Case Report 3

Pseudotumor Cerebriasa Rare Side Effect of Intrathecal Cytarabine

Elias A. Alraqibah MD

Medicine Department, College of Medicine, Qassim University, Kingdom of Saudi Arabia

Abstract

Pseudotumorcerebri (PTC), also known as idiopathic increase in intracranial pressure, is associated with several conditions and as a side effect of many medications.

We are reporting a case of a PTC caused by intrathecalcytarabine as a rare side effect of this medication.

Correspondence:

Elias A. Alraqibah, MD
Medicine of Department,
College of Medicine,
Qassim University,
Kingdom of Saudi Arabia
Mobile: +966554888055
Email: dr.elias@live.com

Introduction

Cytarabine (also known as ara-C) is a pyrimidine analog, classified as an antimetabolite, which is used to treat acute myeloid leukaemia, acute lymphocytic leukaemia, non-Hodgkin lymphoma, and intrathecally for neoplastic meningitis. It is associated with neurotoxic side effects such as transverse myelitis, encephalopathy, acute cerebellar syndrome and aseptic meningitis. [(1)] A rare neurotoxicity side effect of intrathecal cytarabine is PTC. The exact mechanism for this is not fully understood, but this side effect is described in a small number of case reports.[(2, 3)] In our case we will discuss how the patient presented, the diagnosis of PTC and its association with intrathecal cytarabine use.

Case report

A 20-year-old boy presented with fever, weight loss and bony aches. He was diagnosed as a case of precursor-B cell acute lymphoblastic leukemia with CD20 negative, trisomy 21 and his cerebrospinal fluid (CSF) analysis was negative for blasts.

He was started with induction protocol 1423 (Cyclophosphamide, Daunorubicin, Vincristine, Prednisone, L-Asparaginase andintrathecal Methotrexate). On the 28th day, he showed morphologic remission but cytogenetic tests were still positive for trisomy 21.

Post-induction, he received high dose cytarabine-based consolidation. The bone marrow after consolidation attained cytogenetic remission. This was followed by intensifications and maintenance, and he completed 1423 with a total of 8 intrathecal chemotherapies (ITs).

Four months later, he presented to the emergency room complaining of headache, diplopia and blurred vision for 2 weeks. Lumbar puncture (LP) was performed. CSF analysis showed 97% blasts, leading to the confirmation of central nerves system (CNS) relapse. Bone marrow biopsy was negative for systemic relapse, so he was labeled as showing an isolated CNS relapse of acute lymphoblastic leukemia. Magnetic resonant imaging (MRI) of the brain was normal, and he was started on triple intrathecal with folinic acid (FA) salvage chemotherapy, prior to the systemic chemotherapy. He had 3 ITs with cytarabine 50 mg, methotrexate 15 mg and hydrocortisone 50 mg. All CSF analyses were positive for blasts. Then he received another set of 3 ITs (post chemotherapy), in which the last IT CSF analysis was negative for blasts, and his headache improved dramatically during the hospital course.

After recovery of his neutrophil counts, he became febrile, with no identifiable source, and broad spectrum antibiotics were started.

The patient started to complain of headache with no other neurological symptoms. His neurological examination was normal, and the rest of the examination was unremarkable.

LP was done and CSF analysis was normal, with no blasts and culture remaining negative; (LP opening pressure was not done at that time because PTC was not suspected). MRI of the brain showed flattening of the optic nerve-globe junction, minimal papilledema and displacement of the tip of the basilar artery with no evidence of hydrocephalus, mass, structural, or vascular lesion. These findings were suggestive for PTC, The patient was offered to repeat LP to measure the opening pressure but he refused the procedure.

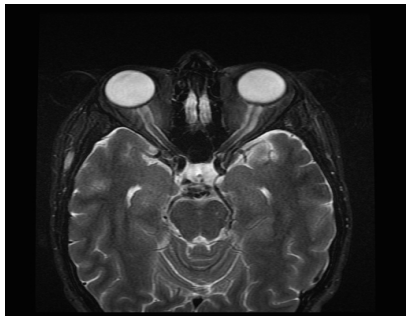

Figure 1: Axial T2 sequence of brain MRI showing significant flattening of optic nerve-globe junction, with expansion of CSF filled peri-optic nerve sheet space.

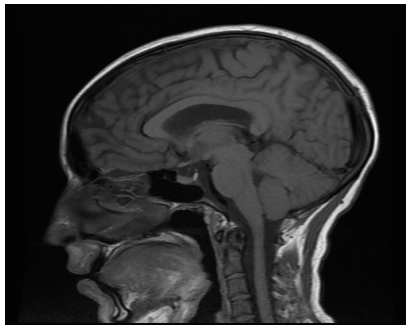

Figure 2: Sagittal T1 sequence of brain MRI showing partial empty sella

Ophthalmology was consulted, and their impression was bilateral optic disc swelling (papilledema). The diagnosis of PTC was made and he was started on Acetazolamide 500 mg BID which was tapered down over time to 250 mg BID and was discharged after his condition stabilized.

After 1 month as follow up in the clinic, his headache had subsided and fundoscopic examination showed normal bilateral optic disc.

Discussion

Pseudotumorcerebri (Idiopathic intracranial hypertension) is a disorder that affects mainly women of child bearing age who are obese. [4] However it can occur in men, non-obese women and in children. [5] The exact pathogenesis of PTC is not fully understood. Association with venous sinus stenosis, obesity-related increased abdominal and intracranial venous pressure; increased cerebrospinal fluid outflow resistance, altered sodium and water retention mechanisms has been described. [6] A number of medications have been associated with development of PTC, mainly; growth hormone, [7] tetracyclines, [8] isotretinoin and to a lesser extent thyroxine, [9] Corticosteroid withdrawal, [10] lithium [11] and nitrofurantoin. [12] Chemotherapeutic agents have also been described as associated with PTC in a small number of case reports, with these agents including all-trans retinoic acid, mitomycin C and cyclosporine. [13]

PTC can be diagnosed based on modified Dandy criteria, which includesymptoms and signs of increased intracranial pressure such as headache, papilledema and visual loss, with no other neurologic abnormalities or change in level of consciousness, increased intracranial pressure (CSF opening pressure above 20 cm H2O in normal-weight individuals and 25 mm H2O in obese individuals) with normal CSF analysis, a neuroimaging study that shows no etiology for intracranial hypertension, and no secondary cause of intracranial hypertension. [14]

PTC has been described as a complication of cytarabine in several case reports. These include the case (in 1999) of an 11 year old boy with acute myeloblastic leukemia who received cytarabine chemotherapy and was diagnosed with PTC secondary to cytarabine, and was treated with cortisone and acetazolamide.[2] The second case was that of a 19 year old female (in 2007) with high CNS risk pre-B ALL, who received 6 IT doses of liposomal cytarabine. The patient was diagnosed with PTC secondary to cytarabine and was treated with ventriculoperitoneal shunt.[3]

Our case is the third case, according to our knowledge from literature review, to describe PTC as a side effect of cytarabine chemotherapy, and the first case in Saudi Arabia.

In our case the diagnosis was made based on symptoms and signs (headache and papilledema), MRI of the brain that excludes structural abnormality with findings suggestive of PTC, CSF analysis excluding the presence of blasts and infectious causes (but opening pressure was not measured), after receiving 6 ITs doses of cytarabine chemotherapy during his hospital stay. We reviewed all medications and associated conditions that may contribute to PTC, and IT cytarabine was the only factor reported to be associated with the diagnosis of PTC.

Conclusion

Cytarabin is a chemotherapeutic agent linked to many central nervous system side effects, and PTC is now being recognized as a side effect of this medication which needs to be suspected, if the clinical scenario is suggestive, in order to avoid serious complications by early diagnosis and proper management.

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