

Central Diabetes Insipidus in Acute Myeloid Leukemia with Cytogenetic Abnormality of 9q34 Deletion

Majd Farajallah¹, Fatima Alkaabi², Arif Alam³ and Raya Almazrouei^{2,4*}

¹Department of Internal Medicine, Tawam Hospital, Tawam, Al Ain, United Arab Emirates.

²Division of Endocrinology, Tawam Hospital, Tawam, Al Ain, United Arab Emirates.

³Department of Hematology & Oncology, Tawam Hospital, Al Ain, United Arab Emirates.

⁴Internal Medicine. Department, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain. United Arab Emirates.

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*Corresponding author rmazrooei@seha.ae.

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Abstract

Acute myeloid leukemia (AML) is rarely associated with central diabetes insipidus (CDI) with unclear underlying pathophysiological mechanism. The most common cytogenetic abnormality reported in cases of AML associated CDI is Monosomy 7 followed by chromosome 3 abnormalities. We report a 42 years old patient with newly diagnosed AML with 9q34 deletion (ABL1 gene region), who developed symptoms of polyuria and polydipsia with investigation confirming CDI. This case highlights an important association between AML and CDI and to our knowledge this is the first case to report the cytogenetic abnormality of 9q34 deletion (ABL1 gene region) in AML with CDI.

Keywords: Central diabetes insipidus, acute myeloid leukemia, polyuria, polydipsia, cytogenetics

Introduction

Central diabetes insipidus (CDI) is caused by decreased secretion of antidiuretic hormone (ADH) which leads to polydipsia and polyuria. The causes could be genetic, idiopathic or secondary to brain insults like infection, granulomatosis, infiltrative conditions, tumor, post traumatic or post-surgical conditions. CDI is rarely associated with AML and currently about 100 cases reported worldwide. The underlying pathophysiological mechanism remains unclear. Common finding is that majority of these cases are associated with cytogenetic abnormality that involves monosomy 7 and inversion (3)(q21q26) (1). Additionally, overall, the cases are associated with poor treatment response and outcome (2). Here, we describe a young woman diagnosed with AML with cytogenetic abnormality of 9q34 deletion (ABL1 gene) and developed CDI that resolved with the initial response to chemotherapy and unfortunately died of relapsed refractory disease post allogenic hematopoietic stem cell transplantation (alloHSCT). To our knowledge, this is the first reported case of AML with cytogenetic abnormality of 9q34 deletion (ABL1 gene) that is associated with CDI.

Case Report

A 42-year-old woman was referred in November 2020 with one-week history of shortness of breath, chest discomfort and bilateral calf muscle pain. She had no past medical history of significance apart from an uncomplicated cesarean section surgery in March 2020. Physical examination showed that she was febrile (38.4 C), tachycardic (121 beat/min) and tachypneic (24 breath/min) with desaturation to 91% in room air. Rest of the examination revealed cervical lymphadenopathy, splenomegaly and bilateral scattered crackles on chest examination. Initial labs (Table 1) showed leukocytosis with neutrophil predominance, anemia and thrombocytopenia. Peripheral blood film showed 61% blasts cells of intermediate to large size with no Auer rods seen. C-reactive protein was raised up to 317.8 mg/L (normal <5 mg/L). Computed Tomography Pulmonary Angiogram (CTPA) confirmed extensive segmental and subsegmental bilateral pulmonary embolism, bilateral airspace consolidations and pleural effusion. Lower limbs deep venous thrombosis was ruled out with doppler ultrasound. Therefore, the patient was admitted as a case of sepsis secondary to pneumonia and pulmonary embolism with suspicion of underlying acute leukemia for further workup and treatment. Supportive measures, broad spectrum antibiotics (Tazocin continued for total 14 days) and

anticoagulation were started and bone marrow biopsy (BMB) was performed. The low molecular weight heparin (enoxaparin) was initiated and the dose was adjusted periodically based on patient's platelets count (full dose with platelets count >50,000 x10⁹/L, prophylactic dose with platelets counts between 20,000-50,000 x10⁹/L and to hold when platelets count less than 20,000 x10⁹/L). Inferior Vena Cava (IVC) filter was placed prophylactically with the prediction of platelets count drop with the chemotherapy initiation. She was continued on this regimen throughout her disease course. Induction chemotherapy with Azacitidine, Venetoclax and Hydroxyurea was started awaiting the BMB results. Subsequent BMB result showed AML with hypercellularity and 63% blasts cells with monocytic differentiation. Cytogenetic analysis revealed that 95% of nuclei had a deletion of the ABL 1 gene region (9q34).

Table 1: Lab results.

	Patient's Result	Reference Range
White blood cell count	226.9	(4.5-13) x10 ⁹ /L
Hemoglobin	98	(117-155) g/L
Platelet count	71	(140-400) x10 ⁹ /L
Neutrophil count	47.66	(1.8-8) x10 ⁹ /L
Abnormal cells %	61.0 %	%
C-Reactive Protein	317.8	<5 mg/L
Serum Sodium	152	136-145 mmol/L
Serum Osmolality	318	275-295 mOsm/Kg
Urine Osmolality	92	300-900 mOsm/Kg

Two weeks post admission, the patient developed polydipsia with drinking more than 5 L of water and polyuria passing 4-5 L of urine. Serum electrolytes showed hypernatremia ranging from 150 to 155 mmol/L (136-145 mmol/L) compared to 143 mmol/L on admission. With the sodium level of 152 mmol/L, she had high serum osmolality of 318 mOsm/Kg and low urine osmolality of 92 mOsm/Kg (Table 1). A trial of intravenous desmopressin 2 mcg resulted in increased urine osmolality to 356 mOsm/Kg and correction of the hypernatremia. Patient's symptoms, labs findings and desmopressin response were highly suggestive of CDI, therefore water deprivation was not performed. Rest of the anterior pituitary hormones panel was within normal. Pituitary magnetic resonance imaging (MRI) was normal with preserved posterior pituitary bright spot and no thickening of the pituitary stalk. Patient's symptoms resolved and sodium level was maintained within normal range after starting oral daily desmopressin 30mg Bedtime.

Around four weeks later, the patient was able to discontinue the desmopressin with resolution of her symptoms and normalization of electrolytes. Initially, the patient achieved remission with second BMB (post treatment) showing blasts of 2.8% on aspirate count and 4% on immunohistochemical stain. After two months of follow up loss, she presented again in February 2021 with disease relapse and BMB cytogenetic analysis showing 34.8% of nuclei with deletion of the ABL 1 gene region (9q34). She did not manifest recurrence of CDI symptom with her disease relapse. The disease was progressive on chemotherapy with 2 cycles of 5 Azacitidine and Venetoclax. This was followed by three cycles of salvage therapy with Mito-FLAG (Mitoxantrone, Fludarabine, Cytarabine, granulocyte-colony stimulating factor G-CSF) and achieved second remission with a drop in blast cell count to 1%. In October 2021, she underwent fully matched allogeneic bone marrow transplantation (BMT) from her sister in Egypt. In April 2022, upon her return to UAE, she was found to be in a relapse and BMB showed 50% blasts while the AML FISH Panel was within normal limits (no cytogenetic abnormality). Again, she did not have CDI manifestation with post BMT relapse. Her disease was refractory and progressive, and she passed away shortly after.

Discussion

CDI is an uncommon manifestation in AML that is estimated to occur in less than 1% of patients with AML (1). The onset of CDI in relation to AML diagnosis is quite variable with the majority of patients developed CDI approximately within two months before or after the time of diagnosis (2). Few cases reported the development of CDI a year later or at the time of relapse (2), while others have reported CDI onset after transformation of MDS into AML (3,4).

Imaging findings is quite variable with more than 60% of cases with MRI showing no abnormalities (2). In the rest of the patients, the main pathological imaging findings were loss of posterior pituitary bright spot and pituitary stalk thickening. Rarely, detection of infundibular mass, empty sella, suprasellar region infiltration were reported (5).

Majority of the reported cases were responsive to desmopressin and had symptoms resolution when achieving AML complete remission and were able to stop the desmopressin (2).

The underlying pathophysiological mechanism of this association still remains unknown. Hypothesis includes leukemic cell infiltration of neurohypophysis, thrombosis, and alteration of neutrophil migration in monosomy 7 due to a reduction in granulocyte cell surface protein (glycoprotein GP130) (3,6). In an autopsy study of 10 patients with AML and CDI, five patients were found to have histological evidence of leukemic infiltration, two had pituitary fibrosis, two had pituitary infarction and one had central toxoplasmosis (5). On the other hand, some patients have evidence of radiological infiltration without diabetes insipidus and others manifests as diabetes insipidus despite the absence of infiltration (7). This suggests that other factors, in addition to leukemic infiltration of neurohypophysis may predispose some patients with AML to CDI.

In terms of cytogenetic analysis, around two thirds of the patients had monosomy 7 followed by inversion (3) (q21q26) (2,7,8)

Others reported cases with normal cytogenetics (4,9,10). It is postulated that the CDI in AML that involve monosomy 7 and inversion 3q21q26 could be the result of ectopic viral integration site 1 (EVI-1) overexpression which, interferes with hypothalamic secretion of ADH or may lead to its inactivation (11). In addition, it is worth exploring whether the association is related to the gene dosage imbalance since in our patient, the CDI manifested when the cytogenetic analysis showed high percentage of nuclei with 9q34 deletion (95% at diagnosis) while the CDI was absent with disease relapse with lower percentage of 9q34 deletion (34.8%) and on post-BMT relapse (no abnormality).

Most of the reported cases of DI in AML associated with the most common cytogenetic abnormalities monosomy 7 and inversion (3) (q21q26), showed poor outcome (12, 13). The one-year survival in such cases regardless of the therapeutic options was 20.3% (2). To our knowledge this is the first case of CDI in AML with 9q34 deletion (ABL1 gene) with unclear underlying pathophysiological mechanism. Whether the development of CDI in AML with this cytogenetic abnormality harbors a worse prognosis is unknown especially that AML with 9q34 showed overall worse prognosis (14).

Further study with many cases is needed to compare the outcomes in AML patients with and without CDI. It is also possible that CDI is underrecognized among AML patients as many patients' hypernatremia is likely controlled by increased water intake.

Conclusion

This case demonstrated a rare association between central diabetes insipidus and acute myeloid leukaemia that could be the first presentation of the disease or its relapse. Additionally, this is the first case to report the CDI in AML with 9q34 deletion (ABL1 gene). Further analysis is needed to clarify the associated genetic abnormalities and reveal the pathophysiological mechanism.

Disclosure

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

References

1. Portela M, Pinal L, Olga S, Dalama B. Diabetes insipidus as an atypical presentation of acute myeloid leukemia. *Endocrinol Nutr.* 2012;59(8):516-519.
2. Ladigan S, Mika T, Figge A, May A, Schmiegel W, Schroers R, Baraniskin A. Acute myeloid leukemia with central diabetes insipidus. *Blood Cells, Molecules and Diseases.* 2019;76: 45–52.
3. Cull EH, Watts JM, Tallman MS, Kopp P, Frattini M, Rapaport F, Rampal R, Levine R, Altman JK. Acute myeloid leukemia presenting with panhypopituitarism or diabetes insipidus: a case series with molecular genetic analysis and review of the literature. *Leuk Lymphoma.* 2014; 55:2125-2129.
4. Levine JA, Pariser A, Bloomgarden E. Acute myeloid leukemia associated leukocytic hypophysitis presenting with central diabetes insipidus. *AACE Clinical Case Rep.* 2018;4 (6) e519.
5. Muller CI, Engelhardt M, Laubenberger J, Kunzman R, Engelhardt R, Lubbert M. Myelodysplastic syndrome in transformation to acute myeloid leukemia presenting with central diabetes insipidus: due to pituitary infiltration association with abnormalities of chromosomes 3 and 7. *Eur J Haematol.* 2002; 69:115 – 119.
6. Ra'anani P, Shpilberg O, Berezin M, Ben-Bassat I. Acute leukemia relapse presenting as central diabetes insipidus. *Cancer.* 1994;73(9):2312–2316.
7. Castagnola C, Morra E, Bernasconi P, Astori C, Santagostino A, Bernasconi C. Acute myeloid leukemia and diabetes insipidus: results in 5 patients. *Acta Haematol.* 1995;93:1-4.
8. Chapelle A, Lahtinen R. Monosomy 7 predisposes to diabetes insipidus in leukaemia and myelodysplastic syndrome, *Eur. J. Haematol.* 39 (1987) 404–411.

9. Harrup R, Pham M, McInerney G. Acute myeloid leukemia with diabetes insipidus and hypophyseal infiltration. *Asia Pac J Clin Oncol*. 2016;12:e350-e351
10. Loukidis K, Papadakis E, Anagnostou N, Kiriklidou P, Gasta E, Karagianni A, Patinakis P, Tsakiris D, Kioumi A, Korantzis I. Polyuria due to central diabetes insipidus presenting as an early manifestation of acute myeloid leukemia. *Clin Adv Hematol Oncol*. 2012;10: 399-400.
11. Ma H, Yang J, Xiang B, Jia Y. Acute myeloid leukemia with monosomy 7, ectopic virus integration site-1 overexpression and central diabetes insipidus: A case report. *Oncology Letters*. 2015 (9): 2459-2462.
12. Harb A, Tan W, Wilding GE, Battiwalla M, Sait SNJ, Wang ES, Wetzler M. Acute myeloid leukemia and diabetes insipidus with monosomy 7. *Cancer Genet Cytogenet*. 2009;190: 97–100.
13. Dohner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Buchner T. et al., Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129(4): 424–447.
14. National comprehensive cancer network. National comprehensive cancer network. <https://www.nccn.org>. Accessed on 1/07/202.