Polyuria Due to Central Diabetes Insipidus Presenting as an Early Manifestation of Acute Myeloid Leukemia

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Introduction

Diabetes insipidus is a polyuric syndrome characterized by a pathologic excretion of large amounts of urine with low osmolality. It can originate from a total or partial lack of antidiuretic hormone (ADH) production from the pituitary gland or from "resistance" of the collecting tubules of the kidney to the ADH.

Acute monocytic leukemia infiltrates the central nervous system in up to 50% of cases. In contrast, the infiltration of the pituitary gland by leukemia cells[1-3] is unusual. As will be described in this case, on rare occasions, polyuria as a result of central diabetes insipidus can precede the manifestation of leukemia.

Case Report

A 55-year-old woman was admitted for investigation of fever (38°C), weakness, and necrotic gingivitis, which had started 20 days before admission. She had type 2 diabetes and a 4-year history of breast cancer. The clinical examination revealed pallor, gum sores, and periumbilical petechiae. A complete blood count showed a hemoglobin level of 4.4 g/dL, a white cell count of 72 x 10^9/L, and a platelet count of 50 x 10^9/L. Blood film, bone marrow biopsy, and immunophenotyping established the diagnosis of acute myeloid leukemia (French-American-British classification M5). Bone marrow karyotyping proved normal.

The patient reported polyuria and polydipsia that had started 2 months before admission. During her hospitalization, polyuria of 10–12 L per 24 hours was confirmed, with a low urine osmolality (specific gravity, 1,008) and serum hypernatremia.

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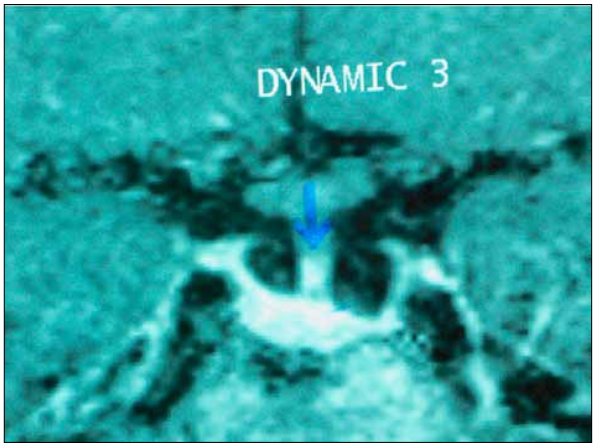

Figure 1. Pathologic enhancement on the pituitary stalk and the optic chiasma due to leukemic infiltration.

The patient received chemotherapy as treatment for acute myeloid leukemia with cytarabine 100 mg/m^2 twice daily for 7 days and idarubicin 10 mg/m^2 on the first, third, and fifth day. Based on suspicion for the presence of diabetes insipidus, we conducted a 12-hour water deprivation test and measured the levels of ADH in her serum. In addition, magnetic resonance imaging (MRI) of the sella turcica was ordered.

The water deprivation test showed worsening hypernatremia (sodium, 158 mEq/L), and the measurements of the serum and urine osmolality showed hyperosmolality of the blood (350 mOsm/kg), with inappropriate low urine osmolality (210 mOsm/kg). The serum ADH value was 3.9 pg/mL (normal value, <8 pg/mL). The MRI showed the sella turcica to be partially void, with pathologic enhancement on the pituitary stalk and the optic chiasma, attributed to leukemic infiltration (Figure 1). These test results confirmed the diagnosis of partial central diabetes insipidus due to leukemic infiltration.

The patient was treated with intranasal desmopressin at 20 mg once a day. In less than 12 hours, the diuresis had decreased from 12 L per 24 hours to 4 L per 24 hours, with a concomitant increase in the urine osmolality (500 mOsm/kg). The serum osmolality decreased (300 mOsm/kg), and the serum sodium normalized (sodium, 144 mEq/L). The patient succumbed to uncontrolled sepsis.

Discussion

The pathogenic mechanism of diabetes insipidus in AML[1-4] is not clear. Although the infiltration of the central nervous system is not uncommon in certain types of leukemia, the infiltration of the sella turcica as a cause of diabetes insipidus,[5-7] as in our case, is rare. In patients with AML, diabetes insipidus is an unfavorable prognostic factor. Leukemic infiltration occurs in the pituitary and its vicinity without causing diabetes insipidus, and diabetes insipidus can occur without leukemic infiltration.[8] Moreover, in the case described, the symptom of polyuria preceded the acute myeloid leukemia manifestation by 2 months. MRI and cerebrospinal fluid examination reveal leukemia involvement of the hypothalamic or pituitary area in only a minority of patients with AML and diabetes insipidus, thus questioning the concept of leukemic infiltration as an etiologic cause. Destruction of hypothalamic cells, instead of temporary dysfunction, has been suggested because diabetes insipidus is seldom affected by chemotherapy. Consequently, CNS therapy should be intensified with intrathecal administration of chemotherapy even in the presence of normal cerebrospinal fluid and MRI findings.[4] The treatment with desmopressin led to remission of polyuria. Apart from our case, only 22 similar cases worldwide are documented, and this is but the second case of diabetes insipidus in AML reported in Greece during the last 30 years.[3,9]

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Review

Central Diabetes Insipidus Presenting as an Early Sign of Acute Myeloid Leukemia

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Loukidis and colleagues describe a rare case of central diabetes insipidus presenting as an early manifestation of acute myeloid leukemia (AML).[1] Magnetic resonance imaging (MRI) with gadolinium (Gd) showed pathologic enhancement of the pituitary stalk and optic chiasma, suggesting leukemic infiltration. Although central diabetes insipidus is controlled by intranasal 1-desamino-8-D-arginine vasopressin (dDAVP), these patients almost always have a poor prognosis, and the pathogenetic mechanisms underlying central diabetes insipidus concomitant with AML are uncertain.

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Clinical Presentation and Diagnosis

Central diabetes insipidus is a rare complication of AML. The incidence of central diabetes insipidus in leukemia is estimated to be at or less than 0.6%,[2] although leukemic infiltrations into the pituitary region are found on autopsy in up to 46% of AML patients in the absence of clinical diabetes insipidus.[3]

The timing of the onset of diabetes insipidus in relation to leukemia is variable. The occurrence of symptoms of diabetes insipidus, such as polyuria and polydipsia, before the diagnosis of AML is not particularly rare. Ra'anani previewed the clinical characteristics of 29 leukemic patients with diabetes insipidus.[4] In 6 patients, dia-

betes insipidus preceded the leukemia by a median period of 2 months, whereas 11 patients showed concomitant presentation of diabetes insipidus and the leukemic process. One case presented with diabetes insipidus at the same time as a recurrence of AML.[4]

The pathogenetic mechanisms for diabetes insipidus in patients with leukemia have been described as leukemic infiltration of the posterior pituitary gland, supraoptic or paraventricular nuclei, thrombosis of the small vessels, hemorrhage, and infection.[2] Clinical features of central diabetes insipidus are polyuria and polydipsia (which causes the patient to drink more than 4–5 L/day), due to a deficiency of antidiuretic hormone (ADH). Laboratory findings show low levels of serum ADH despite high serum osmolality and low urinary osmolality. The symptoms of diabetes insipidus can be relieved using intranasal dDAVP.

ADH is made by the supraoptic and paraventricular nuclei of the hypothalamus and transported through the neural component of the pituitary stalk, then stored in nerve terminals of the posterior pituitary. Central diabetes insipidus is caused by degeneration or destruction of these regions through tumor infiltration, infection, and inflammation. In patients with central diabetes insipidus, T1-weighted MRI shows a lack of hyperintense signals in the posterior lobe, reflecting ADH storage.[5] In addition, MRI occasionally shows abnormal pituitary stalk thickening and abnormal enhancement by Gd, indicating the cause of diabetes insipidus as an infiltrative process.

In the case described by Loukidis and colleagues, the authors suggest leukemic infiltration of the pituitary stalk as the cause of central diabetes insipidus, as indicated by the presence of abnormal enhancement of the pituitary stalk and optic chiasma.[1] There are a few cases in the literature of leukemia with central diabetes insipidus presenting as abnormal pituitary findings on MRI, with suspected leukemic infiltration.[6,7] However, in only 1 case was pathologic examination of the affected region undertaken; it revealed no leukemic infiltration, and the diagnosis was lymphocytic infundibuloneurohypophysitis concomitant with acute lymphoblastic leukemia.[8] Although perihypophyseal leukemic filtration is common in autopsies of AML patients, central diabetes insipidus complicated by leukemia is rare, and central nervous system infiltration does not appear to correlate to the incidence of central diabetes insipidus. The cause of central diabetes insipidus concomitant with leukemia thus appears to involve more than leukemic infiltration.

Central Diabetes Insipidus With AML Chromosomal Abnormality

The patient described by Loukidis and colleagues[1] had a normal karyotype in the bone marrow. However, there are chromosomal abnormalities, such as 3q21q26 and monosomy 7, that may predispose toward the development of central diabetes insipidus.[9] Ecotropic virus integration site-1 (EVI-1) is located at 3q26 and codes for a 1,051-amino acid DNA-binding phosphoprotein that functions as a transcription factor. EVI-1 has been demonstrated to be overexpressed in AML patients with these chromosomal abnormalities. It is hypothesized that overexpression of EVI-1 may result in reduced transcription of ADH and subsequent clinical diabetes insipidus without infiltration of the neurohypophysis.[10]

Conclusion

The case of AML concomitant with central diabetes insipidus described by Loukidis and colleagues is unique because MRI showed abnormal lesions suggesting leukemic infiltration.[1] Further investigation for other cases is required to identify the pathogenesis and clinical prognosis.

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