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CASE REPORT

Stroke-Like Hemiparesis During Acute Lymphoblastic Leukemia Treatment

İnci Yaman Bajin [1,*], [MD]
ORCID: 0000-0003-1305-4326
Barış Kuşkonmaz [1],[MD]
ORCID:0000-0002-1207-4205
Şule Ünal [1], [MD]
ORCID: 0000-0001-8795-6299
Selin Aytaç [1],[MD]
ORCID: 0000-0003-2132-4605
Mualla Çetin [1],[MD]
ORCID: 0000-0002-3005-2288
Selin Ardalı [2],[MD]
ORCID: 0000-0002-4907-3230
Kader Karlı Oğuz [2],[MD]
ORCID: 0000-0002-3385-4665
Fatma Gümrük [1],[MD]
ORCID: 0000-0001-5102-0624

[1] Hacettepe University, Deparment of Pediatrics, Division of Pediatric Hematology 06100 Ankara/ Turkey
[2] Hacettepe University, Department of Radiology 06100 Ankara/ Turkey

*Corresponding Author: İnci Yaman Bajin, MD
Hacettepe University Faculty of Medicine,
Department of Pediatrics
Division of Pediatric Hematology
06100 Ankara/Turkey
e-mail: inciyaman@gmail.com

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ABSTRACT

In this case report; a 12-year-old male with acute lymphoblastic leukemia who developed transient left hemiparesis associated with dysphasia and central facial paralysis 14 days after high dose methotrexate (5g/m^2) and intrathecal methotrexate (12 mg, according to age) treatment has been reported. Cranial magnetic resonance imaging revealed restricted diffusion in bilateral centrum semiovale compatible with methotrexate-induced acute encephalopathy. All clinical symptoms resolved completely without any treatment.

Clinical findings including headache, nausea, emesis, lethargy, altered mental status, blurred vision, aphasia, dysphasia, hemiparesis and cranial magnetic resonance imaging findings of restricted diffusion that does not comply with the territory of any artery should alert the physician for methotrexate-induced acute encephalopathy.

INTRODUCTION

Methotrexate (MTX) is an important chemotherapeutic agent in acute lymphoblastic leukemia (ALL) treatment because it has been shown to increase the surveillance in children with ALL. However, MTX may induce significant neurotoxicity. The MTX neurotoxicity can present as acute or chronic encephalopathy. It has a wide clinical spectrum, ranging from sub-clinical manifestations with complete recovery to a progressive encephalopathy. Methotrexate induced acute encephalopathy is a transient neurological dysfunction that should be considered in patients presenting with stroke-like

hemiparesis, seizures, aphasia, dysphasia, dysphagia, and diplopia 5 to 14 days after MTX therapy [1-3] .

Here, we report a 12-year-old male with ALL who developed transient left hemiparesis associated with dysphasia and central facial paralysis 14 days after high dose MTX (5g/m^2) and intrathecal (IT) MTX (12 mg according to age) treatment. Cranial magnetic resonance imaging (MRI) revealed restricted diffusion in bilateral centrum semiovale compatible with methotrexate induced acute encephalopathy. All clinical symptoms resolved completely without any treatment.

CASE REPORT

A 12-year-old male was admitted to Hacettepe University Faculty of Medicine, Ihsan Dogramaci Children's Hospital, Department of Pediatrics with the complaints of fatigue, loss of apetite, and weight loss for two weeks. On his laboratory studies; anemia and mild thrombocytopenia was noticed. Therefore, he was referred to Pediatric Hematology Unit. His medical history revealed that he was born as the first child of a healthy parents and he was a healthy child without any problem. Physical examination showed pale skin and hepatomegaly (2 cm below costal margin). His complete blood count revealed that hemoglobin (Hb) was 6.8 g/dL, white blood cell (WBC) count 15900/mm3, and platelet (PLT) count 121000/mm3. His peripheral blood smear showed lymphoblasts. On his bone marrow aspiration smear, 98% lymphoblasts were observed. Flow cytometric analysis showed CD2, CD3, CD4, CD7, CD8, and TdT positivity. The results were compatible with T cell ALL. Cytogenetic analysis showed no positive translocation of t(9;22), t(4;11), t(12;21), and t(1;19). All biochemical parameters were within normal range except high serum uric acid (9,3 mg/dL) and LDH (3646 U/L) levels. After the diagnosis of T cell ALL, ALLIC BFM 2009 chemotherapy protocol was started [4]. Diagnostic lumbar puncture (LP) was traumatic so he received extra-intrathecal treatments at 18th and 27th days according to the protocol. At the 8th day of steroid therapy, absolute blast count was 96/mm3 on peripheral blood smear. Therefore, it was considered as prednisolone good response. At the 15th day of the protocol, bone marrow aspiration smear showed no blastic cells with a minimal residual disease (MRD) of 4.5x10-4 (CD3/CD7/TdT). At the 33th day of the protocol, bone marrow aspiration smear showed no blastic cells with a MRD of 0.5x10-4 (CD3/CD7/TdT). After the completion of induction (IA) and consolidation (Augmented IB) parts of the protocol, the bone marrow aspiration showed no blastic cells with a MRD of 0x10-4 (CD3/CD7/TdT). He was considered as 'Intermediate risk group' according to the protocol. Then, he started to M block including four times of high dose MTX (5gr/m2) and intrathecal MTX (12 mg according to age) treatments at a two weeks interval. He completed the first high dose and intrathecal MTX treatments without any complication and he received the second high dose and intrathecal MTX treatments after two weeks. Leucovorin rescue was given at a dosage of 15 mg/m2 at 42nd, 48th, and 54th hours according to the protocol. Six days after the second MTX treatment, he was admitted to the hospital with neutropenic fever and intravenous meropenem treatment was started. Blood culture was negative; fever was under controlled and absolute neutrophil count (ANC) increased over 1000/mm3 within one week. On the 7th day of the antibiotic treatment, hemiparesis occurred on his right side lasting for one hour. Cranial computed tomography (CT) was normal and the symptoms resolved completely. At the next night, hemiparesis occurred again on his right side with dysphasia and central facial paralysis lasting for 2 hours. Cranial MRI revealed lesions with diffusion restriction in bilateral centrum semiovale more prominent on the left. The lesions were not appreciated on T2 weighted and FLAIR imaging and did not show contrast enhancement. As the diffusion restricted areas were bilateral and did not correspond to any single arterial territory, the patient was diagnosed as MTX- induced acute encephalopathy (Figure 1).

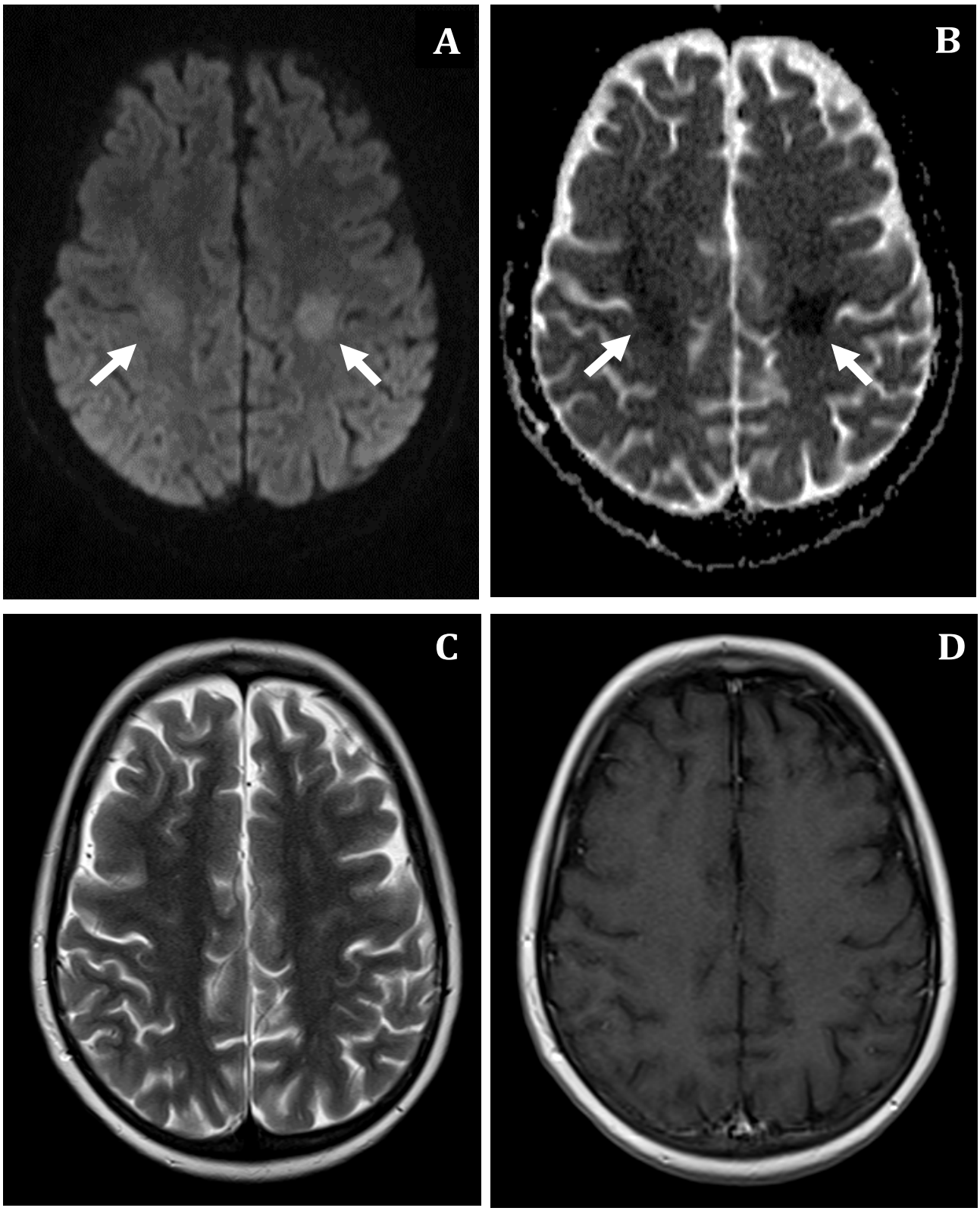

Figure 1. MRI at the symptomatic period. A: Axial diffusion image (b=1000 s/mm2) demonstrates high signal intensity in bilateral centrum semiovale (more prominent on the left, arrows), B: Corresponding ADC map reveals low values at affected sites showing the diffusion restriction (arrows), C: T2 weighted (TR/TE: 5390/106 ms) reveals no apparent signal abnormality corresponding to the areas with restricted diffusion, D: Postcontrast T1 weighted image (TR/TE: 590/14ms) shows no abnormal contrast enhancement in the affected areas.

Clinical symptoms started 14 days after high dose and intrathecal MTX treatments. All the fluctuating symptoms completely resolved within 24 hours.

DISCUSSION

Acute encephalopathy after MTX treatment is a very rare event in children with acute leukemia. The incidence of acute encephalopathy after MTX treatment was 0.8% for patients with leukemia/lymphoma and 4.5% for patients with osteosarcoma or malignant fibrous histiocytoma [5]. This shows that higher incidences of acute encephalopathy are related to higher doses of MTX that used in the treatment of osteosarcoma or malignant fibrous histiocytoma (8-12 g/m2). Clinical findings of acute encephalopathy may include headache, nausea, emesis, lethargy, altered mental status, blurred vision, aphasia, dysphasia, hemiparesis, and seizure [6-8].

In our hospital, MTX-induced acute encephalopathy was observed in only 1/179 (0.5 %) children who have been followed up in Pediatric Hematology Unit with the diagnosis of ALL since January 2010. Therefore, MTX-induced acute encephalopathy is a very rare complication seen in our hospital.

In a study performed by Mahoney et al; cumulative dosage of systemic MTX, a high MTX: leucovorin ratio, and concurrent intrathecal MTX treatment have been shown to increase the risk of acute encephalopathy [9]. Acute encephalopathy generally develops within 5-14 days after MTX treatment and usually resolves within a week. However, recurrences may occur after MTX therapy is resumed. Most patients can resume MTX therapy without permanent neurological sequelae, although 10–56% may experience recurrence on rechallenge. Prophylactic aminophylline treatment is recommended to prevent recurrence of acute encephalopathy [6-10].

In our patient, acute encephalopathy developed after 14 days of MTX treatment. His symptoms became evident after waking up. Dysphasia, facial paralysis, and hemiparesis developed after an episode of headache. He had no seizure. The symptoms evolved over minutes to many hours, progressing, resolving, and involving bilateral brain areas. His cranial MRI revealed restricted diffusion at bilateral centrum semiovale. Restricted diffusion did not comply with the irrigation area of any artery. Therefore, MTX-induced acute encephalopathy was diagnosed with these clinical and cranial MRI findings. All his symptoms resolved within 24 hours. His clinical status is very well now. We decided to resume other doses of MTX treatment with aminophylline prophylaxis.

The pathophysiology of MTX-induced acute encephalopathy is not exactly known. However, it does not appear to be related to MTX pharmacokinetics [6] . Dufourg et al [5] reported that high dose MTX doses of 1.5–8 g/m2 and age >10 years were associated with MTX-induced acute encephalopathy in children with ALL. The tendency of slow MTX clearance in adolescents may contribute to the risk of MTX-induced acute encephalopathy. However, no significant relation between MTX pharmacokinetics and the development of MTX-induced acute encephalopathy has been shown, yet. Although the pathophysiologic mechanisms are unclear, slow waxing and waning of neurologic symptoms indicates progressive depolarization of neuronal and axonal membranes as in migraine-associated cortical spreading depression rather than vascular occlusion [11]. Furthermore, MTX promotes release of adenosine from fibroblasts and endothelial cells and elevated adenosine has been demonstrated in cerebrospinal fluid after MTX treatment. High adenosine levels cause dilatation in cerebral blood vessels, modify the release of pre- and postsynaptic neurotransmitters, and may slow the discharge rate of neurons. Thus, adenosine release may contribute to the pathophysiology of MTX-induced acute neurotoxicity. Aminophylline displaces adenosine from its receptor sites [12]. Although its efficacy is difficult to acertain, aminophylline prophylaxis is recommended to prevent recurrence of MTX-induced acute encephalopathy.

MTX-induced acute encephalopathy may develop in leukemic children who received high dose MTX treatment and age >10 years.. Since treatment strategies are different, differential diagnosis of acute iskemic stroke and MTX-induced acute

encephalopathy should be performed carefully. Anticoagulant treatment is not necessary for MTX-induced acute encephalopathy. Instead of anticoagulation, aminophiline treatment may be useful to decrease the clinical symptoms and also to prevent recurrences. Cranial MRI findings of restricted diffusion that does not comply with the territory of any artery must alert the radiologist. Diffusion weighted imaging (DWI) has been described as the most sensitive modality to show the affected areas in MTX-induced acute encephalopathy in the acute period before T2 weighted and FLAIR signal changes occur. The resolution of DWI findings can be observed on follow-up cranial MRI studies [2].

Thus, pediatric hematologists and neurologists should be aware the clinical picture of MTX-induced acute encephalopathy. Therefore, prompt diagnosis and right treatment strategy may decrease the development of neurological sequelae after MTX-induced acute encephalopathy.

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