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Neurotoxic Effects of Cytarabine in a Patient with Acute Myeloblastic Leukemia: A Case Report

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ABSTRACT

Cytarabine is a chemotherapy agent that has various side effects, including neurotoxicity. In the last 15 years, several case reports show various neurotoxic symptoms caused by Cytarabine high doses. The symptoms also vary from mild to severe. Here we report a case of a patient with acute myeloblastic leukemia who developed neurotoxic effects after Cytarabine administration.

A 52-year-old man came with worsened headaches since one week before being admitted to the hospital. The patient also complained of a left eyelid that seemed to close and was hard to open. The patient's last chemotherapy was eight days before the first headache complained. The electroneuromyography showed a prolonged nerve conduction on median, ulnar, tibial nerves suggesting peripheral neuropathy. Patient were treated with steroid injection, analgetic, and vitamin B Complex. After three days of treatment, the symptoms resolved.

Peripheral neuropathy due to cytarabine administration usually affects the sensory compared to motoric. There is no specific therapy for neuropathy, only symptomatic. Symptoms will improve after discontinuation of therapy but do not experience complete healing in some cases.

Keywords: Cytarabine, chemotherapy, neuropathy.

BACKGROUND

Acute myeloblastic leukemia is one of the most common types of leukemia found globally, with an incidence of 3-5 out of 100,000 population. Cytarabine is a chemotherapy agent that provides complete remission in up to 80% of young patients. [1.] Its antimetabolite has various side effects, including gastrointestinal disturbances, hepatotoxicity, and neurotoxicity.[2]

The neurotoxic effects of Cytarabine might cause cerebral dysfunction, cerebellar dysfunction, and peripheral neuropathy. Symptoms of neuropathy due to cytarabine administration that arise consist of symmetrical sensory and motor disturbances, complaints that arise also vary from mild to severe complaints. The most common complaints of peripheral neuropathy are sensory disturbances such as tingling, numbness, burning sensation in the distal extremities. Motor disturbances in the form of weakness in all four extremities, although in lesser amounts when compared to sensory symptoms. Except for intrathecal chemotherapy, symptoms of the autonomic nervous system are rare. Neurotoxic symptoms appeared when the administration of Cytarabine reached 14%, depending on the patient's age (more common in patients aged >60 years), cumulative dose, schedule of chemotherapy drugs, route of chemotherapy administration (more intrathecally), and the presence of impaired liver and kidney function. [2]

In the last 15 years, several case reports show various neurotoxic symptoms

caused by Cytarabine high doses. The symptoms also vary from mild to severe. There is no specific therapy for neuropathy. Symptoms will improve after discontinuation of therapy but do not experience complete healing in some cases.[3]

Here we report a myeloblastic leukemia patient who presents with neuropathy after receiving chemotherapy with Cytarabine

CASE ILLUSTRATION

A 52-year-old man came with headaches one week before being admitted to the hospital. The headache was felt continuously as a throbbing sensation and worsened. The patient also complained of a left eyelid that seemed to close and was hard to open. The patient denied any difficulty in defecating or urinating. The patient was diagnosed with acute myeloblastic leukemia and underwent chemotherapy with a regimen of Daunorubicin and Cytarabine. The patient's last chemotherapy was eight days before the first headache complained.

The patient was moderately ill on physical examination, with a vital sign within normal limits and a visual analog score of 4/10. On physical examination of the eyes, there was lagophthalmos of the left palpebral; no sign of neck stiffness in the neck. On thoracic examination were within normal limits. Abdominal examination was normal. On examination of the extremities, motor and sensory impressions were normal.

Complete blood count, liver function, and renal function tests were within normal limits. The CT scan with contrast (Fig 1.) and MRI of the head (Fig 2.) showed no bleeding, infarction, or masses. We performed electroneuromyography (ENMG), the result showed prolonged nerve conduction on both hands' median and ulnar nerve. Prolonged distal latency on the right peroneus nerve, right tibial nerve, and left tibial nerve, suggesting peripheral neuropathy.

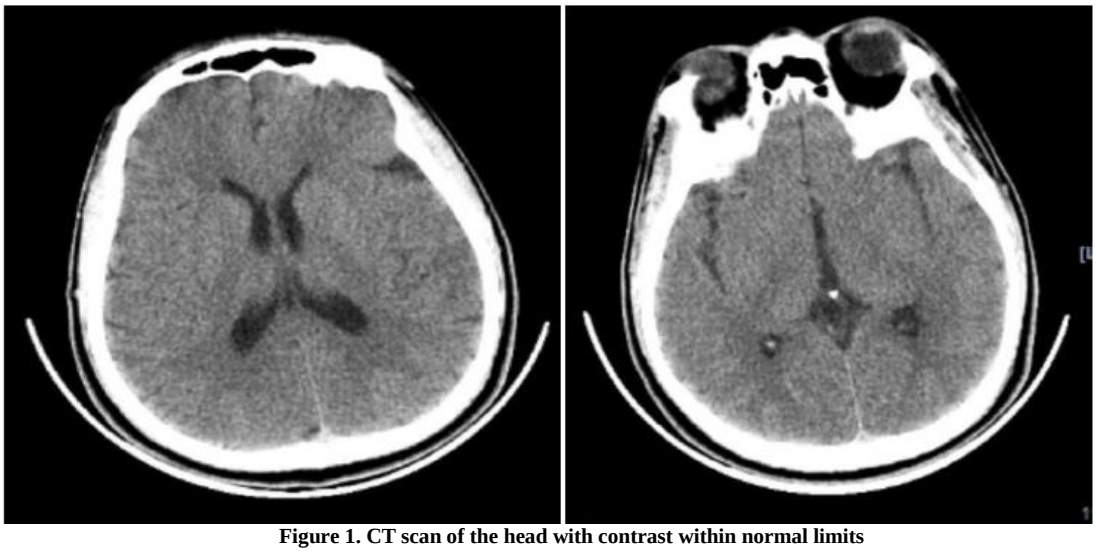

Figure 1. CT scan of the head with contrast within normal limits

Examination of peripheral blood smears did not reveal any young cells (Fig 3.). In contrast, on examination of bone marrow smears (Fig 4.), the impression was hypocellular, M: E ratio = 5:1, decreased erythroid system, myeloid system activity decreased with 2% myeloblast, megakaryocyte system activity decreased slightly.

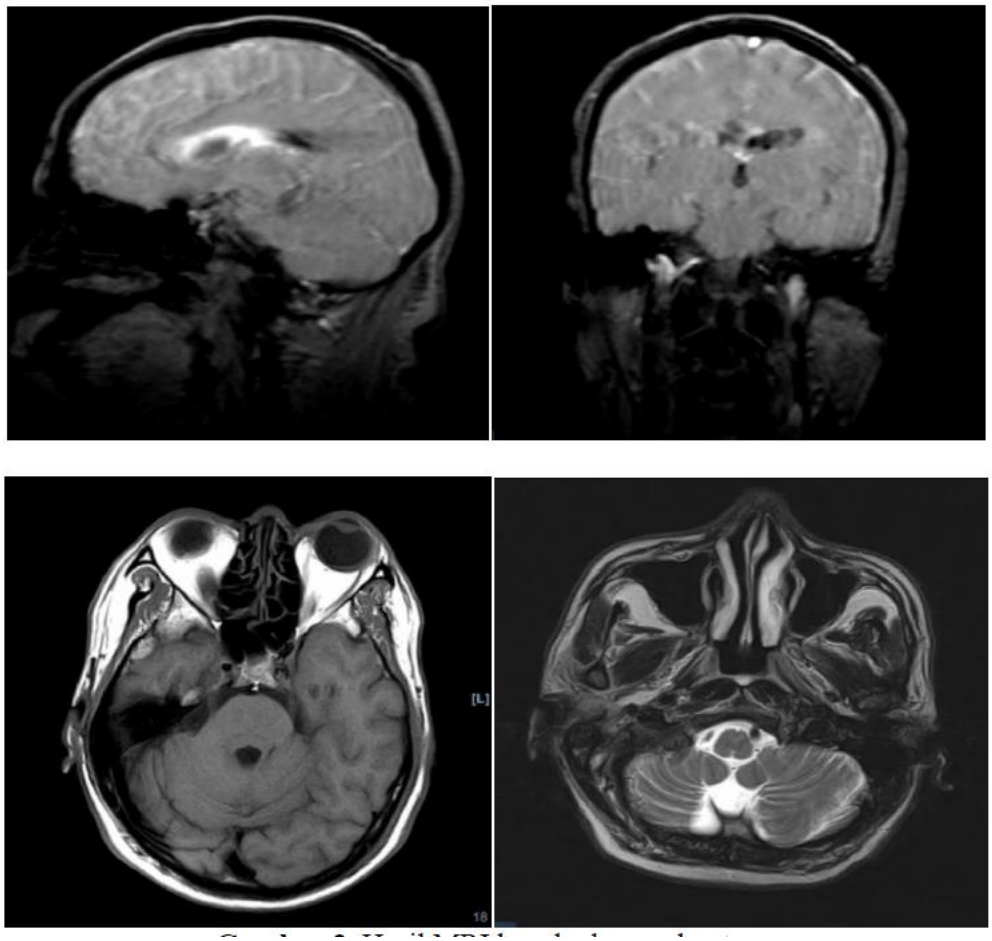

Figure 2. MRI of the head within normal limits

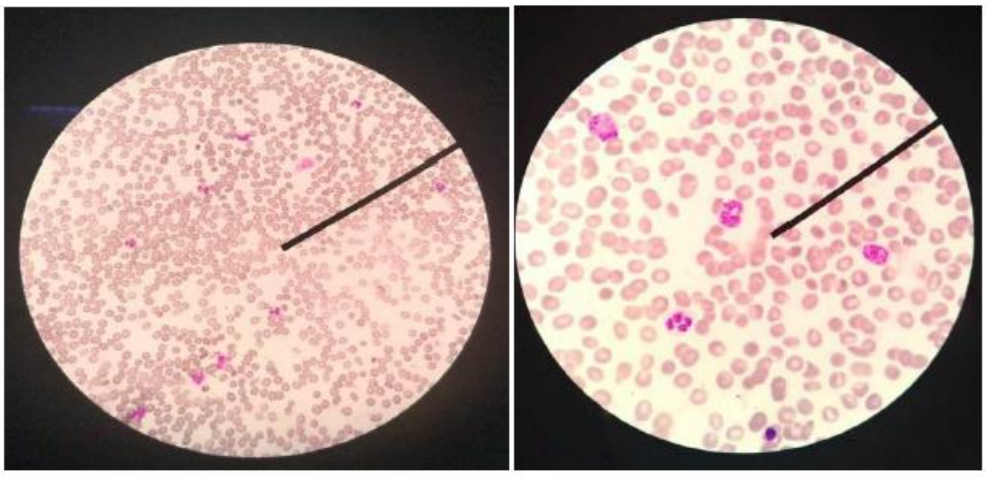

Figure 3. peripheral blood smears did not reveal any young cells

The patient was given Dexamethasone 10 mg every 6 hours IV for three days, vitamin B complex 500 mg every 8 hours, Paracetamol 1000 mg every 8 hours. After three days, the patient's headache felt better, weakness, tingling, and numbness in the hands and feet resolved. Complaints of the left eyelid that seems difficult to open are gone. The patient can take vitamin B complex and paracetamol if the headache appears.

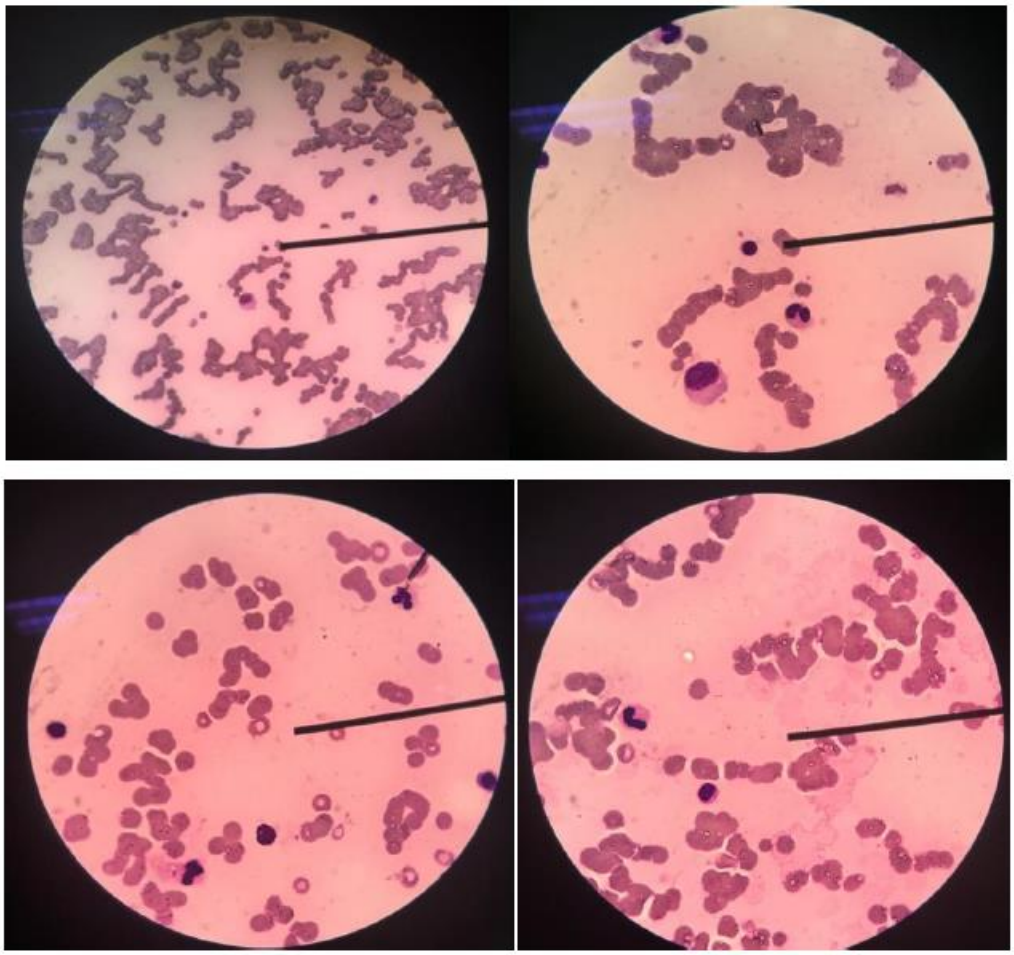

Figure 4. Bone marrow smears showed hypocellular, with M: E ratio = 5:1, decreased erythroid system, myeloid system activity decreased with 2% myeloblast, megakaryocyte system activity decreased slightly.

DISCUSSION

Cytarabine (cytosine arabinoside, Ara-C, 1-β-D arabinofuranosyctosine) is a nucleotide sequence isolated from Cyptothetya Crypta. It was the first trial in 1964 to treat Acute Non-lymphocytic Leukemia (ANL). Since then, Cytarabine has been the drug of choice to treat ANL with a complete response of 25%-45% when used alone and 50-80% in combination with anthracyclines. Cytarabine is now used as a chemotherapeutic agent for ALL and non-Hodgkin's lymphoma.[2] Clinical efficacy of cytarabine administration is highly dependent on the dose and the interval of administration. Various studies reveal that the cytotoxic effect is obtained from the administration by continuous infusion for 5-10 days compared to daily injection.[4]

Cytarabine will be rapidly deaminated into inactive metabolites in circulation by the cytidine deaminase enzyme. Cytidine deaminase is an enzyme with high concentrations in the intestines, liver, and kidneys. The plasma concentrations of Cytarabine decrease biphasically in the first 10-15 minutes after entering the circulation. Furthermore, within 24 hours, about 80% is excreted through the urine.[2]

The recommended conventional dose of Cytarabine is 100-200 mg/m2/day to achieve a plasma concentration of 0.5µmol/L. With this concentration, Cytarabine can diffuse into the intracellular and convert into the active form, namely ara-C triphosphate (ara-CTP), through various enzymatic processes. The mechanism of action, among others, is competition with the normal substrate, deoxycytidine-triphosphate, inhibiting DNA polymerase, inhibiting RNA synthesis. However, the most important mechanism is that Cytarabine directly slows the

elongation of the DNA chain and inhibits the ligation of DNA fragment synthesis.[2] Meanwhile, high dose cytarabine (HIDAC) is thought to overcome cellular resistance by changing the transport of the active ingredient into cells. The most widely used dose is 2-3 grams/m2 in infusion for 2-3 hours and repeated every 12 hours for 12 doses. The plasma concentration will reach one mol/L to achieve higher concentrations than conventional doses with this dose.[5]

After intravenous infusion, Cytarabine is distributed throughout the body, and the concentration in the cerebrospinal fluid will reach 20-50% of the plasma level. Cytarabine will cross the blood-brain barrier through diffusion from the choroid plexus. A clinical trial with mice showed that Cytarabine enters the cerebrospinal fluid through phosphorylation by all tissues that have direct contact with the fluid. This is thought to underlie the highest concentration of ara-CTP in brain cells because most areas are exposed to cerebrospinal fluid. These data are considered the basis for the neurotoxic effect of cytarabine administration.[2]

Some of the neurotoxic symptoms related to the administration of Cytarabine are:

1. Cerebral dysfunction

Seizures are the most common symptom of cerebral dysfunction during intravenous administration. This condition has been reported 13 days after the last dose.[2] Other cerebral dysfunction symptoms range from headaches to severe symptoms such as generalized encephalopathy. On electroencephalography showed a diffuse slowing of wave activity and would improve spontaneously after discontinuation of Cytarabine.[6]

2. Cerebellar dysfunction

An acute cerebellar syndrome is the most common neurotoxic symptom associated with cytarabine administration. Lazarus et al. reported 49 acute cerebellar syndrome events resulting from high doses of Cytarabine (3-4.5 grams/m2/day every 12 hours for 2-8 days), two of which were severe irreversible. Symptoms of cerebellar dysfunction vary by 3-8 days after initiation of Cytarabine. The most common symptoms are dysarthria, dysdiadokinesia, dysmetria, and ataxia.[2] Most of the neurologic dysfunction that occurs improves after five days of discontinuation of Cytarabine, but about 30% are reported to be incomplete and have sequelae. On CT scan, MRI, and cerebrospinal fluid analysis, the results are usually normal.[7]

3. Peripheral Neuropathy

Peripheral neuropathy due to cytarabine administration has not been widely reported. Russell and Powles first reported seven occurrences of peripheral neuropathy due to cytarabine administration, five patients on HIDAC therapy, and two patients on conventional doses. The mean age of the seven patients was 41 years. Symptoms appeared after the total cumulative dose of Cytarabine 600 mg, and the severity of the symptoms was directly proportional to the cumulative dose given. The most severe symptom reported was ascending polyneuropathy (Guillain-Barre-like), which progressed rapidly and left the patient on a ventilator for 34 days. Also reported are patients with bilateral brachial plexopathy manifestations. Symptoms appeared 14 days after the last administration of Cytarabine. On ENMG examination revealed a slowing of the conduction wave velocity indicating a demyelinating polyneuropathy. The pathogenesis of peripheral neuropathy due to cytarabine administration is not fully understood. However, Cytarabine directly affects axonal and myelin metabolism in peripheral nerves.[2]

In this case, the patient was diagnosed with M4 acute myeloblastic leukemia by bone marrow biopsy. Chemotherapy was given Cytarabine with a dose of 100 mg/m2/day (150 mg/day) by continuous infusion for seven days, and daunorubicin 60 mg/m2/day (90 mg/day) given for three days. Eight days after

receiving intravenous Cytarabine, the patient complained of headaches that were getting worse left eyelid that was difficult to open. The patient also complained of weakness, tingling sensation, numbness in both feet and hands.[8]

We found there were symptoms of cerebral dysfunction in the form of headaches and symptoms of peripheral neuropathy, both sensory disturbances characterized by tingling and numbness, and motor disturbances in the form of weakness in both hands and feet. In addition to headaches, other complaints include impaired consciousness, seizures, and the emergence of focal deficits. However, before confirming the diagnosis, it must be ensured that no other causes can cause neurological dysfunction.

To confirm the diagnosis, we performed imaging studies such as a CT scan of the head with contrast and Magnetic Resonance Imaging (MRI) to ensure no bleeding, infarction, or mass. We performed EEG, showing a diffuse slow-wave activity.

Peripheral neuropathy due to cytarabine administration usually affects the sensory compared to motoric. Typical clinical manifestations of sensory disturbances in patients with peripheral neuropathy due to chemotherapy are distal and symmetrical. On ENMG examination, peripheral neuropathy due to chemotherapy showed a slowing of nerve conduction velocity in various peripheral nerves, just as we found in this patient.[9]

There is no specific therapy management of patients with neuropathy due to chemotherapy, only with discontinuation of the chemotherapy regimen and symptomatic therapy.[10] Generally, antidepressant drugs such as amitriptyline, nortriptyline, duloxetine are often used for symptomatic.[11] Antiepileptic drugs such as gabapentin and lamotrigine are widely used because they provide good results without significant side effects.[12]

Vitamin B complex acts as a coenzyme that activates metabolic pathways for neurotransmitter synthesis and neuron membrane synthesis. Schloss et al. found that patients with neuropathy due to chemotherapeutic agents who have given vitamin B complex had a better outcome than those who did not.[12] The neurotoxic effects of Cytarabine will improve with the discontinuation of Cytarabine. In severe cases, especially in cerebellar dysfunction, it usually causes sequelae.[2]

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