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A CASE REPORT ON CENTERAL NERVOUS SYSTEM RELAPSE IN A 12-YEAR-OLD MALE PATIENT WITH PRE-B ACUTE LYMPHOBLASTIC LEUKEMIA FOLLOWING HIGH- DOSE METHOTREXATE ADMINISTRATION

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ABSTRACT:

Introduction: Acute lymphoblastic leukaemia (ALL) is a prevalent paediatric malignancy treated with multi-agent chemotherapy, including high-dose methotrexate. Although effective, methotrexate poses risks such as gastrointestinal toxicity, neurotoxicity, and potential central nervous system (CNS) relapse.

Case Presentation: A 12-year-old male with Pre-B ALL and poor response to Prednisolone was admitted after developing a severe headache during chemotherapy. CNS involvement was confirmed via cerebrospinal fluid analysis, leading to a diagnosis of CNS relapse. Despite intensive treatment including intrathecal chemotherapy and supportive care, the patient's condition

deteriorated, exhibiting gastrointestinal and neurological complications. The treatment plan included ongoing CNS prophylaxis and management of methotrexate toxicity with Leucovorin.

Conclusion: This case underscores the critical balance between the efficacy and toxicity of methotrexate in treating paediatric ALL, highlighting the need for vigilant monitoring and management to prevent severe complications such as CNS relapse.

Keywords: Acute lymphoblastic leukaemia, methotrexate, central nervous system relapse, paediatric oncology, chemotherapy toxicity

INTRODUCTION:

Acute lymphoblastic leukaemia (ALL) is a common hematologic malignancy in paediatric patients, characterized by the proliferation of lymphoid precursor cells. In children, ALL represents approximately 25% of all leukaemia cases and is marked by a rapid onset and progression of disease **[1]**. The treatment of paediatric ALL typically involves intensive multi-agent chemotherapy regimens aimed at inducing remission and preventing relapse. One of the cornerstone drugs in the treatment of ALL is methotrexate, an antimetabolite that interferes with DNA synthesis by inhibiting dihydrofolate reductase, thereby impeding cell proliferation **[1]**.

Methotrexate is a vital component of the chemotherapeutic arsenal against ALL due to its ability to target both rapidly dividing leukaemia cells and residual disease during various treatment phases. High-dose methotrexate is particularly crucial during consolidation and maintenance phases to eliminate residual leukaemia cells and reduce the risk of relapse. Despite its efficacy, methotrexate is associated with a range of potential complications, particularly in high doses. These complications include gastrointestinal toxicity, bone marrow suppression, hepatotoxicity, and renal impairment **[2]**. Methotrexate-induced toxicity can manifest as severe mucositis, myelosuppression, and nephrotoxicity, necessitating vigilant monitoring and supportive care **[3]**.

One of the serious complications of high-dose methotrexate therapy is the potential for central nervous system (CNS) relapse. CNS relapse occurs when leukemic cells infiltrate the CNS, leading to neurological symptoms and potential deterioration in prognosis. Methotrexate can cause CNS relapse through several mechanisms. First, it may lead to increased permeability of the blood-brain barrier, facilitating the entry of leukaemia cells into the CNS. Second, high-dose

methotrexate can cause neurotoxicity, which may contribute to the disruption of normal CNS function and promote leukemic cell proliferation **[4]**. Furthermore, the pharmacokinetics of methotrexate, including its distribution and clearance, can influence its effectiveness and toxicity in CNS settings **[5]**. Gastrointestinal symptoms such as nausea, vomiting, and diarrhoea are common during methotrexate therapy and can exacerbate complications, leading to dehydration and electrolyte imbalances that further compromise patient health **[6]**. Neurological symptoms such as headache, seizures, and altered mental status may indicate severe methotrexate-related neurotoxicity or CNS relapse. In such cases, the presence of leukemic cells in the cerebrospinal fluid (CSF) is a critical diagnostic criterion **[7]**.

To mitigate the risk of CNS relapse, patients undergoing high-dose methotrexate therapy are often given CNS prophylaxis with intrathecal methotrexate or other chemotherapeutic agents. This strategy aims to eliminate any leukaemia cells that may have infiltrated the CNS and prevent their proliferation.(8) Additionally, folinic acid (leucovorin) is administered as an antidote to counteract methotrexate toxicity and minimize its adverse effects on normal tissues **[9]**.

CASE REPORT:

A 12-year-old male patient with a diagnosis of Pre-B Acute Lymphoblastic Leukaemia (ALL) and poor response to Prednisolone, along with negative cytogenetics, was admitted for intensive chemotherapy. Prior to admission, the patient had undergone a six-day chemotherapy regimen that included oral Dexamethasone at a dose of 20 mg/m²/day from day 1 to day 6, intravenous Vincristine at 1.5 mg/m² on days 1 and 6, and Methotrexate infusion at 1 g/m² on day 1. Intrathecal administration of L-asparaginase at 10,000 U/m² was scheduled for day 4. In addition, Methotrexate, Cytarabine, and Prednisolone were administered intrathecally based on the patient's age on day 1. On day 3 of the chemotherapy cycle, the patient was admitted due to a severe headache that had developed over the preceding two days. The headache was insidious in onset, progressively worsening, and did not respond to medication. The patient's body surface area (BSA) was measured at 1.03 m².

Upon admission, patient was treated as per Protocol like acute lymphoblastic leukaemia. the patient was started on intravenous fluids, with a regimen of 3 liters/m²/day, and $NaHCO_3$ was added at 10 cc per drip, with a drip rate of 125 ml/hr. The patient also received oral Dexamethasone at a dose of 4

mg BD. Initial treatment included intravenous Piperacillin-Tazobactam at 2.2 grams three times a day, and Amikacin at 400 mg once daily. To manage potential infection and fever, Paracetamol was administered, and Noradrenaline infusion was started, with the solution being 2 ml of Noradrenaline in 22 ml of normal saline, delivered at a rate of 1 ml/hr with a concentration of 0.1 µg/kg/min. Filgrastim was given subcutaneously at a dose of 0.2 ml once daily. Antifungal treatment with Fluconazole (4 mg BD), Calcium supplementation with Calcimax (500 mg OD), and Pantoprazole (20 mg OD) were also initiated.

Given the patient's deteriorating condition and persistent headache, a cerebrospinal fluid (CSF) analysis was performed, revealing a high percentage of lymphocytes (98%), which indicated central nervous system (CNS) involvement. This finding was concerning for disease progression. The patient's treatment included Methotrexate (100 mg) diluted in 100 ml of 0.9% normal saline, administered over 30 minutes, followed by a triple combination of Methotrexate (12 mg), Hydrocortisone (24 mg), and Cytarabine (36 mg) intrathecally. A high-dose Methotrexate infusion of 930 mg, diluted in 500 ml of 0.9% normal saline, was given over a period of 35.5 hours. The patient's hydration continued at 3 liters/m^2/day, translating to a total of 3090 ml/day or approximately 128 ml/hr. Premedication included Granisetron (2 mg) and Dexamethasone (4 mg).

By day 4 after admission, the patient experienced significant gastrointestinal issues, including three episodes of vomiting and four episodes of loose stools. The intravenous fluid regimen was adjusted to Ringer's Lactate at 68 ml/hr, and antiemetic therapy was modified with the administration of Emeset (4 mg IV) followed by additional doses of Granisetron (2 mg) to control the vomiting. Due to the reported symptoms of unresponsiveness and rolling eye movements, close monitoring for seizure activity was implemented. Levetiracetam (500 mg IV twice daily) and Syp TUS (5 ml four times a day) were introduced to manage potential seizure activity. Folinic Acid (15 mg/m^2) was administered in two doses at 6-hour intervals on day 4, followed by four doses on day 5, and two doses on day 6, to mitigate Methotrexate toxicity.

On day 5, the patient developed fever spikes, with recorded temperatures of 100°F, 100°F, and 101.3°F. The ongoing treatment included intravenous fluids, antibiotics, and supportive medications as previously outlined. The Noradrenaline infusion was adjusted to 4 ml of Noradrenaline in 20 ml of normal saline,

administered at a rate of 1 ml/hr with a concentration of 0.2 µg/kg/min. Filgrastim dosage was increased to 0.25 ml subcutaneously once daily. Despite the adjustments, the patient continued to experience complications, requiring close monitoring and management.

On day 6, a detailed treatment plan was established to manage the patient's Pre-B ALL. The regimen included 6-Mercaptopurine, administered orally at a daily dose of 50 mg/m² for a duration of two years. This medication is commonly used during the induction phase of Pre-B ALL treatment. During the consolidation phase, Methotrexate was administered orally once weekly at a dose of 20 mg/m² for two years. Methotrexate plays a critical role in eliminating residual leukaemia cells post-induction. In the maintenance phase, the patient received Vincristine once monthly at a dose of 1.4 mg/m² for two years, and Dexamethasone at a dose of 6 mg/m² daily for five days, once a month for two years. CNS prophylaxis involved Methotrexate administered intrathecally every three months for two years to prevent leukaemia cell spread to the central nervous system. Toxicity from Methotrexate was managed with prompt administration of Leucovorin (Folinic Acid), which helps counteract the drug's toxic effects**. (Patient explained importance of hospital stay, but went against medical advice.)**

DISCUSSION:

The present case report highlights the significant challenges encountered in treating paediatric Pre-B Acute Lymphoblastic Leukaemia (ALL) with high-dose methotrexate, particularly the risk of central nervous system (CNS) relapse. This patient's poor response to Prednisolone and the subsequent CNS relapse underscores the complexity of balancing chemotherapy efficacy and toxicity.

Previous studies have demonstrated that high-dose methotrexate, although effective in preventing systemic relapse, can lead to increased CNS toxicity. For example, Bhojwani *et al*. **[10]** identified methotrexate as a critical agent in the treatment of ALL but also noted its association with CNS complications, including neurotoxicity and relapse . Moreover, several studies have reported that CNS relapse in ALL patients is often a precursor to systemic relapse, with bone marrow involvement being a common subsequent site of leukemic progression **[11]**. This aligns with our case, where the patient exhibited significant neurological symptoms before the confirmation of CNS relapse.

The use of intrathecal chemotherapy as CNS prophylaxis has been a standard approach, yet

its efficacy in preventing CNS relapse remains variable. For instance, the Children's Oncology Group trial - AALL02P2 **[12]** emphasized the importance of intensive systemic therapy with intrathecal methotrexate to improve outcomes in patients with CNS involvement. However, as demonstrated in our case, even with aggressive CNS-directed therapy, the patient's condition deteriorated, indicating the need for alternative or adjunctive treatment strategies.

One potential approach to mitigate CNS relapse is the modification of methotrexate dosage and scheduling. Studies by Pui *et al* **[13]**. and Matloub *et al*. **[14]** suggested that adjusting methotrexate doses and incorporating other CNS-penetrant agents could reduce the incidence of CNS relapse without compromising overall survival. Additionally, the use of folinic acid rescue, as employed in this case, has been shown to mitigate some of the toxic effects of methotrexate, although its impact on preventing CNS relapse is less clear.

Interestingly, recent advances in molecular profiling have provided insights into the mechanisms underlying CNS relapse. Roberts *et al*. **[15]** identified specific genetic mutations associated with an increased risk of CNS involvement in ALL, suggesting that personalized therapy could be a future direction to prevent relapse. Furthermore, the study by Yeoh *et al*. **[16]** on gene expression profiles in ALL patients highlighted the heterogeneity of the disease and the potential for targeted therapies to address specific risk factors for CNS relapse.

Finally, the long-term outcomes for patients with CNS relapse remain a significant concern. Studies by Bhatia *et al*. **[17]** and Conter *et al*. **[18]** indicated that while aggressive treatment regimens may improve short-term survival, they also increase the risk of long-term neurocognitive deficits and secondary malignancies . These findings emphasize the need for ongoing research into therapies that can balance efficacy with minimizing long-term adverse effects.

CONCLUSION:

This case highlights the intricate challenges of treating paediatric Pre-B Acute Lymphoblastic Leukaemia (ALL), particularly when confronted with central nervous system (CNS) relapse following high-dose methotrexate therapy. The patient's poor response to Prednisolone, coupled with the severe neurological complications, underscores the delicate balance between maximizing therapeutic efficacy and minimizing adverse effects. While high-dose methotrexate remains a cornerstone in ALL

treatment, its associated toxicities, especially neurotoxicity, pose significant risks that require vigilant monitoring and prompt intervention. The CNS relapse in this patient, despite aggressive CNS-directed therapy, calls for a reassessment of current therapeutic strategies. Future directions may include personalized treatment plans based on molecular profiling, optimized methotrexate dosing regimens, and the integration of adjunctive therapies to reduce the risk of CNS relapse. Moreover, the long-term impact of intensive chemotherapy on neurocognitive function and quality of life must be carefully weighed against the benefits of relapse prevention. This case underscores the need for ongoing research and clinical innovation to refine treatment protocols and improve outcomes for paediatric patients with ALL.

DATA AVAILABILITY STATEMENT:

The data supporting the findings of this case report are available from the corresponding author upon reasonable request. However, due to the sensitive nature of the data, some restrictions may apply.

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This research received no external funding. The authors declare no competing interests related to this case report.

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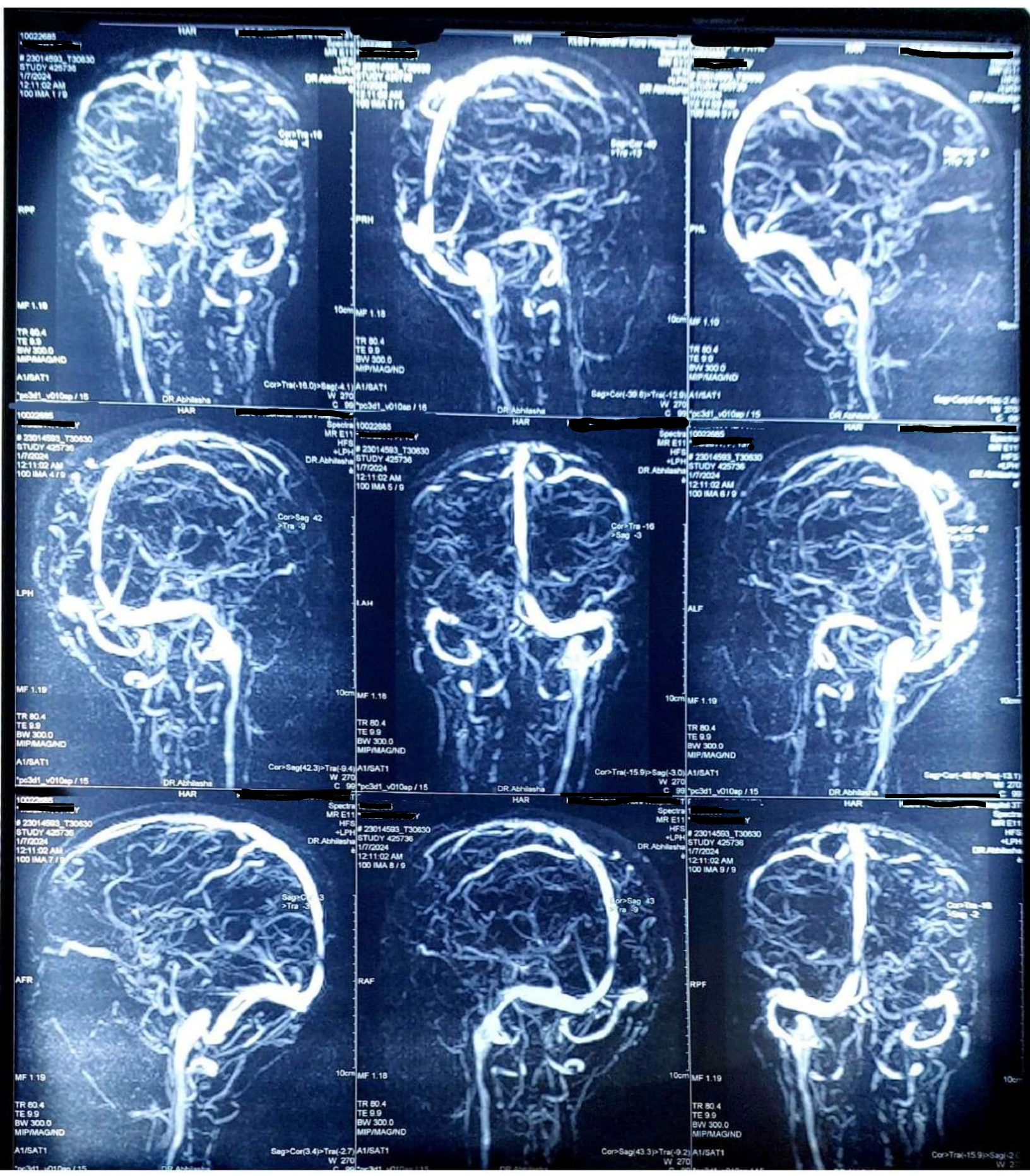
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