



## Progressive Neurotoxicity after Intrathecal Methotrexate and Cytarabine in a Child with Acute Myeloid Leukemia

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### Abstract

**Background:** Progressive encephalomyelitis with fatal course is an uncommon complication of intrathecal chemotherapy in children with acute myeloid leukemia

**Aims:** We describe the clinical and radiological spectrum of progressive neurotoxicity after combined intrathecal use of methotrexate and cytarabine in a child with acute myeloid leukemia

**Methods:** A 10-year-old boy suffering from acute myeloid leukemia developed acute-onset, progressive ascending myelitis followed by encephalopathy after triple intrathecal chemotherapy. He underwent detailed neurological assessments and relevant laboratory and radiological investigations. Intravenous antimicrobials, methyl prednisolone pulse therapy and megavitamins were administered.

**Results:** Examination showed high-frequency horizontal nystagmus, diffuse meningismus, bilaterally symmetrical paraplegia, hypotonia, areflexia and flexor Babinski response in the lower limbs, saddle anaesthesia and urinary retention. Cerebrospinal fluid analysis showed 400 cells (95% polymorphonuclear cells, no blasts). Magnetic resonance imaging of spine showed long-tract myelitis with caudal nerve-root enhancement. Nerve-conduction study showed severe sensory-motor polyneuropathy involving lower limbs. The clinical course evolved from an acute, reversible chemical arachnoiditis to cauda-equina syndrome to a progressive, treatment-refractory, devastating encephalomyelitis over three weeks. He finally succumbed to nosocomial sepsis and cardiac arrest

**Conclusion:** Progressive neurotoxicity following intrathecal chemotherapy, especially with combination of methotrexate and cytarabine needs consideration in pediatric patients of leukemia. Early identification of evolving neurological signs may help in the initiation of early salvage therapy.

**Keywords:** Neurotoxicity; Intrathecal; Methotrexate; Cytarabine; Cauda-Equina; Encephalomyelitis

### Introduction

Intrathecal chemotherapy with methotrexate and cytosine-araboside (cytarabine) is an established modality for central nervous system prophylaxis in pediatric acute myeloid leukemia (AML). Neurotoxicity is a common complication with either drug, however fatal course is exceptional and usually associated with combined use or cumulative doses of methotrexate and cytarabine. We describe the gradually progressive, treatment-refractory, fatal neurotoxicity from combined intrathecal chemotherapy with methotrexate and cytarabine in a 10-year-old boy suffering from AML. Identification of evolving neurological signs is important in anticipating the cause and course of illness. Such atypical progressive neurotoxicity in a single patient is rarely seen with pediatric AML and merits attention.

### Case Report

A 10-year-old boy suffering from AML (stage 2) developed acute-onset, non-projectile vomiting and intermittent, dull headache four hours after triple intrathecal chemotherapy (methotrexate 12 mg, cytarabine 30 mg and hydrocortisone 12.5 mg). Within the next 24 hours, he developed neck stiffness and back pain. Lumbar puncture prior to the institution of intrathecal chemotherapy showed normal glucose and proteins, and no cellular response or blast cells in the cerebrospinal

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Received Date: 20 Nov 2017

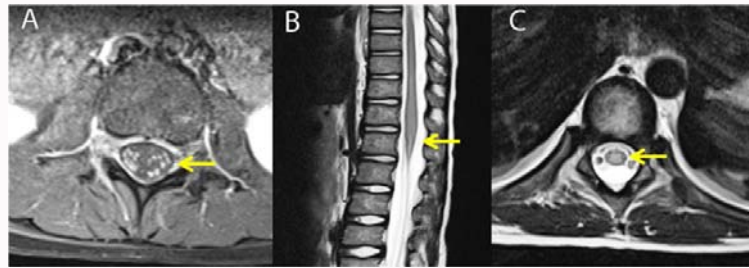
Accepted Date: 21 Dec 2017

Published Date: 29 Dec 2017

#### Citation:

Saini AG, Sahu JK, Mahapatra S, Bansal D, Singh P, Singhi P. Progressive Neurotoxicity after Intrathecal Methotrexate and Cytarabine in a Child with Acute Myeloid Leukemia. *Clin Oncol*. 2017; 2: 1379.

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**Figure 1:** MRI spine: (A) Contrast-enhanced T1-weighted axial sections showing cauda-equina nerve-root enhancement (arrow), (B) T2-weighted sagittal and (C) axial sections showing central hyperintensity (arrow) in thoraco-lumbar cord suggestive of myelitis.

fluid (CSF). He was given supportive treatment for probable chemical meningitis. On second day, parents noticed difficulty in bearing weight on the lower limbs and requirement of support for ambulation. There was no weakness in the trunk or upper limbs. On the third day, he developed moderate-grade intermittent fever and acute-onset urinary retention requiring hospitalization. There was no history suggestive of encephalopathy, seizures, behavioural abnormalities, cranial nerve palsies, vision impairment, extrapyramidal movements or sensory symptoms. The patient had received his first chemotherapy course including the same triple intrathecal drugs one month back. There were no blasts in the CSF or bone-marrow.

Examination at admission showed intermittent, gaze-independent, high-frequency horizontal nystagmus, bilaterally symmetrical weakness (Medical Research Council grade 3/5), hypotonia, absent muscle stretch reflexes and flexor Babinski sign in the lower limbs, saddle anaesthesia, urinary retention, diffuse meningismus with neck rigidity and straight-leg-raising positive at 60°. Higher mental functions, cranial nerve including fundi and upper limb examination was normal. There was no cerebellar ataxia, extra pyramidal or sensory signs, local spine tenderness or hematoma. Clinical syndrome of drug-induced aseptic meningitis with cauda-equina syndrome was considered. CSF showed 400 cells (95% polymorph nuclear cells, no blasts), protein 0.73 g/L, glucose 3.16 mmol/L (blood glucose 5.83 mmol/L) and negative gram-stain and culture. Haemoglobin was 100 g/L, total leucocyte count  $11.7 \times 10^9/L$  (78% neutrophils, 12% lymphocytes, 10% monocytes), platelets  $348 \times 10^9/L$ , prothrombin index 82% and C-reactive-protein was 0.10 g/L (normal <0.08 g/L). Contrast-enhanced magnetic resonance imaging (MRI) spine showed caudal nerve-root enhancement (Figure 1A) and meningeal enhancement at the base of the brain. In view of persisting fever and meningeal signs, he was administered intravenous antimicrobials (vancomycin 50 mg/kg/day q8hourly, meropenem 90 mg/kg/day q6hourly, acyclovir 30 mg/kg/day q8hourly) for possible bacterial meningitis. Fever and meningeal signs subsided within next 48 hours. On sixth day, the patient developed intermittent, irrelevant talking and drowsiness associated with bilateral papilloedema. Contrast-enhanced computed tomography brain scan was normal. He improved with intravenous 3% hypertonic saline infusion. Repeat lumbar CSF showed 60 cells (70% polymorphonuclear cells), glucose 3.22 mmol/L (blood glucose 6 mmol/L) and protein 0.91 g/dL. No organism was identified on gram-stain and culture, triple-antigen testing, viral polymerase chain reaction studies, and mycoplasma serology. From seventh day, weakness gradually progressed to flaccid, symmetric paraplegia (Medical Research Council grade 1/5) with ascending truncal and respiratory weakness, mild upper limb hypotonia, absent joint-position and vibration sense below thoracic cord, and persisting urinary retention. Clinical possibility

of ascending encephalomyelitis due to drug-associated neurotoxicity or infection was considered. Repeat contrast-enhanced MRI-spine showed long-tract myelitis with caudal nerve-root enhancement (Figure 1B-C). Nerve-conduction study on tenth day showed severe sensory-motor polyneuropathy of uncharacterized nature involving the lower limbs alone. Intravenous pulse methylprednisolone (25mg/kg/day q24hourly for 5 days); oral folinic acid (60 mg/day), S-adenosyl methionine (200 mg/day), injection aminophylline (70 mg) and injection B<sub>12</sub> (1000 µg/day) were added. There was gradual progression of encephalopathy and weakness into flaccid quadriplegia and respiratory failure requiring manual ventilation. He finally succumbed to nosocomial sepsis and cardiac arrest on day 22 and could not be revived. Parents denied autopsy on the child.

## Discussion

Our case highlights the clinical and radiological evolution of intrathecal chemotherapy-associated neurotoxicity. It progressed from drug-induced, reversible chemical arachnoiditis, to lumbosacral radiculopathy manifesting as cauda-equina syndrome, to irreversible ascending encephalomyelitis in the same patient. Similar fatal radiculo-encephalomyelitis following intrathecal chemotherapy has been scarcely reported in children and warrants multi-speciality care [1].

Infectious meningitis and leukemic meningeal infiltration constitute important diagnostic considerations and therapeutic priority in such immune-compromised patients. The presence of fever, meningismus and CSF polymorph nuclear pleiocytosis may mimic bacterial infection. However, bacterial and viral studies from CSF did not identify any infectious agent in our patient. Blasts cells were repeatedly absent from the CSF. Absence of compressive lesion on neuroimaging, close temporal relationship and lumbar puncture site via L3/L4 vertebral level (which is free of spinal-cord), support that ascending myelitis in our patient was related to intrathecal administration of methotrexate and cytarabine rather than traumatic or chemical meningitis. The commoner causes of intrathecal drug-induced neurotoxicity are accidental intrathecal administration of the drug instead of intravenous route or miscalculation of intrathecal dose leading to overdosing. These causes were not plausible in our patient as he received a pre-calculated and monitored intrathecal dose. Additionally, cytarabine-induced aseptic meningitis may show 600-1400 polymorph nuclear cells/mm<sup>3</sup> and upto 2g/L proteins in the CSF, possibly due to drug-hypersensitivity or immunologic dysregulation [2]. Whether transverse myelitis is an extreme expression of drug-induced aseptic meningitis remains conjectural.

Both cytarabine and methotrexate are known to cause acute leukoencephalopathy in children and are generally associated with

white-matter hypodensities on computed tomography and areas of diffusion-restriction and T2-hyperintensity on MRI-scan of the brain [3]. However, our patient interestingly had normal MRI scan despite worsening encephalopathy and transient features of raised intracranial pressure. This lack of clear correlation between radiological and clinical manifestations makes the diagnosis of “acute leukoencephalopathy” difficult in these children. The persistent nystagmus in our patient can also be attributed to the prominent neurotoxic effect of cytarabine on the cerebellum [4].

Cauda-equina syndrome due to bilateral lumbo-sacral polyradiculopathy after intrathecal methotrexate and cytarabine has been less commonly described.<sup>5</sup> Partial or completely absent motor responses in lower limbs with sparing of upper limb motor and sensory responses as seen in our case may indicate central damage to the spinal cord or motor roots [5]. The absence of sensory response in our patient could be due to technical difficulties in eliciting sural responses in patients on manual ventilation.

Possible mechanisms of methotrexate-induced leukoencephalopathy include drug-associated alterations in the folate and methyl-transfer pathways in CSF and elevated adenosine levels [6]. In the absence of established treatment guidelines for methotrexate neurotoxicity, there are anecdotal reports of improvement with systemic folinic-acid and competitive adenosine antagonist aminophylline [7]. Our patient remained treatment-refractory despite the use of these rescue medications and intravenous corticosteroid therapy.

## Conclusion

Progressive neurotoxicity following intrathecal chemotherapy, especially with combination of methotrexate and cytarabine needs

consideration in pediatric patients of AML. Early identification of evolving neurological signs may help in the initiation of early salvage therapy. Awareness regarding these manifestations is important for both the pediatric neurologists and hemato-oncologists.

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