Central Pontine Myelinolysis Without Overt Hyponatremia: Case Report and Literature Review

Olfat Khdair-Ahmad¹, Fatena Ajlouni² and Faiha Bazzeh³*

¹Pediatric Hematology/Oncology Fellow, Department of Pediatrics, King Hussein Cancer Center (KHCC), Amman, Jordan
²Assistant Member, Department of Radiology, King Hussein Cancer Center (KHCC), Amman, Jordan
³Assistant Member, Department of Pediatrics, King Hussein Cancer Center (KHCC), Amman, Jordan

*Corresponding Author: Faiha Bazzeh, Assistant Member, Department of Pediatrics, King Hussein Cancer Center (KHCC), Amman, Jordan.

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Abstract

Central pontine myelinolysis (CPM) is a neurological disorder that is classically linked to rapid correction of hyponatremia. Several cases in literature were described in settings of metabolic or electrolytes derangements (other than hyponatremia) and in conditions where the brain's osmolyte response is limited, like in severe or chronic illness or malnutrition. Hematological malignancies, with eu-natremia or mild hyponatremia, complicated by CPM are very rare; herein we report a case of CPM in a teenager with anaplastic large T-cell lymphoma.

Keywords: CPM; Lymphoma; ODS; Eunatremic; Extrapontine Myelinolysis

Introduction

Central pontine myelinolysis (CPM), which is also known as osmotic demyelination syndrome (ODS), was first described by Adams and colleagues in 1959 as a disease affecting alcoholics and the malnourished. The concept was extended in 1962 with the recognition that lesions can occur outside the pons, so-called extrapontine myelinolysis (EPM). In 1976 a link between these disorders and the rapid correction of sodium in hyponatremic patients was suggested and was substantially established by 1982 [1]. While most patients with rapid correction of hyponatremia don’t develop ODS, several cases were reported in patients with appropriate correction of hyponatremia or even in the absence of hyponatremia. There are 111 reported cases of ODS unrelated to hyponatremia published up to December 2017, as reviewed by Shah., et al. [2] hematological malignancies associated with ODS have been rarely reported. Most cases have mild hyponatremia that was not rapidly corrected. Among lymphoma patients, there are only 10 previously reported cases in English language literature [3-12]: majority had either Hodgkin's disease (n = 4), or diffuse large B-cell lymphoma (n = 3) and are adults. Here we report the first case of ODS associated with anaplastic large T-cell lymphoma in a teenager.

Case Description

A 15-year-old male patient with recent diagnosis of stage III ALK-positive Anaplastic large T-cell lymphoma presented to our emergency department (ED) with persistent vomiting, two weeks into starting chemotherapy (POG- 9315 Protocol with Doxorubicin, Prednisone and Vincristine. Brain computed tomography (CT scan) was performed and revealed focal hypodensity at the central aspect of the pons in keeping with central pontine myelinolysis (Figure 1a). Neurological examination was unremarkable. Serum sodium was normal at day of
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this presentation to ED at (139 mmol/L level), however, review of his chart revealed that his initial serum sodium level at diagnosis, two weeks earlier, was slightly low (132 mmol/L). At that time, it was gradually corrected with maintenance IV fluid of 5% dextrose and 0.9% normal saline at rate of 100 ml/hour. The patient was admitted and his CPM was managed conservatively. three weeks later, he returned to the ED with status epilepticus and persistent vomiting. His sodium level was 138 mmol/L. New brain computed tomography (CT) scan, magnetic resonance imaging (MRI) and magnetic resonance venography (MRV) were performed and confirmed CPM. In addition, they showed new sagittal sinus venous thrombosis (SSVT) (Figure 2) and multiple areas of diffusion restriction at grey-white matter junction in bifrontal, bifrontoparietal and bitemporal lobes, which could be areas of Extrapontine myelinolysis (EPM) or ischemic infarcts related to SSVT. He was started on enoxaparin and levetiracetam with good control of the seizure. The vomiting persists despite being on ondansetron, metoclopramide and lorazepam. Follow up brain CT after a month from the first scan showed significant improvement of the pontine lesion (Figure 1b) which appeared less conspicuous on the follow-up scans.

Discussion

The exact pathophysiology of ODS is not fully understood. It is proposed that it is attributed to rapid correction and increase in serum tonicity in patients with chronic hyponatremia. These patients are believed to have made adaptations to the chronic hypotonicity by losing cellular organic osmoles to the extracellular fluid. The rapid correction of hyponatremia creates an osmotic stress that causes shrinkage of brain cells. The problem with rapid correction of hyponatremia is that the re-accumulation of organic osmoles, lost in response to a
hypertonic environment, is not the same process “in reverse” as their loss in adaptation to chronic hyponatremia. If the rate of rise of tonicity is faster than the rate at which organic osmoles can be synthesized and/or transported into the cell, the cell will shrink. It is perhaps here, that the nutritional status of the patient plays its part, influencing the ability to regenerate organic osmoles. Oligodendrocytes, the myelin-forming cells in the brain, are the most susceptible cells to this form of physical damage [1,13]. In addition, there are other interesting theories, on how oligodendrocytes degenerate, that seem more important in lymphoma patients who have increased levels of serum cytokines and are more susceptible to CPM at milder levels of hyponatremia. For example, Todd., et al. suggested that plasminogen activator, complement proteinase, cytokines, immunoglobulins, and neural proteases released from endothelial cells in response to osmotic stress may lead to oligodendrocyte degeneration [14]. DeLuca GC., et al. showed some evidence of apoptosis in CPM in 2002 [15]. In 2008, Patrick Davey proposed his novel hypothesis for ODS causation by suggesting that a pro-apoptotic drive is activated in states of limited brain osmolyte response such as chronic illness and malignancy which renders these patients susceptible to brain injury from minor osmotic stress [13].

The localization in the basis pontis, which is the central part of the pons, has long been one of the most puzzling aspects of the condition. One hypothesis suggests that this particular area is more vulnerable to stress as it is the region of maximal admixture of grey and white matter elements in the brain. In support of this, the lesions of EPM also seem to be in similar regions of grey-white matter apposition [1].

We conducted a Medline search using the keywords lymphoma, pontine and myelinolysis in order to find other reported cases of lymphoma associated CPM/EPM. Only 10 relevant case reports were published up to October 2019 (Table 1). Out of 10, 4 had Hodgkin’s disease, 3/10 had diffuse large B-cell lymphoma, Seven were adults; 4/7 were older than 53 years. Our patient is the first case of ODS identified in anaplastic large T-cell lymphoma.

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<th>Reference</th>
<th>Clinical history</th>
<th>Serum sodium</th>
<th>Outcome</th>
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<tr>
<td>1  Doni E, Tremolizzo L, Patassini M, Piolelli PE, Ferrarese C, Appollonio I. Asymptomatic central pontine myelinolysis without hyponatremia in diffuse large B cell lymphoma. Neurol Sci. 2016 dec; 37(12):2035-2037. Epub 2016 Aug 3</td>
<td>A 68-year-old female, no history of alcoholism, diagnosed with DLBL. One week after first cycle of R-CHOP, had syncope, MRI done showed incidental CPM</td>
<td>No alterations of sodium, baseline 136 mmol/L only once isolated calcium increase was shown (11.3 mg/dL)</td>
<td>MRI repeated after 3rd cycle and showed almost complete normalization</td>
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<td>2  Carrington JM, Sanchez G, Berkeley J. Central Pontine Myelinolysis with Minimal Hyponatremia in the Setting of AIDS. Case Rep Neurol Med. 2015;2015:421923. doi: 10.1155/2015/421923. Epub 2015 Oct 29.</td>
<td>A 53-year-old man, AIDS. A biopsy of leg lesions confirmed intravascular lymphoma. Before starting chemotherapy, he developed acute dysarthria, ataxia, and delirium and became oriented to name only. MRI showed CPM</td>
<td>minimal hyponatremia of 129 mmol/l which had corrected slowly over six days to 136 mmol/L</td>
<td>His neurological deficits had not improved. His family transferred him to hospice on day 18, where he died within 24 hours</td>
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<td>3  Kawata E, Isa R, Yamaguchi J, Tanba K, Tsutumi Y, Nagakane Y, Uchiyama H, Akaogi T, Kobayashi Y, Uoshima N. Diffuse large B-cell lymphoma presenting with central pontine myelinolysis: a case report. J Med Case Rep. 2015 Jun 5;9:131. doi: 10.1186/s13256-015-0614-8.</td>
<td>A 78-year-old female, incidentally found to have CPM on MRI done to investigate generalized weakness in the absence of neurological symptoms. One month later diagnosed as DLBL.</td>
<td>She had severe hypoalbuminemia of 1.64 g/dL, and mild hyponatremia 132 mmol/L, which was slowly and gradually corrected</td>
<td>Patient was treated with THP-COP regimen, pontine lesion decreased in size after 2nd cycle, and completely resolved after 7th cycle. Patient died of her lymphoma 5 months later</td>
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<th>No.</th>
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<td>4</td>
<td>Zhou AY, Barnes C, Razzaq R.</td>
<td>A 62-year-old patient with DLBL presented with intermittent expressive dysphasia and ‘vague’ episodes, 2 weeks after commencing her first cycle of R-CHOP chemotherapy. MRI showed CPM.</td>
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<td>5</td>
<td>Shah SO, Wang A, Mudambi L, Ghuznvi N, Fekete R.</td>
<td>A 26-year-old Hispanic male with history of alcohol abuse. Pancreatic rare and aggressive natural killer T cell lymphoma. MRI was performed for staging purposes which revealed incidental CPM.</td>
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<td>6</td>
<td>Algahtani HA, Attar AA, Young GB, Shami AM.</td>
<td>A 25-year-old female, newly diagnosed gastric B-cell lymphoma. 20 day after her initial hospitalization discharge, she presented to ER with GCS 11/15 due to hyponatremia 109 mmol/l, induced by excessive water intake. Initial brain MRI was normal. However, rapid correction of sodium resulted in the classical pyramidal and extrapyramidal signs of CPM and EPM that were confirmed by Brain MRI.</td>
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<td>7</td>
<td>Chintagumpala MM, Mahoney DH Jr, McClain K, Dreyer ZE, Fishman MA, Carroll CL, Steuber CP.</td>
<td>12-year-old black male who presented with cervical lymphadenopathy, hepatosplenomegaly of 3 month duration, and recent-onset ataxia, nystagmus, dysmetria and increased tone in all extremities. Hodgkin's disease, stage IVB, was diagnosed. Brain MRI demonstrated CPM.</td>
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<td>8</td>
<td>Loizou LA, Rokos J.</td>
<td>CPM was found histologically in a 28-year-old male, who died with Hodgkin lymphoma. Clinically he had developed progressive peripheral sensory deficit, ataxia, quadriparesis, dysarthria, incontinence and drowsiness. Brain CT showed dilatation of lateral and third ventricle together with low density area in the basis of mid-pons.</td>
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Table 1: Review of previously published cases of lymphoma associated ODS.

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<th>Reference</th>
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<th>Findings</th>
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<td>1. R Martin. “Central pontine and extrapontine myelinolysis: The osmotic demyelination syndrome”. Journal of Neurology, Neurosurgery, and Psychiatry 75.3 (2004): iii22–iii28.</td>
<td>A 7-year-old negro boy, Hodgkin’s disease treated for 12 months with vincristine and chlorambucil 2mg/day, and prednisolone 40mg/day. Then referred to kings county hospital. No specific abnormal neurological findings. His condition continued to deteriorate and died 15 days later. Brain autopsy showed CPM.</td>
<td>Not mentioned by authors. Hepatic involvement was considered important in the pathogenesis of CPM in this child.</td>
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Table 1: Review of previously published cases of lymphoma associated ODS.

ODS: Osmotic Demyelination Syndrome; CPM: Central Pontine Myelinolysis; DLBL: Diffuse Large B Cell Lymphoma; R-CHOP: Rituximab, Cyclophosphamide, Doxorubicin Hydrochloride (Hydroxy daunomycin), Vincristine Sulfate (Oncovin) and Prednisone; MRI: Magnetic Resonance Imaging; AIDS: Acquired Immunodeficiency Syndrome; THP-COP: Tetrahydropropyl Adriamycin, Cyclophosphamide, Vincristine and Prednisone; GCS: Glasgow Coma Scale; EPM: Extrapontine Myelinolysis; ABVD regimen: Adriamycin, Bleomycin, Vinblastine and Dacarbazine.

Similar to most of the reported cases of lymphoma associated CPM/EPM, our patient had mild hyponatremia that wasn't rapidly corrected, and his brain imaging showed gradual improvement and resolution of the changes over the interim.

While status epilepticus can be one of the manifestations of CPM [17] it is likely related to SSVT in his case as it was manifested at time of SSVT detection. Out of the 10 previously reported similar cases, one patient presented with seizure [12], four diagnosed incidentally [3,5,7,11] and 50% had different degrees of the classical presentation of ataxia [4,7-9], dysphagia [6], dysarthria [4] and spastic quadripareisis [8-10].

Conclusion

Lymphoma patients have lower threshold to develop ODS at milder degrees of hyponatremia or even in the absence of hyponatremia, due to proposed limited brain osmolyte response and increased serum cytokines that activate pro-apoptotic state in the brain. In these patients, clinical presentation ranges from being asymptomatic to the full clinical picture of pyramidal and extrapyramidal manifestations of CPM/EPM. The aim of reporting this case is to add to the registry of CPM associated with hematological malignancies cases. It is of paramount importance to report such cases in order to understand the exact mechanism of CPM occurrence in this patients’ population and try to prevent it. Further prospective studies on this vulnerable group of patients are recommended.

Bibliography


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