Case Report

Delayed reversible methotrexate-induced leucoencephalopathy in a four-year-old child with acute lymphoblastic leukemia

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ABSTRACT

Intravenous/intrathecal methotrexate (MTX) has been implicated as a major cause of treatment-related neurotoxicity particularly leukoencephalopathy in children with hematological malignancy. We report a 4-year-old boy who presented with apathy and aphasia for 1 day while on the maintenance-phase chemotherapy according to MCP 841 protocol. MRI of brain revealed bilateral symmetrical FLAIR hyperintensities in caudate and putaminal region with FLAIR hypersignal in subcortical U-fiber in left frontal lobe consistent with MTX-induced toxic leucoencephalopathy. There was spontaneous resolution of symptoms within 1 week of onset. So, in Pre-B acute lymphoblastic leukemia patients with subtle neurological deficit, this diagnosis should be kept in mind and further treatment with MTX should be carefully decided.

Key words: Hyperintensities on MR imaging, leukoencephalopathy, methotrexate

INTRODUCTION

The prognosis of childhood acute lymphoblastic leukemia (ALL) has changed considerably in recent years – an important contributing factor being the ability to target the sanctuary site for tumor cells in the central nervous system (CNS). Intravenous/intrathecal methotrexate (MTX) is used as a part of standard treatment protocol due to its ability to cross the blood-brain barrier. But, this drug is also implicated as a major cause of treatment-related neurotoxicity in children with hematological malignancy. Here we report a case of MTX-induced leukoencephalopathy in a 4-year-old child during maintenance phase of MCP-841 protocol for Pre-B ALL. We consider this case to be unique as the imaging findings differ from the usual reported cases.

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CASE REPORT

A 4-year-old male child presented with the complaints of sudden onset generalized apathy and aphasia for the last 1 day, without fever. There was no past history of similar episode. He was a diagnosed patient of Pre-B ALL, on maintenance phase of MCP-841 chemotherapy protocol. He had completed the induction phase 7 months back and was in hematological remission when the maintenance phase was started. The last dose of intrathecal MTX and intravenous vincristine was given 3 weeks back. On initial evaluation, the child was afebrile with stable vital signs. Clinical examination did not reveal pallor, lymphadenopathy, bleeding spots, no palpable organomegaly, or signs of meningeal irritation. CVS and CNS examination was unremarkable. The complete hemogram, liver, and kidney function tests, Arterial blood gas, cerebrospinal fluid study were all within normal limit. No abnormality was detected on CECT-brain. An MRI study revealed bilateral symmetrical FLAIR hyperintensities in caudate and putaminal region [Figure 1] with FLAIR hypersignal in subcortical U-fiber in left frontal lobe [Figure 2]. Suspecting toxic involvement of basal ganglia, other investigations advised were serum ferritin −460 ng/ml, serum ceruloplasmin −28 mg/dl and

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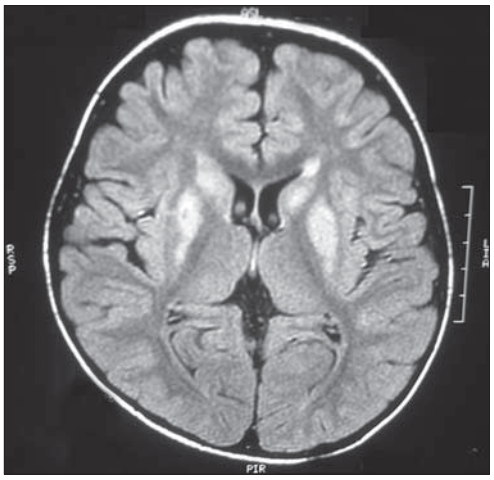

Figure 1: Bilateral symmetrical FLAIR hyperintensities in caudate and putaminal region

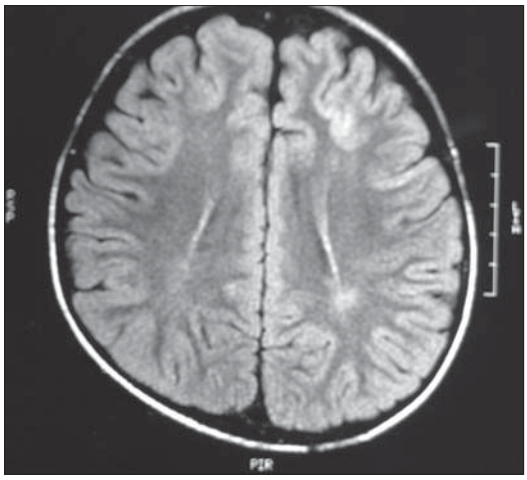

Figure 2: FLAIR hypersignal in subcortical U-fiber in left frontal lobe

24 h urinary copper - 52 mcg/day. The child was put on IV fluids and empirical antibiotic therapy with ceftriaxone. Over the next 48 h he remained afebrile, could take his feed by himself, could communicate with mother in signs and voluntarily regulate his bladder-bowel control. He could obey simple commands. Within 1 week he could verbally communicate as he could before the incident.

DISCUSSION

Leukoencephalopathy is a structural alteration of cerebral white matter affecting the myelin sheath which can result from infection, toxins, and cranial irradiation.[1] Toxic leukoencephalopathy may be considered in a patient with known exposure to toxins causing insult to CNS. Chemotherapeutic drugs like methotrexate, cytarabine, cisplatin, and carmustine are few of such toxins commonly implicated.[2,3] The route of administration influences the outcome. MTX administered intrathecally increases the risk as compared to high-dose intravenous MTX.[2] Concomitant cranial irradiation further increases the toxicity.[4] The suspected etiology of this interaction is increased permeability of the brain tissue to MTX, which increases the concentration of MTX in normal brain tissue.[3] Onset of leukoencephalopathy is variable, with an acute presentation occurring within 12 h of administration of MTX or a delayed presentation occurring several months after completion of therapy.[2] Based on the literature, the time frame for appearance of MTX-induced leukoencephalopathy ranges from immediately to 4 months after administration.[2]

The pathophysiology of MTX-induced leukoencephalopathy is multifactorial. An array of biochemical changes including increased adenosine accumulation, homocysteine elevation, and its excitatory effect on N-Methyl-D-Aspartate (NMDA) receptor and alteration in biopterin metabolism have put forward as a likely etiology.[4] MTX causes a relative excess of homocysteine, which can induce small-vessel vasculopathy. Disturbances of myelin metabolism or inhibition of glucose metabolism, induced by MTX is attributable to a diminished choline to creatine ratio.[5]

The hallmark of MTX-induced leukoencephalopathy is hyperintensities on T2-weighted imaging typically located in the periventricular white matter.[6] For patients with ALL, the incidence of such abnormality is 9-53%.[7] Despite white-matter changes, patients often recover spontaneously from these neurotoxic events, including encephalopathy and stroke-like events.[8]

Our case presented to us 3 weeks following a 12-mg intrathecal MTX received during the maintenance cycle. He had received 12 doses of intrathecal MTX (12 mg each) in the induction phase along with a total of 1800 cGy cranial irradiation in the induction-2 phase of MCP-841 protocol. The maintenance cycle started with oral mercaptopurine daily, and i.v. vincrisine and i.t. MTX at 3-monthly interval. An adequate platelet count and a CT scan of brain ruled out hemorrhagic insult. Clinical examination was not suggestive of CNS infection. The history of intrathecal MTX pointed toward a toxic injury. Our case is unique for its unusual MR findings that show bilateral symmetrical FLAIR hyperintensities in the basal ganglia with FLAIR hypersignal in subcortical U-fiber in left frontal lobe. As McKinney *et al.*, reported, only severe cases involved the basal ganglia in addition to periventricular white matter.[9] But our case had spontaneous resolution of symptoms within 1 week of onset and is presently on follow-up. Manousakis *et al.*,[10] had reported a case of 14-year-old boy with leukemia presenting with numbness and weakness of the left face and hand and ataxia which lasted 20 min and had a history of intrathecal MTX infusion 1 month earlier. MRI of brain showed restricted diffusion at the splenium of the corpus callosum and right frontal white matter.[10] He was diagnosed as delayed reversible

MTX leukoencephalopathy, with transient neurological dysfunction following intrathecal or IV MTX.[10] As our case had a transient neurological deficit with suggestive MRI findings, a provisional diagnosis of delayed MTX-induced leucoencaphalopathy was made.

CONCLUSIONS

Children with Pre-B ALL on chemoradiation may present with subtle neurological deficit due to MTX-induced leukoencephalopathy. Imaging like MRI of brain can detect such toxic CNS insult and further treatment has to be revised with a clinical decision to continue or withhold MTX accordingly. The condition is often transient and reversible but these children should be advised strict follow-up to assess progression of disease.

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