CLINICAL PROBLEM-SOLVING

Stalking the Diagnosis

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In this Journal *feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors' commentary follows.*

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A 58-year-old woman presented to her primary care physician after several days of dizziness, anorexia, dry mouth, increased thirst, and frequent urination. She had also had a fever and reported that food would "get stuck" when she was swallowing. She reported no pain in her abdomen, back, or flank and no cough, shortness of breath, diarrhea, or dysuria. Her history was notable for cutaneous lupus, hyperlipidemia, osteoporosis, frequent urinary tract infections, three uncomplicated cesarean sections, a left oophorectomy for a benign cyst, and primary hypothyroidism, which had been diagnosed a year earlier. Her medications were levothyroxine, hydroxychloroquine, pravastatin, and alendronate. She lived with her husband and had three healthy adult children. She had a 20-pack-year history of smoking but had quit 3 weeks before presentation. She reported no alcohol or drug abuse and no exposure to tuberculosis. Her family history included oral and bladder cancer in her mother, Graves' disease in two sisters, hemochromatosis in one sister, and idiopathic thrombocytopenic purpura in one sister.

An Interactive Medical Case related to this Clinical Problem-Solving article is available at NEJM.org

This patient is urinating frequently and has a fever, which may suggest a urinary tract infection. Dizziness is a common and often vague presenting symptom; it is important to obtain a more detailed description of exactly what she means by "dizzy." In this patient, poor oral intake and fever could be contributing to volume depletion. With a family history of autoimmune thyroid disease and hemochromatosis, diabetes mellitus should be ruled out, as should other causes of polyuria, such as hypercalcemia, hypokalemia, and renal failure. In addition, the patient's dysphagia could be the result of esophagitis caused by alendronate, which should be withheld; further evaluation will be needed if the dysphagia persists.

On physical examination, the patient was afebrile. Her weight was 57.6 kg (127 lb), her blood pressure 120/70 mm Hg, and her heart rate 90 beats per minute. She appeared pale and nonicteric. The rest of her examination was reportedly unremarkable.

The white-cell count was 5200 per cubic millimeter, with 67% neutrophils, 14% lymphocytes, 7% monocytes, 11% eosinophils, and 1% basophils. Her hematocrit was 36.3%, and her platelet count 476,000 per cubic millimeter. The serum sodium level was 135 mmol per liter; potassium, 4.3 mmol per liter; bicarbonate, 26 mmol per liter; blood urea nitrogen, 7 mg per deciliter (2.5 mmol per liter); creatinine, 1.4 mg per deciliter (124 μmol per liter); glucose, 80 mg per deciliter (4.4 mmol per liter); and thyrotropin, 4.7 mIU per liter. A urine dipstick was positive for leukocyte esterase and nitrites. The patient was given a prescription for ciprofloxacin for a urinary tract infection and was advised to drink plenty of fluids.

On a follow-up visit with her physician 3 days later, her fever had resolved, but she reported continued weakness and dizziness despite drinking a lot of fluids. She felt better when lying down. Her supine blood pressure was 120/80 mm Hg, and her pulse was 88 beats per minute; on standing, her systolic blood pressure was 84 mm Hg, and her pulse was 92 beats per minute. A urine specimen obtained at her initial presentation had been cultured and grew more than 100,000 colonies of *Escherichia coli,* which is sensitive to ciprofloxacin. Another series of laboratory studies revealed serum sodium levels of 137 mmol per liter; potassium, 3.4 mmol per liter; chloride, 98 mmol per liter; bicarbonate, 24 mmol per liter; blood urea nitrogen, 3 mg per deciliter (1.1 mmol per liter); and creatinine, 1.1 mg per deciliter (98 μmol per liter). The levels of other electrolytes and the results of a complete blood count were essentially unchanged, and liver function was normal. The patient was referred to the emergency department, where she received normal saline and supplemental potassium, and her symptoms abated. She was discharged with instructions to complete a 1-week course of ciprofloxacin. One week later, she returned to the emergency department with continued weakness, frequent urination, intermittent vomiting, dysphagia, and increased thirst and fluid intake.

Persistent dizziness and orthostasis suggest hypovolemia despite robust fluid intake. Urosepsis is possible but seems unlikely, given the appropriate antibiotic selection, assuming the patient is taking it as directed. Vomiting could also explain the hypovolemia and hypokalemia, but one would then expect a contraction alkalosis, and her serum bicarbonate level is 24 mmol per liter. Furthermore, the ratio of blood urea nitrogen to creatinine does not suggest clinically significant volume contraction. Although the polydipsia may be driven by hypovolemia, other causes of polydipsia should be explored. The serum glucose level is normal. The patient could have diabetes insipidus, manifested as urinary frequency, but her initial hyponatremia argues against this diagnosis. In addition, diabetes insipidus does not usually cause clinically significant volume contraction and would not explain her symptoms of dysphagia and intermittent vomiting, which need to be explored more thoroughly.

A review of symptoms revealed difficulty swallowing and occasional emesis of solid foods because of a feeling of "sandlike" dryness in her mouth; she also had an involuntary weight loss of 4.5 kg (10 lb) over the past month. She reported no hematemesis and no cardiac, pulmonary, neurologic, or visual problems.

On physical examination, her temperature was 37.2°C; pulse, 89 beats per minute; blood pressure, 100/60 mm Hg; respiratory rate, 18 breaths per minute; and oxygen saturation, 98% while she was breathing ambient air. Her mucous membranes were dry, and she had angular cheilosis. Physical examination revealed a nontender left cervical lymph node, 2 cm in diameter; her thyroid, lungs, heart, breasts, and abdomen were normal. She had no hepatomegaly or splenomegaly and no edema, cyanosis, or clubbing. Neurologic examination showed no focal deficits, although she had a flat affect.

Additional testing showed a serum sodium level of 132 mmol per liter; potassium, 2.9 mmol per liter; chloride, 96 mmol per liter; bicarbonate, 25 mmol per liter; blood urea nitrogen, 4 mg per deciliter (1.4 mmol per liter); creatinine, 0.9 mg per deciliter (80 μmol per liter); glucose, 94 mg per deciliter (5.2 mmol per liter); calcium, 8.8 mg per deciliter (2.1 mmol per liter); magnesium, 1.3 mg per deciliter (0.5 mmol per liter); phosphorus, 2.7 mg per deciliter (0.9 mmol per liter); and albumin, 3.4 g per deciliter. Her white-cell count was 6700 per cubic millimeter, her hematocrit 37%, and her platelet count 438,000 per cubic millimeter.

The patient continues to have clinical signs of dehydration. Fluid and electrolyte repletion would be reasonable steps in her care at this point, while the search continues for the underlying cause or causes of her condition. The palpable left cervical lymph node is of concern and warrants further evaluation, including biopsy, to determine whether there may be a tumor.

The patient's history of cutaneous lupus and hypothyroidism, as well as her family history of autoimmune disease, suggests that an associated autoimmune disorder, such as Sjögren's syndrome, may be causing dry mouth or that scleroderma or polymyositis may be causing esophageal dysmotility and dysphagia.

Her mild hyponatremia remains unexplained. Determining the status of her blood volume is critical for identifying the cause of the hyponatremia. The syndrome of inappropriate secretion of antidiuretic hormone can be manifested as hy-

ponatremia and as low levels of blood urea nitrogen, but this syndrome is generally associated with euvolemia, and the patient's very low level of blood urea nitrogen may alternatively be explained by protein malnutrition or liver disease. Her symptoms and the findings on physical examination suggest volume depletion. Primary adrenal insufficiency could cause hypovolemia and hyponatremia, both of which can result from mineralocorticoid deficiency, although this deficiency is typically associated with hyperkalemia. Hyponatremia can also be caused by glucocorticoid deficiency, which can alter renal tubular water excretion and diminish the tonic physiologic central inhibition of vasopressin by cortisol. I would measure urinary output and check the urine specific gravity and sodium concentration. Measuring the serum cortisol level is also warranted.

The patient was admitted for intravenous hydration, management of electrolyte disturbances, and further evaluation. She was hydrated with normal saline, with 5% dextrose and 20 mmol of potassium chloride per liter. Laboratory studies the next morning showed normalization of serum sodium and potassium levels to 139 and 3.8 mmol liter, respectively. The sodium level in a randomly collected urine specimen was under 10 mmol per liter. The serum cortisol level in a blood specimen obtained in the morning was 3.2 μg per deciliter (89 nmol per liter). A chest radiograph was normal, and an evaluation of speech and swallowing revealed no functional swallowing impairment. Tests for antinuclear antibodies, rheumatoid factor, and anti-Rho, anti-La, and anti–SCL-70 antibodies were negative. The patient was scheduled for a biopsy of the left cervical lymph node and computed tomographic (CT) scans of the chest, abdomen, and pelvis.

On the second hospital day, transient hypotension developed after the intravenous fluids had been discontinued. Treatment with intravenous fluids was resumed and high-dose dexamethasone was administered, and her blood pressure returned to normal. After the administration of 250 μg of cosyntropin intravenously, the serum cortisol level rose from a baseline of 2.5 μg per deciliter (69 nmol per liter) to 13.0 μg per deciliter (359 nmol per liter) at 30 minutes and to 18.2 μg per deciliter (502 nmol per liter) at 60 minutes.

A stimulated cortisol level above 18 μg per deciliter 60 minutes after the administration of synthetic corticotropin indicates that the adrenal glands are capable of responding normally to corticotropin. This response, coupled with the patient's low basal cortisol level, suggests secondary adrenal insufficiency of recent onset. This condition probably explains her initial hyponatremia. Imaging of her pituitary gland is warranted.

Chest, abdominal, and pelvic CT scans revealed axillary, mediastinal, upper abdominal, retroperitoneal, and pelvic lymphadenopathy (Fig. 1). No lesions were seen in the liver or the lung parenchyma or adnexa. The next day, the patient was scheduled for biopsy of the left cervical lymph node. Although she was taking nothing by mouth, her serum sodium level increased over a period of several hours, from 144 to 159 mmol per liter, without any change in blood pressure or mental status. With an infusion of 5% dextrose and liberalization of water intake, the serum sodium level normalized. The serum osmolality was 332 mOsm per kilogram, the urine osmolality was 106 mOsm per kilogram, and the specific gravity of urine was 1.004. Her urine output was 4 liters over a period of 24 hours.

The development of hypernatremia during a period of fluid restriction and glucocorticoid replacement suggests diabetes insipidus, which is likely to be of pituitary–hypothalamic origin given the concurrent diagnosis of secondary adrenal insufficiency. Testing is warranted to assess other pituitary hormonal axes. Although it is generally preferable to measure the thyroxine level rather than the thyrotropin level in order to screen for

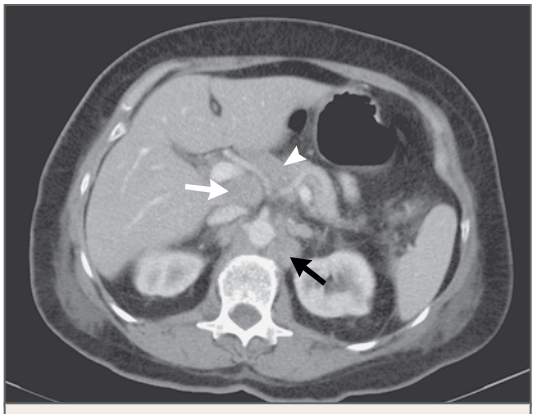

Figure 1. CT Scan of the Lymph Nodes.
The CT scan shows enlargement of a portocaval lymph node (white arrow), a left para-aortic lymph node (black arrow), and a celiac lymph node (arrowhead).

central hypothyroidism (since the level of thyrotropin may be normal), this patient is likely to have a normal thyroxine level, given the administration of levothyroxine. Normally, high levels of follicle-stimulating hormone would be expected in a postmenopausal woman; a low level would suggest secondary hypogonadism. A low level of insulin-like growth factor 1 (IGF-1) (also called somatomedin C) would suggest a deficiency of growth hormone, but there is already ample evidence of a central process. I would proceed with magnetic resonance imaging (MRI) of the pituitary to look for a mass or infiltrative lesion of the pituitary–hypothalamic axis, particularly given the worrisome findings on the CT scans. My major concern at this point is cancer, with lymphoma and metastatic solid tumor high on the list. Less likely possibilities would be sarcoidosis, autoimmune destruction of the pituitary, or tuberculosis.

The serum thyrotropin level was 0.703 mU per liter (normal range, 0.5 to 5.0) and the total thyroxine level 6.4 μg per deciliter (normal range, 5.0 to 11.0); the thyroid-binding hormone ratio was 1.09. The prolactin level was 14.6 ng per milliliter (normal range, 2.7 to 26.7); follicle-stimulating hormone, 6.3 mIU per milliliter; luteinizing hormone, 0.7 mIU per milliliter; and IGF-1, 47 ng per milliliter (normal range, 42 to 272). An MRI scan of the brain revealed a symmetric gadolinium-enhancing mass (1.0 cm by 1.0 cm by 1.1 cm) at the base of the third ventricle, surrounding the infundibular recess, without impingement on the optic tracts (Fig. 2). The pituitary gland was normal in size and signal intensity. The results of radiography suggested lymphoma or sarcoidosis; lymphocytic hypophysitis, eosinophilic granulomatosis, and metastatic disease were considered less likely. A biopsy specimen of the left cervical lymph node showed features of a reactive process, with no diagnostic features of a malignant or lymphoproliferative disorder. The results of flow cytometry were negative.

The MRI results confirm the suspicion that a mass lesion in the area of the hypothalamus is causing pituitary insufficiency. In light of the diffuse lymphadenopathy, I am particularly concerned about the possibility of lymphoma or another malignant condition. The negative biopsy results do not rule out the possibility of an underlying cancer, and further tissue confirmation must be pursued.

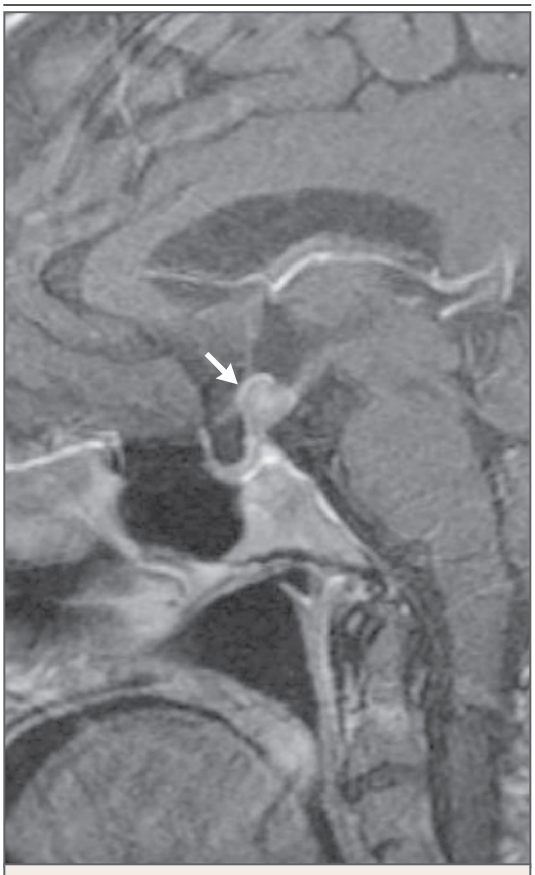

Figure 2. MRI Scan of the Brain.
A symmetric, gadolinium-enhancing mass (arrow), measuring 1 cm by 1 cm by 1.1 cm, can be seen at the base of the third ventricle, surrounding the infundibular recess.

Prednisone, at a dose of 7.5 mg daily, was substituted for dexamethasone, and the patient was treated with desmopressin acetate, after which her urine output normalized and her serum sodium level remained normal. Despite the negative results obtained on biopsy of the left cervical lymph node, clinical suspicion of lymphoma remained high; there was concern that the stress doses of glucocorticoids administered earlier during this admission may have masked the findings of lymphoma in the biopsy specimen. The patient was discharged home with a plan to return in 3 weeks for further imaging and another biopsy.

A biopsy of the left axillary lymph node performed 3 weeks later showed breast carcinoma, with negative results for estrogen and progesterone receptors and positive results for human epidermal growth factor receptor type 2 (HER2) and with extranodal extension and extensive lymphovascular invasion (Fig. 3). A mammogram revealed

a spiculated mass with a diameter of 0.5 cm in the left breast, which had not been seen on a mammogram obtained 18 months earlier. To confirm the presence of metastatic rather than node-positive disease, a biopsy of the hypothalamic lesion was performed, which showed breast carcinoma that was consistent with the primary tumor. The patient had progressive failure to thrive and impairment of her thirst mechanism, which complicated the management of her diabetes insipidus. Stereotactic radiation therapy was initiated for the brain lesion. Shortly after receiving this treatment (and 4 weeks after her initial diagnosis), the patient had an aspiration episode, became unresponsive, and died from a pulseless electrical activity arrest. The family declined a postmortem examination.

COMMENTARY

Hypopituitarism can result from various conditions affecting either the pituitary or the hypothalamus, including tumors, infiltrative lesions, infarction, apoplexy, trauma, and infection; it can also be caused by radiation therapy. Only in rare instances is hypopituitarism caused by malignant primary or metastatic tumors of the pituitary. Pituitary metastasis is also an unusual manifestation of systemic cancer, with a reported incidence of 1 to 3.6% of patients with cancer.[1-4] Breast and lung cancer are the most common tumors that metastasize to the pituitary gland.[2,5-7] The posterior pituitary may be more prone to metastases because of its direct systemic supply of arterial blood, whereas the adenohypophysis receives blood from the hypophyseal portal system[2,5-8]; some investigators have reported a greater predilection for the involvement of the anterior pituitary in breast cancer.[2,9,10] Pituitary-stalk thickening, or enhancement, has been reported in cases of metastasis to the pituitary–hypothalamic axis.[7] The incidence of associated hypothalamic invasion is unknown, but retrograde degeneration of the cells in the hypothalamic nuclei in association with malignant involvement of the pituitary stalk and neurohypophysis has been described.[8]

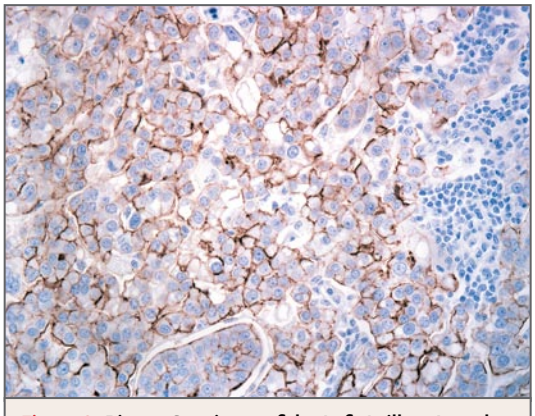

Figure 3. Biopsy Specimen of the Left Axillary Lymph Node.

The lymph node shows positive staining for human epidermal growth factor receptor type 2 (HER2), indicating the presence of ductal breast carcinoma.

Pituitary metastases are often asymptomatic. Among symptomatic cases, diabetes insipidus is the most frequently reported finding.[5,7,11-14] Headache, ophthalmoplegia, visual-field defects, and anterior pituitary dysfunction are also common in such cases. In this patient, electrolyte disturbances resulting from hormonal deficiencies were the first manifestation of underlying cancer; in such cases, differentiation from an adenoma on clinical grounds is difficult.[15]

In considering the consequences of pituitary insufficiency, it is important to look for corticotropin deficiency, which can lead to adrenal crisis and death if it is not recognized. Secondary adrenal insufficiency generally has a less dramatic presentation than primary adrenal insufficiency because aldosterone levels, which are controlled predominantly by the renin–angiotensin system, are preserved. The neurons that produce vasopressin are located in the hypothalamus and project axons to nerve terminals in the posterior pituitary gland; as a result, diabetes insipidus is seen more commonly with hypothalamic conditions than with pituitary disease. In addition to hormonal deficiencies, hypothalamic involvement is often manifested as impairment of thirst, which is regulated by osmostats in the hypothalamus, and as imbalances in energy homeostasis due to loss of normal appetite and energy regulation. Loss of circadian rhythms results in altered sleep–wake cycles. Dysregulation of body temperature, memory loss, and personality changes are also common.

This case also highlights the fact that "normal" results on hormonal testing do not necessarily indicate normality in the entire hormonal axis. As the discussant notes, an appropriate rise in the serum cortisol level in response to stimulation with corticotropin indicates that the adrenal glands

are intact, but such a rise in association with a low baseline morning cortisol level is characteristic of secondary adrenal insufficiency of recent onset. Similarly, if the thirst mechanism is intact and free water intake is sufficient, hypernatremia may not be present in patients with diabetes insipidus. This patient's presentation was particularly unusual, because she initially had low levels of serum sodium in the context of adrenal insufficiency.

This case illustrates an unusual presentation of breast cancer — that is, metastasis to the pituitary gland. In retrospect, the patient presented with a number of typical symptoms and signs of hypopituitarism, including weakness, intermittent nausea, orthostasis, polydipsia, and polyuria. Her fever and positive urine culture, as well as her dysphagia and dry mouth, initially distracted the clinicians from a consideration of the primary disease process. The recognition of the hormonal deficiencies caused by a lesion on the pituitary stalk and the reconciliation of these developments with the diffuse lymphadenopathy led to the definitive diagnosis that unified this seemingly incongruent set of clinical findings.

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