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Intracerebral Hematoma as a Complication of Intrathecal Methotrexate Administration

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Neurotoxicity of methotrexate is a well-documented issue, but development of an intracerebral hematoma following administration of intrathecal methotrexate is an extremely rare entity. A 6-year-old male with the diagnosis of non-Hodgkin lymphoma was put on a treatment regimen, including intrathecal methotrexate. Six days following the last intrathecal methotrexate administration, the patient developed a deteriorating state of consciousness. There was no history of trauma. Coagulation studies and platelet count were normal. Magnetic resonance imaging of the brain demonstrated a large left frontoparietal hematoma. Intracerebral hematoma may be a very rare, but serious, complication of intrathecal methotrexate administration. Pediatr Blood Cancer 2008;50:152–154.

Key words: intracerebral hematoma; lumbar puncture; methotrexate; non-Hodgkin lymphoma

INTRODUCTION

Neurotoxicity of methotrexate is a well-documented issue [1]. However, intracerebral hematoma following administration of intrathecal methotrexate is an extremely rare entity, with only two cases having been reported in the literature till now [2,3]. In this paper, we describe a case of intracerebral hematoma developing

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Received 17 January 2006; Accepted 13 March 2006

DOI 10.1002/pbc.20861

after intrathecal methotrexate administration without any underlying cause.

CASE REPORT

A 6-year-old male with the diagnosis of non-Hodgkin lymphoma (NHL) was treated on the revised NHL-BFM 90 treatment regimen for stage III, risk group III, including; prednisone, cyclophosphamide, vincristine, ifosfamide, cytosine arabinoside, etoposide, doxorubicin, and methotrexate with leucovorin rescue, along with triple intrathecal treatment with methotrexate, cytosine arabinoside, and prednisone. In the pre-treatment period, central nervous system involvement was excluded by both an enhanced cranial magnetic resonance imaging (MRI) and negative cerebrospinal fluid (CSF) cytology. Six days following the last intrathecal methotrexate administration, during the 4th week of the treatment, the patient developed a deteriorating state of consciousness, right-sided hemiparesis and right-sided focal seizures. There was no history of trauma. Coagulation studies showed normal prothrombin time, partial thromboplastin time, and fibrinogen. Platelet count was $195 \times 10^3/\mu l$, white blood cell count was $10.9 \times 10^3/\mu l$, and hemoglobin was 9.7 g/dl. There was no clinical evidence for significant CSF leak at the site of dural puncture. MRI of the brain demonstrated a large left frontoparietal hematoma causing a significant midline shift (Fig. 1A). The neurosurgery team recommended surgical evacuation of the hematoma, but this plan was refused by the patient's parents. Phenytoin, dexamethasone, and mannitol were initiated. The patient's symptoms began to improve and the intracerebral hematoma resolved spontaneously over 6 weeks (Fig. 1B). The patient recovered with a persistent slight right-sided hemiparesis and aphasia. An MRI angiogram after the resolution of hematoma was negative for an underlying vascular malformation. The patient died 5 months later because of progressive disease.

DISCUSSION

Methotrexate is an anti-neoplastic agent utilized in prophylaxis for central nervous system involvement. The association between methotrexate therapy and idiosyncratic neurological complications is well recognized in children [4–7]. Although the hematological and mucocutaneous toxicities are dose limiting, its neurotoxicity can be problematic because the adverse effects may be more severe and irreversible, especially in patients undergoing cranial irradiation [4]. Acute cerebral dysfunction with paresis, aphasia, behavioral abnormalities, and seizures are observed in 5–15% of patients receiving high-dose methotrexate [5]. Acute cerebral dysfunction has also been reported to occur with a similar frequency after intermediate dose intravenous therapy or even oral administration [6]. Acute chemical arachnoiditis with severe headaches, nuchal rigidity, seizures, vomiting, fever, and an inflammatory cell infiltrate in the CSF can be observed immediately after intrathecal administration [5]. A chronic form of neurotoxicity manifesting as a demyelinating encephalopathy with dementia and motor paresis can develop 2–4 months after the treatment [5–8].

Although neurotoxicity from methotrexate exposure is well-documented, intracerebral hematoma following intrathecal methotrexate administration is an extremely rare complication. There are only two letters in the literature reporting the development of an intracerebral hematoma following administration of intrathecal methotrexate; one in a 67-year-old man with NHL and the other in a 6-year-old boy with acute lymphoblastic leukemia (ALL) [2,3].

One of the pathological mechanisms in the development of intracerebral hematoma is probably the CSF leak following dural puncture. Up to 240 ml of CSF can leak from the dural puncture site per day [9]. This leak results in decreased intracranial pressure, leading to compensatory expansion of intracerebral veins [10]. In addition, loss of CSF also results in caudal displacement of intracranial structures, applying traction on dilated veins. This mechanical traction suddenly increases when the patient changes from recumbent position to upright position, which may result in tearing of the dilated veins leading to subdural or intracerebral hematoma. On the other hand, post dural-puncture CSF leak is unlikely to be the sole mechanism because there are no reports of intracerebral or subdural hematoma in the literature following diagnostic lumbar puncture [11,12]. Thus, methotrexate is likely to play a role in the pathogenesis of development of a hematoma.

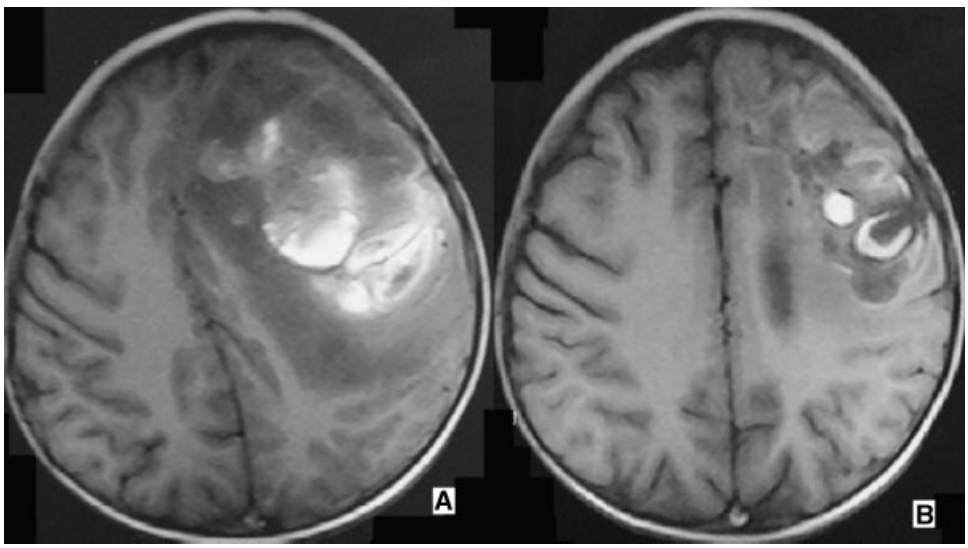

Fig. 1. Magnetic resonance imaging of the brain demonstrating large frontoparietal hematoma (**A**), and control imaging performed 6 weeks after the bleeding (**B**).

Colosimo et al. [13] have reported their experience for 657 patients undergoing bone marrow transplantation. They have administered intrathecal methotrexate in 197 patients as a part of the conditioning regimen; they showed subdural hematoma in 14 patients. When they omitted methotrexate from the regimen, they had no new cases of hematoma in the following 100 consecutive patients.

Previous reports indicate that methotrexate has adverse effects on cerebral vasculature. Shapiro et al. [14] reported that fibrinoid degeneration occurs in the cerebral vessels in case of methotrexate encephalopathy. Fibrinoid degeneration and hyaline thrombus of the penetrating cortical vessels as a direct toxic effect of methotrexate after intra-arterial administration has also been reported [15]. Elevation of CSF homocysteine may even be more relevant since homocysteine is known to be directly toxic to vascular endothelium [16]. Furthermore, Osterlundh et al. [17] have examined regional cerebral blood flow of six patients with ALL receiving intrathecal methotrexate therapy, using single-photon emission computed tomography (SPECT). They have reported that every patient had various degrees of disturbed regional cerebral blood flow.

Intracranial hemorrhage following intrathecal methotrexate administration can be due to a combination of two or more of the above mechanisms. Intracerebral hematoma may be a very rare, but serious, complication of intrathecal methotrexate administration.

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Renal Failure After High-Dose Methotrexate in a Child Homozygous for MTHFR C677T Polymorphism

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We report the case of an 11-year-old female treated for mediastinal T-cell lymphoma who presented renal failure following the second cycle of high-dose methotrexate (HDMTX). Because of life threatening plasma methotrexate (MTX) levels, carboxypeptidase G2 (CPDG2) was administered resulting in a dramatic decrease within 1 hr. The patient recovered from renal failure and no other side effects were observed. Homozygosity for the methylentetrahydrofolate reductase (MTHFR) C677T polymorphism diagnosed by molecular genetic analysis was the only explanation for this toxicity. Pediatr Blood Cancer 2008;50:154–156. © 2007 Wiley-Liss, Inc.

Key words: high-dose methotrexate; methotrexate (MTX) toxicity; MTHFR polymorphism; renal failure

INTRODUCTION

High-dose methotrexate (HDMTX) is an important component in the treatment regimens for a variety of cancers [1–3]. The drug acts as a strong, competitive inhibitor of the enzyme dihydrofolate reductase (DHFR), and thus depletes intracellular tetrahydrofolate (THF), the active form of folate, essential for the synthesis of DNA, RNA, and proteins. The enzyme methylentetrahydrofolate reductase (MTHFR) catalyzes the reduction of

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Received 24 January 2006; Accepted 26 December 2006

DOI 10.1002/pbc.21176