Case report

Dorsal column myelopathy following intrathecal chemotherapy for acute lymphoblastic leukemia

Prathap Jacob Joseph^{1,2,3}, Maria Regina Reyes³

¹Department of Physical Medicine and Rehabilitation, University of Texas Houston Medical School, Houston, TX, USA, ²TIRR Memorial Hermann, Houston, TX, USA, ³Department of Rehabilitation Medicine, University of Washington School of Medicine, University of Washington Medical Center, Seattle, WA, USA

Objective/context: To describe a distinctive clinical and radiographic pattern of myelopathy following intrathecal chemotherapy. Myelopathy is a rare complication of intrathecal chemotherapy used in the treatment of acute lymphoblastic leukemia (ALL). We present a 42-year-old female with T-cell ALL who developed a myelopathy primarily involving the dorsal columns.

Method: Case report and literature review.

Findings: Within 24 hours of an injection of intrathecal methotrexate, cytarabine, and hydrocortisone, the patient developed ascending lower limb numbness and balance difficulties progressing to the inability to ambulate. Clinical examination showed profound loss of lower limb proprioception and light touch sensation below T5, mild proximal limb weakness, but preserved pinprick and temperature sensation with intact bowel and bladder function. Initial thoracic and lumbar spine magnetic resonance imaging (MRI) at 1 week revealed no abnormalities. However, repeat imaging at 6 weeks showed abnormal signal in the posterior cord with sparing of the anterior and lateral columns, diffusely involving the lower cervical cord through the conus medullaris. Dermatome somatosensory-evoked potential (DSEP) conduction abnormalities were consistent with thoracic myelopathy. An empiric trial of high-dose intravenous corticosteroids during inpatient rehabilitation more than 6 weeks later produced no significant clinical improvement.

Conclusion/clinical relevance: Preferential and persistent dorsal column myelopathy is a distinctive clinical and radiographic presentation of a rare complication of intrathecal chemotherapy. The MRI abnormalities were initially absent, but evolved to consist of multi-level spinal cord T2 and STIR hyperintensity with regional gadolinium enhancement. DSEPs more accurately reflected the clinical level of spinal cord dysfunction.

Keywords: Chemotherapy, Intrathecal injections, Leukemia, Myelopathy, Spinal cord injuries, Somatosensory-evoked potential

Introduction

T-cell acute lymphoblastic leukemia (ALL) is a rare malignancy with an age-adjusted United States incidence of 1.5 per 100 000 people,¹ and is expected to account for 6050 of the projected 1.6 million new cancer diagnoses in the United States in 2012.² Primarily affecting children aged 2–5 years and adults over age 50 years, ALL is characterized by excessive and abnormal lymphocyte production in the bone

marrow, and is known for its rapid progression in the absence of therapy. At the time of diagnosis, central nervous system (CNS) involvement is identified in less than 10% of adults with ALL. However, this incidence is likely underestimated.³ The pathogenesis is thought to be related to leptomeningeal disease and is described in five phases:⁴

1. Destruction of the arachnoid trabeculae and penetration of the blood–brain barrier.
2. Cranial nerve palsies secondary to compression ischemia and direct nerve fiber infiltration.
3. Obliteration of cerebrospinal fluid channels leading to hydrocephalus.

Correspondence to: Maria R. Reyes, Department of Rehabilitation Medicine, University of Washington School of Medicine, 1959 NE Pacific Street, Box 356490, Seattle, WA 98199, USA. Email: mrreyes@u.washington.edu

4. Hypoperfusion encephalopathy related to arachnoid blood vessel compression.
5. Destruction of the pial–glial membrane and direct infiltration of neural tissue.

While treatment is fairly successful in children, achieving remission in adults has been a greater challenge, with a long-term survival rate of only 40%.¹ Therapy involves multi-agent systemic chemotherapy combined with CNS prophylaxis, usually consisting of intrathecal (IT) chemotherapy and craniospinal radiation. This approach has resulted in high rates of complete remission (91%) with a low incidence of CNS relapse (4%).⁵ Systemic chemotherapy is commonly implicated in neurologic dysfunction, especially polyneuropathy. Adverse effects from intrathecal chemotherapy are rare but more severe, including arachnoiditis, leukoencephalopathy, and transient or permanent myelopathy.¹

Clinical presentation

A 42-year-old woman was initially diagnosed with T-cell ALL 18 months prior to this hospital admission, and had received induction and consolidation therapy over 5 months following the diagnosis. Treatment consisted of hyper-CVAD chemotherapeutic regimen (cyclophosphamide, vincristine, doxorubicin) and eight cycles of intrathecal therapy using high-dose methotrexate and cytarabine. Residual mediastinal disease was discovered 8 months after diagnosis, and the patient received radiation therapy with a total dose 3960 cGy to the supraclavicular, hilar, anterior superior mediastinum. Seven months later, recurrent disease was identified in the cerebrospinal fluid and bone marrow. The patient was treated with a course of nelarabine (two cycles) followed several weeks later by two cycles of intrathecal

chemotherapy with methotrexate, cytarabine, and hydrocortisone.

Within 24 hours of the last dose of intrathecal chemotherapy, the patient began to develop ascending, symmetric circumferential numbness in both lower limbs. The symptoms were initially attributed to a prior history of presumed chemotherapy-related peripheral polyneuropathy. However, the sensory deficits progressed over the next week, leading to balance problems requiring initially a walker for ambulation, and later a manual wheelchair for primary mobility.

The clinical examination was remarkable for a profound loss of proprioception, absent even at the hip. There was loss of vibratory sensation to the level of the anterior superior iliac spine. Light touch sensation was impaired below the T5 dermatomal level bilaterally, with preserved pinprick and temperature sensation. Strength was initially preserved, but later in the hospital course the patient developed mild, non-progressive bilateral proximal lower limb weakness. Reflexes were normal in the upper limbs and patella but diminished at the bilateral Achilles tendons. Bowel and bladder function were preserved.

Diagnostic evaluation

Imaging

Initial magnetic resonance imaging (MRI) of the thoracic and lumbar spine 1 week after onset of symptoms showed no abnormalities related to the spinal cord or nerve roots (Fig. 1). Nerve conduction studies showed minimally prolonged sural sensory latencies, likely representing her known pre-existing mild polyneuropathy. Cerebrospinal fluid testing and serum laboratories,

Figure 1 Initial sagittal MR image of thoracic spine at 1 week post-symptom onset. No cord abnormality detected in both T2-weighted (A) and STIR imaging (B).

including serum B12 levels, were normal; there was no evidence for megaloblastic anemia.

Six weeks later, thoracic and lumbar spine MRI was repeated (Figs. 2–4) and demonstrated abnormal high T2 and STIR signal in the posterior cord, primarily localized to the posterior columns but with some involvement of the central cord. These signal changes were diffuse, and involved the visualized lower cervical segments through the entire thoracolumbar spinal cord, to the level of the conus medullaris. Gadolinium enhancement was observed from T11 to the conus (Fig. 5). MR angiography of the thoracic spine did not reveal any vascular anomaly.

Electrodiagnostic studies

Nerve conduction studies conducted 2 weeks after symptom onset showed normal fibular (peroneal), tibial, and median nerve F-wave latency. Tibial somatosensory-evoked potential (SEP) studies performed at 6 weeks following the onset of sensory loss recorded normal responses at the popliteal fossa, but absent responses proximally. Dermatome SEP (DSEP) studies 10 days later yielded normal cortical responses

with stimulation at the T2 dermatome bilaterally, but absent cortical responses with stimulation of the T4 and T6 dermatomes bilaterally. Unlike the MRI, the DSEP findings demonstrated better correlation with the clinical sensory examination.

Treatment/clinical course

The patient elected to proceed with a matched, unrelated peripheral blood stem cell transplant 3 weeks following the onset of her sensory loss. In preparation for this, she received total-body irradiation totaling 12 Gy. It was noted that her previous total radiation exposure to her spinal cord was a mean dose of 1872.4 cGy and maximum dose of 4221.9 cGy. During her craniospinal radiation, the spinal cord was blocked from receiving any further radiation. She received an additional two courses of intrathecal methotrexate uneventfully.

Six weeks after symptom onset, the patient was transferred to an inpatient rehabilitation unit. In addition to standard functional retraining, strategies to improve proprioceptive function were utilized, including the use of ankle weights, ace-wrapping, gait training, and

Figure 2 Sagittal T2-weighted (A) and STIR (B) MR images of the thoracic spine at 6 weeks after symptom onset. The arrows identify the intramedullary signal abnormality.

Figure 3 Sagittal MR image of the lumbar spine at 6 weeks after symptom onset. Arrows identify the intramedullary signal abnormality to the level of the conus in the T2-weighted (A) and STIR images (B).

Figure 4 MR axial STIR image of lumbar (A) and T2-weighted thoracic (B) spine 6 weeks after symptom onset. The arrow localizes the posterior spinal cord lesion.

biofeedback. These treatments were successful in improving functional independence with adapted mobility and daily living skills, but failed to produce clinically detectable improvement in lower limb sensation or motor control.

At nearly 7 weeks following symptom onset, an empiric trial of high-dose steroids – consisting of a

5-day course of intravenous methylprednisolone – failed to result in any measurable change in the patient's strength or sensory examination.

No further intrathecal chemotherapy was administered. By 3.5 months after onset, the profound sensory loss remained stable. The patient reported improved ability to compensate for the gait dysfunction related

Figure 5 Axial contrast-enhanced T1-weighted MR images of the thoracic (A) and lumbar (B) spine at 6 weeks after symptom onset. The arrows localize the posterior spinal cord lesion and contrast enhancement.

to the proprioceptive loss, but continued to require use of a walker for safety during household-level ambulation. She expired 11 months following the onset of myelopathy, due to complications related to her ALL.

Discussion

A well-described neurologic sequela of systemic cancer therapy is peripheral polyneuropathy related to specific chemotherapy regimens. This patient's description of sensory loss in the fingers and toes during the initial chemotherapy treatment regimen is consistent with a previous non-progressive polyneuropathy, likely related to vincristine.

Myelopathy resulting from IT chemotherapy with methotrexate, cytosine arabinoside, and steroids has been described in isolated case reports and case series. The clinical presentation in adults and children ranges from transient paraparesis to complete tetraplegia associated with variable amounts of sensory as well as bowel and bladder dysfunction.⁶⁻⁹ Although the incidence rates for myelopathy following IT chemotherapy have not been described, the occurrence of this entity appears to be highly infrequent. This case demonstrates the acute onset and rapid progression of myelopathy with predominantly dorsal column involvement following intrathecal chemotherapy. The pathophysiology behind this complication remains unclear. Lu *et al.* demonstrated a similar clinical presentation in two patients who had undergone IT chemotherapy. However, in contrast to this case, the symptoms had evolved over months.⁸ Lu *et al.* also noted that the imaging findings associated with the suspected IT chemotherapy-induced myelopathy were similar to those observed in subacute combined degeneration

of the cord, with degeneration of the posterior and lateral columns often attributed to vitamin B₁₂ deficiency. However, in this patient, the serum B₁₂ level was normal. Elevated plasma homocysteine and methylmalonic acid levels are more specific at detecting B₁₂ deficiency,¹⁰ but these levels were not obtained in this patient. No megaloblastic anemia was detected.

Although MRI is the primary diagnostic study used to identify this complication, it is often initially normal.^{9,11} MR abnormalities due to IT chemotherapy are non-specific and include cord swelling, T2 hyperintensity, and contrast enhancement.⁹ Subsequent T2-weighted and STIR MRI images 6 weeks after symptom onset revealed cord signal hyperintensity localized primarily to the dorsal columns.

The MR abnormalities in this case noted extensive longitudinal involvement of the dorsal greater than central spinal cord, from the lower cervical segments down to the conus. However, the patient primarily manifested clinical dysfunction of the dorsal columns in the mid-thoracic spinal cord. The reason for the discrepancy in radiographic and physical examination findings is unclear.

DSEPs performed 6 weeks after symptom onset reflected better correlation than MRI with the sensory deficit below T5. A previous study by Vainionpää *et al.*¹² prospectively examined tibial mixed nerve SEPs in children treated with IT chemotherapy, and documented conduction delay when compared to age- and height-matched controls, even in children who were clinically asymptomatic. These findings suggest that SEPs may be a more sensitive test for detecting sub-clinical or evolving myelopathy following intrathecal

chemotherapy. Further studies would be needed to assess this possibility.

To explore other potential causes for spinal cord dysfunction in this case, we considered possible contributions from the prior radiation exposure, nelarabine therapy, and the possibility of ischemic myelopathy.

The patient had received mediastinal radiation therapy 7 months prior to symptom onset. This is within the timeframe for development and manifestation of radiation myelopathy, which rarely occurs before 6 months post-exposure.⁹ However, there have been no reports of radiation myelopathy below doses of 4500 cGy, which is greater than the level of exposure for this patient.¹³

Nelarabine, a purine nucleoside analog, has been approved for use in refractory T-cell ALL since 2005. The potential for neurotoxicity has been one of the greatest concerns with nelarabine use. Most commonly, adverse neurologic effects include somnolence and gradual onset of peripheral neuropathy.¹¹ Although the acuity and severity of our patient's symptoms were not consistent with nelarabine toxicity, it is unclear as to whether the use of nelarabine contributed to greater vulnerability to IT chemotherapy, and therefore resulted in a cumulative myelopathic effect.

Diffuse or longitudinal MRI cord signal abnormalities, particularly evident on T2-weighted imaging, can be seen with ischemic injuries, but can also be seen with inflammatory, demyelinating, or infectious disease, traumatic or compressive lesions, tumor, or vasogenic edema of the spinal cord.^{14–17} The patient's MRI and clinical presentation were inconsistent with CNS demyelinating disease or invasive tumor. The time course of the patient's symptom development could be consistent with the development of syringomyelia or hydromyelia; however, MRI findings at 6 weeks showed no evidence of syrinx formation. No vascular anomaly of the thoracic cord, acute traumatic or infectious etiology was identified.

Spinal cord infarctions have been associated with aortic disease or surgery, trauma, vertebral artery dissection/atherosclerosis/stenosis, hypotension, cocaine misuse, fibrocartilaginous embolism, infrarenal aortic aneurysmal repair, vasculitis, and prothrombotic state.^{14–16,18} Toxic etiology has not been a known association. However, the majority of cases of spinal cord infarction cannot be clearly attributed to a specific etiology.^{15,17} The range of associated conditions, variable radiographic and clinical presentation, and the often normal initial MRI can confound and delay the acute diagnosis of spinal cord ischemia. Follow-up MRI is usually confirmatory.^{14,15,18,19}

The pattern of primarily bilateral posterior column abnormality would specifically implicate ischemia in the territory of both posterior spinal arteries, a highly infrequent diagnosis versus the more commonly expected anterior spinal artery syndrome, due to the former's bilateral occurrence and extensive vascular anastomotic network. The MRI and clinical features of this case are similar to those described in association with posterior spinal artery syndrome.^{14–16,18} Clinical features include acute loss of proprioceptive function associated with variable amounts of motor and superficial sensory loss. MRI features include symmetric T2-weighted hyperintensities in the dorsal spinal cord. Sagittal T2-weighted MR imaging assisted in identifying the level of the lesion, while the pattern of abnormalities on the axial images may assist in localizing the vascular lesion.^{15,17}

The temporal association between the symptom onset and the administration of intrathecal chemotherapy suggests a causal relationship. However, we can neither implicate nor completely exclude ischemia as the primary or contributing mechanism to this presentation. No hypotensive episodes occurred with the injection, and the patient had no history of vascular risk factors, or prior thrombotic event. No epidural or cord hemorrhage was noted.

One study suggests a potential mechanism for direct drug toxicity resulting in myelopathy in animal subjects. Burch *et al.* studied patterns of penetration by labeled methotrexate and cytarabine administered into the intrathecal space of rabbits, administered by lumbar puncture or by intraventricular injection. This study demonstrated drug penetration into an extensive section of spinal cord tissue, involving >96% of the total spinal cord area within 1 hour of administration by lumbar puncture, with the greatest drug concentration involving the substantia gelatinosa and peripheral white matter of the spinal cord.²⁰

Currently, no pharmacologic intervention has been reported as beneficial in reversing or diminishing myelopathy associated with IT chemotherapy. A trial of high-dose intravenous corticosteroids administered 7 weeks after the onset of symptoms produced no change in clinical examination. Despite the relative strength preservation, the patient's sensory deficits were significant enough to impair ambulation. Once transferred to the rehabilitation unit, the treatment focused on developing adaptive strategies to compensate for the proprioceptive and light touch impairments. These were successful in improving functional independence prior to discharge. However, clinical reassessment 3 months later showed no further improvement in proprioception.

Conclusion

The preferential and profound dorsal column involvement and associated proprioceptive loss in this case is a distinctive presentation of myelopathy likely resulting from intrathecal chemotherapy treatment for ALL, and was associated with marked functional consequences. Although a very rarely identified complication of intrathecal chemotherapy, the diagnosis of myelopathy should be considered in any patient with motor or sensory deficits following administration of intrathecal chemotherapy. This case demonstrates that even individuals who have previously tolerated the same IT chemotherapy regimens without complications may be susceptible. The mechanism for the development of myelopathy following intrathecal chemotherapy is unknown. Serial MRI focusing on T2-weighted and STIR sagittal and axial images, and possibly SEP evaluation, may be useful in the evaluation of this entity. Additional descriptive reports about the clinical, radiographic, and electrodiagnostic presentation of suspected intrathecal chemotherapy-related toxic myelopathy would better define the range of manifestations, most appropriate diagnostic evaluations, and outcomes. Postmortem pathological evaluation of the spinal cord may be helpful at evaluating the mechanism of this unusual spinal cord dysfunction. Exploring the potential role of diffusion-weighted MRI in the early detection of suspected toxic myelopathic complication may be helpful.

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