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ACUTE TOXIC LEUKOENCEPHALOPATHY FOLLOWING STANDARD-DOSE CYTARABINE DURING INDUCTION THERAPY FOR PEDIATRIC ACUTE MYELOID LEUKEMIA-PEDIATRIC CASE REPORT

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ABSTRACT

Background: Acute toxic leukoencephalopathy (ATL) is an uncommon but potentially reversible neurological complication of several chemotherapeutic agents, including cytarabine. Although neurotoxicity is well recognised with high-dose cytarabine, it is rarely reported following standard-dose induction therapy in children with acute myeloid leukemia (AML). Early recognition is important because timely supportive management can lead to complete neurological recovery.

Keywords: Acute toxic leukoencephalopathy; Cytarabine; Acute myeloid leukemia; Pediatric oncology; Chemotherapy-induced neurotoxicity; Magnetic resonance imaging; Encephalopathy; Standard-dose cytarabine.

Case presentation: We report a 14-year-old boy with newly diagnosed AML who developed acute encephalopathy ten days after completing induction chemotherapy with standard-dose cytarabine and daunorubicin (7+3 regimen). He initially presented with fever, vomiting and loose stools, followed by altered sensorium and generalized weakness. Examination revealed a Glasgow Coma Scale score of 13/15, axial and truncal weakness, exaggerated deep tendon reflexes, bilateral ankle clonus and extensor plantar responses.

Outcome: Brain MRI demonstrated multifocal diffusion restriction involving the bilateral deep white matter with corresponding T2/FLAIR hyperintensities, highly suggestive of acute toxic leukoencephalopathy. Cerebrospinal fluid examination, electroencephalography and microbiological investigations were unremarkable, making infective meningoencephalitis unlikely. The child improved completely with supportive care, treatment of febrile neutropenia and neuroprotective measures without any residual neurological deficit.

Conclusion: This case highlights that cytarabine-induced toxic leukoencephalopathy may occur even with standard-dose therapy during pediatric AML induction. Prompt recognition of characteristic MRI findings and exclusion of alternative causes allow appropriate management and may prevent unnecessary interventions while improving neurological outcomes

KEYWORDS: Acute toxic leukoencephalopathy; Cytarabine; Acute myeloid leukemia; Pediatric oncology; Chemotherapy-induced neurotoxicity; Magnetic resonance imaging; Encephalopathy; Standard-dose cytarabine.

INTRODUCTION

Acute myeloid leukemia (AML) accounts for approximately 15–20% of childhood leukemias and requires intensive multi-agent chemotherapy for remission induction. Standard induction therapy commonly consists of cytarabine combined with an anthracycline in the conventional 7+3 regimen, which has substantially improved survival over the past few decades. Despite these advances, treatment-related toxicities continue to contribute significantly to morbidity during induction because of prolonged cytopenias, severe infections and organ-specific adverse effects [1,2].

Cytarabine remains the backbone of AML treatment because of its potent antileukemic activity. Although generally well tolerated at conventional doses, it has been associated with a spectrum of neurological complications ranging from transient cerebellar dysfunction and encephalopathy to the much less common entity of acute toxic leukoencephalopathy (ATL). The exact mechanism is not completely understood but is believed to involve direct injury to oligodendrocytes and cerebral white matter, resulting in cytotoxic edema [3,4].

Acute toxic leukoencephalopathy is an uncommon clinicoradiological syndrome characterized by altered mental status, behavioural changes, motor deficits or seizures accompanied by characteristic magnetic resonance imaging (MRI) abnormalities. Diffusion-weighted imaging (DWI) typically demonstrates early areas of restricted diffusion within the cerebral white matter, often before conventional T2-weighted or fluid-attenuated inversion recovery (FLAIR) changes become evident, making MRI the investigation of choice for early diagnosis [5,6].

Most published reports of cytarabine-related neurotoxicity involve high-dose cytarabine administered during consolidation therapy in adults. Reports following standard-dose induction therapy in children remain uncommon, making diagnosis challenging, particularly in patients who simultaneously present with febrile neutropenia where infective meningoencephalitis is often the initial clinical concern [2,6,7].

We describe a 14-year-old boy with newly diagnosed AML who developed acute toxic leukoencephalopathy shortly after completion of standard-dose cytarabine induction chemotherapy. Recognition of the characteristic imaging findings together with exclusion of infectious central nervous system involvement enabled appropriate supportive management, resulting in complete neurological recovery. This case highlights the importance of maintaining a high index of suspicion for chemotherapy-induced neurotoxicity even after conventional-dose cytarabine administration during pediatric AML induction [7,8].

Case presentation

A 14-year-old boy with newly diagnosed acute myeloid leukemia was admitted for induction chemotherapy. He received standard induction treatment consisting of intravenous cytarabine and daunorubicin according to the institutional 7+3 protocol.

He remained clinically stable during chemotherapy. Approximately ten days after completion of induction, he developed high-grade intermittent fever associated with multiple episodes of vomiting and loose stools for one day. Over the next several hours, his parents noticed progressive reduction in activity and responsiveness. He became less interactive, responded only to repeated verbal commands and appeared increasingly drowsy, prompting emergency evaluation.

On examination, he was febrile and markedly pale(Figure 1). Multiple discrete, non-tender cervical and generalized lymph nodes were palpable. Mild hepatosplenomegaly was present. His pupils were equal and reactive to light bilaterally. Glasgow Coma Scale score was 13/15 (E4V4M5). Cranial nerve examination was otherwise unremarkable, and gag reflex was preserved. Motor examination revealed generalized weakness with muscle power greater than 3/5 in all four limbs, associated with axial and truncal weakness. Deep tendon reflexes were exaggerated with bilateral ankle clonus and bilateral extensor plantar responses. There were no meningeal signs or focal cranial nerve deficits.

Figure 1. Child having pallor and chemotherapy induced rashes in face

Given the background of profound neutropenia during AML induction, an initial diagnosis of febrile neutropenia with acute encephalopathy was considered, and evaluation for infectious as well as treatment-related neurological complications was initiated simultaneously.

Investigations

Initial hematological investigations showed profound pancytopenia consistent with induction chemotherapy. Hemoglobin was 2.7 g/dL, total leukocyte count 320/mm³, and platelet count 3,000/mm³. Inflammatory markers were elevated with an ESR greater than 120 mm/hour and CRP 17.1 mg/L. Serial blood counts gradually improved following packed red blood cell and platelet transfusions together with supportive care.

Contrast-enhanced CT brain performed at presentation was normal.Lumbar puncture showed clear, colourless cerebrospinal fluid without pleocytosis. CSF glucose and protein were within normal limits. Gram stain, fungal smear and bacterial culture were negative.

Electroencephalography demonstrated no epileptiform discharges or diffuse encephalopathic slowing.

MRI brain with contrast revealed multifocal ill-defined areas of diffusion restriction with corresponding low apparent diffusion coefficient (ADC) values involving the bilateral centrum semiovale, periventricular and subcortical deep white matter of both frontal lobes and bilateral occipital lobes. These lesions demonstrated corresponding T2/FLAIR hyperintensities with subtle post-contrast enhancement. The imaging appearance was highly suggestive of acute toxic leukoencephalopathy.

Peripheral blood smear demonstrated severe pancytopenia with circulating blast cells consistent with AML under induction chemotherapy. (Figure 2).

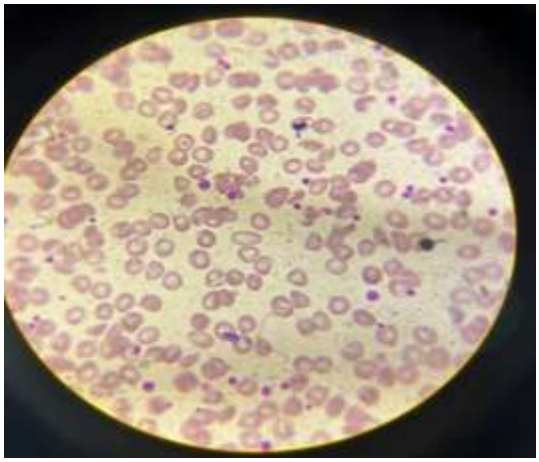

Figure 2 .Blood Smear picture showing severe pancytopenia with blast cells

Differential diagnosis

The principal differential diagnosis was infective meningoencephalitis, particularly in view of febrile neutropenia. However, sterile cerebrospinal fluid, absence of pleocytosis, normal glucose and protein concentrations, negative microbiological studies and characteristic MRI findings argued strongly against this diagnosis.

Posterior reversible encephalopathy syndrome (PRES) was also considered. However, PRES usually demonstrates vasogenic edema involving predominantly cortical and subcortical parieto-occipital regions, whereas our patient showed symmetrical deep white matter diffusion restriction, favouring cytotoxic injury.

Radiation-induced leukoencephalopathy was excluded because the child had not received cranial irradiation.

Other chemotherapy-related neurotoxicities, particularly methotrexate-induced leukoencephalopathy, were unlikely as methotrexate was not part of the induction regimen. The temporal relationship between symptom onset and recent cytarabine administration strongly supported cytarabine-induced toxic leukoencephalopathy.

Treatment

The child was managed according to institutional febrile neutropenia protocols with immediate initiation of broad-spectrum intravenous antibiotics after obtaining appropriate cultures. Intravenous fluids, electrolyte correction and close neurological monitoring were continued throughout admission.

Supportive hematological care included repeated packed red blood cell and platelet transfusions along with correction of mild coagulation abnormalities when indicated.

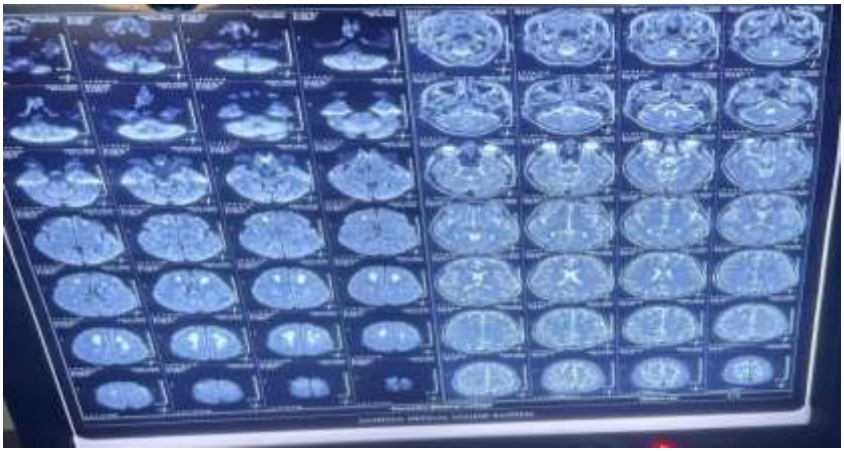

Figure 3. Magnetic resonance imaging of the brain demonstrating acute cytarabine-induced toxic leukoencephalopathy

Considering the characteristic MRI findings and exclusion of infectious central nervous system involvement, conservative management with neuroprotective supportive measures was continued. No additional cytarabine doses were administered during the acute neurological episode. Serial neurological examinations were performed to monitor recovery.

Outcome and follow-up

Over the following several days, the child's neurological status improved steadily. Sensorium returned completely to normal with restoration of full Glasgow Coma Scale score (15/15). Motor strength improved progressively, and upper motor neuron signs resolved without residual neurological deficits.

The febrile neutropenia also resolved with antimicrobial therapy and supportive care. Blood counts recovered gradually, allowing continuation of planned leukemia treatment. The patient subsequently received the second cycle of induction chemotherapy under close neurological surveillance and remains on regular hematology follow-up.

DISCUSSION

Acute toxic leukoencephalopathy (ATL) is an uncommon neurological complication of chemotherapy resulting from toxic injury to the cerebral white matter. Although several chemotherapeutic agents including methotrexate, 5-fluorouracil, ifosfamide and cytarabine have been implicated, cytarabine-associated ATL remains relatively rare in children, particularly following standard-dose induction therapy [3,4]. Most clinicians are familiar with cerebellar toxicity associated with high-dose cytarabine, whereas diffuse white matter involvement causing encephalopathy is encountered much less frequently. Consequently, early diagnosis requires a high index of suspicion, especially in pediatric patients with AML receiving induction chemotherapy.

Cytarabine is converted intracellularly to its active metabolite, cytarabine triphosphate, which inhibits DNA polymerase and DNA synthesis. Although its exact mechanism of neurotoxicity remains uncertain, experimental and clinical studies suggest that accumulation of toxic metabolites within the central nervous system results in oligodendrocyte dysfunction, disruption of myelin metabolism and cytotoxic edema involving the cerebral white matter [2,9]. The onset of neurological manifestations is variable and may occur during treatment or several days after completion of chemotherapy, as observed in our patient who developed symptoms approximately ten days after induction therapy. Similar delayed presentations following conventional-dose cytarabine have also been described in isolated pediatric reports [7,13,16].

Our patient initially presented with fever and altered sensorium during profound chemotherapy-induced neutropenia. In this clinical setting, infective meningoencephalitis remains the foremost differential diagnosis and must always be excluded promptly because delayed treatment can be life-threatening. However, cerebrospinal fluid examination in our patient was completely acellular with normal biochemical parameters, Gram stain and fungal smear were negative, and cultures showed no growth. In addition, electroencephalography did not reveal evidence of encephalitis or seizure activity. These findings, together with the characteristic MRI appearance, made an infectious etiology unlikely and favored chemotherapy-induced neurotoxicity [3,14,15].

Magnetic resonance imaging plays a central role in the diagnosis of ATL. Diffusion-weighted imaging is particularly sensitive because diffusion restriction appears early due to cytotoxic edema and often precedes conspicuous abnormalities on conventional sequences. In our patient, MRI demonstrated multifocal diffusion restriction involving the bilateral centrum semiovale, frontal subcortical and periventricular white matter, together with bilateral occipital white matter involvement and corresponding low apparent diffusion coefficient values. Mild T2/FLAIR hyperintensities with subtle contrast enhancement were also noted. This imaging pattern closely resembles previously reported cases of chemotherapy-induced toxic leukoencephalopathy and supports the diagnosis of acute white matter injury [8,14].

The principal radiological differential diagnosis was posterior reversible encephalopathy syndrome (PRES), another recognized neurological complication during leukemia treatment. PRES typically demonstrates symmetrical vasogenic edema predominantly affecting the cortical and subcortical parieto-occipital regions, whereas our patient showed multifocal deep white matter diffusion restriction reflecting cytotoxic rather than vasogenic edema. Furthermore, the absence of severe hypertension, seizures and the characteristic imaging distribution made PRES less likely [3,14,15]. Methotrexate-induced leukoencephalopathy was also considered but excluded because methotrexate was not administered during this phase of treatment.

Most published literature associates cytarabine neurotoxicity with high-dose consolidation regimens, advanced age and renal impairment [2,9]. However, increasing reports suggest that clinically significant neurotoxicity may also occur with intermediate or conventional doses, particularly in susceptible individuals [6,7,13]. Our case further supports this observation by demonstrating that standard-dose cytarabine administered during pediatric AML induction can produce reversible toxic leukoencephalopathy despite the absence of classical risk factors. This highlights the importance of considering ATL whenever new neurological symptoms develop after cytarabine exposure, irrespective of the administered dose.

Management of ATL remains largely supportive because no specific antidote exists. Early discontinuation or avoidance of further exposure during the acute episode, maintenance of adequate hydration, correction of metabolic abnormalities, prompt treatment of coexisting infections and careful neurological monitoring constitute the mainstay of management [9,20]. Simultaneously, patients with AML require aggressive supportive care for febrile neutropenia, including early administration of broad-spectrum intravenous antibiotics, blood component therapy and close monitoring of hematological recovery. Our patient received comprehensive supportive management for both febrile neutropenia and neurological dysfunction, resulting in gradual improvement without the need for intensive neurocritical interventions.

The prognosis of chemotherapy-induced ATL is generally favorable when recognized early. Clinical improvement is usually accompanied by gradual resolution of diffusion abnormalities on follow-up MRI, although radiological recovery may lag behind neurological improvement [8,14]. Our patient recovered completely with restoration of normal sensorium and neurological examination and was subsequently able to continue planned AML therapy under close clinical surveillance. Similar reversible outcomes have been described in pediatric case reports when diagnosis is established early and supportive measures are instituted promptly [7,10,18].

Our case emphasizes an important clinical message for pediatric hematologists and intensivists. During AML induction, altered sensorium is often initially attributed to central nervous system infection because of profound neutropenia. However, when cerebrospinal fluid findings are non-contributory and MRI demonstrates characteristic diffusion-restricted white matter lesions, cytarabine-induced toxic leukoencephalopathy should be strongly considered. Early recognition not only avoids unnecessary investigations and prolonged antimicrobial escalation but also facilitates timely supportive management, leading to favorable neurological recovery while allowing continuation of definitive leukemia treatment.

Learning points

- Acute toxic leukoencephalopathy should be considered in any child receiving cytarabine who develops new-onset encephalopathy, even after standard-dose induction chemotherapy.

- Diffusion-weighted MRI is the most sensitive investigation for early diagnosis and helps distinguish toxic leukoencephalopathy from infective meningoencephalitis and posterior reversible encephalopathy syndrome.
- Normal cerebrospinal fluid findings together with characteristic MRI abnormalities strongly support the diagnosis of chemotherapy-induced neurotoxicity.
- Early supportive management, treatment of concurrent febrile neutropenia and close neurological monitoring are associated with good clinical recovery in most pediatric patients.
- Recognition of this uncommon complication allows continuation of planned AML therapy with appropriate neurological surveillance during subsequent treatment cycles.

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