

Intracranial Hemorrhage Following Intrathecal Methotrexate Therapy for Acute Lymphoblastic Leukaemia

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Background: Acute toxic leukoencephalopathy following intrathecal methotrexate administration is well documented but intracranial haemorrhage is extremely rare. **Case Characteristics:** A 2½-year-old girl with acute lymphoblastic leukemia developed sudden onset neurological deterioration following intrathecal methotrexate. **Observations:** Computed tomography scan of brain demonstrated intraventricular and subarachnoid hemorrhage. **Outcome:** Child improved gradually on conservative management. Follow-up neuroimaging showed resolution of hemorrhage. **Message:** Intracranial haemorrhage is a rare but serious complication of intrathecal methotrexate.

Keywords: *Chemotherapy, Complications, Malignancy, Neurological events.*

Acute lymphoblastic leukemia (ALL) is one of the most common haematological malignancies of childhood treated with high dose methotrexate not only to prevent central nervous system (CNS) recurrence but also hematologic relapses. The association between methotrexate therapy and idiosyncratic neurological complications is well documented [1] but intracranial hemorrhage following intrathecal methotrexate administration is extremely rare. We report a 2½-year-old girl who developed both intraventricular and subarachnoid hemorrhage following intrathecal methotrexate administration.

CASE REPORT

A 2½-year-old girl presented with a 2 week history of fever, progressive pallor, petechial spots, hepatosplenomegaly and generalized lymphadenopathy. She was diagnosed as ALL Type L1 (FAB classification); CNS involvement was excluded by cerebrospinal fluid (CSF) analysis in the pre-treatment period. She was categorized as standard risk group and was then put to induction phase 1A of chemotherapy with prednisolone, vincristine, daunorubicine, L-asparaginase and intrathecal methotrexate.

Following completion of induction phase 1A, patient showed initial remission as evident by repeat bone marrow examination. Phase 1B of induction therapy was then started with 6-Mercaptopurine, cylophosphamide, cytarabine and intrathecal methotrexate. On 3rd day after receiving last dose of intrathecal methotrexate, patient developed vomiting, sudden onset generalized tonic-clonic seizure and alteration of consciousness. Blood

pressure was measured as 112/78 mmHg. There was no history of trauma or any leak of CSF from the lumbar puncture site. Patient was shifted to pediatric intensive care unit. Complete blood count (CBC) revealed hemoglobin 9.7 g/dL, white blood cell count $3.6 \times 10^3/\mu\text{L}$ and platelet count $140 \times 10^3/\mu\text{L}$. Coagulation profile showed normal prothrombin time and activated partial thromboplastin time. Non-contrast axial computed tomography (CT) scan of brain showed ventricular and subarachnoid hemorrhage (*Fig. 1*).

Patient was treated conservatively by adequately controlling raised intracranial tension, seizures and providing constant supportive and nursing care. Patient regained consciousness and was able to take oral feeds. MRI of brain after four weeks showed resolution of hemorrhage with mildly dilated ventricles as a sequel. Magnetic resonance angiography (MRA) could not demonstrate any underlying vascular malformation. Presently, she is receiving chemotherapy as per the above mentioned protocol.

DISCUSSION

Intracerebral hemorrhage (ICH) following intrathecal methotrexate administration is an extremely rare but serious life threatening complication. A few cases have been reported in the literature till date [2-4]. As the other possible etiologies of ICH like arteriovenous malformation, hypertension, thrombocytopenia, coagulopathy, history of major head trauma or thrombolytic therapy were excluded in the present case, intrathecal methotrexate was considered to be the probable cause in our patients.

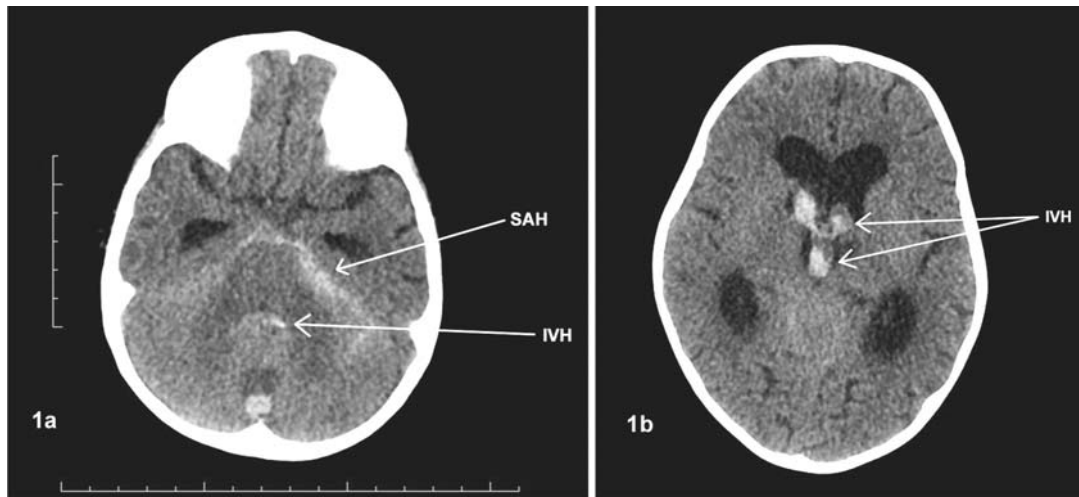


FIG. 1 Non-contrast axial CT scan of brain showing (a) subarachnoid haemorrhage in prepontine cisterns and hemorrhage within 4th ventricle; and (b) haemorrhage in 3rd and both lateral ventricles.

The exact pathogenesis for intracranial bleeding following intrathecal administration of methotrexate is unknown. Faulty technique during lumbar puncture can cause significant CSF leakage resulting in low intracranial pressure leading to traction and rupture of the dilated, thin-walled dural blood vessels [5-7].

In our case, there was no such history of CSF leak. Intraventricular and subarachnoid hemorrhage in our case occurred possibly due to vasculopathic effect of methotrexate in the central nervous system. The vasculopathic effect of methotrexate may be due to fibrinoid degeneration and hyaline thrombus of the cerebral vessels as described earlier [8, 9]. Alteration in the regional cerebral blood flow could be another pathogenic mechanism for ICH [10].

Intrathecal methotrexate is routinely used for prevention of CNS involvement in patients with ALL. Mild and transient neurological complications following IT methotrexate are common but intraventricular and subarachnoid hemorrhage may rarely occur. Clinicians should be aware of this rare but serious adverse effect of intrathecal methotrexate.

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