

Transverse myelopathy following intrathecal administration of chemotherapy

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ABSTRACT

Transverse myelopathy is one of the rare complications following administration of intrathecal chemotherapy. We report two cases of transverse myelopathy following administration of intrathecal methotrexate and cytarabine arabinoside. One patient was a 17-year-old Malay man who had lymphoblastic lymphoma in the leukaemic phase, while the other patient was a 40-year-old Malay man with relapsed Hodgkin's lymphoma. Both cases demonstrated variability in onset of symptoms, clinical progression and final outcome from the complication.

Keywords: chemotherapy complications, cytarabine arabinoside, intrathecal methotrexate, transverse myelopathy

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INTRODUCTION

Neurological complications of anti-cancer therapy may result from direct toxic effects on the nervous system, or indirectly from drug-induced metabolic derangements or cerebrovascular accidents.⁽¹⁻⁴⁾ Their

recognition is important because of potential confusion with metastatic disease. Furthermore, discontinuation of the offending agent may prevent irreversible injury. Common neurological complications of chemotherapy include peripheral neuropathy, cranial neuropathies, acute encephalopathy, acute vasculopathies, headaches and seizures.⁽¹⁻⁴⁾ Transverse myelopathy, a much less common sequela following intrathecal (IT) administration of chemotherapy, is defined as the development of isolated spinal cord dysfunction over hours or days in the absence of a compressive lesion. It has been rarely reported following IT methotrexate (MTX), cytarabine arabinoside (Ara-C) and thiotepea.⁽⁵⁻⁷⁾

CASE REPORTS

Case 1

A 17-year-old Malay man was diagnosed to have lymphoblastic lymphoma in the leukaemic phase in July 2004, and underwent autologous peripheral blood stem cell transplantation (PBSCT) five months later (Fig. 1). Six weeks after PBSCT, he developed sudden onset of isolated left facial nerve palsy. Leukaemic infiltration of the central nervous system (CNS) was confirmed with the presence of malignant lymphoid cells noted in the cytopsin

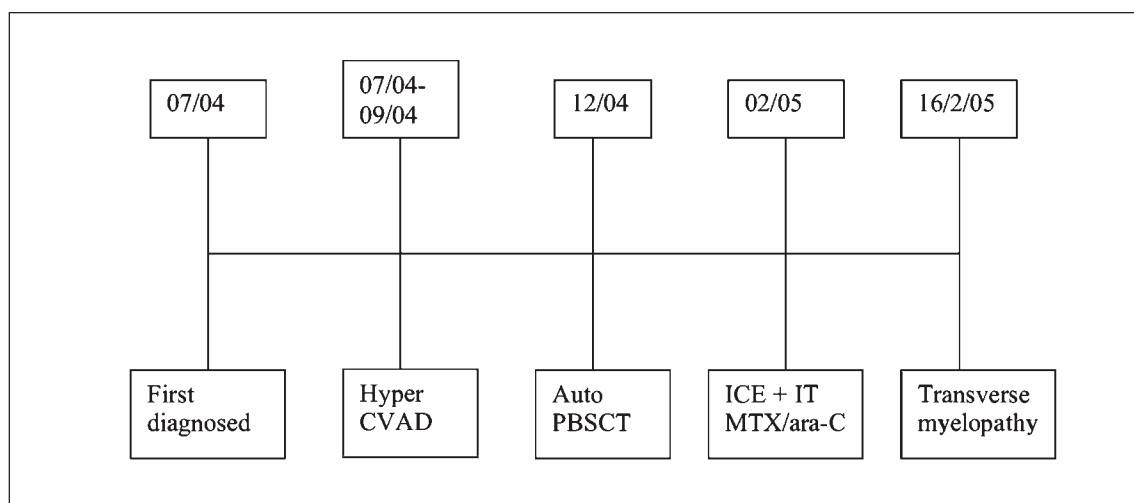


Fig. 1 Timeline of events for Case 1.

Hyper-CVAD: Hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone.

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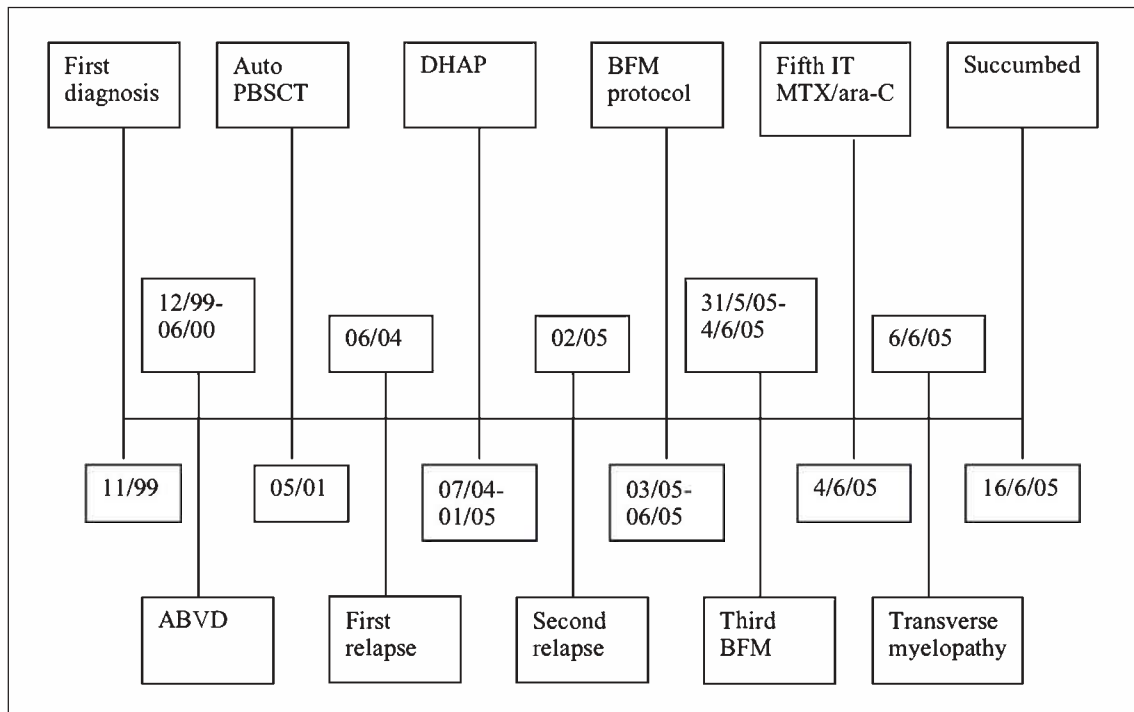


Fig. 2 Timeline of events for Case 2.

DHAP: Dexamethasone, high-dose Ara-C and cis-platinum; ABVD: Adriamycin, bleomycin, vinblastine and dacarbazine.

of the cerebrospinal fluid (CSF). He was given the first IT (via the third and fourth lumbar intervertebral space) MTX 12.5 mg immediately following the diagnostic lumbar puncture. After confirming CNS relapse, he was given IT MTX 12.5 mg, Ara-C 40 mg and dexamethasone 4 mg about one week after the first IT MTX. Soon after completion of IT injection, he felt numbness of his left lower limb, followed by development of paraplegia and paraesthesia of the lower parts of the body. There was no urinary or bladder incontinence.

Physical examination revealed that the blood pressure was high (200/120 mmHg) and he was tachycardic, pulse rate of 120 beats per minute. Sensory loss was noted from lower extremities up to T4 vertebral level. Intravenous (IV) hydrocortisone 100 mg and piriton 10 mg were given immediately. Contrast-enhanced computed tomography of the brain was done on the same day and was normal. The power of his lower limbs improved from 0/5 to 3/5 (Medical Research Council Scale) 45 minutes after the IT injection. Power and sensory deficit of the lower limb were normalised after the next day.

As the neurological complication occurred following IT administration of MTX in combination with Ara-C and not MTX alone, Ara-C was thought to be the most likely offending agent. However, he developed paraplegia a week later, following IT MTX 12.5 mg and dexamethasone 4 mg, in the absence of Ara-C.

The symptoms completely resolved 30 minutes after IV hydrocortisone 100 mg and piriton 10 mg. Magnetic resonance (MR) imaging of the brain and thoracolumbar spine revealed no abnormality. Repeated CSF examination during the neurological event was unremarkable.

Case 2

A 40-year-old Malay man underwent autologous PBSCT for relapsed Hodgkin's lymphoma in 2001 (Fig. 2). Following that, he had another two relapses in 2004 and 2005. He presented with low backache without neurological deficit in February 2005 and MR imaging showed lymphomatous infiltration of L4 vertebra, upper sacral region and right thigh. He was treated with Berlin-Frankfurt-Munster (BFM) protocol (Table I), which included high doses of IV MTX, and IT MTX and Ara-C. CSF examination revealed a high protein content of more than 1 g/L which was suggestive of meningeal infiltration. Repeat MR imaging after two courses of BFM regime showed a reduction of the sacral mass from 2 cm to 1 cm thickness and resolution of the right thigh mass, but the L4 infiltration persisted and the patient continued to receive weekly IT MTX.

He developed sudden onset of paraplegia and urinary retention two days after the fifth IT MTX during the second BFM cycle. Four days after the event, his Glasgow Coma Scale (GCS) deteriorated from

15/15 to 10/15, and he developed respiratory distress. He was electively intubated for respiratory distress and poor GCS. Repeat MR imaging of the spine and brain showed no evidence of disease progression, spinal cord compression or brain metastasis. He continued to deteriorate and succumbed ten days later.

DISCUSSION

Transverse myelopathy, an unusual complication of IT MTX/Ara-C, is defined as the development of isolated spinal cord dysfunction over hours or days in the absence of a compressive lesion.⁽⁵⁻⁷⁾ The incidence was reported in approximately 3% of all cases treated with IT MTX or Ara-C. Our patients demonstrated a typical transverse myelopathy with paraplegia, level of sensory deficit as well as bladder and respiratory muscle involvement following administration of IT MTX and Ara-C. The symptoms developed within few minutes and two days, respectively, after completion of the medication. This was similar to other patients previously described who developed symptoms within minutes to 48 hours after treatment, although some may even persist up to two weeks.⁽⁵⁻⁷⁾ Repeated MR imaging of the spine and brain which excluded a compressive lesion, close temporal relationship and lumbar puncture site via L3/L4 vertebral level which was free of spinal cord, supported that the transverse myelopathy was related to IT administration of MTX and Ara-C.

In the first patient, all the symptoms (weakness and sensory loss) started to improve in less than one hour and completely resolved in less than 24 hours. The rapid development and resolution of the symptoms suggest that it is most likely a neuropraxia caused by sudden osmolality changes in CSF, or direct toxic or irritation by the IT medication. Hence, recovery occurred rapidly when the offending agents were cleared from the spinal CSF. This was consistent with the half-lives of IT administration of MTX and Ara-C in CSF, which are 4.5–14 hours^(8,9) and 2–11 hours, respectively. Although the majority of cases reported showed clinical improvement, the extent of recovery was variable.⁽⁵⁻⁷⁾

In contrast to the first case that developed neurological symptoms after the second IT MTX, the second patient developed the symptoms only after the fifth IT MTX. Additionally, the neurological deficit was more extensive and progressive. The more severe neurological manifestation may be partly attributed to systemic IV MTX in high doses. Besides, the pre-existing CNS involvement observed in the second case also contributed to the increased risk and severity of neurotoxicity of IT MTX.⁽⁵⁻⁷⁾

Documented risk factors for the development of MTX-related transverse myelopathy include high dose MTX of more than 50 mg given intrathecally,

Table 1. Chemotherapy regime.

Chemotherapy agents	Manufacturer	City/state	Country
HyperCVAD cycle A			
Cyclophosphamide	Baxter	Frankfurt	Germany
Vincristine	Mayne Pharma	Mulgrane	Australia
Doxorubicin	Dabur	Solan	India
Dexamethasone	Zydus Cadila	Ahmedabad	India
HyperCVAD cycle B			
Methotrexate	Mayne Pharma	Mulgrane	Australia
Ara-C	Dabur	Solan	India
ICE			
Ifosfamide	Baxter	Frankfurt	Germany
Carboplatin	Mayne Pharma	Mulgrane	Australia
Etopoxide	Dabur	Solan	India
ABVD			
Doxorubicin	Dabur	Solan	India
Bleomycin	Nippon Kayaku	Tokyo	Japan
Vincristine	Mayne Pharma	Mulgrane	Australia
Dacarbazine	Mayne Pharma	Mulgrane	Australia
DHAP			
Dexamethasone	Zydus Cadila	Ahmedabad	India
Cis-platinum	Pfizer	Bentley	Australia
Ara-C	Dabur	Solan	India
BFM cycle A			
Dexamethasone	Zydus Cadila	Ahmedabad	India
Vincristine	Pfizer	Bentley	Australia
Ifosfamide	Baxter	Frankfurt	Germany
Methotrexate	Mayne Pharma	Mulgrane	Australia
Etopoxide	Dabur	Solan	India
Ara-C	Dabur	Solan	India
BFM cycle B			
Dexamethasone	Zydus Cadila	Ahmedabad	India
Vincristine	Pfizer	Bentley	Australia
Cyclophosphamide	Baxter	Frankfurt	Germany
Methotrexate	Mayne Pharma	Mulgrane	Australia
Adriamycin	Dabur	Solan	India

repeated injection with close interval less than one week, concurrent cranial radiotherapy, systemic MTX, active CNS disease (e.g. meningeal leukaemia).^(8,9) Since the occurrence and clinical course of IT-induced transverse myelopathy is unpredictable, we should try to avoid high dose IT MTX, close interval of administration, concurrent cranial radiotherapy and systemic MTX as far as possible. Those high-risk patients should be counselled properly about the possible side effects before administration of the medication. Any further administration of IT MTX or Ara-C must be stopped once the complication has occurred.⁽⁵⁻⁷⁾ The patients should be reassured regarding

the clinical course and given appropriate supportive treatment accordingly. It is advisable to monitor the CSF MTX level to make sure that it has declined to an acceptable value before the subsequent dose is administered.

In conclusion, history of uncomplicated IT administration of MTX or Ara-C does not exclude one from developing transverse myelopathy during subsequent chemotherapy as illustrated in the second case. The onset can vary from a few minutes to a few hours after IT injection. The clinical course also can vary from complete resolution of symptoms to continued deterioration, merely paraplegia to respiratory muscle involvement and even death.

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