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SUBACUTE MYELOPATHY FOLLOWING INTRATHECAL CHEMOTHERAPY ADMINISTRATION.

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ABSTRACT

Methotrexate and cytarabine are intrathecal chemotherapy agents for acute lymphoblastic leukaemia. We report a case of a paediatric patient with late onset CNS relapse of Pre-B acute lymphoblastic leukaemia who developed chemotherapy-induced myelopathy secondary to triple intrathecal chemotherapy (TIT) with its imaging findings. Imaging plays a role in localising abnormality within the spinal cord for diagnosis and aids clinicians to prevent further axonal damage by stopping the causative chemotherapic agents.

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Keywords: Acute lymphoblastic leukemia, Chemotherapy-induced, Intrathecal, Myelopathy, Magnetic resonance imaging.

INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is a malignant disease of the bone marrow, in which proliferation of the early lymphoid cells replace the normal hematopoietic cells. The treatment of childhood central nervous system (CNS) ALL includes intrathecal (IT) chemotherapy of methotrexate (MTX), cytarabine (ARA-C) and dexamethasone.[1] MTX functions by suppressing the DNA synthesis and proliferation of tumour cells by preventing a conversion pathway of dihydrofolate to tetrahydrofolate.[2] As MTX is minimally absorbed through the blood-brain barrier, it is usually administered intrathecally to maximise its CNS anti-cancer effect and minimising systemic toxicity. As for ARA-C, systemic administration causes rapid conversion to inactive metabolite (ARA-U) by cytidine deaminase. Because of low levels of cytidine deaminase in the brain and cerebrospinal fluid (CSF), negligible conversion occurs here,[3] hence, higher drug concentration can be achieved with much lower dosage via intrathecal route. However, complications related to IT chemotherapy have been reported in literature which include arachnoiditis, progressive myelopathy, and leukoencephalopathy.[1,3] We report here such a case in a 12-year old boy with CNS relapse of his pre-B ALL which was treated with IT chemotherapy,

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with subsequent development of IT chemotherapy myelopathy and described the MRI findings related to his myelopathy.

CASE REPORT

AF is a 12-year-old boy diagnosed with Pre-B ALL who was in remission status post-induction chemotherapy. He complained of intermittent mild frontal headache at the end of the fourth cycle of maintenance chemotherapy. Lumbar puncture showed presence of blast cell in CSF however, bone marrow aspirate (BMA) showed remission status. These findings conform to isolated CNS relapse of pre-B ALL.

Induction phase for relapse protocol ALL Relapse Berlin-Frankfurt-Münster (ALL-REZ BFM) was started, which includes triple intrathecal (TIT) chemotherapy (MTX, ARA-C, Dexamethasone). Repeat CSF examination post-induction phase showed remission status. The following maintenance chemotherapy regime included TIT, intravenous (IV) vincristine (VCR), IVI MTX, oral dexamethasone, oral 6 thioguanine, IVI Ifosfamide, daunorubicin, and IM asparaginase.

After the fourth cycle, he developed bilateral foot pain and difficulty in walking, which was initially treated as presumed VCR induced neuropathy. However, whilst waiting for the subsequent chemotherapy block, the neurological symptoms worsened to lower limb weakness, paraesthesia, urinary and faecal incontinence. On examination, temperature and pain sensation were reduced from T6 level downwards. The proprioception and vibration sensations were intact. Babinski sign was positive.

Nerve conduction study showed absent combined motor action potential (CMAP) of bilateral common peroneal nerves and sensory nerve action potential (SNAP) of bilateral sural nerves, consistent with diffuse axonal neuropathy. CSF study showed increased protein of 0.34. No infective cause found from culture and sensitivity. Blood investigation were unremarkable.

An urgent magnetic resonance imaging (MRI) of the brain and spine (1.5T Signa Excite, GE Healthcare, Milwaukee) was performed. MRI brain showed bilateral symmetrical white matter T2W/FLAIR hyperintensity involving both cerebral hemispheres sparing the grey matter and subcortical u-fibres (Figure 1). No restricted diffusion on DWI/ ADC or enhancement post-gadolinium. MRI whole spine showed long segment T2W/ STIR hyperintensity from C5 to T11 levels involving the peripheral white matter and sparing central grey matter. There was also patchy contrast enhancement of the dorsal aspect of the cord from T5 to T10 levels (Figure 2a-d). These features were in-keeping with cervicothoracic dorsal column myelopathy with symmetric leukoencephalopathy.

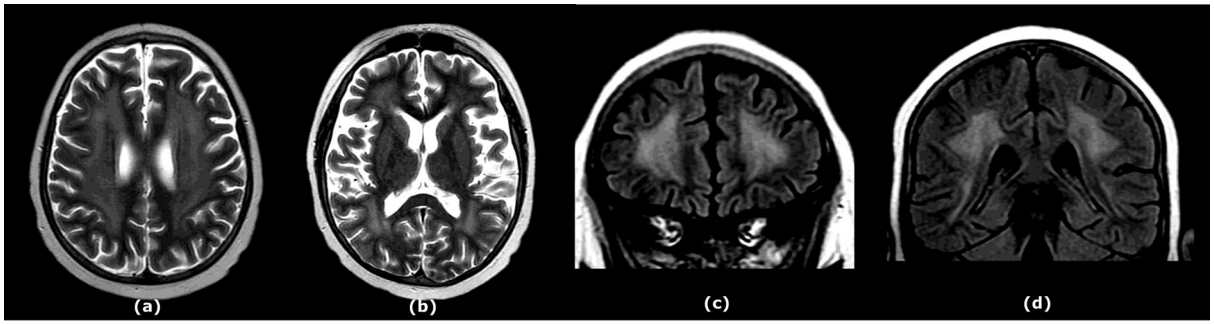

Figure 1: Bilateral symmetrical white matter in axial T2W (a and b) and coronal FLAIR (c and d) hyperintensity involving both cerebral hemispheres sparing the grey matter and subcortical u-fibres.

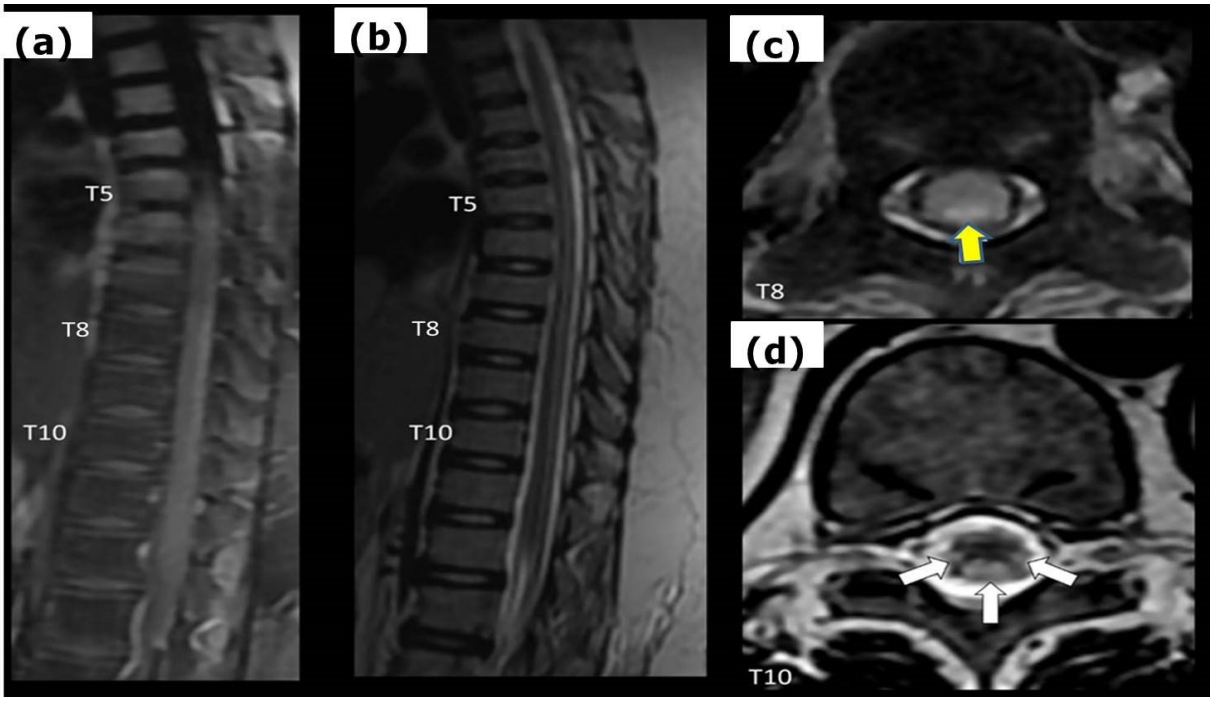

Figure 2: MRI spine in sagittal T1W post-gadolinium (a) with its corresponding axial cut at T8 level (c), which showed patchy contrast enhancement at dorsal spinal cord (Yellow arrow). Sagittal T2W (b) with its corresponding axial cut at T10 level (D) showed dorsal and lateral T2W high signal intensity (White arrows). (Click to enlarge)

In view of these findings, intrathecal chemotherapy was withheld. He was started on oral maintenance therapy instead, which consisted of daily oral 6-mercaptopurine and weekly oral MTX. He was treated supportively under neurorehabilitation team, which included routine physiotherapy and occupational therapy. Unfortunately, patient passed after contracting a pneumonia.

DISCUSSION

Leukoencephalopathy and myelopathy from intrathecal chemotherapy has been reported since its early use in 1960s.[4] Myelopathy from IT chemotherapy with MTX, ARA-C, and steroids has been described in isolated case reports and case series.[5] Clinically, as in our case, patient usually present with bilateral lower limb weakness, paraesthesia and urinary incontinence. There will usually be a sensory level, either at thoracic or lumbar, with ascent of levels in small number of cases causing quadriplegia or death. The preferential dorsal and lateral spinal column involvement with distinctive clinical presentation in this case lead to the diagnosis of myelopathy likely secondary to intrathecal chemotherapy. This also leads to long-term disability for the patient.

In post-mortem study, microvacuolar degeneration of the spinal cord white matter with no inflammatory cells infiltration is the main pathological findings in MTX myelopathy.[2] Axonal swelling and myelin loss has also been reported.[6] Demyelination is usually more prominent at the posterior funiculus, however, there are cases of lateral and anterior funiculi involvement.[7] Furthermore, more severe demyelination occurs at the surface of spinal cord in contact of CSF compared to central cord.[2] This is suggestive of progression of demyelination from the surface to central spinal cord.

Potential neurotoxicity from methotrexate is divided into acute, subacute or late

onset.[3] The most common is acute toxicity, which occurs within days of drug administration. It presents as chemical arachnoiditis with headache, back pain, fever and CSF pleocytosis. Subacute neurotoxicity occurs within weeks or months, as in our case, whereby patient present with either reversible or permanent paraplegia, limb weakness, seizures, cranial nerve palsy, or coma. Late or chronic onset usually occurs in cases that combines intrathecal MTX therapy with central nervous system irradiation.

The theories in pathophysiology of MTX neurotoxicity includes alterations in folate metabolic pathways, adenosine accumulation in the CNS, homocysteine accumulation in CSF with production of sulphur containing excitatory amino acids and impairment of dopamine and serotonin synthesis.[3]

A study by Burch *et al*. suggested a potential mechanism for direct chemotherapy toxicity resulting in myelopathy in animal subjects.[6] The patterns of MTX and ARA-C penetration administered by lumbar puncture into intrathecal space of rabbits demonstrated involvement of extensive spinal cord tissue segment, which encompassed >96% of the total spinal cord area within 1 hour of injection with the greatest drug concentration involving the substantia gelatinosa and peripheral white matter of the spinal cord.[6]

In terms of radiological findings, it is somewhat similar to subacute combined degeneration of the cord in cases of vitamin B12 deficiency with involvement of the dorsal and lateral spinal columns. Vitamin B12 plays a role in the remethylation of homocysteine to methionine and S-adenosylmethionine, which is necessary for methylation of myelin sheath phospholipids.[8] Deficiency in Vitamin B12 causes accumulation of homocysteine as in IT MTX induced myelopathy, hence, the possible explanation for the similarity in imaging findings.

Although MRI of the spine is the primary diagnostic tool to detect myelopathy, it may initially be normal.[5] MR features of spinal cord abnormality due to IT chemotoxicity includes cord swelling, T2W hyperintensity and post-gadolinium enhancement.

There are now reports on the use of dextromethorphan as adjunct therapeutic agent in patients using MTX with neurological symptoms [9] and as prevention against childhood neurotoxicity in ALL cases.[10] Fustino *et al.* reported 7 cases of paediatrics ALL that underwent prophylactic dextromethorphan and none developed neurotoxicity.[10] There was also report of substitution of multiple metabolites of folate for subacute MTX-induced neurotoxicity in an adult.[11] In most cases, patients are subjected to rehabilitation and long term adaptive support for activity of daily living.

CONCLUSION

Though rare, myelopathy should be considered in any patient with motor or sensory deficits following administration of intrathecal chemotherapy. The definitive mechanism for the development of intrathecal chemotherapy induced myelopathy is still unknown. MRI plays a role in localising abnormality within the spinal cord and pinpoint the diagnosis. It also aids clinicians to prevent further axonal damage by stopping the causative chemotherapy.

CONFLICTS OF INTEREST STATEMENT

The authors have no conflicts of interest to declare and consent has been obtained from patient and hospital authority to publish this article.

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