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Behenoyl Cytarabine-Associated Reversible Encephalopathy in a Patient with Acute Myelogenous Leukemia

We report a case of reversible encephalopathy syndrome in a 16-year-old girl with acute myelogenous leukemia (AML), who is undergoing during consolidation chemotherapy composed of BH-AC (N^4-behenoyl-1-β-D-arabinofuranosyl cytosine) and idarubicin. On the 6th day of chemotherapy, she was in a drowsy state following generalized tonic clonic seizure lasting 20 minutes. MR images revealed extensive cortical and subcortical white matter brain edema. Alertness returned over the 24 hr following by the discontinuation of BH-AC and intravenous administration of diphenylhydantoin, although she complained of intermittent headaches and visual disturbance. She gradually recovered from these symptoms during subsequent 7 days. Previously noted abnormal signal intensities have nearly disappreared on follow-up MRI obtained on the 22nd day after the first seizure. She was discharged without any neurologic sequela. This case suggests that BH-AC, a derivative of cytosine arabinoside (1-β-D-arabinofuranosylcytosine) could be a cause of reversible encephalopathy syndrome.

Key Words : *Cytarabine; Brain edema; Drug toxicity; Leukemia, myelocytic, acute*

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INTRODUCTION

BH-AC (N^4-behenoyl-1-β-D-arabinofuranosyl cytosine, Behenoyl cytarabine, Enocitabine) is an analogue of cytosine arabinoside (1-β-D-arabinofuranosylcytosine) whose activity is long lasting and less toxic regardless of the treatment schedules or the presence of cytarabine-inactivating enzyme, cytidine deaminase compared with parent compound (1, 2). Although central nervous system (CNS) toxicities related to systemic administration of high-dose cytarabine are well-recognized, BH-AC-associated CNS toxicities have not been reported yet (3, 7). Here we report a case of extensive transient cerebral edema, so-called reversible encephalopathy syndrome, in a patient with acute myelogenous leukemia (AML) during consolidation chemotherapy with BH-AC and idarubicin.

CASE REPORT

A 16-year-old girl was diagnosed having acute myelogenous leukemia (AML, M1, FAB classification) in November 1995. Chemotherpay was initiated with daunorubicin (DNR, 85 mg/daily/IV/days 1-3) and cytarabine (ARA-C, 140 mg/day/CIV/days 1-7). A follow-up bone marrow examination revealed a complete remission state of AML. In January 1996, she received consolidation chemotherapy, which is consisted of idarubicin (IDA, 17 mg/daily/IV/days 1-2) and BH-AC (290 mg/day/CIV/days 1-5). She was asymptomatic at the beginning of consolidation therapy and had a non-specific neurologic examination. On the 6th day of chemotherapy, BHAC was withdrawn because she underwent generalized tonic clonic seizure which lasted 20 minutes and repeated 4 times in spite of the treatment with anticonvulsants. She did not have any history of seizure disorder, and this attack was the first. Blood pressure was 180/130 mmHg, pulse rate was 110/min and temperature was 36.8℃ when she had the seizure.

Laboratory data revealed a hemoglobin of 13.5 g/dL, white blood cell count of 8,400/μL, platelet count of 81,000/μL, BUN of 28 mg/dL, creatinine of 0.9 mg/dL, total protein of 7.0 g/dL, albumin 4.5 g/dL, total bilirubin 0.8 mg/dL, AST of 28 IU/L, ALT 25 IU/L and LDH 350 U/L. Urinalysis revealed a 5-7 RBCs/HPF. Cerebrospinal fluid (CSF) was clear and colorless with no white cells, glucose concentration 65 mg/dL, and protein concentration of 34 mg/dL. Electroencephalogram showed diffuse posticteric changes. MRI showed extensive cortical and subcortical brain edema in cerebellar hemispheres, temporoccipital lobes, posterior parietal lobes (Fig. 1). She gradually recovered over the sub-

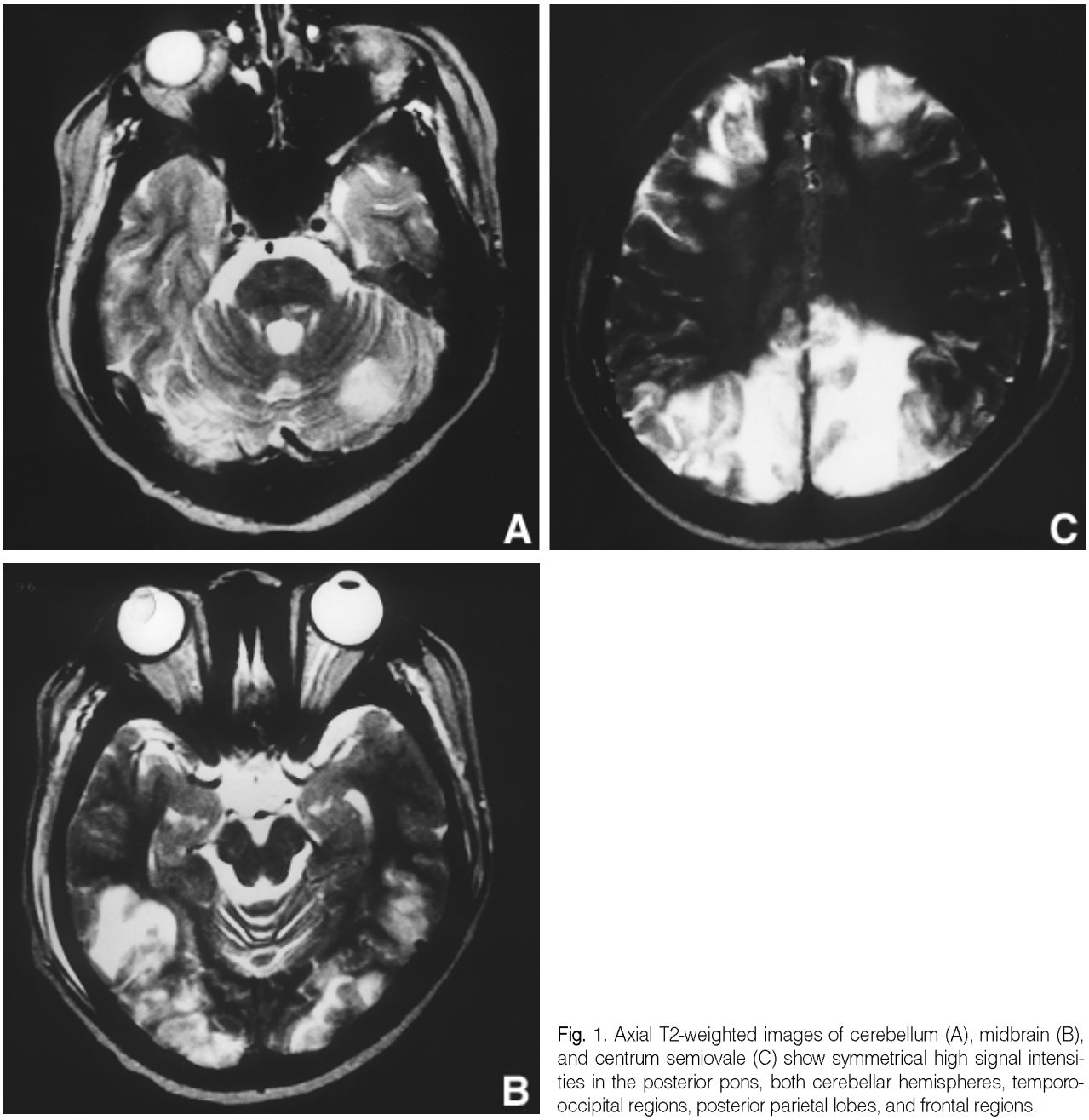

Fig. 1. Axial T2-weighted images of cerebellum (A), midbrain (B), and centrum semiovale (C) show symmetrical high signal intensities in the posterior pons, both cerebellar hemispheres, temporo-occipital regions, posterior parietal lobes, and frontal regions.

sequent 24 hours following intravenous administration of diphenylhydantoin. She returned to her normal mental status, but complained of intermittent headaches and visual disturbance. Blood pressure normalized over the next 3 days. She subsequently recovered from these symptoms over the next 7 day. She was kept on a maintenance dose of 300 mg of diphenylhydantoin without any seizure attacks. Follow-up of MRI was performed on the 22nd day after chemotherapy. Previously noted hyperintensities were nearly disappreared on the follow-up MRI obtained on the 22nd day of the seizure attack except for both posterior parietal lobes (Fig. 2). Abnormal signal nearly disappeared. She was discharged without any neurologic sequela (Table 1).

DISCUSSION

Reversible posterior leukoencephalopathy syndrome is characterized by headache, altered mental function, seizure, and a loss of vision associated with findings indicating pre-

Table 1. Summary of clinical course during chemotherapy

Hospital day	Chemotherapy		Clinical course		MRI study
D1	IDA	BH-AC			
D2	IDA	BH-AC			
D3	IDA	BH-AC			
D4		BH-AC			
D5		BH-AC			
D6	*discontinuing*	*BH-AC*	*seizure(4 times)*	*drowsy*	*extensive edema*
D7				*alert*	
D8-D21					
D22			*no neurologic sequela*		*complete resolution*

Abbreviations: IDA, idarubicin; BH-AC, N^4-behenoyl-1-β-D-arabinofuranosyl cytosine

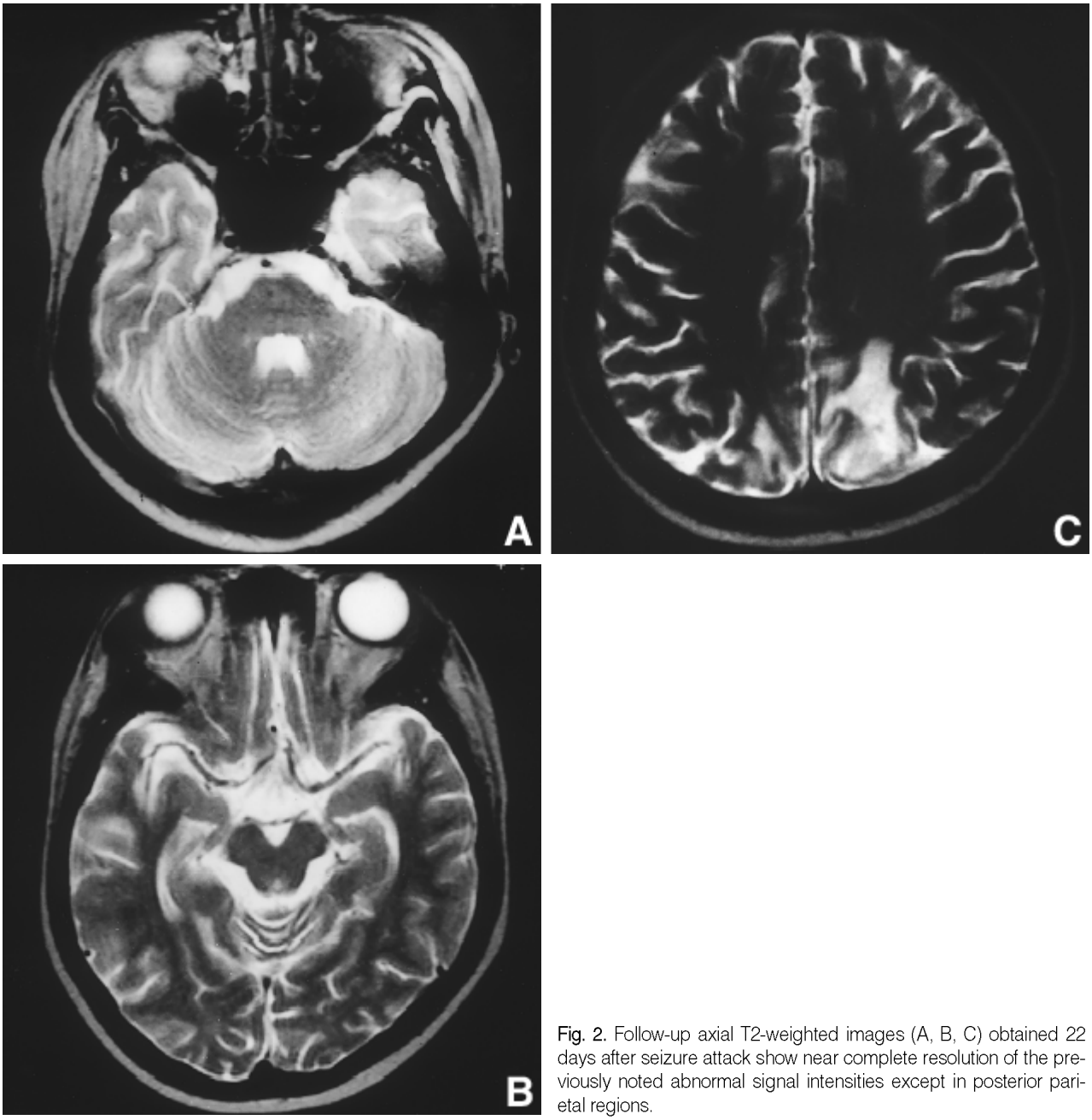

Fig. 2. Follow-up axial T2-weighted images (A, B, C) obtained 22 days after seizure attack show near complete resolution of the previously noted abnormal signal intensities except in posterior parietal regions.

dominantly posterior encephalopathy on imaging studies (8). However, these neurologic deficits improve within two weeks. The most common abnormality, on neuroimaging of the patients with this syndrome, is edema involving the white matter in the posterior portion of cerebral hemisphere. Additional reported areas of the brain, which are involved, include the brain stem, cerebellum, basal ganglia and frontal lobes. In patients who have follow-up MRI scans, there is an improvement or resolution of white-matter abnormalities, suggesting transient edema rather than infarction (8, 9).

Hypertensive leukoencelphopathy (10, 11), eclampsia of pregnancy (12), and acute intermittent porphyria (13) have been known to have transient brain edema, predominantly in the posterior cerebral white matter.

Recently, cyclosporine and other immunosuppressive agents have been reported to be a causal agent in this syndrome (14, 15). In previous reports, some chemotherapeutic agents such as cisplatin-based combination chemotherpy (16), high-dose ARA-C (6) and induction chemotherapy for acute lymhocytic leukemia (17), were associated with ischemic vascular events (3-7). Although the mechanism for this syndrome remains to be elucidated, it is probably a brain-capillary leak syndrome related to hypertension, fluid retention, and possibly the cytotoxic effect of immunosuppressive agents on the vascular endothelium (8).

In this case, the involvement of hypertensive encephalopathy could be excluded to be involved because the patient's blood pressure was elevated to 180/130 mmHg only when she had a generalized tonic clonic seizure. Additionally, the possibility of idarubicin-associated transient ischemic change could be ruled out because idarubicin was administered for two days (day 1-2) and has not been reported to be associated with this syndrome. BH-AC might be more neurotoxic than ARA-C because it is more lipophilic and pass easily through blood-brain barrier. Therefore, it seemed highly likely to be involved in reversible encephalopathy in this case. Especially this case showed more extensive lesions including posterior pons, both cerebellar hemispheres, temporo-occipital regions, posterior parietal lobes, and frontal regions than previous reports (8).

In summary, although BH-AC, a derivative of ARA-C has not been reported to be associated with reversible encephalopathy, this case suggests that it could be involved in this syndrome. One should keep in mind that this syndrome is reversible if it is recognized early and readily treated by controlling blood pressure and seizure and discontinuing the offending agents.

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