Case Report

High dose Cytarabinearabinoside (Ara-C) as a culprit of leukoencephalopathyin a patient of acute myeloid leukemia

Saxena M[1], Panchal H P[2], Parikh S K[3], Anand A S[2], Patel A A[2], Shah S A[3], Talati S S[2], Gharote M A[1]

ABSTRACT

Leukoencephalopathy is known complication of cancer chemotherapy but cytarabinearabinoside (Ara-C) is only rarely associated with it and that too usually with intrathecal administration or in patients with prior cranial irradiation. Leukoencephalopathy secondary to systemic Ara-C alone is very rare.

Here we report a case of acute myeloid leukaemia treated with three courses of high dose Ara-C who developed acute neurological deterioration seven days after final infusion of third course. It was suggestive of leukoencephalopathy Confirmation was done on MRI Spectroscopy. Patient recovered completely.

Our case report highlights importance of considering chemotherapy induced leukoencephalopathy as an etiology of acute neurologic deterioration following high-dose chemotherapy.

Key words : Acute myeloid leukemia, CytarabineArabinoside, Leukoencephalopathy

Introduction -

Leukoencephalopathy is known complication of cancer chemotherapy. Methotrexate is common offending agent. Cytosine arabinoside (Ara-C) associated leukoencephalopathy is usually seen with intrathecal administration of Ara-C especially when given in combination with methotrexate or in patients who received cranial irradiation. Systemic Ara-C alone is only rarely associated with leukoencephalopathy.

Ara-C as single agent or preferably in combination is among most effective agents in treatment of acute leukemia. High dose Ara-C is standard consolidation therapy of acute myeloid leukemia. It is usually given in dose of 1.5 to 3 gm/m^2 intravenous over 2 hours at interval of 12 hours alternate day with total six doses in a course (total dose - 9 to 18 gm/m^2 in a course) as consolidation for acute myeloid leukaemia. Three to four cycles of high dose Ara-C are required. The reported neurological complications of high dose Ara-C are cerebellar dysfunction, altered mental status and seizure disorder. Here we report a case acute myeloid leukaemia treated with high dose Ara- C as consolidation therapy who developed leukoencephalopathy 7 days after completion of third cycle of high dose Ara-C. The clinical picture, imaging and other investigations highly suggested that Ara-C played central role in the pathogenesis of leukoencephalopathy.

[1]DM Resident, [2]Professor, [3]Associate Professor, Dept. of Medical & Paediatric Oncology, GCRI, Ahemedabad

Address for Correspondence -
Dr. Mohit Saxena
E-mail : dr.mohitsaxena@yahoo.in

Case Report -

A 34 year old male came to our institute in November 2013 with history of febrile illness and pancytopenia diagnosed as acute myeloid leukaemia on basis of bone marrow examination and immunophenotyping. Patient was non-smoker and had no past history of diabetes, hypertension or any cardiovascular co-morbidity. Conventional cytogenetics was normal and fluorescence in situ hybridization (FISH) analysis for inversion 16 and t (8,21) translocation was negative. He was treated with standard induction chemotherapy in form of three days of daunorubicin (60mg/m^2/day) and seven days of Ara-C (100mg/m^2/day) and underwent remission after it. Then he was consolidated with three courses of high dose Ara-C (1.5 gm/m^2 intravenous over 2 hours at interval of 12 hours alternate day on day 1, day 3 and day 5; six doses and

total 9 gm/m^2 in each course). Cumulative dose of Ara-C was 27.7 gm/m^2. Seven days after final infusion of third course, he developed febrile neutropenia, was admitted and treated with intravenous antibiotics and antifungal agents. Eight hours after admission, he developed two episodes of generalized tonic clonic seizure lasting for 15 to 20 seconds 15 minutes apart. His blood pressure was 140/90 mm of Hg. He was confused and disoriented after the episode. However, no focal neurological deficit was seen and rest of neurologic examination including cranial nerves, motor, sensory and cerebellar function was within normal limit. Rest of general physical and systemic examination was unremarkable. Patient was immediately treated with intravenous antiepileptic medication, anti-oedema measures were started and patient was stabilized. He became conscious and oriented after three to four hours of the episode. At that time his Hemoglobin was 7.1g/dl, total leukocyte counts were 700/mm^3 and platelet counts were 15000/mm^3. Non contrast computerized tomography (NCCT scan) of brain was done immediately to rule out intracranial haemorrhage which was normal. Serum biochemistry including renal function, liver function, blood sugar, serum sodium, potassium, calcium and magnesium levels were within normal limit. Patient was sero-negative for human immunodeficiency virus (HIV) infection. The cerebrospinal fluid (CSF) examination showed 3-4 cells/hpf and most of them were lymphocytes. CSF protein and glucose levels were within normal limit. No malignant cell was seen in CSF examination. Magnetic resonance (MR) imaging of brain was done which revealed ill-defined hyperintense areas in subcortical white matter in bilateral fronto-parietal and occipital region without mass effect on T2 weighted images ***(Figure1).***

Serum homocystine level, total lipid profile, two dimensional echocardiography (2-D Echo) and colour doppler study of both carotid arteries were within normal limit. MR spectroscopy examination was done after complete recovery from febrile neutropenia. On MR spectroscopy, prominent choline, reduced creatine, mildly reduced N-acetylaspartate (NAA), prominent lipid and reduced

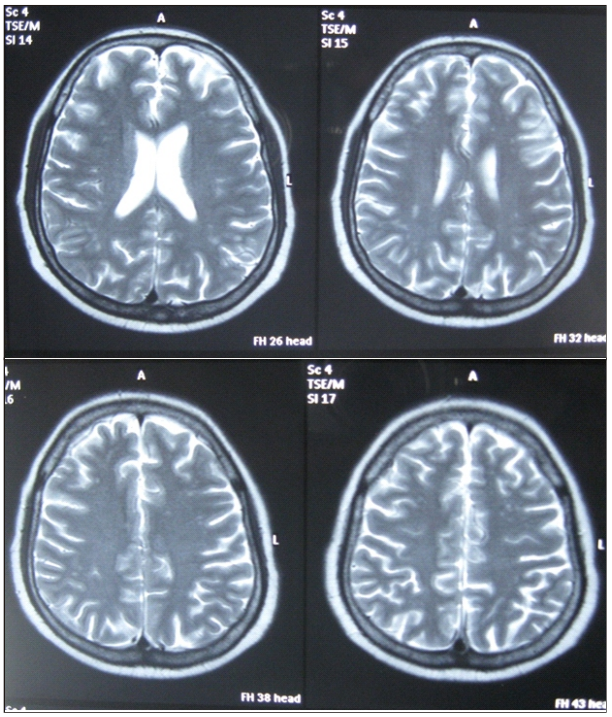

Figure 1 : **MRImaging of brain of patient showing ill-defined T2 hyperintense areas in subcortical white matter in bilateral fronto-parietal & occipital region**

lactate were seen within the above mentioned areas of white matter ***(Figure 2A & 2B).*** These abnormalities were consistent with leukoencephalopathy. Patient did not have any neurological deficit; he recovered completely from episode and discharged on oral antiepileptic medication. After this episode, he was never treated with Ara-C again and he did not develop neurological deterioration again. High dose Ara-C was likely culprit as other causes were excluded.

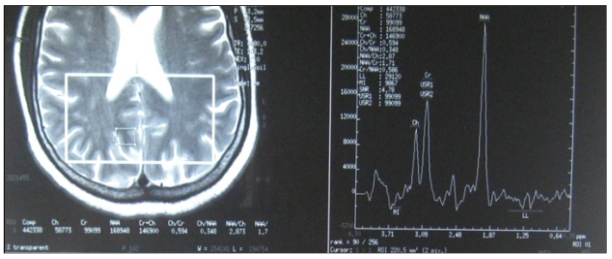

Figure 2A : **MR Spectroscopy focussing abnormal area of brain of patient**

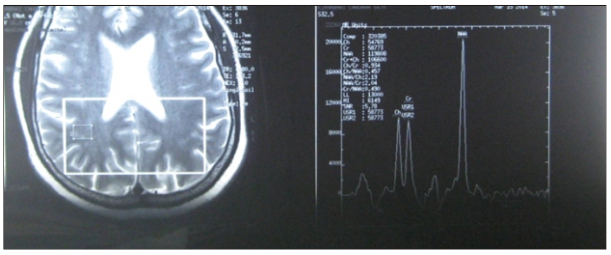

Figure 2B : **MR Spectroscopy of patient showing mildly prominent choline with reduced creatinine with mildly reduced NAA in affected areas of white matter**

Discussion -

Leukoencephalopathy is a neurologic syndrome characterized by headache, seizure, visual disturbance, and altered mental function associated with cerebral edema1. Regions of vasodilatation and vasoconstriction develop, especially in arterial boundary zones, and there is a breakdown of the blood-brain barrier, with focal transudation of the fluid and petechial hemorrhages. The lesions of posterior leukoencephalopathy are best visualised with MR imaging, which, at the height of symptoms, characteristically show diffuse hyperintensity on T2 weighted MR images selectively involving the white matter of posterior parietal and occipital lobe. In patients with extensive involvement other structures such as brain stem, cerebellum, basal ganglia, and frontal lobes can also be affected. The imaging abnormalities are often symmetrical; however, asymmetrical involvement is not unusual. At times the grey matter is also extensively affected. It is often difficult to distinguish leukoencephalopathy from bilateral infarctions of the occipital lobes secondary to top of basilar syndrome. Seizure almost always occurs and the calcarine and paramedian occipital lobe structures are usually spared in leukoencephalopathy which help to differentiate it from infarction.

Now a day, MR spectroscopy is commonly used which shows elevated choline, reduced NAA, reduced creatine and reduced lactate in patients with leukoencephalopathy. It helps in differentiating this condition from infection (reduced to absent NAA, elevated lactate, reduced choline), acute infarction (elevated lactate, elevated choline, reduced NAA, reduced creatine) and infiltration of malignant cells (elevated choline, reduced NAA, reduced creatine, normal or slightly elevated lactate)[2].

Although leukoencephalopathy has been reported primarily in association with hypertension, eclampsia, and administration of immunosuppressive drugs like cyclosporine, tacrolimus, interferon-alpha, the disease is also triggered by various types of cytotoxic chemotherapy drugs, including cytarabine[3]. It is reversible with conservative management like control of blood pressure and withdrawal of offending agent. Many other causes of leukoencephalopathy are also known like sarcoidosis, lupus erythematosus, multiple sclerosis etc. but these are usually progressive in nature. These diseases do not cause reversible neurological damage. Our patients had blood pressure much less than that seen in patients with hypertension inducedleukoencephalopathy. His renal function and serum electrolytes were within normal limit. He was not taking any immunosuppressive drugs. He was seronegtive for HIV infection making JC virus related progressive multifocal leukoencephalopathy unlikely as cause of symptoms. Moreover, normal CSF examination of our patient had ruled out most of infective and autoimmune causes as these conditions usually show CSF pleocytosis and altered CSF protein and glucose levels. MR spectroscopy findings of elevated choline, reduced NAA, reduced creatine and reduced lactate of this patient had ruled out infection, infarction and malignant infiltration as cause of symptoms making high dose Ara-C likely culprit. Temporal course of events was also consistent with Ara-C as likely culprit as patient developed neurological symptoms 7 days after completion of high dose chemotherapy, recovered completely and did not suffer from similar complaints on withdrawal of offending agent (Ara-C). Autoimmune and degenerative causes of leukoencephalopathy are not reversible so these are ruled out.

Ara-C related leukoencephalopathy is usually seen with intrathecal administration of the drug especially in combination with intrathecal

methotrexate or in patients with prior history of cranial irradiation. Systemic therapy alone is very rare to cause this complication so our patient is unique in this regard. In 1986, two patients with acute myelomonocyticleukemia in central nervous system relapse were reported to develop clinical signs and computerized tomographic evidence of leukoencephalopathy five to seven days after intravenous high dose Ara-C therapy, one received 30 gm of intravenous Ara-C with cranial irradiation and intrathecalAra-C for an intracerebralchloroma and leptomeningealleukemia and other patient had received 24 gm of intravenous Ara-C infusion with prior history of intrathecal administration of Ara-C and methotrexate five and one-half months back[4]. Our patient also developed leukoencephalopathy seven days after administration of intravenous high dose Ara-C but never received intrathecal chemotherapy or cranial irradiation. Two decades later, anothercase of reversible posterior leukoencephalopathy syndrome was reported tooccur 21 days after repeat intermediate dose cytarabine therapy (cumulative dose 9.2 gm/m^2) with white matter changes in MRI brain but along with slight leukocytosis in CSF5. In contrast, our patient developed leukoencephalopathy 7 days after high dose Ara-C (cumulative dose 27.7gm/m^2) and no CSF leukocytosis was found.

The details of how cytarabine, as well as the other chemotherapeutic drugs, causes leukoencephalopathy are largely unknown. Initially, it was thought that direct neurotoxicity,by passage of drug across blood-brain barrier at dose greater than 36 g/m^2, was responsible for development of neurologic abnormalities but later, it was postulated that some type of allergic response might have been involved in the development of leukoencephalopathy and CNS toxicity of Ara-C might not limited to high dose regimens of the drug[5]. Risk factors for Ara-C related neurotoxicity were also postulated : creatinine greater than or equal to 1.2 mg/dL, age greater than or equal to 40 years, and serum alkaline phosphatase greater than or equal to 3 x normal[6]. None of these risk factors were seen in our patient and he still developed this complication.

Conclusion -

Knowledge of chemotherapy induced leukoencephalopathy is of great significance in everyday clinical practice. The diagnosis is suggested by cerebral white matter abnormalities seen on T2 weighted MR imaging, and by the presence of headache, altered mental status, seizures, and disturbances of vision. Although intrathecal therapy is the cause in most cases, high dose chemotherapy like Ara-C can also cause this complication. The condition is reversible by conservative measures, control of raised blood pressure, and withdrawal of offending agent.

Conflicts of interest : None Reported by Authors

References :

1. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, et al. A reversible posterior leukoencephalopathy syndrome. N Engl J Med 1996 Feb; 334(8):494500.
2. Ross BD, Colletti P, Lin A : MR spectroscopy of the brain : Neurospectroscopy. in Edelman, Hesselink, Zlatkin & Crues, eds., Clinical Magnetic Resonance Imaging, 3rd edition, Saunders-Elsevier, Philadelphia, 2006, pp 1840-1910.
3. Tam CS, Galanos J, Seymour JF, Pitman AG, Stark RJ, Prince HM. Reversible posterior leukoencephalopathy syndrome complicating cytotoxic chemotherapy for hematology malignancy. Am J Hematol 2004 Sep; 77(1):726.
4. Hwang TL, Yung WK, Lee YY, Borit A, Fields WS. High dose Ara-C related leukoencephalopathy. J Neurooncol 1986; 3(4):335-9.
5. Saito B, Nakamaki T, Nakashima H, Usui T, Hattori N, Kawakami K, et al. Reversible posterior leukoencephalopathy syndrome after repeat intermediate-dose cytarabine chemotherapy in a patient with acute myeloid leukemia. Am J Hematol 2007 Apr; 82(4):304-6.
6. Rubin EH, Andersen JW, Berg DT,Schiffer CA, Mayer RJ, Stone RM.Risk factors for high-dose cytarabine neurotoxicity : an analysis of a cancer and leukemia group B trial in patients with acute myeloid leukemia. J ClinOncol 1992 Jun; 10(6): 948-53.