Case report

Central Diabetes Insipidus – An uncommon presentation of Acute Myeloid Leukaemia: A Case Report and Literature Review

Abstract

Introduction:

Central diabetes insipidus (CDI) is a rare manifestation of Acute myeloid leukaemia (AML). Patients can present with polyuria, polydipsia, weight loss and electrolyte disturbances either at the time of diagnosis or while on treatment. Due to the underlying haematological malignancy, management of this condition might become challenging.

Case summary:

We report a 65-year-old gentleman diagnosed with acute myeloid leukaemia. Post 2 cycles of azacytidine therapy, he presented with polyuria, polydipsia and weight loss.
On evaluation, he was diagnosed with CDI after performing water deprivation test and correlating biochemical parameters. Concurrent MRI of the brain showed well defined homogeneously enhancing posterior pituitary lesions suggestive of leukemic deposits confirming the diagnosis of CDI.
Diagnosis of diabetes insipidus (DI) was made 2 months after the diagnosis of AML. The patient was started on oral desmopressin at a dose of 0.2 mg per day. Upon initiation of the therapy there was significant relief of symptoms. He was simultaneously continued on therapy with hypomethylating agent (Azacytidine) and Venetoclax for AML. Upon initiation of therapy, the symptoms significantly subsided. He continued receiving treatment for AML with Venetoclax and azacytidine. However, the patient succumbed to the disease 9 months post the diagnosis of CDI.

Conclusion:

AML- M4/M5 with monocytic differentiation have a propensity to invade various extramedullary tissues, including the skin, gingiva, brain, and endocrine organs. If patients with AML present with symptoms of increased urination, excessive thirst, and weight loss, it is crucial to consider the possibility of CDI and conduct a thorough assessment for this condition.

Key Words:

Acute myeloid leukaemia, central diabetes insipidus, water deprivation test, desmopressin.

Introduction

Acute myeloid leukaemia (AML) associated Central Diabetes Insipidus (CDI) is a rare but increasingly recognized complication of AML. Patients can present either upfront with symptoms of CDI or can develop later on through the course of AML treatment. (1)

CDI is characterized by the inability to concentrate urine due to deficiency of antidiuretic hormone (ADH). It is commonly idiopathic or may be secondary to tumours, infections, trauma, or infiltrative diseases affecting the brain. (2) Patients with CDI present with polyuria, polydipsia, dyselectrolytemia and weight loss.Click or tap here to enter text.

AML causing central DI secondary to infiltration of the pituitary gland is being increasing recognised these days, especially with a few cytogenetic abnormalities of chromosome 3 and chromosome 7 like inversion 3 or monosomy 7(3). These patients usually respond to desmopressin and show good response.

There are very limited reports from India on AML with CDI. We report a case report of CDI in a patient with AML with monocytic differentiation, that was diagnosed after initiating treatment, which is rare manifestation of myeloid neoplasms. Informed consent was taken from the patient and family for publishing anonymized case report.

Case Presentation

Patient information:

A 65-year-old gentleman, resident of Punjab with co-morbidities of hypertension presented with complaints of incidentally detected elevated leucocyte count of 38,400 /mm^3 on routine outpatient evaluation and health check-up. He was later evaluated at our centre under the haematology unit in January 2022. Bone marrow showed hypercellular marrow with < 5% blasts and dysmegakaryopoesis. Patient was under regular outpatient follow ups as patient was asymptomatic.

In March 2022 (Two months post initial presentation) his hemogram showed increasing leukocyte count of 67200/cu.mm with blasts in the peripheral smear. Immunophenotyping done showed 31% cells gated in the blast region to be CD45 (dim) positive. Gated population showed moderate expression for CD34, CD38 and HLA-DR; dim expression of CD13, CD33, CD11b and CD117. Fifteen percentage of the cells in the monocytic region showed expression of CD4, CD11b, CD14, CD13, CD64, CD117, CD38, CD33 and MPO which was suggestive of AML with monocytic differentiation in the month of April,2022

Patient's EDTA blood was analysed for AML mutations as per ELN criteria which was negative for all AML mutations and fusions.

Treatment history and timeline of events:

Patient was initiated on therapy with hypomethylating agent (Azacytidine) and Venetoclax (BCL2 inhibitor) in the month of May 2022. He responded to the therapy and there was decrease in total count.

Post 2 cycles of Azacytidine and Venetoclax, in the month of July 2022, he presented with complaints of increased frequency of micturition, increased thirst, and nocturia for 2 weeks. He would consume nearly 6 litres of water a day and would wake up at least 10 times at night to urinate. This compromised sleep quality and there was a documented unintentional weight

loss of 5 kg. A possibility of uncontrolled sugars leading of polydipsia, psychogenic polydipsia, nephrogenic diabetes insipidus and CDI were the differential diagnosis entertained.

The endocrinology team subjected him for a water deprivation test which was done over a period of 8 hours starting at 9AM to 5 PM the subsequent day. His blood sugars were within normal range. There was no previous history of diabetes, psychiatric illness, kidney disease, antipsychotic, antifungal or antibiotic medications use.

Diagnostic assessment:

Water deprivation test was done in the index case to diagnose CDI.

Table 1. Pre desmopressin injection

Time	Weight (Kg) (1 Hourly)	Urine Osmolality (mOsm) (2 Hourly)	S. Na+ (2 Hourly)	Hourly Urine output chart
8.00 a.m.	-	-	-	-
9.00 a.m.	59.05 kg	74.38	140	100ml
10.00 a.m.	58.80 kg			
11.00 a.m.	58.80 kg	84.45	144	280ml
12.00 p.m.	58.80kg			250ml
01.00 p.m.	58.50 kg	84.45	144	150ml
02.00 p.m.	58.50 kg			-
03.00 p.m.	58.35 kg	110.94	146	300ml
04.00 PM	58.05 kg			200ml
05.00 PM	57.90 kg	145.34	145	90ml
				1370ml

Before any fluids were administered the patient received Desmopressin 10 mcg intranasal spray.

Table 2. Two hrs post desmopressin

Urine Osmolality (mOsm) (2 Hourly)	S. Na+ (2 Hourly)
236.02	145

Table 3. Interpretation

Post Dehydration Osmolality (mOsm/Kg)	**Post DDAVP Osmolality (mOsm/Kg)**	**Diagnosis**
Urine	Urine	Normal
> 750	> 750	Normal
< 300	< 300	Nephrogenic D. I
< 300	> 750	Cranial D. I
300-750	> 750	Chronic Polydipsia
300-750	> 750	Partial Nephrogenic D.I or Primary Polydipsia
300-750	> 750	Partial Cranial D. I

During the water deprivation test, the patient's urine osmolality remained below 160mOsm, and serum sodium levels were stable between 140 to 145 over six hours. Post-administration of 0.2 mg Minirin (desmopressin), urine osmolality rose to 236 mOsm within two hours, suggesting the ability to concentrate urine due to desmopressin, pointing to a central origin of diabetes insipidus. MRI brain revealed distinct, uniformly enhancing lesions in the posterior pituitary, indicative of leukemic infiltration. The CDI diagnosis was confirmed by synthesizing clinical symptoms, lab results, water deprivation test outcomes, and MRI evidence.

Therapeutic intervention:

The patient was continued on oral desmopressin at a dose of 0.2mg once a day and there was significant resolution of symptoms with decreasing thirst and frequency of micturition. Desmopressin is the treatment of choice for CDI because it specifically targets the underlying problem of vasopressin deficiency in central DI, as opposed to nephrogenic DI where the kidney is unresponsive to vasopressin.

This patient had cranial diabetes insipidus secondary to acute myeloid leukemia due to leukemic deposits in the posterior pituitary. The leukemic deposits in the posterior pituitary in this case caused cranial diabetes insipidus, which was a complication of acute myeloid leukaemia.

Patient was discharged on once-a-day tablet Minirin (desmopressin) 0.2 mg. Patient reported remission of symptoms during outpatient follow up with desmopressin tablet.

Follow up and outcome:

Subsequently patient was followed up for 9 months and he succumbed at 11 months post diagnosis of AML with disease progression.

Methodology of literature review

Following search terms were used in PubMed Central to perform the review of literature.

(“leukemia, myeloid, acute”[MeSH Terms] OR (“leukemia”[All Fields] AND “myeloid”[All Fields] AND “acute”[All Fields]) OR “acute myeloid leukemia”[All Fields] OR (“acute”[All Fields] AND “myeloid”[All Fields] AND “leukemia”[All Fields])) AND (“diabetes insipidus”[MeSH Terms] OR (“diabetes”[All Fields] AND “insipidus”[All Fields]) OR “diabetes insipidus”[All Fields])

Discussion

Central diabetes insipidus (CDI) is a rare manifestation of Acute myeloid leukaemia (AML). In around 0.6% cases of leukaemias, pituitary involvement is documented. Due to the lack of a consistent relationship between pituitary involvement and the occurrence of diabetes insipidus, the actual prevalence of CDI linked to leukaemia remains uncertainClick or tap here to enter text..(1,4)

CDI is secondary to the destruction of the neurons of the hypothalamus/posterior pituitary axis, with decreased ADH secretion. This syndrome is caused by a wide variety of congenital and acquired lesions.(2)

AML causing CDI has been increasingly reported these days and the symptoms of CDI can either present before the diagnosis of AML, during the course of treatment or at relapse.

PubMed search revealed 70 case reports/case series since 1955. Cases were increasingly linked to monocytic differentiation (6/70, 9%), monosomy 7 (11/70, 16%) and erythroleukemia (4/70, 6%).

Clinical presentations included polyuria, polydipsia, dehydration either before the diagnosis of AML or during the course of treatment or at relapse.

Seventy five percent of the patients will be diagnosed with CDI concurrently with their AML diagnosis, with most remaining cases presenting no more than 2 months prior to or following their AML diagnosis.Click or tap here to enter text. In our patient, he was diagnosed 2 months after the diagnosis of AML.(5)

Ra’anani et al described 2 patients in whom diabetes insipidus symptoms preceded the diagnosis of AML relapse (One patient with acute lymphocytic leukaemia and 1 with AML)(6)

Similar to this, in a case reported by Konstantinos Loukidis et al patient presented with symptoms of CDI 2 months preceding the diagnosis of AML.(7)

Our index patient here presented with CDI symptoms two months after the diagnosis and had MRI abnormalities in the form of well-defined homogeneously enhancing posterior pituitary lesions likely representing leukemic deposits.

Most of the individuals (about 61%) suffering from AML-related CDI will not display any abnormal results in brain imaging, while a portion might exhibit pathological findings such as the disappearance of the bright spot in the posterior pituitary or the development of nodular thickening/attenuation in the pituitary stalk. (8)

In this case, the patient was diagnosed with Central Diabetes Insipidus (CDI) two months following their Acute Myeloid Leukemia (AML) diagnosis. This timing aligns with the pattern observed in most CDI cases associated with AML, as 75% are identified concurrently with or within two months of AML diagnosis. Similar to prior reports, such as those by Ra’anani et al.(6)and Konstantinos Loukidis et al.,(7) our patient displayed CDI symptoms post-AML diagnosis and MRI revealed indicative posterior pituitary lesions, suggesting leukemic infiltration.

While a majority (about 61%) of AML-related CDI cases show no abnormal brain imaging, some do exhibit notable changes. (5)The pathogenesis of AML-related CDI, though not fully understood, is thought to involve multiple factors, including direct leukemic infiltration. Historical autopsies, like the one by Virginia Miller and Wallace Campbell identified diabetes insipidus linked to lesions in the supraoptic hypophyseal system and other neural changes (9). Moreover, Muller et al. reported a case where MRI changes correlated with chemotherapy response, suggesting leukemic cells as a potential underlying cause for CDI.

Theories also suggest a role for abnormal platelet function and dysmegakaryopoiesis in AML-induced DI, affecting vasopressin function.(10) Our patient lacked typical chromosomal aberrations often seen in CDI, specifically on chromosomes 3 and 7(9,11–13). These aberrations are frequently linked to poor chemotherapy responses and adverse outcomes.

In AML with 3q26 breakpoints, the activation of the EVI-1 protein, crucial for neurodevelopment, might disrupt neuroendocrine secretion.(10) Notably, about 90% of AML-associated CDI cases respond to vasopressin analogs like DDAVP/desmopressin, as seen in our patient who showed rapid symptom improvement with this treatment. (8) However, despite treatment, CDI in AML is often a marker of poor prognosis, as our patient experienced disease worsening and succumbed to the condition within a few months post-CDI diagnosis.

Conclusion

AML with monocytic differentiation has a propensity to infiltrate various tissues, including the skin, gingiva, brain, and endocrine organs. If patients with AML present with symptoms of increased urination, excessive thirst, and weight loss, it is crucial to consider the possibility of CDI and conduct a thorough assessment. Patients respond well to oral desmopressin on diagnosis of CDI, with significant resolution of symptoms and metabolic abnormalities.

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