

Case Report

Background

Dorsal column degeneration has been typically described in B12 deficiency. An unusual case of dorsal column degeneration in a leukemic patient in remission with neurotoxic drug nelarabine is being described.

History and Physical

15-year-old African American male with T-cell ALL on remission status post nelarabine chemotherapy as third line presented with progressive weakness pain and paresthesia starting in lower extremities and spreading to upper extremities. Symptoms commenced from completion of first cycle of nelarabine and progressed to inability to walk with worsening neuropathic pain. Patient further developed in 3-4 weeks zoster rash in trigeminal distribution with altered mental status due to opioid toxicity and encephalopathy.

Neuro exam was suggestive of severe motor & sensory neuropathy with distal greater than proximal in terms of involvement. There were no radicular features and he did not have a sensory level or neurogenic bowel or bladder to suggest cord involvement. Patient had loss of both vibration sense and position sense in lower extremities and distal upper extremities with more preservation of position sense. Imaging was consistent with myelitis involving central and dorsal columns.

He was treated with acyclovir and physical therapy and some improvement was noted clinically in 2 months with regaining ability to stand and barely walk with support. However follow up MRI spine showed progression of lesions with later imaging indicating atrophic changes.

However systemically he developed secondary fungal infection, graft versus host reaction and finally succumbed to his disease.

CSF Studies

Proteins 158, sugar was 35, WBC was 26, with 71% lymphocytes, IGG CSF was 20.5, Varizella Zoster PCR 6,600 copies trending to 300 in a week with no blast cells

Blood studies

B12, folate, MMA, homocysteine, vit E, TSH all were normal.

EMG/NCS

Diffuse axonal more than demyelinating neuropathy

Imaging

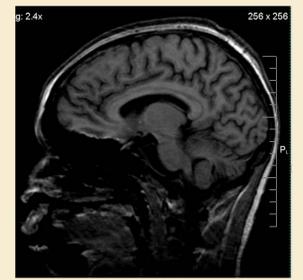
MRI spine - subtle diffuse symmetric enhancement of the nerve roots of cauda equina anterior > posterior with no nodularity
 MRI spine (6 weeks) - Confluent, mildly expansile nonenhancing lesion of entire length of spinal cord with central and dorsal columns involved.

MRI spine (2 months) progression of lesions with slightly more enhancement in posterior columns
 MRI spine (5 months) atrophy of spinal cord, T2 hyperintensity of dorsal columns

Brain MRI - some brain atrophy

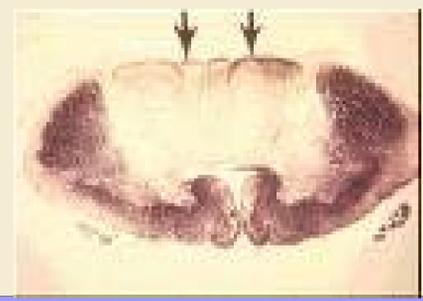
Studies

Brain MRI



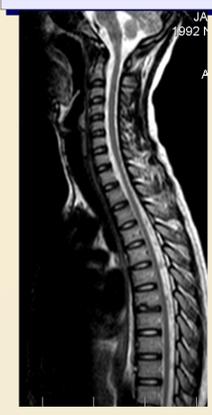
MRI brain - showed volume loss.

Autopsy of spinal cord



Autopsy of spine dorsal column degeneration

MRI 1



MRI 2 T2 / T1 /T1 post



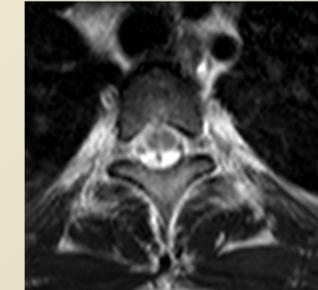
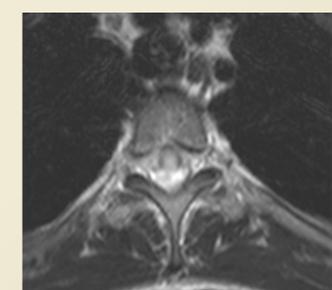
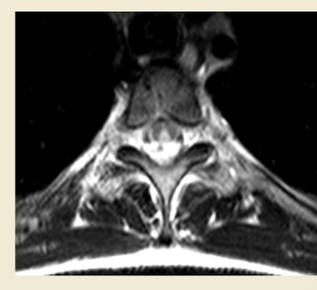
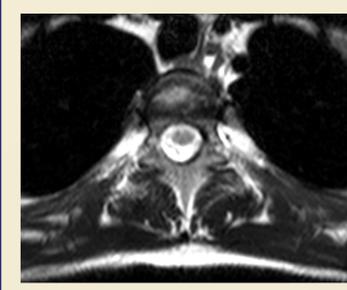
MRI 3



MRI 4



MRI spine series of sagittal and axial views showing no involvement to progressive involvement of dorsal columns with subsequent atrophy of the dorsal columns



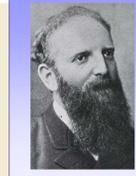
MRI 1

MRI 2

MRI 3

MRI 4

Discussion



Ludwig Lichtheim described subacute combined degeneration of spinal cord called as Lichtheim's disease.

Nelarabine is a second line drug for T-cell acute lymphoblastic leukemia. Nelarabine inhibits DNA synthesis and induces apoptosis. Metabolism is in the liver by methylation.

Nelarabine is neurotoxic, damaging the highly metabolic neuronal cell. Symptoms of central neurotoxicity are somnolence, seizures, dizziness, confusion, and ataxia; symptoms of peripheral neurotoxicity included paresthesias, pain in the extremities, and peripheral neuropathy. A guillian Barre type of ascending paralysis, hypoesthesia, coma, status epilepticus, craniospinal demyelination have all been described. Risk of neurotoxicity is increased with chemotherapy or irradiation.

In this case patient developed progressive leg weakness even with first cycle and worsened over 2-3 months. Though his weakness stabilized and disease achieved remission there was progressive worsening noted in MRI images of spine with atrophic changes. He had zoster myelitis like CSF changes with elevated PCR for zoster virus but the onset and temporal progression was more suggestive of drug toxicity. CNS leukaemia was unlikely as he remained in remission with no CSF blast cells.

The pattern of predominant posterior column is more difficult to explain. In myeloproferative disorders B12 levels are unreliable. The requirement of methylation for degradation of nelarabine may increase demand for tetrahydrofolate/ methyl cobalamine associated pathways. This might induce a similar type of metabolic insult on dorsal column tracts leading to axonal loss.

Conclusions

- The grave neurotoxicity of the drug should be discussed to all patients planning for such a regime and close follow up for neurological side effects should be practised including EMG/NCS and neuro imaging.
- Alteration of metabolic pathways with the chemotherapy resulting in secondary insults to neural tissue needs to be considered.

Reference:

Buie L.W, Epstein SS, LindleyCM. Nelarabine: A novel purine antimetabolite antineoplastic agent: Clin Ther.2007 Sep;29(9):1887-99.