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Double Trouble – Severe Hypernatremia Secondary to Central Diabetes Insipidus Complicated by Hypercalcemic Nephrogenic Diabetes Insipidus: A Case Report

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Patient: Female, 40
Final Diagnosis: Combined central and nephrogenic diabetes insipidus
Symptoms: Confusion • polyuria
Medication: —
Clinical Procedure: —
Specialty: Nephrology

Objective: Rare disease

Background: Patients with malignancies often have electrolyte abnormalities. We present a case of a patient with central diabetes insipidus secondary to metastatic pituitary invasion complicated by hypercalcemic nephrogenic diabetes insipidus.

Case Report: We present a case of 40-year-old female with a history of stage IV breast cancer with skeletal and leptomeningeal metastasis, who was admitted with polyuria, polydipsia, and recent onset of confusion. The patient was found to have profound hypernatremia and severe hypercalcemia with normal parathyroid and vitamin D serum levels. Urine studies showed low urine osmolality and high urine output, despite the higher serum osmolality. The patient received 5% dextrose for rehydration, 1 dose of intravenous (IV) pamidronate, 1 dose of IV desmopressin, and 4 days of subcutaneous calcitonin 200 international units Q12H. Initially, her urine output in the hospital was in the range of 350–400 milliliters/hour, which responded well to 1 dose of 1-desamino-8d-arginine vasopressin (DDAVP). In the subsequent days, her confusion resolved with normalization of serum sodium and calcium, but she died because of the extensive malignancy.

Conclusions: Our case emphasizes the importance of identification of causes and complications of electrolyte abnormalities associated with metastatic cancers. These electrolyte abnormalities can be primary or paraneoplastic and should be actively pursued and treated in such cases.

MeSH Keywords: Diabetes Insipidus • Hypercalcemia • Hypernatremia • Polyuria

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Background

The serum sodium concentration is strictly controlled by water homeostasis, which is mediated by thirst, antidiuretic hormone (ADH), and the renin-angiotensin-aldosterone system. A disruption in the water balance leads to abnormality in the serum sodium concentration (hyponatremia, with serum sodium <135 milliequivalent) or hypernatremia (serum sodium >145 milliequivalents) [1]. ADH is synthesized in the hypothalamus and is stored and secreted by the posterior pituitary in response to higher serum osmolality to absorb free water at distal convoluting tubules of the kidney [2]. Among the several causes of hyponatremia due to excessive secretion of ADH leading to a syndrome of inappropriate antidiuretic hormone (SIADH), malignancy is one of the most likely causes of SIADH. Small cell lung cancer is the most common malignancy associated with hyponatremia due to ectopic ADH production by cancer cells. Hypernatremia of malignancy might be due to anticancer drug therapy blocking ADH production or its action on renal tubules. Anticancer drugs can cause hypovolemic hyponatremia, as well as drug-induced diarrhea and vomiting [3]. Diabetes insipidus (DI) is due to loss of ADH function, which is characterized by hypotonic polyuria (urine output > 3 liters/day with a urine osmolality < 250 milliosmoles/kilogram) with extensive compensatory polydipsia and hypernatremia [4,5]. DI is an uncommon condition with a prevalence of 1: 25 000. DI equally affects males and females, with a 1: 1 ratio. Fewer than 10% of cases are inherited, and of these, about 90% are X-linked, with a frequency of 4–8/million male live births, and the remaining 10% of cases are autosomally inherited. All inherited cases are NDI type. Age of disease onset depends upon underlying etiology. DI has 2 types. The first and most common is central diabetes insipidus (CDI), which results from impaired synthesis or release of ADH from the posterior pituitary gland due to underlying hereditary or acquired conditions. Stroke, traumatic brain injury, neurosurgery, and primary or secondary pituitary tumors are some of the common causes of CDI. The second and less frequent is cause is nephrogenic diabetes insipidus (NDI), which stems from failure of the kidneys to respond to ADH secondary to drugs (e.g., lithium, foscarnet, and clozapine) or electrolyte disturbances typically due to hypercalcemia and/or hypokalemia [6].

DI (CDI and NDI), like many other conditions such as psychogenic polydipsia, diuretics, or alcohol abuse, is a polyuria state. Correct diagnosis is mandatory, as some causes are reversible and treatment varies between the 2 types of DI. The water deprivation test is diagnostic for DI because it can differentiate between other polyuric states. Serum and urinary electrolytes and osmolality are tested before and after ADH ingestion. Sometimes, an accurate diagnosis cannot be made due to improperly performed laboratory tests. However, difficulties may arise due to body weight, urine volume, and serum and urine osmolality measurements [7].

In DI, hypernatremia can impair normal neuronal functioning, and it can lead to confusion, psychosis, seizure, or coma, or no symptoms at all, depending on the acuity *vs.* chronicity of development of hypernatremia [8,9]. We present the case of a patient with metastatic pituitary cancer who presented with polyuria and polydipsia and was found to have hypercalcemia, which responded to DDAVP (1-desamino-8d-arginine vasopressin).

Case Report

Our patient was a 40-year-old white female with a history of metastatic stage 4 estrogen (ER) and progesterone receptor (PR)-positive and HER2 receptor-negative breast cancer (Ca). It metastasized to bone, lung, liver, and leptomeninges. She underwent lumpectomy of breast Ca and received her last dose of chemotherapy a few days before her hospital admission. She was initially getting doxorubicin, which was changed recently to eribulin. The family reported that she was having confusion, excessive thirst (5 gallons of water intake), and excessive urination. On presentation, she was febrile and hypotensive with a mean arterial pressure (MAP) in the 50s, tachycardia, and tachypnea. The patient was intubated on arrival at the hospital. A physical exam showed sunken eyeballs, reduced skin turgor, no jugular venous distension (JVD), no pedal edema, and no focal neurological deficit. Her weight on admission was 48 kg. On workup, she was found to have hypernatremia (167 milliequivalents/liter [mEq/L]) and hypercalcemia (16.5 milligrams/deciliter [mg/dL]). Serum and urine electrolytes are shown in Table 1. Other relevant lab studies were parathyroid hormone (PTH)=24 picogram/mL, PTH-related peptide (PTH-rP)=2.4 picomol/L, 25-OH vitamin D=25.9 nanogram/mL, serum phosphate=2.2 mg/dL, creatinine=0.8 mg/dL, blood urea nitrogen (BUN)=13 mg/dL, random blood sugar 158 mg/dL, serum potassium 3.2 mEq/L, WBC count 2.8×10^9/L, hemoglobin 7.9 g/dL, hematocrit 25%, and platelet count 65×10^9/L. Arterial blood gases done on admission showed pH 7.43, pCO2 37.4 mmHg, pO_2 184 mmHg, and bicarbonate 25.3 mmol/L. She had a free water deficit of 5.6 L. Hypotonic 5% dextrose was started at 150 mL/h intravenously. One dose of intravenous (IV) pamidronate 90 mg, desmopressin (DDAVP) 2 microgram, and 4 days of subcutaneous calcitonin 200 international units (IU) every 12 h were given. Initially, urine output in the hospital was 350–400 mL/h, which reduced to 50–150 mL/h (Table 1). In the subsequent days, serum sodium and calcium levels normalized. Unfortunately, the patient died a few days later due to extensive tumor burden.

Discussion

Individuals with malignancies are at risk of several fluid and electrolyte abnormalities stemming from their paraneoplastic

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Table 1. Urine and serum electrolyte and urine output trends.

Timeline and trends	Serum Na mEq/L	Serum osmolality mOsm/kg	Urine Na mmol/L	Urine osmolality mOsm/kg	Serum Ca mg/dL	Urine output mL/hour
Baseline – Prior to admission	151	334	20	115	8.8	N/A
Day 0 – On admission	167	347	72	185	16.5	350–450
Day 1 (DDAVP + Calcitonin + Pamidronate)	158	N/A	189	451	12.2	100–150
Day 2	158	N/A	N/A	N/A	11.5	50–150
Day 3	148	303	151	455	9.3	75–150

Na – Sodium; Ca – Calcium; N/A – not available; DDAVP – desmopressin; mOsm – milliosmoles; kg – Kilogram; mmol – millimoles; mg – milligrams; dL – deciliter; L – liters; mL – milliliters; mEq – milliequivalent.

processes and the aggressive chemotherapy regimen. Common abnormalities include hyponatremia from SIADH, hypercalcemia, or, rarely, hypernatremia from CDI as a result of local compression of pituitary by distant cancer metastasis. Lung and breast cancers are the most common malignancies to metastasize hematogenously to the pituitary, with a predilection for the posterior pituitary lobe due to direct blood supply from circulation, thus causing CDI. Most cases with pituitary metastasis are asymptomatic except for the 2.5–18% of patiends who present with a DI history [10]. There have been cases reported in which CDI was the first presenting symptom of underlying malignancy [11]. Hypercalcemia in advanced malignancy is probably the common electrolyte imbalance, affecting up to 1 in 5 cancer patients during the course of their disease [12]. It is particularly prevalent in breast, lung, and hematologic malignancies and often results from multiple entities such as PTH-rP-induced osteolysis, hypercalcemia related to osteolytic metastases, and 1, 25 vitamin D-mediated hypercalcemia. PTH-rP acts on osteoblasts, leading to the enhanced synthesis of RANKL, which subsequently activates osteoclasts and results in bone resorption with calcium release into the bloodstream. PTH-rP also enhances calcium reabsorption at the level of the kidney [13]. Cancer-related hypercalcemia is most commonly due to the systemic release of these bone-resorbing factors such as PTH-rP rather than local bone dissolution [14]. Studies show that PTH-rP level was over 1.5 pmol/L in more than 90% of patients with nonhematological malignancies [15].

Hypercalcemia of malignancy can cause NDI by decreasing the sensitivity of distal nephrons to ADH, leading to polyuria and dehydration. One studied underlying mechanism is that higher calcium level in distal convoluted tubules causes autophagic degradation of aquaporin-2 and decreased expression of aquaporin-2 on the tubular surface, which leads to a decreased sensitivity of distal convoluted tubular cells to ADH [16,17].

Patients with DI with underlying malignancy present mainly with symptoms of persistent polyuria (8–16 L of dilute urine per day) and polydipsia (intake of up to 20 L fluid per day). Other symptoms may be present due to hypernatremia secondary to free water loss, such as fatigue, weakness, signs of dehydration (dry skin and mucous membranes, weight loss, hypotension, and tachycardia), dizziness, personality changes, altered level of consciousness, and. A 24-h total urine volume is used to confirm polyuria [6]. The water deprivation test is the criterion standard test to differentiate DI from primary polydipsia (psychogenic polydipsia) in a patient with a history of polyuria and polydipsia. In DI, the primary pathology is polyuria, which leads to compensatory polydipsia, while in primary polydipsia, the main pathology is excessive water intake, which leads to polyuria. In healthy individuals, water deprivation causes a rise in plasma osmolality above 280–290 mOsm/kg, which leads to the release of ADH from the posterior pituitary gland into the systemic circulation. In the collecting ducts of the kidney, ADH binds to the vasopressin type 2 receptor, followed by expression of aquaporin 2 channels, thereby resulting in increased water reabsorption, with a rise in urine osmolality up to a maximum of 1000–1200mOsm/kg and fall in plasma osmolality towards the reference range. In DI, hypotonic polyuria continues upon water deprivation, despite the presence of high plasma osmolality. During water deprivation, body weight and urine osmolality are measured hourly [18]. The test is stopped when 2–3 samples vary by <30 mOsm/kg (or <10%), or until the patient loses 5% of body weight [6]. Previously, serum ADH level towards the end of the water deprivation test was used to differentiate between CDI and NDI, but due to its short half-life and instability, it is not recommended. The desmopressin challenge test serves this purpose well and recent small studies suggest using copeptin, which is co-secreted with ADH precursor physiologically [18]. The diagnostic algorithm of DI is described in Figure 1 [6].

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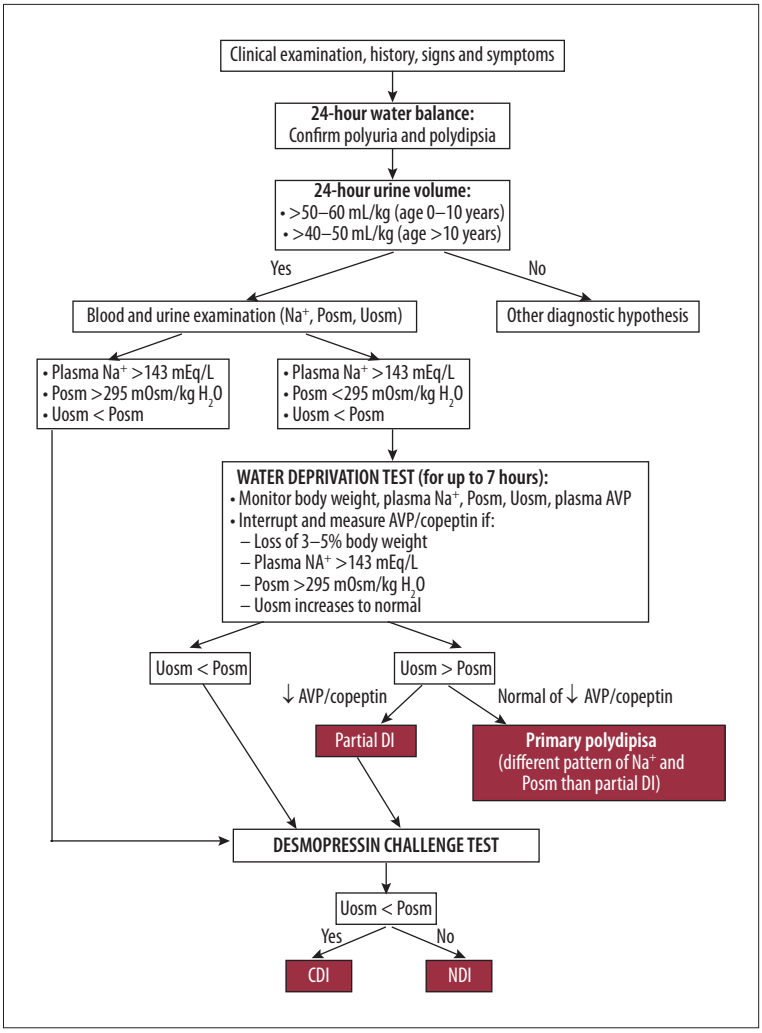

Figure 1. Diagnostic algorithm for CDI and NDI. AVP – arginine vasopressin (ADH); Posm – plasma osmolality; |Uosm – urine osmolality.

Bisphosphonates administration is at present the mainstay of tumor-related hypercalcemia management, while calcitonin, gallium nitrate, and mithramycin have limited activity and several adverse effects [19]. Anti-RANKL therapy (denosumab) and antibodies against PTH-rP are promising therapies, but their clinical use is not well studied. The hypercalcemia-induced nephrogenic component of CDI can lead to a subnormal response to desmopressin administration and delay the final diagnosis. This may have been the situation with our patient. Such patients require prompt treatment of both hypernatremia and hypercalcemia with rehydration, calcitonin, and bisphosphonates [20]. Hypernatremia secondary to DI should be corrected slowly to avoid serious complications. Organic osmolytes accumulated during the adaptation to hypernatremia are slow to leave the cells during rehydration. Therefore, if the hypernatremia is corrected too rapidly, cerebral edema can result due to relatively more hypertonic ICF accumulating water. To avoid cerebral edema, the rate of correction should not exceed 10–12 mEq/liter/day [8]. At our hospital-based setting in the city center of Philadelphia, we encounter few NDI patients and even fewer CDI patients. CDI and simultaneous hypercalcemia NDI is rarely seen.

Conclusions

Our case emphasizes the importance of identification of causes and complications of electrolyte abnormalities associated with metastatic cancers. These electrolyte abnormalities can be primary or paraneoplastic and should be actively pursued and treated in such cases.

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