CASE REPORT

Oman Medical Journal [2024], Vol. 39, No. 4: e661

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

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ARTICLE INFO

Article history:
Received: 22 July 2022
Accepted: 28 March 2023

Online:
DOI 10.5001/omj.2024.22

Keywords:
Central Diabetes Insipidus; Acute Myeloid Leukemia; Polyuria; Polydipsia; Cytogenetics; United Arab Emirates.

ABSTRACT

Acute myeloid leukemia (AML) is rarely associated with central diabetes insipidus (CDI) with unclear underlying pathophysiological mechanisms. The most commonly reported cytogenetic abnormality in cases of AML-associated CDI is monosomy 7, followed by chromosome 3 abnormalities. We report a case of a woman with newly diagnosed AML with 9q34 deletion (*ABL1* gene region), who developed symptoms of polyuria and polydipsia with an investigation confirming CDI. This is the first reported case of cytogenetic abnormality of 9q34 deletion (*ABL1* gene region) in AML with CDI.

Central diabetes insipidus (CDI) is caused by decreased secretion of antidiuretic hormone, leading to polydipsia and polyuria. The causes could be genetic, idiopathic, or secondary to brain insults such as infection, granulomatosis, infiltrative conditions, tumors, or post-traumatic or post-surgical conditions. CDI is rarely associated with acute myeloid leukemia (AML), with only about 100 cases reported worldwide. The underlying pathophysiological mechanism remains unclear. Most cases had cytogenetic abnormalities involving monosomy 7 and inversion 3 (q21q26).[1] Overall, this condition is associated with poor treatment response and outcome.[2]

Here, we describe a case of a 42-year-old woman diagnosed with AML with a cytogenetic abnormality of 9q34 deletion (*ABL1* gene) and developed CDI that initially resolved with chemotherapy. Thereafter, she underwent allogenic hematopoietic stem cell transplantation, but later succumbed to relapsed refractory disease. To our knowledge, this is the first reported case of AML with a cytogenetic abnormality of 9q34 deletion associated with CDI.

CASE REPORT

In November 2020, a 42-year-old woman was referred to us with a 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 in March 2020. Physical examination showed that she was febrile (38.4 °C), tachycardic (121 beats/min), and tachypneic (24 breaths/min) with desaturation to 91% in room air. The rest of the examination revealed cervical lymphadenopathy, splenomegaly, and bilateral scattered crackles from the lungs. Initial laboratory tests revealed leukocytosis with neutrophil predominance, anemia, and thrombocytopenia [Table 1]. Peripheral blood film showed 61% blast cells of intermediate-to-large size with no Auer rods seen. C-reactive protein was elevated at 317.8 mg/L (normal < 5 mg/L). Computed tomography pulmonary angiogram confirmed extensive segmental and subsegmental bilateral pulmonary embolism, bilateral airspace consolidations, and pleural effusion. Lower limbs deep venous thrombosis was ruled out by Doppler ultrasound.

The patient was admitted as a case of sepsis secondary to pneumonia and pulmonary embolism with suspicion of underlying acute leukemia for further

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Table 1: Laboratory test results.

Test	Patient's result	Reference range
White blood cell count, $\times 10^9$/L	226.9	4.5–13.0
Hemoglobin, g/L	98	117–155
Platelet count, $\times 10^9$/L	71	140–400
Neutrophil count, $\times 10^9$/L	47.66	1.8–8.0
Abnormal cells, %	61.0	
C-reactive protein, mg/L	317.8	< 5.0
Serum sodium, mmol/L	152	136–145
Serum osmolality, mOsm/Kg	318	275–295
Urine osmolality, mOsm/Kg	92	300–900

workup and treatment. Supportive measures were initiated and the broad- spectrum antibiotic Tazocin was given for 14 days. Anticoagulation treatment was started and a bone marrow biopsy (BMB) was performed. The low molecular weight heparin (enoxaparin) was initiated and the dose was adjusted periodically based on the patient's platelets count—full dose was given if platelets rose to > 50 000 × 10^9/L, the prophylactic dose was given if platelets ranged 20 000–50 000 × 10^9/L, and holding the dose if platelets remained < 20 000 × 10^9/L. An inferior vena cava filter was placed prophylactically with the prediction of platelet count drop with the chemotherapy initiation. She continued on this regimen throughout her disease course. Induction chemotherapy with azacitidine, venetoclax, and hydroxyurea was started while awaiting the BMB results. Subsequent BMB results showed AML with hypercellularity and 63% blast cells with monocytic differentiation. Cytogenetic analysis revealed that 95% of nuclei had a deletion of the *ABL1* gene region (9q34).

Two weeks post-admission, the patient developed polydipsia and polyuria—drinking more than 5 L of water and passing 4–5 L of urine daily. Serum electrolytes showed a hypernatremia of 150–155 mmol/L compared to 143 mmol/L on admission (ref. range = 136–145 mmol). With a 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 antidiuretic (desmopressin of 2 mcg) increased urine osmolality to 356 mOsm/Kg and corrected her hypernatremia.

As the patient's symptoms, laboratory findings, and desmopressin response were highly suggestive of CDI, water deprivation was avoided. The rest of the anterior pituitary hormone panel was normal. Pituitary magnetic resonance imaging (MRI) was normal with preserved posterior pituitary bright spot and no thickness of the pituitary stalk. The patient's symptoms resolved and sodium level was maintained within normal range after starting oral daily desmopressin of 30 mg at bedtime.

About four weeks later, the patient discontinued the desmopressin with a resolution of her symptoms and normalization of electrolytes. Initially, the patient achieved remission with a second BMB (post-treatment) showing blasts of 2.8% on the aspirate count and 4% on the 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 *ABL1* gene region (9q34). This time she did not manifest recurrence of symptoms of CDI. The disease was progressive despite giving two cycles of chemotherapy with 5-azacitidine and venetoclax. This was followed by three cycles of salvage therapy with Mito-FLAG (mitoxantrone, fludarabine, cytarabine, and granulocyte-colony stimulating factor) and achieved a second remission with a drop in blast cell count to 1%. In October 2021, she underwent (in Egypt) fully matched allogeneic bone marrow transplantation (BMT) from her sister. In April 2022, after her return to the 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 continued to be refractory and progressive, and she passed away shortly afterward.

DISCUSSION

CDI is an uncommon manifestation in AML, estimated to occur in fewer than 1% of patients with AML.[1] The onset of CDI with AML diagnosis is quite variable with the majority of patients developing CDI approximately within two months before or after the time of diagnosis.[2] In a few reported cases, the development of CDI occurred a year later or at the time of relapse,[2] while others have reported CDI onset after the transformation of MDS into AML.[3,4]

Imaging findings are quite variable with MRI showing no abnormalities in more than 60% of cases.[2] MRI did detect pathologies, these included loss of posterior pituitary bright spot and pituitary

stalk thickening. Rarely, detection of infundibular mass, empty sella, and suprasellar region infiltration were reported.[5] The majority of reported cases were responsive to desmopressin with CDI resolution when complete AML remission was achieved.[2]

The underlying pathophysiologic mechanism of the AML and CDI association remains unknown. Hypotheses include 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 had 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 manifest 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 with AML and CDI 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 3 (q21q26) could be the result of ectopic viral integration site-1 overexpression which interferes with hypothalamic secretion of antidiuretic hormone or may lead to its inactivation.[11] In addition, it is worth exploring whether the association is related to gene dosage imbalance, since in our patient, the CDI manifested when the cytogenetic analysis showed a high percentage of nuclei with 9q34 deletion (95% at diagnosis), while the CDI was absent with disease relapse with a lower percentage of 9q34 deletion (34.8%) and on post-BMT relapse (no abnormality).

Most reported cases of CDI in AML associated with the most common cytogenic abnormalities monosomy 7 and inversion 3 (q21q26), have shown poor outcomes.[3,12,13] The one-year survival in such cases regardless of the therapeutic options was 20.3%.[2]

To our knowledge, we are reporting the first case of CDI in AML with 9q34 deletion (*ABL1* gene) with unclear underlying pathophysiological mechanisms. Whether the development of CDI in AML with this cytogenetic abnormality harbors a worse prognosis is unknown, especially as AML with 9q34 showed an overall poor prognosis.[14]

Further research with more cases is needed to compare the outcomes among 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 CDI and AML. Further analysis is needed to clarify the associated genetic abnormalities and reveal the pathophysiological mechanism of this extremely rare disorder.

Disclosure

The authors declared no conflicts of interest. Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

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