Case Report / Olgu Sunumu

DOI: 10.4274/cayd.galenos.2025.66934
J Pediatr Emerg Intensive Care Med 2025;12(3):201-4

Toxic Encephalopathy Developing After High-dose Cytarabine in a Child with Burkitt Lymphoma: A Successful Treatment Case

Burkitt Lenfomalı Bir Çocuk Hastada Yüksek Doz Sitarabin Sonrası Gelişen Toksik Ensefalopati: Başarılı Bir Tedavi Olgusu

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Abstract

Chemotherapy drugs used in the treatment of leukemia and lymphoma can occasionally cause side effects. We present here a rare case of neurotoxicity that occurred after high-dose cytarabine (HiDAC) administration. A 13-year-old girl presented with right eye diplopia while receiving the high-risk non-Hodgkin lymphoma (NHL)-Berlin-Frankfurt-Münster 95 chemotherapy protocol. Magnetic resonance imaging (MRI) screening revealed four new parenchymal lesions, none of which showed contrast enhancement. The patient underwent a detailed evaluation for diplopia. Neurotoxicity occurred after the first HiDAC administration in our 13-year-old patient. Cytarabine is one of the key agents in the treatment of NHL, but complications of cytarabine toxicity include seizures, ataxia, and even death. The patient was treated with pulsed methylprednisolone for three days, which was then tapered and discontinued. A follow-up brain MRI performed at the end of the month showed that the lesions had reduced by more than 90%. This case highlights the importance of recognizing cytarabine-induced neurotoxicity, especially in pediatric patients undergoing intensive chemotherapy. Early diagnosis and prompt management can lead to significant clinical improvement and radiological resolution.

Keywords: High-dose cytarabine, magnetic resonance imaging, non-Hodgkin lymphoma, neurotoxicity, cytarabine

Öz

Lösemi ve lenfoma tedavisinde kullanılan kemoterapi ilaçları zaman zaman yan etkilere yol açabilir. Bu yazıda, yüksek doz sitarabin (YDS) uygulamasından sonra gelişen nadir bir nörotoksisite olgusunu sunuyoruz. On üç yaşında, non-Hodgkin lenfoma (NHL) tanısıyla izlenen kız hasta, yüksek riskli NHL-Berlin-Frankfurt-Münster 95 kemoterapi protokolü sırasında sağ gözünde çift görme (diplopi) şikayetiyle başvurdu. Manyetik rezonans görüntülemesinde (MRG), kontrast tutmayan dört yeni parankimal lezyon saptandı. Hasta diplopi açısından ayrıntılı olarak değerlendirildi. Nörotoksisite, 13 yaşındaki hastamızda ilk YDS uygulamasından sonra gelişti. Sitarabin, NHL tedavisinde önemli kemoterapi ajanlarından biridir. Literatürde, sitarabin toksisitesine bağlı olarak nöbet, ataksi ve ölüm gibi ciddi tablolar bildirilmektedir. Hastaya üç gün süreyle intravenöz pulse metilprednizolon tedavisi verildi ve ardından tedavi kademeli olarak azaltılarak sonlandırıldı. Bir aylık tedavi sonunda çekilen beyin MRG'de lezyonların %90'dan fazla gerilediği görüldü. Bu olgu, özellikle yoğun kemoterapi alan pediatrik hastalarda sitarabin kaynaklı nörotoksisitenin tanınmasının önemini vurgulamaktadır. Erken tanı ve hızlı tedavi, belirgin klinik iyileşme ve radyolojik düzelme sağlayabilir.

Anahtar Kelimeler: Yüksek doz sitarabin, manyetik rezonans görüntüleme, non-Hodgkin lenfoma, nörotoksisite, sitarabin

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Received/Geliş Tarihi: 14.02.2025 **Accepted/Kabul Tarihi:** 13.05.2025 **Epub:** 22.08.2025 **Publication Date/Yayınlanma Tarihi:** 01.12.2025
Cite this article as: Kütükçü Görgülü MK, Acıpayam C, Kandemir Gülmez T, Kırık S, Yurttutan N. Toxic encephalopathy developing after high-dose cytarabine in a child with burkitt lymphoma: a successful treatment case. J Pediatr Emerg Intensive Care Med. 2025;12(3):201-4

Introduction

Lymphoma treatment is a process that involves the use of multiple chemotherapeutic agents, and various toxicities may occur due to these drugs. Cytarabine, a chemotherapeutic agent commonly used in the treatment of leukemia and lymphoma, is a pyrimidine analogue that can cause neurological side effects in up to 14% of cases when administered at high-doses.[1] Neurotoxicity usually begins 6 to 8 days after high-dose cytarabine (HiDAC) administration and may manifest as acute cerebellar toxicity or cerebral dysfunction. These effects can last for 3 to 14 days.[2] It has been suggested that the accumulation of cytarabine metabolites in the central nervous system (CNS) is responsible for the neurotoxicity observed following HiDAC administration.[3] In this report, we present the case of a 13-year-old patient who developed neurotoxicity after receiving HiDAC. The patient showed significant improvement, with more than a 90% reduction in symptoms, following steroid treatment.

Case Report

A 13-year-old girl diagnosed with common disease phase-3 Burkitt's lymphoma, presented with a complaint of diplopia in her right eye while receiving treatment according to the high-risk non-Hodgkin lymphoma (NHL)-Berlin-Frankfurt-Münster 95 chemotherapy protocol. Informed verbal and written consent was obtained from the patient's family for the presentation of this case.

On physical examination, her body weight was 43 kg (10^{th}-25^{th} percentile), her height was 163 cm (75^{th}-90^{th} percentile), her blood pressure was 100/60 mmHg, and her pulse rate was 98 beats per minute. The visual field of the left eye was normal, whereas the right eye exhibited inferior field limitation. Systemic examination was unremarkable, with no pathological findings detected.

Laboratory tests showed hemoglobin 10.6 g/dL, hematocrit 31.5%, white blood cell count 3,090/mm³, absolute neutrophil count 1,130/mm³, C-reactive protein 3 mg/L, and platelet count 224,000/mm³. Biochemical parameters were within normal limits.

Visual acuity was found to be normal in both eyes. However, visual field testing revealed a defect in the upper temporal quadrant of the left eye. Diplopia was present only in upward gaze. Fundus examination and ocular motility were normal. No signs of papilledema were observed.

Given the presence of diplopia, CNS involvement was initially suspected. Cerebrospinal fluid (CSF) analysis following lumbar puncture revealed no malignant cells on cytology; however, elevated protein levels were observed on CSF biochemistry.

Cranial magnetic resonance imaging (MRI) revealed four new parenchymal lesions: one in the left anterior frontal subcortical area, one adjacent to the left genu of the corpus callosum, one in the right posterior parietal white matter, and another in the left temporal periventricular white matter (Figure 1). Visual evoked potentials were within normal limits. Chest and abdominal computed tomography scans showed no evidence of metastasis, instead, some regression of previously detected lesions was observed. The patient's diplopia developed shortly after the first HiDAC administration (16 g) within the chemotherapy protocol, five days following subsequent treatment with 3x9 mg dexamethasone, vincristine, etoposide, HiDAC, and intrathecal methotrexate-cytarabine-prednisolone. Consequently, the sporadic white matter lesions were attributed to cytarabine-induced toxic leukoencephalopathy. Although high-dose methotrexate was also part of the chemotherapy regimen, the patient did not experience diplopia or any neurological symptoms after methotrexate administration. Therefore, methotrexate was excluded as the likely cause of neurotoxicity. Due to suspected cytarabine-related neurotoxicity, a one-month corticosteroid

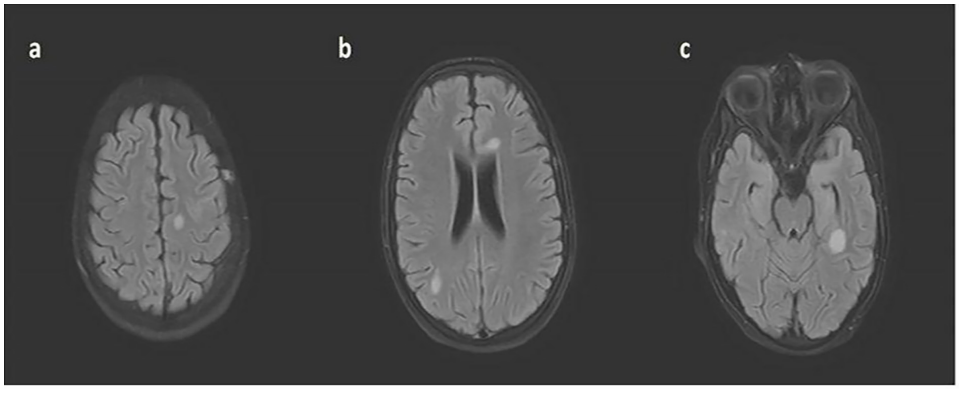

Figure 1. The 13-year-old treated patient diagnosed with Burkitt lymphoma had following lesions present: in the leftparaceptal subcortical area (a), next to the left segment of thecorpus callosum genus (b), in the right posterior parietal area (b) and in the left temporal periventricular white matter (c). The hyperintense lesions detected at FLAIR sequence werefound without significant round shaped edema rings. Thepresence of a corpus callosum lesion firstly raised suspicionfor chemotoxic leukoencephalopathy. The lesions had nopathologic contrast enhancement after the applicated IV contrast material

therapy was initiated. The patient was treated with one gram intravenous methylprednisolone daily for three days, followed by 24 milligrams oral methylprednisolone twice daily, for one week. The steroid dose was gradually tapered each week. During follow-up, the visual field defect in the left eye resolved completely. Cranial MRI at the end of treatment showed near-complete resolution of the lesions (Figure 2).

Discussion

Neuroimaging findings in cases without CNS metastasis during the treatment of extracranial tumors may result from direct chemotherapeutic toxicity, radiation exposure to tissues near the brain, or paraneoplastic effects of the primary tumor. Among these, direct toxicity can particularly manifest as white matter involvement.[4,5]

Several chemotherapeutic agents have been implicated in the development of leukoencephalopathy, including methotrexate, 5-fluorouracil, topotecan, cisplatin, cytarabine, carmustine, and thiotepa.[6-8] Cytarabine is one of the key agents used in the treatment of NHL and acute myeloid leukemia. Neurotoxic side effects such as seizures, ataxia, and in rare cases, death, have been reported following cytarabine administration.[9]

In high-risk NHL treatment protocols, HiDAC is commonly used at a dose of 3 g/m². Neurotoxicity, although rare, is a potentially devastating adverse effect that may present as acute cerebellar toxicity or cerebral dysfunction.[2] In a small cohort study, cases of cerebral toxicity and paraplegia were reported following intravenous HiDAC and intrathecal cytarabine administration.[10] Neurotoxicity typically begins 6 to 8 days after administration of HiDAC and may persist for 3 to 14 days.[2] It is believed that increased levels of cytarabine metabolites in the CNS are responsible for this toxicity.[3]

Pathologically, the loss of Purkinje cells in the cerebellar hemispheres and vermis has been identified as a hallmark of cytarabine-induced neurotoxicity. Additionally, peripheral neuropathy may result from direct cytotoxic effects on axonal and myelin metabolism.[3,11,12] Several cases in the literature describe successful treatment of cytarabine-induced neurotoxicity either through discontinuation of the drug, plasmapheresis, or corticosteroid therapy alone.[13] In a case series published by Dotson and Jamil[14], two patients who developed neurotoxicity after HiDAC were successfully treated with corticosteroids.

In our case, CNS metastasis was initially considered, as the patient developed diplopia five days after receiving a chemotherapy regimen including HiDAC. However, CSF cytology obtained via intrathecal therapy revealed no malignant cells. Given this, cerebral diffusion MRI was performed, which revealed leukoencephalomalacic lesions suggestive of chemotherapy-related toxicity rather than metastatic disease.

When evaluating the chemotherapy protocol for drug-induced neurotoxicity, cytarabine was identified as the causative agent, as the patient developed diplopia only after receiving HiDAC. The patient was treated with pulsed intravenous methylprednisolone for three days, followed by gradual tapering. A follow-up cerebral MRI at the end of one month showed more than 90% regression of the lesions, and the normalization of the visual field. The resolution of diplopia and imaging findings strongly supports the efficacy of corticosteroid therapy in treating cytarabine-induced neurotoxicity.

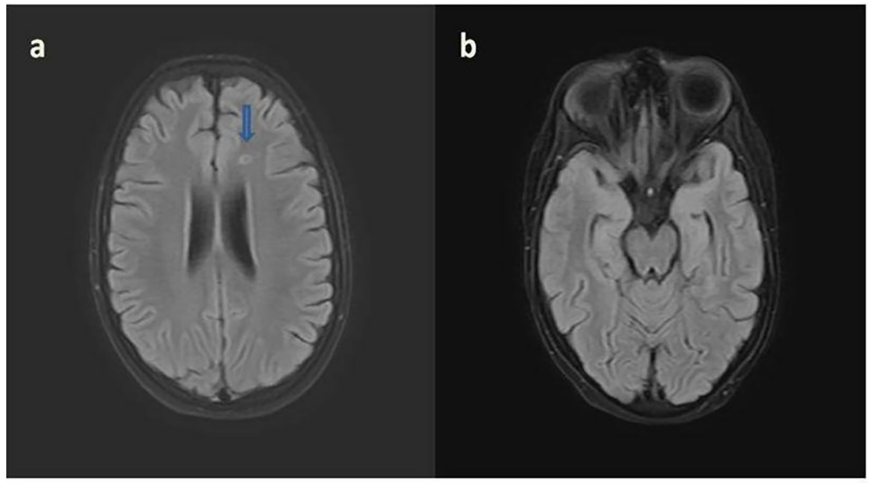

Figure 2. The lesion at the left frontal anterior periventricular white tissue with a cystic encephalomalasy at the center (arrow) had retrieved greatly after the application (a). Other white tissue lesions could not be elected apart at the current examinations (b)

To the best of our knowledge, this case has no direct equivalent in the current literature. It represents the first pediatric case of drug-induced neurotoxicity from cytarabine successfully treated with corticosteroids. Previously reported cases involved only minor white matter lesions.[14] In contrast, our patient exhibited multiple, widespread MRI-documented lesions, with complete clinical and radiological recovery.

Conclusion

In conclusion, this case highlights a rare but critical complication of HiDAC and demonstrates the potential of corticosteroids as an effective treatment option for cytarabine-induced neurotoxicity in pediatric patients. As such, it adds valuable insight to the existing literature and may serve as a reference for managing similar complications in future cases.

Ethics

Informed Consent: Written informed consent was obtained from the patient's legal guardian for the publication of this case report.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.K.K.G., C.A., T.K.G., N.Y., S.K., Concept: M.K.K.G., N.Y., Design: M.K.K.G., T.K.G., N.Y., Data Collection or Processing: M.K.K.G., N.Y., Analysis or Interpretation: M.K.K.G., T.K.G., N.Y., Literature Search: M.K.K.G., T.K.G., N.Y., Writing: M.K.K.G., T.K.G., N.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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