagnosed with B-cell Acute Lymphoblastic Leukemia (B-ALL). Immunophenotyping indicated the leukemia was CALLA (Common Acute Lymphoblastic Leukemia Antigen, or CD10) positive. While CALLA positivity is generally a favourable prognostic indicator in pediatric populations, adult B-ALL carries a higher risk profile and requires aggressive induction chemotherapy. He was diagnosed 1 month back and used chemotherapy (Tab Prednisolone 20mg, Inj. Methotrexate 12mg Intrathecal, Inj. Daunorubicin 55mg, Inj. L-Asparaginase 10,000U) for 4 weeks.

Patient presented to ER after 2 weeks of chemotherapy with involuntary movements, uprolling of eyeballs, involuntary micturition, weakness of both upper and lower limbs since 3 days. Symptoms were sudden in onset and rapidly progressive.

At presentation, patient was in altered sensorium. Neurological evaluation showed decrease in tone & power in both upper and lower limbs with diminished reflexes.

Patient was sent for MRI Brain which revealed multiple well defined T2/FLAIR hyperintensities, T1 iso to hypointensities showing restriction of diffusion in centrum semi ovale, parietal lobes on both sides, right anterior temporal lobe, temporal and occipital lobes on left side (Figures 1-3) sparing subcortical U-fibres suggestive of white matter disease. No evidence of blooming (calcifications / hemorrhage) on gradient sequences within. No evidence of necrosis within. No perilesional edema noted.

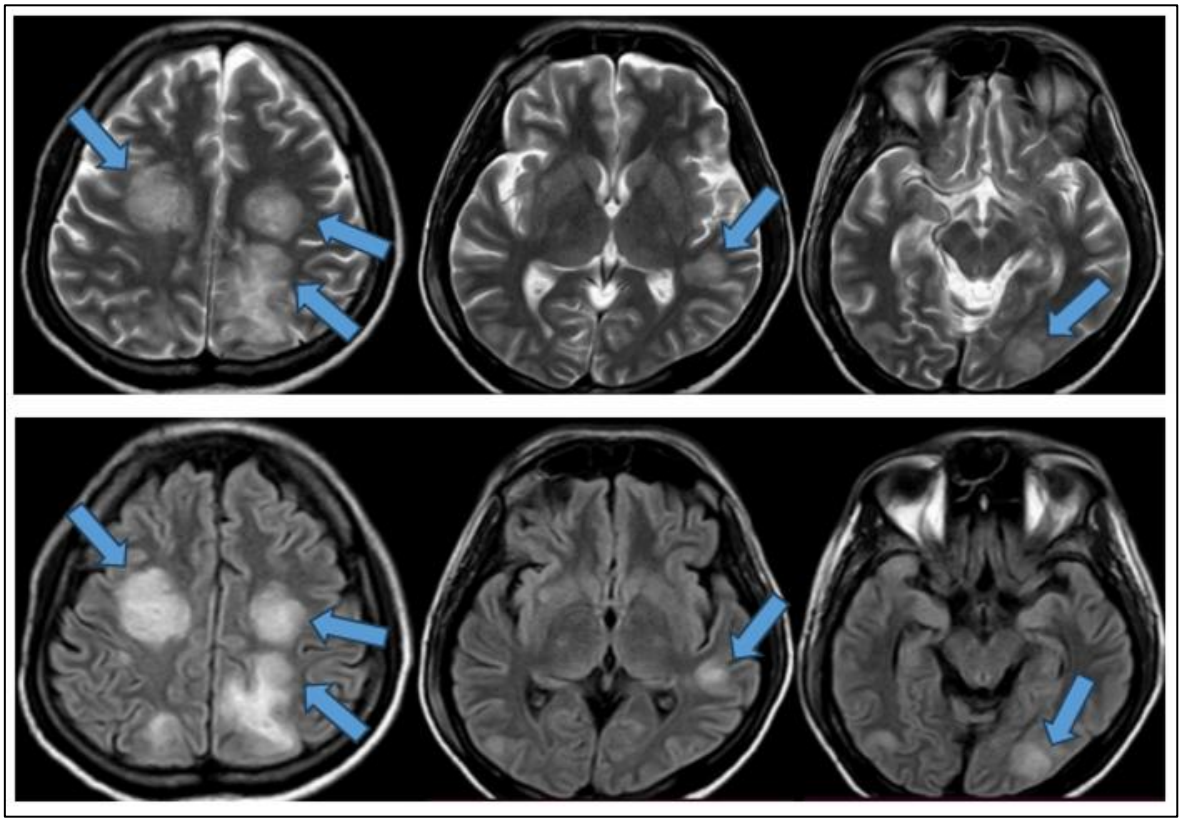

Fig 1a: Axial T2 & Fig 1b: Axial FLAIR Sequences Showing Hyperintensities in Centrum Semiovale on Both Sides, Right Anterior Temporal Lobe, Left Temporal and Occipital Lobes Sparing Subcortical U-Fibres.

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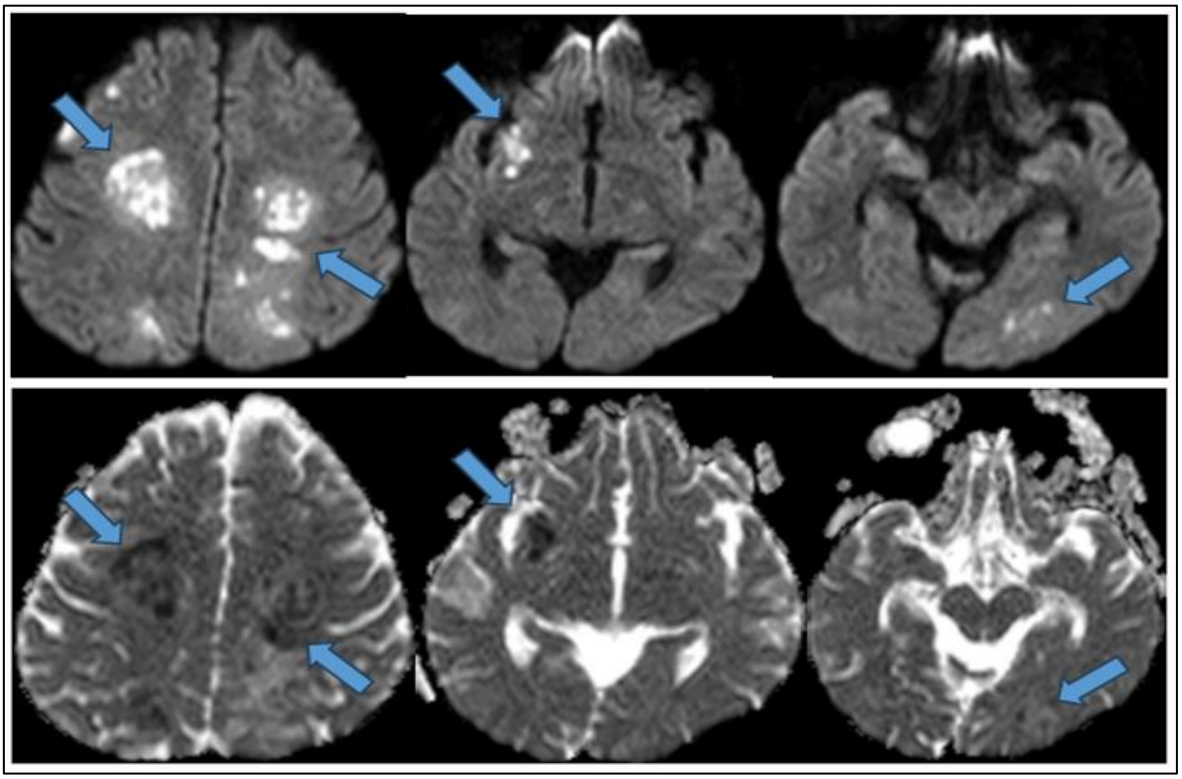

Fig 2a: Axial DWI, Fig 2b: Axial ADC Sequences Showing Restriction of Diffusion in Centrum Semi Ovale on Both Sides, Right Anterior Temporal Lobe, Left Temporal and Occipital Lobes.

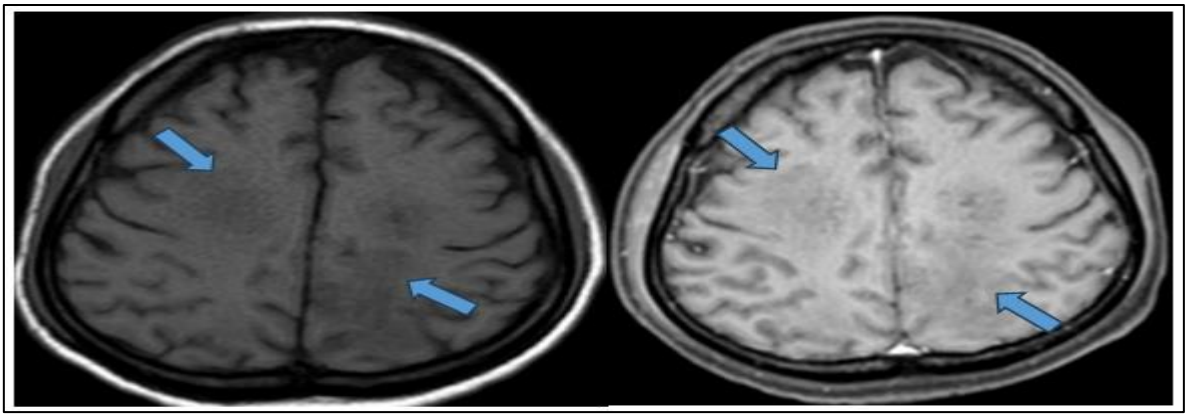

Fig 3a: Axial T1WI, Fig 3b: T1c+ Shows Isointense to Hypointense Non-Enhancing Lesions in Centrum Semiovale on Both Sides.

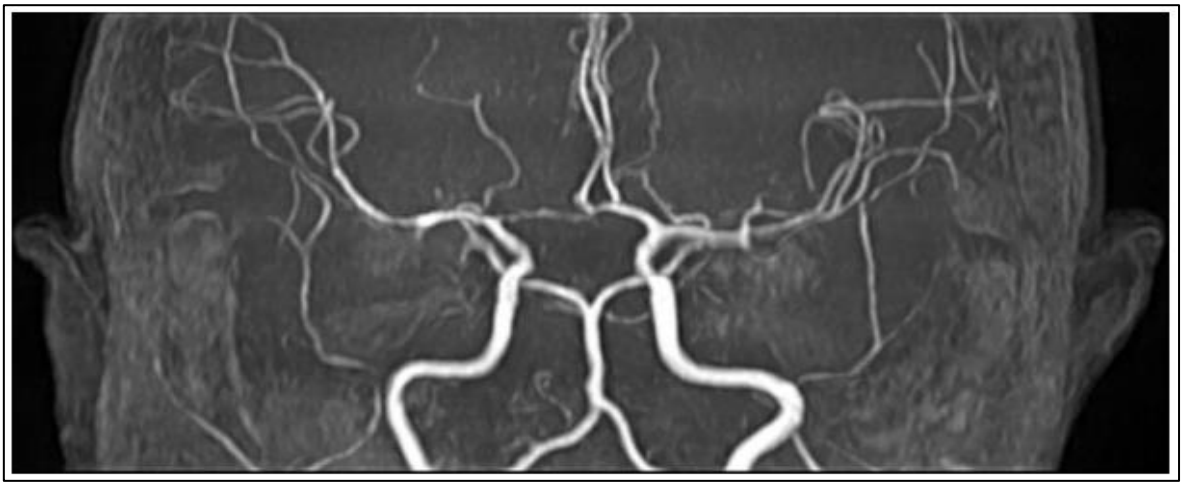

Fig 4 MR Angiogram (TOF) Revealed Normal Arterial Anatomy with No Significant Luminal Stenosis / Thrombosis.

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Suspecting to be metastasis secondary to B-ALL, contrast study was done which shows no enhancement (Figure 3) confirming the lesions as Stroke mimic which is Drug (Methotrexate) induced subacute leukoencephalopathy. MR Angiogram (Figure 4) revealed no abnormality.

Lab investigations revealed decreased cell counts and elevated LDH suggesting Pancytopenia secondary to chemotherapy.

Complete urine examination revealed no abnormality.

ECG (Figure 5) revealed first degree AV block (PR interval > 200 ms). While a first-degree block is often benign, in the context of acute toxicity, it serves as a sentinel sign of AV nodal conduction suppression—a known effect of adenosine toxicity.

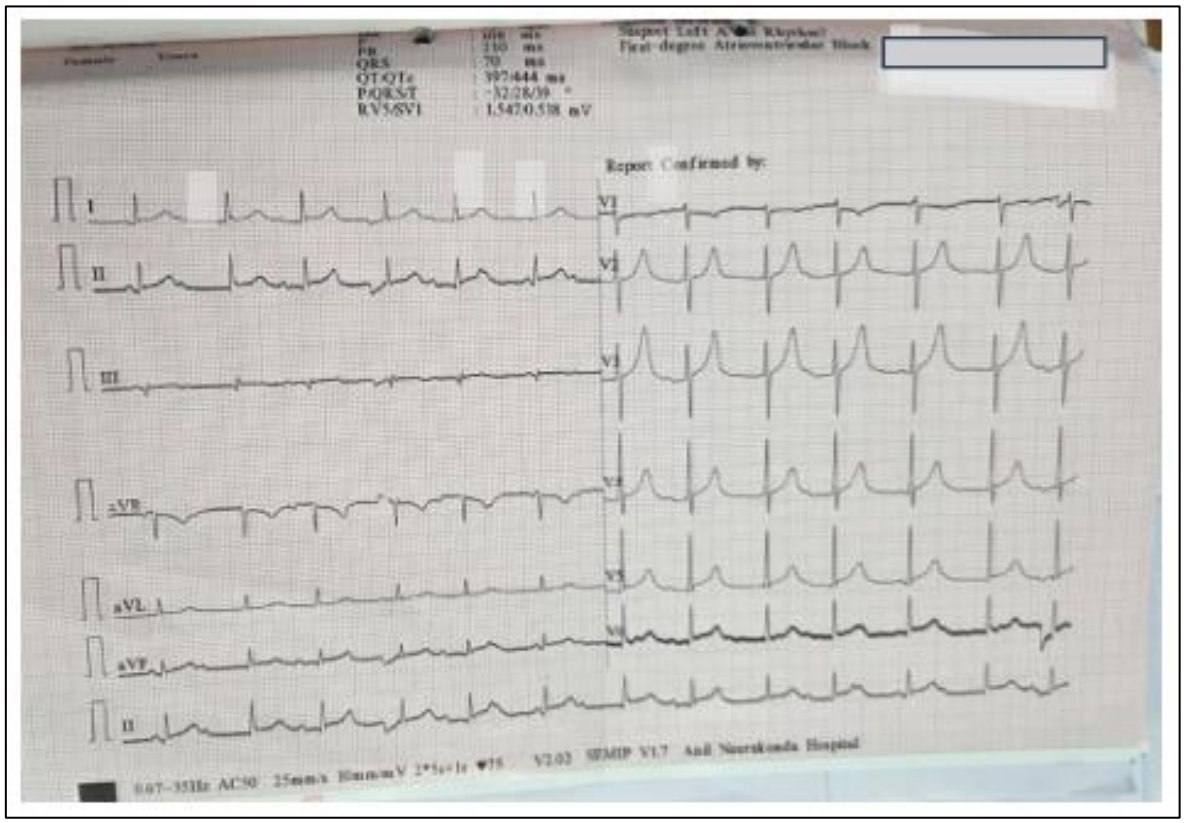

Fig 5 ECG of the Patient Showing PR Interval > 200 ms – First Degree AV Block.

A 2D Echocardiogram demonstrated normal cardiac anatomy, with a Left Ventricular Ejection Fraction (LVEF) of 64% and no evidence of intracardiac thrombus, ruling out a cardioembolic source for the neurological deficit.

ABG analysis revealed metabolic alkalosis.

III. DISCUSSION

Methotrexate (MTX) is a folate antagonist that inhibits enzymes critical for nucleotide biosynthesis, thereby impairing DNA synthesis, repair and cell proliferation ultimately leading to cell death (7,15). It has been a cornerstone in the management of hematologic malignancies, particularly acute lymphoblastic leukemia (ALL) as well as in various autoimmune disorders. In ALL, high-dose MTX (HD-MTX) and intrathecal MTX (IT-MTX) often combined with leucovorin rescue are routinely employed across multiple phases of therapy which includes induction, consolidation and maintenance (4,7). These treatment strategies have been refined over decades, contributing significantly to improved survival rates in ALL with current long-term remission rates exceeding 85–90% in many centres.

Despite its therapeutic benefits, MTX is associated with a spectrum of toxicities which include myelosuppression, mucositis, nephrotoxicity, hepatotoxicity, cardiotoxicity and neurotoxicity (3,7). Neurotoxicity, although uncommon, is one of the most clinically significant complications because of its potential for sudden onset, diagnostic confusion and occasionally severe outcomes. MTX-induced neurotoxicity may present in acute, subacute or chronic forms. Acute toxicity is generally transient and non-permanent with a reported cumulative incidence of approximately 3% after HD-MTX administration (4). Common clinical manifestations include somnolence, confusion, headache, vomiting and seizures often resembling meningitis. Subacute and chronic neurotoxicity may produce progressive neurological deterioration involving the brain, spinal cord and in rare cases may result in coma or death (3,13).

MTX-induced neurotoxicity is a well-documented yet unpredictable complication with an incidence ranging from

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3% to 15% depending on the dose, route of administration and patient age (4,7). The toxicity manifests in three temporal forms:

- Acute: Occurring within hours of administration characterized by chemical arachnoiditis (headache, nausea, vomiting, nuchal rigidity), typically self-limiting.
- Subacute: Occurring days to weeks (typically 2–14 days) after exposure, presenting as encephalopathy, seizures or the distinct "stroke-like" syndrome (1,4,11).
- Chronic / Delayed: Occurring months to years later, often manifesting as a progressive, irreversible leukoencephalopathy with cognitive decline particularly in patients who received concomitant cranial irradiation (13).

Subacute leukoencephalopathy is a particularly rare entity but important form of MTX-induced neurotoxicity. It typically occurs within two weeks of HD-MTX or IT-MTX administration and often resolves within a week. Clinically, it can present acutely mimicking ischemic stroke which poses a significant diagnostic challenge. Neurological manifestations may include headache, seizures, dysarthria, facial droop, aphasia, hemiparesis and other focal deficits (6,8,9). The stroke-like presentation can lead to misdiagnosis causing inappropriate interventions or treatment and may delay targeted supportive care.

The subacute "stroke-like" syndrome poses the most acute diagnostic dilemma for the neuroradiologist and treating physician. Patients present with sudden-onset hemiparesis, aphasia, dysarthria or facial droop indistinguishable on physical examination from a thromboembolic event (6,8). In the hyper-acute setting, where the window for thrombolysis (tPA) or mechanical thrombectomy is narrow (typically <4.5 hours), the pressure to diagnose and treat is immense. However, administering anticoagulants or fibrinolytics to a leukemia patient with chemotherapy-induced thrombocytopenia and coagulopathy carries an increased risk of intracranial hemorrhage (18). Therefore, the rapid and accurate identification of MTX neurotoxicity using advanced neuroimaging is a critical patient safety competency.

Magnetic resonance imaging (MRI) is the modality of choice for diagnosing MTX-induced leukoencephalopathy. Typical findings on T2-weighted and FLAIR sequences include transient hyperintensity in the centrum semiovale while initially sparing subcortical U-fibres (4,5). These changes may appear unilaterally or bilaterally. Diffusion-weighted imaging (DWI) frequently demonstrates diffusion restriction reflecting cytotoxic edema which can occur across multiple vascular territories and may precede observable changes on FLAIR sequences (5,10). Rarely, leukoencephalopathy may present without diffusion restriction (6,16). Recognizing these imaging patterns is essential to differentiate MTX-induced leukoencephalopathy from true cerebrovascular events, demyelinating disorders or infectious encephalopathies. MRI-detectable leukoencephalopathy may be more common than clinical symptoms alone and that subclinical CNS changes do not necessarily correlate with overt neurological deficits.

The pathophysiology of MTX-induced neurotoxicity is complex and multifactorial. While direct neuronal damage and homocysteine-mediated excitotoxicity are major theories, the "Adenosine Hypothesis" provides a compelling explanation for the transient, fluctuating nature of the stroke-like symptoms (11,15). MTX inhibition of purine biosynthesis leads to an intracellular accumulation of aminoimidazole carboxamide ribonucleotide (AICAR) which inhibits adenosine deaminase resulting in a profound increase in extracellular adenosine levels. Adenosine is a potent neuromodulator that suppresses neuronal firing and causes cerebral vasodilation, theoretically mimicking the functional deficits of a stroke without the structural infarction.

MTX is believed to exert direct neurotoxic effects damaging neuronal tissues. Additionally, it disrupts several critical metabolic pathways including folate-dependent reactions, excitatory amino acids, homocysteine metabolism, S-adenosylmethionine / S-adenosylhomocysteine balance, adenosine pathways and biopterin metabolism. Acute toxicity appears to be partially mediated by adenosine, whereas subacute and chronic manifestations may involve homocysteine, S-adenosylmethionine / S-adenosylhomocysteine, excitatory amino acids and biopterins. These biochemical disturbances contribute to neuronal dysfunction, myelin injury and cytotoxic edema ultimately leading to the observed neurological symptoms. Given these mechanisms, careful monitoring of patients receiving HD-MTX or IT-MTX is critical to identify early signs of neurotoxicity and provide supportive care which may mitigate long-term complications.

Crucially, adenosine receptors are not confined to the CNS. The massive accumulation of adenosine drives a dual toxicity: cerebral (neuronal hyperpolarization/stroke mimic) and cardiac (AV nodal suppression). The heart, specifically the atrioventricular (AV) node is rich in A1 adenosine receptors, stimulation of which induces negative dromotropy (conduction slowing) (11). While the neurotoxic effects of MTX are widely reported, the potential for simultaneous cardiac conduction toxicity (17) driven by the same adenosine surge is largely absent from the major neuroradiology literature. This case report aims to bridge this knowledge gap by detailing a case where severe leukoencephalopathy was mirrored by significant cardiac conduction defects suggesting a unified systemic toxicity.

A novel insight from this case is the correlation between the neurotoxic event and the cardiac findings. The patient's ECG showed a first-degree AV block with other features raising suspicion of an atrial rhythm disturbance. Adenosine is a potent negative dromotrope used clinically to terminate supraventricular tachycardias by creating a transient AV block. It acts by binding to A1 receptors in the AV node activating acetylcholine-sensitive potassium channels and inhibiting L-type calcium channels thereby hyperpolarizing the cell and slowing conduction velocity.

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In a state of massive MTX-induced systemic adenosine accumulation, it is physiologically consistent that the patient would experience both CNS suppression (leukoencephalopathy) and cardiac conduction suppression (AV block). While the recorded block was first-degree, severe adenosine toxicity can progress to high-grade block, bradycardia and asystole. This "cardio-neuro" axis (19) provides a plausible mechanism for the fatal outcome: a terminal progression from metabolic encephalopathy to hemodynamic collapse driven by profound adenosine-mediated myocardial depression and conduction failure.

The management of MTX-induced leukoencephalopathy remains largely supportive with limited evidence supporting specific pharmacologic interventions. Leucovorin rescue with aminophylline is commonly employed and generally well tolerated while dextromethorphan has been explored as a potential therapeutic option (9,14). However, the transient and self-limiting nature of acute MTX neurotoxicity complicates the evaluation of treatment efficacy, as many patients improve spontaneously without pharmacologic intervention. This highlights the importance of supportive care, close monitoring and early recognition of symptoms to prevent unnecessary procedures and optimize outcomes.

Continuing CNS-directed MTX therapy after neurotoxic episodes poses a therapeutic dilemma. Omitting or permanently discontinuing MTX can increase the risk of CNS relapse. This underscores the importance of balancing neurotoxicity management with the need to maintain optimal leukemia-directed therapy. Rechallenge is generally delayed until complete neurological recovery which typically occurs within a week resulting in only a minimal delay in therapy. Most patients can resume standard treatment without major alterations, substitutions or prophylactic medications (7,14).

Our case highlights the severe and potentially fatal course of MTX-induced leukoencephalopathy and cardiac conduction defects. The patient developed acute neurological deficits following MTX administration and MRI revealed bilateral centrum semiovale diffusion restriction confirming the diagnosis. No thrombolytic therapy (1,10) was administered as the clinical suspicion of stroke was reconsidered after imaging. This outcome underscores the critical importance of early recognition of MTX-induced neurotoxicity especially in patients presenting with stroke-like symptoms and the need for heightened vigilance among clinicians and radiologists.

IV. CONCLUSION

Methotrexate-induced leukoencephalopathy is an uncommon but potentially severe complication of high-dose or intrathecal MTX therapy particularly in patients with acute lymphoblastic leukemia. Its clinical presentation can closely mimic acute ischemic stroke posing a significant diagnostic challenge and risking delays in appropriate supportive care. MRI plays a pivotal role in early recognition with characteristic diffusion restriction and transient T2/FLAIR hyperintensities that do not conform to a vascular territory thereby guiding accurate diagnosis and preventing mismanagement (1,5).

While many cases are transient and resolve spontaneously, MTX-induced neurotoxicity can occasionally progress rapidly and result in fatal outcomes. This case further highlights a rare but important association between MTX-induced leukoencephalopathy and cardiac conduction abnormalities suggesting a shared adenosine-mediated systemic mechanism affecting both the central nervous system and the heart. Awareness of this “cardio-neuro” axis (19) among clinicians, hematologists, radiologists is therefore essential to avoid misdiagnosis and prevent unnecessary, potentially catastrophic interventions such as thrombolysis in thrombocytopenic patient to ensure timely supportive management (1,6,13). It may have significant implications for monitoring and management advocating for simultaneous neurological and cardiac surveillance in affected patients.

Early recognition of MTX-induced neurotoxicity allows for appropriate monitoring and informed decisions regarding safe continuation or rechallenge of MTX therapy which is crucial for preventing CNS relapse and optimizing overall leukemia treatment outcomes. A multidisciplinary approach with early identification, vigilant neurological, cardiac surveillance & coordinated care remains key to improving patient safety and prognosis in this rare but serious complication.

➢ *Declaration of Patient Consent:*

The authors certify that appropriate written informed consent was obtained from the patient for publication of clinical details and images. The patient’s identity has been adequately anonymized.

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➢ *Conflict of Interest:*

- None declared.

➢ *Funding:*

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➢ *Institutional details:*

- NRI Institute of Medical Sciences, Visakhapatnam, India.

➢ *Ethical Committee:*

- Not applicable. Case reports based on de-identified clinical findings do not require IEC approval.

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➢ *Approval Number:*

- N/A

➢ *Informed Consent:*

- Informed written consent was obtained from the patient for publication of clinical details and images.

➢ *Author's Contribution:*

- Dr. Gorle Siva Sai: Conceptualization of the case report, literature review and drafting of the manuscript.
- Dr. Tavva Pradeep: Supervision of radiological analysis, imaging interpretation, manuscript review and approval of the final version.
- Dr. Kanduri Soumya: Clinical evaluation of the patient, neurological assessment, contribution to clinical interpretation and critical revision of the manuscript.
- Dr. Sivani Reddy Demali: Clinical data collection, patient management details, integration of clinical and laboratory findings and contribution to manuscript drafting.
- Dr. Bhamidipaty Kanaka Durga Prasad: Overall supervision, case conceptualization, guidance on manuscript structure, critical revision and final approval of the manuscript for publication.

➢ *Data Availability:*

All data related to this case report are included in the manuscript. Further details available upon request.

➢ *Use of Artificial Intelligence:*

No generative AI tools were used in the preparation of this manuscript.

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