Case Report

We report a case of cervical and thoracic dorsal column myelopathy in a 41-year-old man with T-cell acute lymphoblastic leukemia (ALL) associated with nelarabine treatment.

He presented with chest pain and was found to have multiple mediastinal masses up to 8 centimeters in diameter. He had a peripheral WBC count of 45,000, more than 80% of which was composed of blasts. He was diagnosed with T-cell ALL expressing CD5, CD7, CD34, CD38, and cytoplasmic CD3 and was terminal deoxynucleotidyl transferase positive. Blasts also contained myeloperoxidase. At the time of initial presentation, a few suspicious cells were noted in the examination of the CSF, but these were later determined to be hema-togones. He was, therefore, treated with standard prophylactic intrathecal methotrexate because of the high risk of relapse for ALL in known sanctuary sites (CNS, testes). At presentation, he had a normal neurologic exam. He was treated then with standard combination chemotherapy along with standard prophylactic dose intrathecal methotrexate.1

After one cycle, his treatment was changed to hyperfractionated cyclophosphamide, coupled with vincristine, doxorubicin, and dexa-methasone (hyperCVAD) at the request of a consulting transplantation physician who thought the patient would be better prepared for an allogeneic transplant after hyperCVAD.2 The patient subsequently received seven cycles of hyperCVAD, receiving seven doses of intrathecal methotrexate during each of the first six courses of hyperCVAD and during the initial induction. Cell counts, protein, and glucose levels were normal at the time of intrathecal installation of methotrexate (Fig 1). Each treatment was delivered through the L4-L5 interspace under fluoroscopic guidance; the patient refused placement of an Ommaya reservoir.

He subsequently received oral 6-mercaptopurine and methotrexate as part of what was to be a 2-year course of maintenance but then relapsed systemically after 4 months. The patient had no neurologic symptoms, and at the time of relapse, there was no CNS involvement. At the time of relapse, an analysis of the patient’s CSF initially suggested the presence of leukemic blasts, but these were later determined to be contaminants from the systemic disease.

Results of cerebrospinal fluid analysis, intrathecal chemotherapy dosage, systemic chemotherapy, and systemic progression of neurotoxicity.

Fig 1.
given one course of daunorubicin, vincristine, prednisone, and L-asparaginase, but he experienced no reduction in disease burden. In preparation for an allogeneic bone marrow transplant, he was then given nelarabine (three cycles of 1500 mg/m² on days 1, 3, and 5 of every 21-day cycle) and one intrathecal installation of “triple therapy,” which included methotrexate, cytarabine, and hydrocortisone.

One month after completion of the last dose of nelarabine and three months after the one intrathecal methotrexate, cytarabine and hydrocortisone treatment dose, he developed left-sided foot drop, loss of sensation in the left lower extremity, and gait ataxia (Fig 1, week 70). Initial magnetic resonance imaging (MRI) without contrast of the cervical, thoracic, and lumbar spine revealed a small contiguous hyperintense T2/fluid-attenuated inversion recovery (FLAIR) lesion limited to the dorsal columns of the thoracic spine from T6 to T12 (Figs 2 and 3; arrow highlights the evolving hyperintensity of the dorsal columns). He was treated with high-dose dexamethasone (24 mg per day in four divided doses) along with cyanocobalamin, folate, and a multivitamin. In anticipation of an upcoming allogeneic bone marrow transplant, dexamethasone was tapered after 10 days. Six weeks after the last cycle of nelarabine (Fig 1, week 72), he developed a frank ascending myelopathy, manifesting as bilateral lower extremity paraplegia, and he became completely insensate to light touch and painful stimuli below the midchest (approximately at the T4-T6 dermatomal level), along with constipation and urinary retention. Eight weeks after the last nelarabine treatment, he developed progressive bilateral upper extremity weakness, limb ataxia, and dystonia (Fig 1, week 74). Repeat MRI of the cervical, thoracic, and lumbar spine with and without contrast revealed an enlarging contiguous nonenhancing hyperintense T2/FLAIR lesion involving the dorsal columns of the cervical and thoracic spine from the foramen magnum to T12 (Figs 4 and 5, arrows); however, no spinal cord expansion was noted. Bone marrow biopsy at this time showed no evidence of ALL.

Throughout his treatment course and subsequent neurologic deterioration, he experienced no cognitive or visual deficits. MRIs of the brain were normal throughout his treatment. After his myelopathy progressed, he was retreated with decadron 24 mg once per day in four divided doses and a 10-day course of plasma exchange (Fig 1, week 72). There was no neurologic improvement. A third MRI of the cervical and thoracic spine obtained 34 days after the onset of symptoms, with and without contrast, revealed an evolving contiguous
partially enhancing further expansive hyperintense T2/FLAIR lesion involving the dorsal columns of the cervical and thoracic spine from the foramen magnum to T12 (Figs 6 and 7, arrows). In summary, then, the radiographic imaging revealed an initial nonenhancing process that started in the dorsal portion of the low thoracic spinal cord (Figs 2 and 3), rapidly expanded within the cord, extended cephalad to involve the entire length of the cord (Figs 4 and 5, sagittal and axial views), eventually becoming a partially enhancing process involving the dorsal columns of the entire cord (Figs 6 and 7, sagittal and axial views), and culminating in subtle enhancement in the cervical spinal cord only. The brain remained uninvolved throughout. The patient had a follow-up lumbar puncture performed with large volume CSF aspiration, obtained specifically for flow cytometry, which showed no evidence of recurrent leukemia in that compartment. Fifty-one days after the onset of neurologic symptoms (Fig 1, week 77), the patient’s flaccid paralysis was complete from the cervical spine distally; repeat scans documented some lessening of the inflammation within the cord 60 days after the onset of paralysis; however, leukocytosis, anemia, and thrombocytopenia evolved. Bone marrow biopsy performed at that time was consistent with a florid recurrence of leukemia. He died several months later.

Discussion

We considered alternative possibilities that might account for a selective dorsal column myelopathy including Foix-Alajouanine syndrome, tapering of corticosteroids, nutritional deficiency, infection, and a paraneoplastic syndrome. The patient had no history of alcohol consumption, drug abuse, or any significant antecedent medical history.

Foix-Alajouanine is a rare cryptogenic necrotic thoracic myelopathy thought to be related to selective impairment in the vascular supply of the dorsal columns; this rare syndrome is unlikely to be related to malignancy or exposure to chemotherapy. The possibility that tapering of corticosteroids could have precipitated in the worsening of his neurologic symptoms was considered; however, there did not appear to be any improvement in his symptoms with reinstatement of corticosteroid therapy. B12, homocysteine, methylmalonic acid, and folate levels were normal.
(relevant laboratory studies are listed in Table 1). HIV and syphilis testing were negative. B6 level was less than 2 mg/mL (normal range, 2.1-21.7); however, it is unlikely that B6 deficiency caused the myelopathy in this case. B6 supplementation was administered at 100 mg per day without improvement. Anti-Hu and anti-Yo antibodies were not detectable in serum, making a paraneoplastic etiology of the myelopathy unlikely. Final CSF sampling (after clinical worsening and after the MRI images shown in Fig 4 were obtained) revealed clear and colorless CSF with 0 RBCs, 1 WBC, glucose 60 mg/dL, protein 169 mg/dL, and negative gram stain and culture.

This is a second case of T-cell ALL associated with severe and irreversible neurologic toxicity in the dorsal columns.6 A rapidly worsening transverse myelopathy associated with nelarabine, a new purine analog, has been reported once previously. In the initial phase I study of nelarabine in children with relapsed T-cell leukemias, cumulative neurotoxicity in the form of hypoesthesias, paresthesias, or peripheral neuropathies was dose-limiting and occurred (1.2 g/m²; 30 and 60 mg/kg).7 In the pivotal study of adults with relapsed T-cell leukemias, there were no grade 4 adverse events involving the CNS.8

Nelarabine is a soluble prodrug of 9-beta-D-arabinofuranosylguanine (ara-G), a novel purine antimetabolite, antineoplastic that preferentially accumulates in T cells. Ara-G is phosphorylated in T cells to ara-G triphosphate, which exerts cytotoxic effects. Animal and in vitro models exist for neurologic toxicity secondary to chronic intrathecal administration of chemotherapy and systemic use of nucleoside analogs.9-10 Mitochondrial damage has been implicated. Direct toxic effects on neuronal cells in vitro by adenosine analogs and nitrous oxide have also been reported. Adenosine has not been reported to damage spinal cord morphology, even with chronic intrathecal administration.11

A rapidly ascending myelopathy has not been associated with other nucleoside analogs other than nelarabine or with chronic intrathecal administration of chemotherapy. CNS leukemia has never been reported to result in selective destruction of the dorsal columns, nor has intrathecal administration of either methotrexate or cytarabine. Clofarabine, which is strikingly similar to nelarabine and which is often used in combination with cytarabine, has only occasionally been associated with severe neurotoxicity.12-13 Neither cladribine, the mainstay of hairy cell leukemia for the last 20 years, nor fludarabine, which is often used for
the treatment of chronic lymphocytic leukemia have been noted to cause myelopathies.\(^{14-15}\) It is possible that a selective destruction of the dorsal columns can be mediated by nelarabine under certain unknown conditions.

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**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**
The author(s) indicated no potential conflicts of interest.

**REFERENCES**

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<th>Table 1. Selected Laboratory Neurologic Studies</th>
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<td><strong>Study</strong></td>
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<tr>
<td>B12</td>
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<td>Oligoclonal banding</td>
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<td>Syphilis (IgG)</td>
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NOTE: Values in parentheses indicate normal laboratory ranges for laboratory studies listed. Abbreviation: IgG, immunoglobulin G.