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NEUROTOXICITY IN A YOUNG PATIENT WITH DIFFUSE LARGE B-CELL LYMPHOMA AFTER FIRST DOSE OF INTRATHECAL TRIPLE THERAPY.

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ABSTRACT:

Background: Intrathecal triple chemotherapy (ITT) including cytarabine arabinoside, methotrexate and glucocorticoids is a standard regimen for prophylaxis and treatment of hematological malignancies, owing to their high proclivity for invasion of the neuraxis. Unfortunately, intrathecal chemotherapy is associated with various neurological adverse effects including seizures, encephalopathy, myelopathy, arachnoiditis and cauda/conus syndrome. We present a case of 33-year-old lady with primary bone diffuse large B-cell lymphoma. She had received 4 cycles of R-CHOP* and later 2 cycles of R-DHAP**. The first dose of ITT was administered along with the last cycle of R-DHAP. On the third day post-ITT, she developed acute bilateral lower limb flaccid paralysis followed by one episode of generalized tonic clonic seizure. Brain and spine imaging revealed diffuse meningeal enhancement with abnormal signal intensity predominantly in central gray matter, extending from C7 to T6 spine. Patient was given methylprednisolone, parenteral folic acid and vitamin B12 replacement, followed by five sessions of intravenous immunoglobulin with no clinical benefit. No further intrathecal chemotherapy was given after the event. Attempts to predict risk factors and treat intrathecal chemotherapy-induced severe neurological adverse effects are largely discouraging.
* Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone
** Rituximab, dexamethasone, high-dose cytarabine and cisplatin

Keywords: Intrathecal triple therapy; Diffuse large B cell lymphoma; Aseptic meningitis; myelopathy; Conus medullaris syndrome; Cauda equina syndrome

INTRODUCTION: Owing to the high proclivity for invasion of the neuraxis by hematological malignancies,[1] intrathecal chemotherapy along with systemic chemotherapy and optional cranial irradiation are standard components for the regime used for prophylaxis and treatment.[2] The intrathecal chemotherapeutics include traditional methotrexate (MTX) or cytarabine arabinoside (Ara-C) alone or in combination with intrathecal glucocorticoids and contemporary monoclonal antibodies e.g. rituximab and trastuzumab. Considering at least additive, if not synergistic, effects of the MTX and Ara-C together with glucocorticoids,[3-5] various study groups prefer use of conventionally labelled intrathecal triple therapy (ITT) as a preferred regime.[6] Regrettably, intrathecal chemotherapy is associated with well documented neurological adverse effects including headache, visual loss, seizures, aseptic meningitis, pseudotumor cerebri, encephalopathy, leukoencephalopathy, transverse myelopathy, radiculopathy, arachnoiditis and cauda/conus syndrome.[3,7-8] We present a case of a young lady with primary bone diffuse large B-cell lymphoma that developed aseptic meningitis, acute myelopathy, and cauda/conus syndrome after the first dose of ITT.

Case presentation:

A 33-year-old lady presented in our Emergency Department (ED) with an acute onset bilateral lower

limb numbness that progressed to bilateral lower limb weakness within a few hours. It was associated with band-like chest pain, urinary retention and mild headache. Three days prior to presentation, she had received her first prophylactic ITT (Ara-C 50 mg, hydrocortisone 50 mg and MTX 12.5 mg) as a part of diffuse B-cell lymphoma treatment. On arrival, she had an episode of generalized tonic clonic seizure in the hospital, which was aborted with IV diazepam. Five months back, she was first diagnosed with primary diffuse large B-cell lymphoma of bone. It involved pelvic bones, sternum and vertebral column (cervical, dorsal and lumbar vertebrae) without spinal cord or leptomeningeal involvement. Prior to her ITT, she had received four cycles of standard R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) followed by two cycles of R-DHAP chemotherapy (rituximab, dexamethasone, high-dose cytarabine and cisplatin). Cerebrospinal fluid (CSF) studies and CSF cytology were unremarkable prior to ITT. On examination, the patient was awake and alert with intact higher mental functions. Cranial nerve examination was unremarkable. Fundus examination revealed normal optic discs bilaterally. There were no signs of meningeal irritation. Motor examination revealed normal tone and power in bilateral upper limbs with Medical Research Council (MRC) grade of 5/5, while the tone was reduced in bilateral lower limbs and power was of MRC grade 0/5. Knee and ankle reflexes were absent with equivocal plantar responses. On sensory examination, all sensation modalities were absent up-to sensory level T4. Abdominal reflex was absent.

Investigations

With an initial impression of disease progression, MRI of the brain and the whole spine with contrast were done. MRI brain revealed diffuse meningeal enhancement while MRI whole spine revealed new longitudinal abnormal signal intensities in the spinal cord, predominantly central gray matter, extending from C7 to T6 levels. These signals were isointense on T1 and hyperintense on T2 (Figure 1) with minimal post contrast enhancement (Figure 2), along with enhancement of the conus medullaris and cauda equina nerve roots (Figure 3). The heterogeneous T1 and T2 signal intensities in cervical, thoracic and lumbar vertebral bodies and left iliac bone with patchy post contrast enhancement suggesting old lymphomatous deposits were also seen, which showed no interval progression of disease.

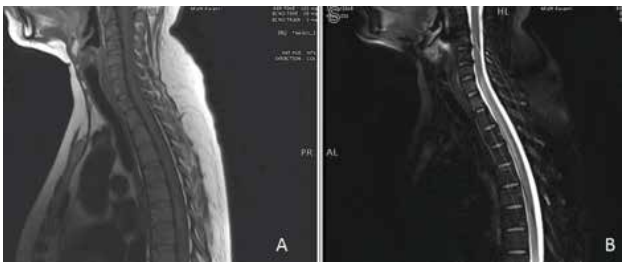

Figure 1. MRI cervical and upper thoracic spine showing isointense signals on T1 (left) and hyperintense on T2 MRI (right)

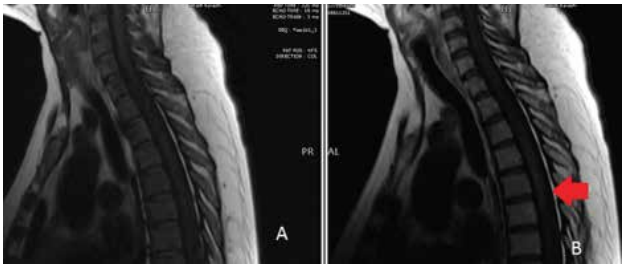

Figure 2. Pre and post contrast T1 MRI cervical and upper thoracic spine showing minimal post contrast enhancement (red arrow)

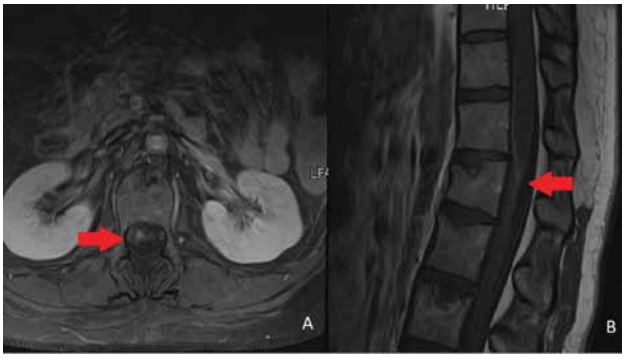

Figure 3. MRI lumbosacral spine showing enhancement of the conus medullaris and cauda equina nerve roots.

Nerve conduction studies and electromyography (NCS/EMG) revealed no definite evidence of large fiber sensory motor polyneuropathy. There was a complete absence of voluntary motor unit potential activation in lower limbs pointing towards a central disorder of motor unit control. Serum B12 and folate levels were within normal range.

CSF examination revealed CSF glucose of 68 mg/dL, protein 294 g/dL and TLC 285/mm3, with polymorphonuclear predominance (95%). Gram and fungal stain were negative. A CSF biofire film array panel for meningitis (DNA/RNA PCR panel) was sent to detect 14 most common pathogens (including

Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, Herpes simplex, Varicella zoster, Cytomegalovirus and Cryptococcus neoformans/gatti) was also negative. CSF and blood culture did not grow any organism. CSF cytology was negative for malignancy.

Treatment and Follow Up

She was initially started on meningitic doses of vancomycin, ceftriaxone and acyclovir, which were later stopped after negative cultures. IV methylprednisolone was also administered for three days (1000 mg/day) as an empirical treatment for myelopathy. For suspicion of methotrexate induced myelitis, leucovorin 15 mg IV every 8 hours and cyanocobalamin 1000 mcg IV once daily were also administered. During the course of treatment, she remained afebrile and alert. Due to lack of response to high-dose steroids, possibility of paraneoplastic myelopathy was considered but serum paraneoplastic antibodies were negative. She was also administered five sessions of intravenous immunoglobulins (IVIG). There was no neurologic improvement and she was discharged with close follow-up. No further intrathecal chemotherapy was given after the event.Our initial differential diagnosis included primary disease progression, paraneoplastic neurotoxicity or chemotherapy induced neurotoxicity. Primary disease progression was excluded as MRI revealed no interval disease progression and two CSF cytology studies were negative for malignancy. Workup and treatment for paraneoplastic neurotoxicity were also unrevealing. Hence, the diagnosis of ITT-induced neurotoxicity i.e. aseptic meningitis, myelopathy and cauda/conus syndrome was made as a diagnosis of exclusion.

Discussion:

In the context of aggressive hematological malignancies, with potential or established central nervous system invasion, chemotherapy-induced neurotoxicity poses potential diagnostic confusion with disease advancement. The concern of disease progression compels a physician to continue or upgrade antineoplastic drugs. At the same time there is risk of irreversible self-harm by the chemotherapy. Predictable risk factors for intrathecal chemotherapy-induced neurotoxicity still remain to be evaluated. Few documented risk factors include intrathecal MTX dose of 50 mg or higher, repeat intrathecal injection within a week, concurrent systemic chemotherapy, cranial irradiation and active CNS disease.[7,9]

Numerous mechanisms for non-leukemic neurotoxicity have been postulated, varying from direct toxicity/irritation by chemotherapeutics to neuropraxia secondary to osmolarity changes.[10] While cytarabine arabinoside directly hampers DNA synthesis of tumor cells by inhibiting DNA polymerase, methotrexate targets the same indirectly by inhibiting folic acid enzymatic pathways.[7] The exact mechanism of cytarabine neurotoxicity is unknown, Both cytarabine and its metabolites can cause neurotoxicity through a DNA synthesis-independent process since adult neurons are postmitotic.[11] Immune-mediated mechanism by cytarabine might be also involved.[12] Intrathecal methotrexate depletes local active tetrahydrofolate synthesis, leading to methylcobalamin and ultimately S-Adenosyl Methionine deficiency, an indispensable requirement of myelin production.[13] It results in central nervous system demyelination, which is morphologically similar to that of subacute combined degeneration of the spinal cord seen in vitamin B12 deficiency.[14] Finally, such rare but devastating adverse effects in the presence of wide variety of dosages, preservative compositions, dilutions, timings and preparation protocols point toward potential of idiosyncratic reactions and individual susceptibility threshold to toxic effects of intrathecal chemotherapy.[7] Classically, intrathecal chemotherapy-induced myelopathy has been reported to affect predominantly posterior-lateral column.[10,14,15] However, exceptions are not unusual and MRI findings often lag behind clinical findings. Imaging may be initially normal or show non-specific findings including cord edema, central gray matter T2 hyperintensity and subtle peripheral or diffuse meningeal enhancement along the cord, conus medullaris and/or cauda equina.[8,14,16] In our case, MRI spine shows predominantly central gray matter involvement similar to only reported case by Counsel P. et al. [16] Enhancement of conus medullaris and cauda equina is also an established finding.[8,14] Due to myelopathy at cervical and thoracic area, cauda/conus syndrome symptoms were likely masked and could not be assessed clinically in our patient until appreciated on MRI of the spine. Although CSF studies were suggestive of acute bacterial meningitis in our patient, the close temporal association of intrathecal chemotherapy and symptoms, unremarkable workup for infection and lack of clinical deterioration after stopping antibiotics in first few days favor aseptic meningitis. CSF studies in chemotherapy-induced chemical meningitis may vary from predominant mononuclear cells to polymorphonuclear reaction with increased proteins. [17] Cachia D. and colleagues reported a case series of 7 patients with intrathecal

chemotherapy-induced myelopathy and cauda/conus syndrome. None of the patients had low CSF glucose on CSF analysis, and only one patient had CSF white cell count >5 while protein was elevated in all subjects. Five out of seven patients also had EMG/NCS done and 3 of them had evidence of concurrent severe polyneuropathy or polyradiculoneuropathy after intrathecal triple therapy, with 2 of the patients also showing contrast enhancement along conus medullaris and cauda equina.[14] In our patient, EMG NCS done within 24 hours, was unrevealing and suggestive of central cause with no evidence of neuropathy in the presence of imaging evidence of enhancement along conus medullaris and cauda equina which could not be clinically assessed due to concurrent myelopathy.

Our patient did not respond to parenteral high dose folic acid and B12 replacement. Although, dextromethorphan, high-dose leucovorin, cyanocobalamin and methionine replacement have been tried with optimistic results in few studies.[13,14] Since further intrathecal chemotherapy is contraindicated in case of severe neurotoxicity, despite a persistently low but definite index of suspicion of disease progression, we did not give further intrathecal chemotherapy after the event. This is in contrast to Cachia. D. et al who continued IT chemotherapy for at least one further cycle in all 7 patients with intrathecal myelopathy. 2 patients out of 7 improved temporarily after discontinuation of chemotherapy and treatment with dextromethorphan. However, they were also given other concurrent treatments (e.g. steroids, IVIG) making it difficult to attribute it to single treatment alone. The treatments for these 7 patients ranged from the use of high dose steroids to intravenous immunoglobulin to radiation therapy with no difference in the outcome as in our case.[14] Though intrathecal chemotherapy-induced aseptic meningitis is usually reversible without any definitive treatment,[17] myelopathy, conus medullaris and cauda equina syndrome are notoriously irreversible with promising response to folic acid metabolite replacements in few cases only and no response to steroids, plasmapharesis and IVIG in various studies.[13,14]

Limitations:

The well admitted fact regarding the diagnostic uncertainty between malignant CNS infiltration and side effect of chemotherapeutics lingers in our study.[8,14] The confusion can probably be offset by considering close temporal association of new symptoms and chemotherapeutic administration, and ruling out alternative differentials using direct/indirect evidences of disease progression. Since the sensitivity of serial CSF cytology approaches 70%, 90% and 95%, [18] two unremarkable CSF cytology studies, done within a week of intrathecal chemotherapy, make malignant infiltration less likely in our case.

Learning Points:

1. Triple intrathecal chemotherapy (ITT) is associated with well-documented neurological adverse effects including aseptic meningitis, pseudotumor cerebri, transverse myelopathy, arachnoiditis and cauda/conus syndrome.
2. Due to variable ITT protocol, predictability of risk factor is difficult, few documented risk factors include intrathecal MTX dose of 50 mg or higher, repeat intrathecal injection within a week, concurrent systemic chemotherapy, cranial irradiation and active CNS disease.
3. Temporal association of new symptoms following intrathecal chemotherapy creates a high-index of suspicion of intrathecal triple therapy associated neurotoxicity but other causes should be excluded first.
4. Treatment options are limited, with variable response to dextromethorphan, leucovorin, cyanocobalamin and methionine replacement in literature.
5. Further intrathecal chemotherapy is contraindicated in case of severe neurotoxicity.

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Dr. Ali Sajjad: Study concept and design, protocol writing, data collection, data analysis,manuscript writing, manuscript review.
Dr. Sajid Hameed: Study concept and design, data collection, data collection, data analysis, manuscript writing, manuscript review.
Dr. Sara Khan: Study concept and design, data analysis, manuscript writing, manuscript review.