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Spinal cord atrophy and myelomalacia following triple intrathecal chemotherapy in a patient of relapsed acute lymphoblastic leukemia

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ABSTRACT

Paraplegia in a case of leukemia is an uncommon finding. It can be disease related, therapy related, or both. It may or may not be reversible or curable. Here, we are discussing an unusual acute life-threatening, therapy related condition, where triple intrathecal therapy in a relapsed acute lymphoblastic leukemia child led to severe spinal cord atrophy and myelomalacia causing acute paraplegia with urinary retention. Subsequently, the patient developed respiratory failure and succumbed to death. There is very few case reported of this complication. The aim of this case report is to sensitize, the pediatricians and pediatric oncologists about this life-threatening complication of chemotherapy.

Key words: *Acute lymphoblastic leukemia, Intrathecal therapy, Methotrexate, Myelomalacia, Relapse*

Only a few cases of "myelomalacia with spinal cord atrophy" after intrathecal methotrexate and cytosine arabinoside (ara-C) alone or in combination have been reported [1-9]. In general, it is a chronic, cumulative dose-related condition but the onset may be acute also. Paraplegia in the context of malignancy has many potentially different causes and diagnostic techniques or procedures that clarify the diagnosis are helpful to the treatment team. In this paper, we describe a patient in whom acute onset paraplegia developed after the intrathecal administration of combined methotrexate, ara-C, and hydrocortisone. The magnetic resonance imaging (MRI) suggestive of myelomalacia was dramatically abnormal and unique for this condition.

CASE REPORT

A 6-year-old male child diagnosed as acute lymphoblastic leukemia was on treatment according to MCP 841 protocol. On the 17th day of 6th cycle maintenance phase chemotherapy (6-mercaptopurine and weekly methotrexate), he developed severe headache and vomiting. Lumbar puncture was done, and blasts were found in the cerebrospinal fluid (CSF). Bone marrow aspiration and biopsy did not show any blasts. The patient was diagnosed as "early isolated central nervous system relapse."

Triple intrathecal chemotherapy with methotrexate, hydrocortisone, and cytarabine was planned weekly, till three consecutive normal documented CSF examinations. After 5th cycle of intrathecal chemotherapy, the patient developed weakness in both lower limbs with urinary retention. The weakness progressed over 3 days to complete paraplegia with power 0/5, absence of deep tendon reflexes and absent plantar reflex. Sensory perception was normal.

The CSF examination at this time showed no blast cells or pleocytosis and a very mild increase in protein. CSF culture for bacteria, fungus, and tuberculosis produced no growth. CSF viral culture for poliovirus, echovirus, Coxsackie virus, herpes simplex virus, and mumps virus was negative. The previous (4th cycle) CSF examination was also negative for blast. Hypocalcemia was noted (serum calcium 6.2 mg/dl) and corrected by intravenous calcium infusion. MRI spine showed decreased signal intensity in the central portion of lower dorsal and upper lumbar spinal cord suggestive of spinal cord atrophy and myelomalacia. There were neither any leukemic infiltrations of the spinal cord which can explain paraplegia nor any spinal cord hematoma (Figs. 1 and 2).

Subsequently, he developed weakness in both upper limbs with difficulty in respiration. He was intubated and given ventilator support for 7 h. The patient finally succumbed to death as paraplegia progressed to quadriplegia and respiratory failure. The progressively deteriorating condition of the patient did not allow us to do an MRI brain; hence, leukoencephalomalacia could not be confirmed.

DISCUSSION

The possible causes of spinal cord atrophy and myelomalacia are leukemic infiltrates, spinal cord hematoma, transverse myelitis, bacterial or viral meningitis, and hypocalcemia [1-12]. The possible causes of myelomalacia such as leukemic infiltration of spinal cord, transverse myelitis, and spinal cord hematoma were excluded by MRI as well as the absence of pleocytosis in CSF. The paraplegia due to hypocalcemia is of gradual onset and is non-progressive and generally responds to correction of hypocalcemia which was not seen in our case. We finally concluded that patient developed chemotherapy-induced myelopathy, based on specific MRI findings and exclusion of other possible causes.

The syndrome of myelopathy associated with intrathecal administration of chemotherapy has been reported since the introduction of this mode of treatment in the mid-1960s [10]. The clinical syndrome is characterized by leg weakness, urinary retention or incontinence, and paresthesia. Some patients report pain in the hips or low back. Sometimes the weakness and sensory level ascend,

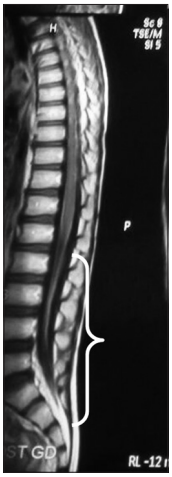

Figure 1: Magnetic resonance imaging (contrast) dorsolumbar region showing spinal cord atrophy

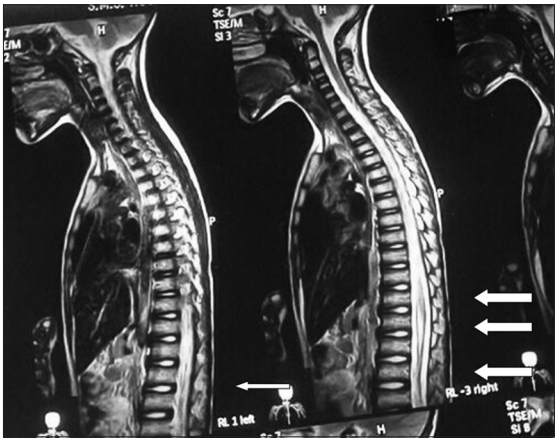

Figure 2: Magnetic resonance imaging (T1) dorsolumbar region showing spinal cord atrophy

resulting in quadriplegia and death [7]. Pain seems to be present in patients with absent reflexes, suggesting nerve root involvement as the cause of this symptom. The symptoms may occur as acute onset (within minutes) to as long as 6 months after intrathecal therapy [9]. Those with immediate paralysis generally lose reflexes and experience pain, and the disease involves the nerve roots [6]. When the onset is delayed, the disease involves the spinal cord [3,4]. The prognosis is variable: Some patients recover completely, whereas others make an incomplete or no recovery. Usually, the maximal involvement is in the thoracic cord [3]. In a systematic analysis of spinal cord disease in the children who died of acute lymphatic leukemia, Price described an entity called "subacute necrotizing leukomyelopathy." This was observed in 20 of 65 spinal cords examined. 75% of the children receiving a cumulative dose of 200 mg or more of intrathecal methotrexate showed white matter disease [11].

The pathogenesis of paraplegia after intrathecal chemotherapy remains obscure. Several hypotheses postulated to explain it. The acute syndrome occurring immediately after injection seems related to the preservative used in the diluents. This complication has not been reported since its cause was recognized. Second, the location of the disease matches the intraspinal penetration of labeled intrathecal methotrexate administered experimentally. Hence, a direct toxic effect of the drug has been postulated [8]. Third, the possible mechanism can be high CSF drug level. The syndrome develops in patients who, for one or another reason have high CSF drug levels. When CSF methotrexate levels were measured prospectively, side effects and paraplegia correlated with the highest CSF level [12]. High levels can also be obtained by more frequent administration; one patient was reported in whom the syndrome developed after 5 consecutive days of intrathecal administration [5]. The lesions may be due to local folate deficiency related to methotrexate penetration into the spinal cord. However, this does not explain how ara-C produces the lesion. The diagnosis of paraplegia occurring in the context of treated malignancy remains difficult.

CONCLUSION

Intrathecal methotrexate and/or cytarabine-induced acute myelomalacia is relatively lesser reported complication from India. These cases are increasing in number as more facilities are available to treat pediatric cancers. We should always keep in mind that these drugs can lead to severe adverse effects which can cost the life of the patient also. A baseline MRI brain and spine should be ordered to each patient before starting the high dose/combination intrathecal chemotherapy.

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