Lymphocytic Hypophysitis in a Man Presenting with Hypercalcemia

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ABSTRACT: A 59-year-old man with a 30-year history of type 2 diabetes mellitus presented with fatigue, confusion, and weight loss over a 3-month period. He was found to be hypercalcemic (11.8 mg/dL) and dehydrated, and his hypercalcemia improved with intravenous fluids. While in the hospital, he developed hypotension, hypoglycemia, and hypotension. He was found to have a subnormal cortisol level of 2.3 μg/dL at baseline, which increased to only 5.6 μg/dL 60 minutes after a 250-μg corticotropin intravenous stimulation test.

The patient developed pneumonia and adult respiratory distress syndrome and died of an acute myocardial infarction. During the autopsy, he was found to have lymphocytic hypophysitis with a severe reduction in corticotropin-producing anterior pituitary cells. No malignancy was identified at autopsy. He is the first male patient to be described in the literature who presented with hypercalcemia caused by lymphocytic hypophysitis.


Corticotropin (ACTH) and cortisol secretion increase in response to physical stress, illness, and hypoglycemia. Primary adrenal insufficiency results commonly from either autoimmune adrenalitis or tuberculosis. Secondary adrenal insufficiency results most often from exogenous glucocorticoid therapy. Other causes of secondary adrenal insufficiency include tumor of the hypothalamus or pituitary, infectious processes, infarction, hemorrhage of the pituitary, isolated ACTH deficiency, and lymphocytic hypophysitis.

Hypercalcemia is an unusual presentation of adrenal failure. The cause of hypercalcemia in glucocorticoid insufficiency is thought to be both a decrease in calcium excretion by the kidneys and an increase in calcium release from bone that may be mediated by thyroid hormone. All previously reported cases of hypercalcemia associated with secondary adrenal insufficiency were in women. The present report delineates the clinical course and pathophysiology associated with secondary adrenal insufficiency in a 59-year-old man with type 2 diabetes mellitus.

Case Report

A 59-year-old Korean man was brought in by his family, who had noted fatigue, weight loss of 60 pounds over 3 months, and a recent fall at home. He was unable to give a full history, but he did complain of right leg pain. He had been diagnosed with type 2 diabetes mellitus 30 years before, and his glycosylated hemoglobin level was 11.8% (HbA1c). He had no prior history of diabetic ketoacidosis. He denied headaches, chest pain, or abdominal pain. On physical examination, he weighed 98 pounds and was febrile, with a pulse of 75 beats/min and blood pressure of 90/60 mm Hg. His heart, lungs, and abdominal examination were unremarkable. Axillary and pubic hair were normal, and testicles were of normal size. His stool was guaiac negative. He walked with a wide, shuffling gait. Motor and sensory exams were grossly intact. Serum electrolytes were normal. Blood glucose level was 99 mg/dL, serum urea nitrogen level was 25 mg/dL, and creatinine level was 1.4 mg/dL. Hemoglobin level was 11.2 g/dL, calcium level was 11.8 mg/dL, and albumin level was 2.6 g/dL. Intact parathyroid hormone level was reduced at 3 pg/mL (reference range, 10–65 pg/mL). Urine and serum protein electrophoresis were normal, and prostate-specific antigen level was 0.3 ng/mL. Bone scan showed no lesions. Thyrotropin (TSH) level was 2.82 μIU/mL (reference range, 0.4–4.6 μIU/mL), total thyroxine level was 9.2 μg/dL (reference range, 4.5–12 μg/dL) and total triiodothyronine level was 168 ng/dL (reference range, 80–220 ng/dL).

His hypercalcemia responded to rehydration, and he was initially eating most of his meals. Serum calcium level was 10.3 mg/dL on day 2, and his corrected calcium level (0.8/g of albumin) was still mildly increased at 11.4 mg/dL (reference range, 8.5–11 mg/dL). On hospital day 8, his calcium level decreased to 10.0 mg/dL (corrected 10.8), but he developed a mild hyponatremia (130 mmol/L). On hospital day 9, his calcium was 9.5 mg/dL (corrected to 10.5 mg/dL) and his blood glucose was normal. The next day, however, his serum sodium was 118 mEq/L and he had a tonic-clonic seizure and was intubated for apnea. His head CT showed a normal sella and no hemorrhage or mass lesions. Lumbar puncture showed no cells, normal glucose, and mildly elevated protein at 100 mg/dL (reference range, 20–50 mg/dL). He developed hypothermia and became hypertensive at 60/20 mm Hg. Intravenous dopamine was started, and later norepinephrine, for

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blood pressure control. The next day (day 11), the hyponatremia had improved (124 mmol/L), but he developed hypoglycemia (56 mg/dL) while receiving daily glyburide therapy and 2 U of a sliding scale insulin order. He subsequently became more confused and agitated. He was given 1 ampule of D50 and started on intravenous dextrose (D20) infusion for his hypoglycemia. His oral hypoglycemic medication was held; however, his mental status did not improve. His blood pressure was also noted to be 84/36 mm Hg, and he was given normal saline infusion. His chest radiograph showed a right upper lobe infiltrate, for which broad spectrum antibiotics were started. He was found to have a sub-normal cortisol level of 2.3 μg/dL at baseline, which increased to only 5.6 μg/dL 60 minutes after a 250-μg Cortrosyn (ACTH) stimulation test. Intravenous hydrocortisone (100 mg every 8 hours) was begun. His blood pressure increased in response to the intravenous hydrocortisone. The next day, he had an episode of ventricular fibrillation followed by pulseless electrical activity. After successful resuscitation, he had anterior ST segment elevation and became asystolic 4 hours later.

Histologic Examination. Formalin-fixed, paraffin-embedded tissue from autopsy was examined by hematoxylin and eosin staining and immunohistochemistry, which was performed using avidin-biotin conjugated antispecies technique for localization of CD45 (Leukocyte common antigen (LCA)), CD20 (L26), CD45RO (UCHL-1), and a pituitary panel consisting of prolactin, TSH, ACTH, human growth hormone, luteinizing hormone, and follicle-stimulating hormone. (DAKO, Carpinteria, CA).

Results

After fixation for autopsy, the pituitary weighed 0.6 g and was of normal size. Histologic sections of the pituitary showed focal aggregates of mononuclear cells in the anterior lobe. In a few areas, there were nodular aggregates of mature lymphocytes, but no germinal centers were observed (Figure 1). In most areas, the lymphocytes infiltrated diffusely into the parenchyma, with patchy fibrosis of the stroma and loss of parenchymal cells. Some of the remaining cells showed a marked degree of karyorrhexis and karyolysis. Immunohistochemistry indicated that the inflammatory cells were uniformly positive for the T-cell marker CD45RO (LCA) (Figure 2); a majority were also positive for CD43 (UCHL-1). About 20% of the cells were positive for the B-cell marker CD20 (L26). The immunohistochemical panel of pituitary hormones revealed that the cells localizing prolactin, follicle-stimulating hormone, luteinizing hormone, and growth hormone were decreased in number in areas of active inflammation but normal in areas that were histologically intact. ACTH showed few weakly positive cells and were selectively depleted in the patient’s pituitary compared with control pituitary. The TSH stain showed no positive cells. The thyroid weighed 20 g. The microscopic sections showed follicles of various sizes with homogeneous colloid. There was no evidence of atrophy. One parathyroid was identified with nests of clear cells and a few chief cells. There was no evidence of hyperplasia. The paired adrenals weighed 15 g. Both cortices were very thin and atrophic with a 0.1-cm thickness, and fat was tightly adherent to the outer cortex. There were no areas of focal inflammation or signs of chronic adrenalitis. The pancreas weight was 85 g. Microscopic sections demonstrated normal pancreatic ducts, acini, and islets of Langerhans. There was no evidence of type 1 diabetes mellitus. The lungs had diffuse alveolar damage, pulmonary edema, and pneumonia. The heart demonstrated an acute anterior wall myocardial infarction. Kidneys demonstrated nodular diffuse glomerulosclerosis. The bone showed no evidence of increased osteoclastic activity or resorption. There was no evidence of cancer on autopsy.

Discussion

Hypercalcemia is seen in approximately 6 to 20% of patients with adrenal insufficiency and is seen in 21% of dogs who present with adrenal insufficiency. The cause of the hypercalcemia is unknown. In a group of 16 patients with lymphocytic hypophysitis, 19% (3 of 16 patients) presented with hypercalcemia. These 3 patients were all women and all had

Figure 1. Lymphocytic (small round cell) infiltration of anterior pituitary (50×)

Figure 2. LCA immuno-peroxidase stain highlights the lymphocytes in an area of parenchymal damage (horseradish peroxidase conjugate with hematoxylin counterstain, 200×)
Lymphocytic Hypophysitis and Hypercalcemia

Symptoms of glucocorticoid insufficiency; 1 had parathyroid hyperplasia. Ten of the 14 cases in women were associated with pregnancy. The two men in this group of 16 patients with lymphocytic hypophysitis presented with panhypopituitarism but normal calcium concentration. 2

Our patient presented with hypercalcemia that persisted after correction for serum albumin. Several factors may have contributed, including reduced calcium delivery to the glomerulus, increased proximal tubular reabsorption, 2 and enhanced calcium mobilization of skeletal origin. 3 This is probably caused by the ability of thyroid hormone to mobilize bone when cortisol concentrations are reduced. 6 In our patient, hypercalcemia was resolved on hospital day 8, after the patient had received large amounts of normal saline.

Over 50 cases of lymphocytic hypophysitis have been reported in the English language literature. As mentioned above, almost all of these cases have been in women and many were related to pregnancy or immediately postpartum. As little as 12% of these cases were in men. 7 Some patients had adrenal insufficiency, and other patients had associated autoimmune disease, such as Hashimoto thyroiditis, adrenalitis, or pernicious anemia. 1,7 In some reported cases of lymphocytic hypophysitis, there was enlargement of the pituitary gland on CT or MRI, prompting transphenoidal surgery, and in a few cases, the patients had visual field defects or diabetes insipidus (not seen in our case). The histopathologic findings in the cases reported range from edema and lymphocytic infiltration in the more acute setting, often associated with a mass lesion in the pituitary, to mixed cell infiltrate (eosinophils, macrophages, lymphocytes, and plasma cells) associated with a predominance of fibrosis representing involutional change as the result of ongoing inflammation. Germinal centers and lymphoid nodules are present in most patients, but others have a more diffuse infiltration. The absence of granulomas or giant cells distinguishes lymphocytic hypophysitis from a related disorder, granulomatous hypophysitis. 7 In our case, we noted lymphocytic infiltration with ongoing parenchymal destruction. Neither lymphoid follicles nor extensive fibrosis was seen. Also, no granulomas were seen. The absence of pituitary thyrotrophs may have been relatively acute because the thyroid gland was normal in size. In comparison, the severe reduction in ACTH cells resulted in adrenocortical atrophy identified at autopsy.

Symptoms of primary adrenal insufficiency include fatigue, weakness, weight loss, and orthostatic hypotension. Laboratory abnormalities include hyponatremia, hyperkalemia, hypoglycemia, and mild normocytic anemia. 1 In secondary adrenal insufficiency, reduced blood glucose or elevated serum calcium level may be the only abnormality because ACTH deficiency does not reduce aldosterone production. In a diabetic patient (such as ours) the blood glucose may be of limited value and the only abnormality may be an elevated calcium concentration.

Hypercalcemia is seen in approximately 6 to 20% of patients with adrenal insufficiency and may be equally frequent in patients with lymphocytic hypophysitis. 7 This critically ill patient most likely had developed secondary adrenal insufficiency over the few months before his death. This was characterized by weight loss, fatigue, and ultimately by recurrent episodes of hypoglycemia and hyponatremia with normal potassium concentrations. His cortisol was abnormally low, even 60 minutes after ACTH administration. Two days after he started on appropriate therapy for glucocorticoid insufficiency, he died of a myocardial infarction and we discovered lymphocytic hypophysitis at autopsy. Hypercalcemia, with normal electrolytes, fatigue, and weight loss should prompt the provider to test for glucocorticoid insufficiency and consider earlier therapy with hydrocortisone. Diagnosis of glucocorticoid insufficiency in patients with diabetes is difficult, and greater attention to abnormal sodium concentrations and clinical features such as weight loss and hypotension should be identified. Earlier therapy for the patient may have ameliorated his hypoglycemia and hypercalcemia and may have improved his clinical outcome.

References