Casereport

iMedPub Journals
www.imedpub.com

Journal of Clinical and Molecular Endocrinology
ISSN 2572-5432

2023
Vol.8 No.1:001

# Central Diabetes Insipidus, a Red Flag and Key Presentation of Rare Neoplasms: A Propos Two Cases

**Georges Khalil*, Amine Wehbe, Elie Raad, Georges Jabbour, Elio Mikhael and Anthony Fata**

Department of Medical Microbiology, Saint Joseph University, Beirut, Lebanon

***Corresponding author:** Georges Khalil, Department of Medical Microbiology, Saint Joseph University, Beirut, Lebanon, Tel: 009613758600; E-mail: grkhalil@gmail.com

**Received date:** October 18, 2022, Manuscript No. IPJCME-22-14827; **Editor assigned date:** October 21, 2022, PreQC No. IPJCME-22-14827 (PQ); **Reviewed date:** November 07, 2022, QC No. IPJCME-22-14827; **Revised date:** December 27, 2022, Manuscript No. IPJCME-22-14827 (R); **Published date:** January 04, 2023, DOI: 10.36648/2572-5432/8.1.001

**Citation:** Khalil K, Wehbe A, Raad E, Jabbour G, Mikhael E, et al. (2023) Central Diabetes Insipidus, a Red Flag and Key Presentation of Rare Neoplasms: A Propos Two Cases. J Clin Mol Endocrinol Vol:8 No:1

## Abstract

Central Diabetes Insipidus (CDI) is a rare condition in which your body doesn't have enough Antidiuretic Hormsone (ADH or vasopressin), which causes you to pee large volumes of urine and become very thirsty. Your hypothalamus produces ADH, but your pituitary gland stores and releases it. You can get central diabetes insipidus if your pituitary gland or hypothalamus is damaged.

**Keywords:** Diabetes; Central Diabetes Insipidus (CDI); Hypothalamus; Chromogranin, Synaptophysin; Neutrophils, Lymphocytes

## Introduction

People with diabetes insipidus pee large volumes of urine several times a day and drink large amounts of water because they feel constantly thirsty. If you have CDI and don't drink enough fluid to replace water loss through urine, you can become dehydrated, which is dangerous to your health.

## Case presentation

### Case 1

A 64-year-old female presented to the ED of our hospital because of intense fatigue and worsening of pre-existing polyuria, nycturia and polydipsia over the last 6 months, stating that she had persistent thirst despite an intake of 10 to 14 liters of water daily. She also noted losing 10 Kg in 4 months [1]. On admission, capillary blood glucose was 121 mg/dl and on physical examination, the patient had a cachectic appearance, with a BMI of 14.6. Following her admission, diuresis was persistently high at up to 10.4 L/day despite a lower intake of 3 L sodium chloride 0.45% intravenous infusions [2]. We conducted an overnight water deprivation test, followed by the administration of 2 µg of desmopressin. Urine osmolality was 122 mOsm/kg after overnight water deprivation and increased from 122 mOsm/Kg to 271 mOsm/Kg after taking desmopressin. Given this increase of >50% from baseline, the diagnosis of central diabetes insipidus was retained. Her Arginine Vasopressin (AVP) plasma value was at the lower limit (0.8 ng/L) [3]. The patient was then started on oral desmopressin 50 µg twice daily. This dose was progressively increased up to 120 µg thrice a day to control her diuresis [4]. Tests upon admission and additional workup are shown in Table 1.

**Table 1:** Tests upon admission and additional workup (patient 1).

| Tests upon admission | Patient's results | Normal values |
|---|---|---|
| Complete blood count | | |
| Hemoglobin (g/dL) | 13.2 | 11.5-15.5 |
| Leukocytes (/mm$^3$) | 8000 | 4000-10000 |
| Platelets (/mm$^3$) | 288000 | 150000-500000 |
| Metabolic panel | | |

| | | |
|---|---|---|
| Creatinine (mg/dL) | 0.24 | 0.50-0.90 |
| ASAT (UI/L) | 34.99 | <29 |
| Alcaline phosphatase (UI/L) | 517.56 | <141 |
| γGT (UI/L) | 410.47 | <37 |
| C-reactive protein (mg/L) | 57.67 | <3 |
| HbA1C (%) | 5.8 | 6-Apr |
| Electrolytes-Blood | | |
| Sodium (mmol/L) | 139 | 135-145 |
| Chloride (mmol/L) | 98.4 | 92-104 |
| Potassium (mmol/L) | 3.9 | 3.5-5.1 |
| Blood osmolality (mOsm/Kg) | 299.6 | 280-290 |
| Electrolytes-Urine | | |
| Sodium (mmol/L) | 16 | |
| Potassium (mmol/L) | 6.3 | |
| Chloride (mmol/L) | 14 | |
| Urine osmolality (mOsm/Kg) | 122 | 100-1400 |
| Tumor markers | | |
| Ca 15-3 (KU/L) | 29.06 | <30 |
| Ca 19-9 (KU/L) | 140.4 | <37 |
| Carcinoembryonic antigen (ng/ml) | 43.3 | <10 |
| Additional workup | | |
| ADH (ng/L) | 0.8 | <14.1 |
| Prolactine (ng/ml) | 24.00 | 3.2-23.3 |
| Morning Cortisol (nmol/l) | 384.1 | 101.2-535.7 |
| Morning ACTH (ng/L) | 17.2 | May-60 |
| PTH (pg/ml) | 59.21 | 15-65 |

Given the diagnosis of central diabetes insipidus, we performed a brain and pituitary MRI [5]. The findings of brain imaging were as follows: An intrasellar lesion with marked contrast enhancement, causing enlargement of the sella turcica, infiltrating the cavernous sinuses bilaterally, surrounding the left intracavernous internal carotid segment with an effacement of the venous structures of the left cavernous sinus, infiltrating the left sphenoidal sinus anteriorly and displacing the pituitary gland superiorly [6]. There was a homogeneous enhancement of the pituitary parenchyma [7]. The posterior pituitary gland was displaced anteriorly with a normal signal. A neurosurgical consultation was requested to schedule a transsphenoidal biopsy [8]. However, the biopsy was not performed as it carried a high risk given the serious and advanced general condition of the patient. In parallel, the patient underwent an abdominal MRI that revealed a cephalic mass of the pancreas measuring 3.2 cm x 4 cm, hepatic metastases and peritoneal epiploic carcinomatosis with ascites [9]. The chest CT-scanner showed

mediastinal lymphadenopathies. An abdominopelvic CT-scan done 2 years earlier for abdominal pain and low appetite revealed a pancreatic mass measuring 2 centimeters. At that time, the patient was complaining of polydipsia and polyuria [10]. No further workup was performed at that time and the medical decision was clinical surveillance and a follow-up with imaging after 6 months. Due to the COVID-19 pandemic and lockdown, the patient did not follow up with any physician for 2 years and no assessment or imaging was done [11]. Upper and complete lower digestives endoscopies did not show any abnormalities. We performed CT-guided biopsy of the hepatic and peritoneal epiploic lesions. Due to the refractory ascites, pancreatic mass biopsy was not performed. Immunohistochemical studies on tumor cells revealed high expression of CK7 and TTF1, moderate expression of CDX2 and focal expression of CK19-9. CD56, chromogranin and synaptophysin were highly and diffusely expressed among tumor cells, while CK20 was negative and KI67 antigen expression was inferior to 20%. A microscopic study revealed mild to moderate nuclear atypia, with weak mitotic activity. Immunohistochemical and microscopic studies were compatible with intermediate grade (grade 2) neuroendocrine tumor. Additional tests included gastrin, insulin, glucagon and VIP blood levels. All were within normal ranges. Ascitic fluid analysis showed increased cellularity with atypical cells containing abundant cytoplasm and an increased nucleocytoplasmic ratio. Immunohistochemical staining was positive for BerEP4. This ascitic fluid analysis suggested the metastasis of an adenocarcinoma. Tumor marker analysis revealed markedly elevated CA 19-9 and CEA blood levels. The prognosis of the patient was poor, complicated by severe ascites, hypotension and anuria, ultimately resulting in her death 2 months after her admission.

## Case 2

A 52-year-old female presented to the ED because of recent worsening of her symptoms of polyuria and polydipsia. The patient drank 12 liters of water per day. These clinical manifestations had started insidiously 2 years earlier and were attributed to psychogenic polydipsia and sicca syndrome. She had no personal history of diabetes mellitus as her fasting blood glucose and HbA1c values were normal. On admission, we noted high plasma osmolality (298.6 mOsm/Kg) and low urine osmolality (129.1 mOsm/Kg). The plasma sodium concentration was 145 mmol/L, while urinary sodium spot revealed a low urine sodium concentration (2012 mEq/L). The AVP plasma value was at the lower limit (1.0 ng/L). The protein electrophoresis test was normal. A complete immunological test was negative for all immunoglobulins. A water deprivation test confirmed the diagnosis of central diabetes insipidus [12]. Tests upon admission and additional workup are shown in Table 2.

**Table 2:** Test upon admission and additional workup (Patient 2).

| Tests upon admission | Patient's results | Normal values |
|---|---|---|
| Complete blood count | | |
| Hemoglobin (g/dL) | 13.2 | 11.5-15.5 |
| Leukocytes (/mm$^3$) | 8000 | 4000-10000 |
| Platelets (/mm$^3$) | 288000 | 150000-500000 |
| Metabolic panel | | |
| Creatinine (mg/dL) | 0.24 | 0.50-0.90 |
| ASAT (UI/L) | 34.99 | <29 |
| Alcaline phosphatase (UI/L) | 517.56 | <141 |
| γGT (UI/L) | 410.47 | <37 |
| C-reactive protein (mg/L) | 57.67 | <3 |
| HbA1C (%) | 5.8 | 45022 |
| Electrolytes-Blood | | |
| Sodium (mmol/L) | 139 | 135-145 |
| Chloride (mmol/L) | 98.4 | 92-104 |
| Potassium (mmol/L) | 3.9 | 3.5-5.1 |

| | | |
|---|---|---|
| Blood osmolality (mOsm/Kg) | 299.6 | 280-290 |
| Electrolytes-Urine | | |
| Sodium (mmol/L) | 16 | |
| Potassium (mmol/L) | 6.3 | |
| Chloride (mmol/L) | 14 | |
| Urine osmolality (mOsm/Kg) | 122 | 100-1400 |
| Tumor markers | | |
| Ca 15-3 (KU/L) | 29.06 | <30 |
| Ca 19-9 (KU/L) | 140.4 | <37 |
| Carcinoembryonic antigen (ng/ml) | 43.3 | <10 |
| Additional workup | | |
| ADH(ng/L) | 0.8 | <14.1 |
| Prolactine (ng/ml) | 24.00 | 3.2-23.3 |
| Morning Cortisol (nmol/l) | 384.1 | 101.2-535.7 |
| Morning ACTH (ng/L) | 17.2 | 22037 |
| PTH (pg/ml) | 59.21 | 15-65 |

A cerebral MRI showed a prominent aspect of the pituitary gland with no other abnormalities. An enhanced pituitary MRI showed a pituitary stalk thickening with a diameter of 6.2 mm and a bright spot (an area of hyperintensity in the posterior pituitary observed in sagittal views on T1-weighted images). The patient was then lost to follow-up as she moved to Canada. Two years later, she developed increasing abdominal, back and bilateral leg pain. She underwent a thoracic, abdominal and pelvic CT scan, which showed the following abnormalities: A mediastinal nodal enlargement, a normal-size but slightly heterogeneous liver with a 6 mm hypodense nodule in the left liver, a prominent pancreatic body and multiple hyperdense round images in several vertebral bodies. Tumor markers CEA and Ca 19-9 were within normal ranges [13]. CT-guided bone biopsy of a vertebral body revealed a clonal neoplastic proliferation with the expression of the markers CD1a, CD207 and S100, as well as an eosinophilic granuloma including eosinophils, neutrophils, lymphocytes, macrophages and Langerhans cells. This was consistent with the diagnosis of langerhans cell histiocytosis. The patient was referred to medical oncology for assessment and treatment.

## Results and Discussion

Central Diabetes Insipidus (CDI) is characterized by decreased AVP release leading to decreased renal water reabsorption that may be caused by neoplasms of the hypothalamic/pituitary area (craniopharyngioma, meningioma, germinoma and metastasis), infiltrative diseases like sarcoidosis or histiocytosis, traumatic events, neurosurgical operations or anoxia of the brain and which in some cases have no clinical explanation (idiopathic). In the first case, the patient had had polyuria and polydipsia for at least 3 years. She arrived with an advanced metastatic mixed cancer with involvement of the hypothalamus-pituitary complex. She presented with features of a metastatic digestive adenocarcinoma (cytology of ascites fluid, elevated CA 19-9 and CEA values, metastasis on radiology, rapid evolution). She had radiological and histological features of Multiple Endocrine Neoplasia type 1 (pancreatic and pituitary tumors, high chromogranin A/synaptophysin/and CD56 expression…). However, the age of the patient, the absence of family history and the rapid progression of the tumor were more in favor of an advanced metastatic digestive tumor with a pituitary metastasis. Although the differentiation of a pituitary metastasis from other pituitary tumors can be difficult on imaging, the presence of a digestive tumor with metastasis to the liver and peritoneal carcinomatosis, as well as the invasive character of the tumor, were all in favor of a pituitary metastasis. Pituitary metastasis is very rare. Among intracranial masses, pituitary metastasis only accounts for 1 to 3.8% of masses. According to a review performed by Javanbakht et al., the total number of reported pituitary metastases over a period of 60 years between 1957 and 2018 was only 289, with slightly more than half of patients being females, aged 56.6 on average. Although the most

common pituitary metastases originate from the breast and lungs, any type of solid or hematological cancer can metastasize to the pituitary fossa. The tumor cells can reach the pituitary either *via* the hypothalamus-hypophyseal portal circulation system, causing tumor cells to spread to the anterior pituitary or hematogenous spread through the inferior hypophyseal artery, causing tumor cells to spread to the posterior pituitary; extension of parasellar malignancies to the pituitary fossa and spread through the cerebrospinal fluid are also possible. The prognosis is poor following the diagnosis of a pituitary metastasis and patients die within a few months. The main cause of death is the progression of the primary tumor. Our first case was exceptional, as it involved a pituitary metastasis from a mixed digestive tumor with neuroendocrine and adenocarcinoma features. Our patient's prognosis was poor given the metastatic spread of the tumor and the pituitary involvement. The aggressive development of the carcinosis ultimately led to the patient's death. An important presentation and red flag of mixed metastatic digestive adenocarcinoma/ neuroendocrine was polyuria and polydipsia, which turned out to be CDI caused by the large infiltrating pituitary tumor. The compression and displacement of the pituitary, which was infiltrated by the tumor, probably disrupted AVP release from the hypothalamus, which explains the low AVP blood levels and the development of CDI. In fact, the extension of the tumor to the hypothalamus can lead to the destruction of supraoptic and paraventricular nuclei, disrupting the production of posterior pituitary hormones, including AVP, which leads to CDI.

In our second case, the underlying cause of CDI was Langerhans Cell Histiocytosis (LCH). LCH is a rare disease characterized by the abnormal proliferation of mononuclear phagocytes. The clinical presentation of LCH is widely variable, as it can range from single eosinophilic indolent lesions to life-threatening multisystem disease. While the incidence among children younger than 15 years of age is 4 to 5 cases per million per year, the incidence among adults is 1 to 2 cases per million per year, making LCH a very rare disease, especially among the adult population. The most commonly affected system is the skeleton, as 80% of patients with LCH present bone lesions. Hence, our patient's presentation was very rare, given the low incidence of langerhans cell histiocytosis in the general population and among adults and the initial involvement of the pituitary stalk. Since the pituitary stalk has a critical location, the biopsy of lesions in this area is very delicate and difficult to perform, so the diagnosis is usually based on other accessible sites when present, such as bone or skin lesions. In our case, the delayed appearance of bone lesions, 2 years after the initial CDI presentation, was helpful for the final diagnosis. We confirmed the diagnosis by vertebral body biopsy, which showed the specific markers CD1a, CD207 (Langerin) and S100.

Every clinician should be aware of the significance of polyuria and polydipsia. A series of advanced paraclinical and biological testing may be necessary to search for a rare underlying cause presenting with such symptoms. These cases are important to show that CDI can be an early clinical presentation and red flag of rare diseases. The clinician should perform a multisystem workup when needed, as the dysfunction of an organ could be due to a multisystem disease and the presentation may sometimes be atypical. In the case of CDI with a normal MRI or nonspecific pituitary lesion, after performing a full clinical examination, complemented by biochemical blood tests including pituitary hormones, a specific evaluation should be done to screen for several diseases, such as LCH, primary hypophysitis, sarcoidosis and germinoma.

## Conclusion

CDI can be an important feature of multisystem diseases and a red flag for neoplastic diseases. In our cases, it was a key feature of a metastatic mixed digestive tumor and an initial presentation of LCH. Physicians should be fully aware of the possible etiologies of CDI, which should be properly investigated with an oriented workup. In the case of CDI, brain imaging is important and should be complemented by additional workup in order to establish the etiological diagnosis.

## References

1. Refardt J (2020) Diagnosis and differential diagnosis of diabetes insipidus: Update. Best Pract Res Clin Endocrinol Metab 34:101398
2. McCormick PC, Post KD, Kandji AD, Hays AP (1989) Metastatic carcinoma to the pituitary gland. Br J Neurosurg 3:71-79
3. Javanbakht A, D'Apuzzo M, Badie B, Salehian B (2018) Pituitary metastasis: A rare condition. Endocr Connect 7:1049-1057
4. Max MB, Deck MD, Rottenberg DA (1981) Pituitary metastasis: Incidence in cancer patients and clinical differentiation from pituitary adenoma. Neurology 31:998-1002
5. Sioutos P, Yen V, Arbit E (1996) Pituitary gland metastases. Ann Surg Oncol 3:94-99
6. Komninos J, Vlassopoulou V, Protopapa D, Korfias S, Kontogeorgos G, et al. (2004) Tumors metastatic to the pituitary gland: Case report and literature review. J Clin Endocrinol Metab 89:574-580
7. Shimon I (2020) Metastatic spread to the pituitary. NEN 110:805-808
8. Morita A, Meyer FB, Laws ER (1998) Symptomatic pituitary metastases. J Neurosurg 89:69-73
9. Habu M, Tokimura H, Hirano H, Yasuda S, Nagatomo Y, et al. (2015) Pituitary metastases: Current practice in Japan. J Neurosurg 123:998-1007
10. Allen CE, McClain KL (2018) Langerhans-cell histiocytosis. N Engl J Med 13
11. Su M, Gao Y-J, Pan C, Chen J, Tang J-Y (2018) Outcome of children with Langerhans cell histiocytosis and single-system involvement: A retrospective study at a single center in Shanghai, China. Pediatr Hematol Oncol 35:385-392
12. Weitzman S, Egeler RM (2005) Histiocytic disorders of children and adults: Introduction to the problem, overview, historical perspective and epidemiology. Histiocytic Disorders Children Adults 1:13
13. Christ-Crain M, Winzeler B, Refardt J (2021) Diagnosis and management of diabetes insipidus for the internist: An update. J Intern Med 290:73-87