

Transverse myelopathy occurring with intrathecal administration of methotrexate and cytarabine chemotherapy: A case report

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Received March 14, 2015; Accepted March 18, 2016

DOI: 10.3892/ol.2016.4519

Abstract. Paraplegia following spinal injury is a rare complication subsequent to the administration of intrathecal chemotherapy; however, it is also one of the rare clinical features of central nervous system leukemia (CNSL). Distinguishing between the two is extremely important. The present study reports the case of a 46-year-old man who was diagnosed with acute lymphoblastic leukemia and subsequently achieved remission in the blood and bone marrow following the initial course of chemotherapy. However, the patient developed a sudden onset of paraplegia and urinary retention due to spinal cord infiltration of leukemia cells following the administration of intrathecal methotrexate and cytarabine. The paraplegia was initially reversible. However, a few weeks later, the patient developed irreversible paraplegia due to a complication of the intrathecal administration of chemotherapy (methotrexate and cytarabine arabinoside). The patient gave up further treatment in May 2013 and succumbed to the disease in June 2013.

Introduction

Acute lymphocytic leukemia (ALL) is a malignant hematological disease, which originates from B or T lymphoid progenitor cells (1). The central nervous system (CNS) is a region in which direct infiltration and involvement or relapse occurs in adults with ALL (1). If no preventative therapy is administered, a total of 30-50% of adults with ALL eventually present with CNS leukemia (CNSL) (2). Following advances in chemotherapy and effective CNS prophylaxis, the incidence of CNS relapse in cases of ALL has decreased to 5-10% (1). Intrathecal administration of chemotherapy, high dose chemotherapy and brain radiotherapy are the primary measures used for the prevention of CNSL (3,4).

The central nervous system (CNS) has long been recognized as a site, and indeed a sanctuary, for leukemic cells (1). However, few patients (<5%) with ALL present with overt CNSL initially (1). The clinical manifestation of CNSL ranges from mild to severe, and infiltration of the arachnoid membrane and dura mater is the most common, followed by the brain parenchyma and cranial nerves; spinal cord infiltration is the most rare presentation (1,3,4).

The most commonly used treatment for CNSL is intrathecal (IT) administration of chemotherapy (1,3-5). However, IT chemotherapy is associated with certain complications, which most frequently include peripheral neuropathy, cranial neuropathies, acute encephalopathy, acute vasculopathies, headaches and seizures (5). Transverse myelopathy is a rare complication (5). The current study reports the case of a patient who experienced a reversible spinal cord injury as clinical feature, and subsequently developed irreversible spinal cord injury following the IT administration of methotrexate (MTX) and cytarabine (Ara-C).

Case report

A 46-year-old man was diagnosed with B-cell ALL (Philadelphia chromosome-positive and hyperleukocytosis) morphology, immunology, cytogenetics and molecular biology by morphology, immunology, cytogenetics and molecular biology at The Second Hospital of Anhui Medical University (Hefei, China) in November 2012. Philadelphia chromosome was tested using the G-banding technique, and a routine blood test demonstrated that the white blood cell count was $32.93 \times 10^9/L$, which indicated the presence of hyperleukocytosis. The patient underwent induction chemotherapy consisting of DVCP (daunorubicin 80 mg, day 1, 15 and 22; vindesine 4 mg, day 1, 8, 15 and 22; cyclophosphamide 1.0 g, day 1 and 15; and desamethasone 15 mg, days 1-28) plus imatinib (400 mg, days 19-28) for 1 cycle. However, in January 2013, the patient developed a sudden onset of numbness in his two lower limbs (also known as transverse myelopathy) in addition to bladder incontinence, shortly after achieving remission in the blood and bone marrow following the initial course of chemotherapy. Magnetic resonance (MR) imaging (MAGNETOM Verio 3.0T; Siemens AG, Munich, Germany) revealed lymphomatous infiltration at the T12 vertebra (Fig. 1A). Leukemic infiltration of the CNS was confirmed by the presence of malignant leukemia cells detected in the cytospin of the cerebrospinal fluid (CSF) (Fig. 2).

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Key words: transverse myelopathy, chemotherapy, B-cell acute lymphocytic leukemia



Figure 1. (A) Magnetic resonance images of the thoracic spinal cord following induction chemotherapy demonstrated a lesion at the T12 vertebra.

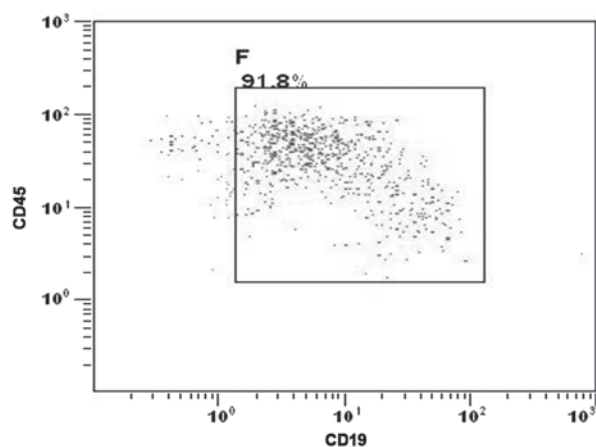


Figure 2. The malignant leukemia cells in the cerebrospinal fluid (gate F) had an abnormal immunophenotype: CD19⁺CD45^{dim-++}. CD, cluster of differentiation.

The patient was subsequently administered IT (via the 3rd and 4th lumbar intervertebral space) MTX (15 mg) and Ara-C (50 mg) immediately following a diagnostic lumbar puncture every other day 8 times, without other therapy, from January 7 to 21, 2013. After experiencing CNSL remission, the patient was given IT MTX (10 mg), Ara-C (50 mg) and dexamethasone (10 mg) once per week for 4 weeks. Soon after the completion of IT injections, the patient reported feeling that his numbness and bladder incontinence had recovered. Repeat MR imaging showed no infiltration in the spinal cord (Fig. 3A). The patient was subsequently administered consolidation chemotherapy once consisting of cyclophosphamide (1.2 g; day 1), vincristine (2 mg; day 1), Ara-C (0.2 g; days 1-5), teniposide (150 mg, days 1-4) and dexamethasone (10 mg; days 1-7) for 1 cycle.

However, in April 2013, the patient developed a sudden onset of paraplegia and urinary retention again. Repeat MR imaging of the spine and brain revealed no evidence of disease progression, spinal cord compression or brain metastasis (Fig. 3B). A repeat CSF examination during this neurological event was normal. Supportive treatment, which included neuro nutrition

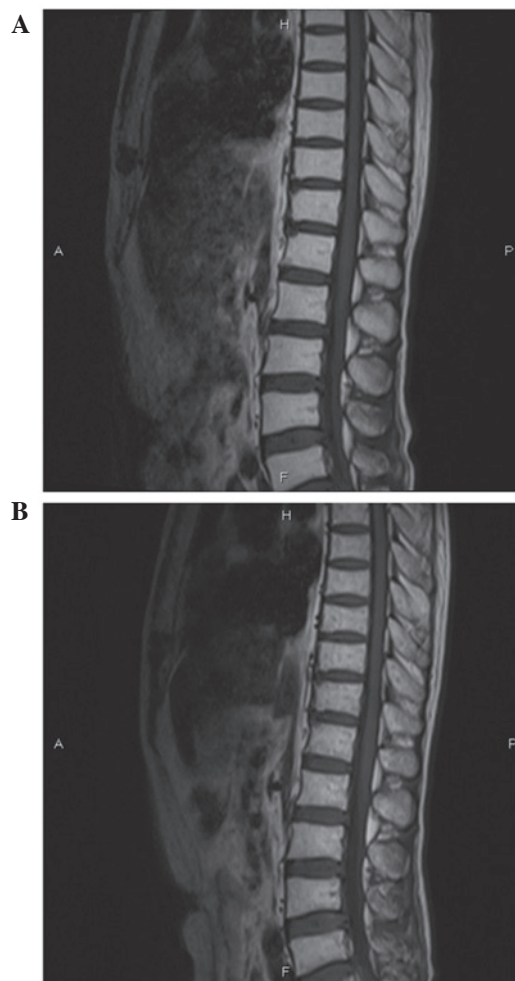


Figure 3. No infiltration was observed in the spinal cord in magnetic resonance images (A) when the paraplegia recovered and (B) when the patient developed irreversible paraplegia.

drugs, was administered accordingly; however, the paraplegia was irreversible. The patient gave up further treatment due to economic factors in May 2013, and at the last follow-up the numbness and bladder incontinence had alleviated, but had not fully recovered.

Discussion

The CNS is a location in which direct infiltration and involvement or relapse may occur in ALL (1). The majority of ALL relapses occur during treatment or within the first 2 years after the completion of treatment; however, relapses have been reported to occur even 10 years after diagnosis. The main mechanism of CNS infiltration in leukemia is associated with blood brain barrier (7). CNSL most frequently involves infiltration of the arachnoid membrane and dura mater, less commonly the brain parenchyma, choroid glands and cranial nerve, and rarely the spinal cord (5).

There are several high risk factors associated with the occurrence of CNSL, including hyperleukocytosis at diagnosis, the presence of extramedullary infiltration, certain types of acute leukemia [including acute myelomonocytic leukemia and acute monocytic leukemia (M5a)], T-cell immunophenotype, Burkitt's lymphoma (mature), relapsed acute promyelocytic

leukemia, and high-risk genetic abnormalities [such as t(4;11) and the Philadelphia chromosome] (8). The current patient, who developed the symptom of paraplegia, had two high risk factors for CNSL: Hyperleukocytosis at diagnosis and the Philadelphia chromosome.

There are numerous methods for the treatment of CNSL, including IT chemotherapy, systemic chemotherapy and radiation therapy (9). The role of IT chemotherapy has been emphasized in modern clinical usage; however, it is associated with various possible side effects. Transverse myelopathy, which is defined as the development of isolated spinal cord dysfunction over hours or days in the absence of a compressive lesion, is an unusual complication of IT MTX/Ara-C chemotherapy (10-12). The most important MTX-associated risk factors for the development transverse myelopathy are high dose IT MTX, systemic MTX, repeated injection with an interval of <1 week, concurrent use with other medication or cranial radiotherapy, and active CNS disease (13,14). The symptoms usually develop between several minutes and 2 weeks after treatment (13,14); however, the current patient developed the neurological symptoms 3 months after the first administration of IT MTX and Ara-C.

Although the incidence of transverse myelopathy is low (~3% of all patients who undergo intrathecal injection) and its occurrence is unpredictable, doctors must be aware of this complication and attempt to avoid the aforementioned high risk factors (15). Once the complication has occurred, administration of IT MTX or Ara-C must be discontinued and the patient should be reassured (15).

In conclusion, the most vital difference between the current case and other cases in which transverse myelopathy developed was that the neurological symptoms of the current patient were identical when he developed CNSL and when the complication of the subsequent IT chemotherapy occurred. To distinguish the two is crucial as the appropriate therapies for each are completely opposite (5). It is advisable to monitor the CSF by light microscopy and flow cytometry. Repeated MR imaging must also be conducted.

Acknowledgements

This study was supported by the Foundation of Anhui Medical University (grant no. 2015xkj018) and the National Natural Science Foundation of China (grant no. 81401293).

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