Multiple endocrine neoplasia type I in a cat

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- Multiple endocrine neoplasia is a well-recognized syndrome in humans.
- Functional endocrine tumors of the pancreas, adrenal gland, and parathyroid gland are uncommonly diagnosed in cats; detection of one of these tumors should prompt further examination of the patient for signs of other endocrine tumors.
- In cats, resection of functional endocrine tumors may result in the resolution of clinical signs and return to health.

A 13-year-old 4.6-kg (10.2-lb) neutered male domestic long hair cat was evaluated by a referring veterinarian because of a history of lethargy, exercise intolerance, and ventroflexion of the cervical portion of the vertebral column. The cat also had intermittent bouts of constipation during the previous months, which would resolve without medical intervention. Two years previously, the cat underwent extracapsular thyroidectomy because of a palpable mass on the right side of the ventral portion of the neck; during that procedure, both parathyroid glands associated with the right lobe of the thyroid gland were also removed. Clinicopathologic analyses conducted before and after surgery revealed that serum concentrations of thyroid hormones and calcium were within reference limits. Findings of a histologic examination of the excised mass were consistent with an adenoma of the parathyroid gland. During the more recent evaluation by the referring veterinarian, laboratory analyses revealed hypokalemia; a dietary potassium supplement was administered orally to the cat every other day. With this regimen, the hypokalemia and clinical signs of lethargy, exercise intolerance, and ventroflexion of the cervical portion of the vertebral column were initially well controlled.

Five months after the inception of clinical signs, the cat returned to a lethargic state and a palpable mass was detected in the left side of the cervical region in the area consistent with the location of the left lobe of the thyroid gland. The cat's thyroid gland function was assessed by the referring veterinarian. The serum concentrations of total and free triiodothyronine as well as total and free thyroxine were measured via radioimmunoassay; values were within reference limits. Clinicopathologic abnormalities included high serum calcium concentration (11.3 mg/dL; reference range, 8.2 to 10.8 mg/dL), low blood glucose concentration (38 mg/dL; reference range, 64 to 170 mg/dL), and high serum sodium concentration (163 mEq/L; reference range, 145 to 158 mEq/L). A grade 2/6 heart murmur was detected on physical examination; subsequently, thoracic radiography revealed generalized cardiomegaly. Consultation with a cardiologist was obtained, and a pericardial cyst with resultant turbulence in the right ventricular outflow tract was diagnosed. Pericardiocentesis was performed, and 30 mL of fluid (described as being clear) was removed from the cyst. Fluid analysis was not performed.

In an effort to further elucidate potential causes of hypernatremia and previously diagnosed hypokalemia, a serum aldosterone assay was performed. Results of this assay confirmed a high serum concentration of aldosterone (1,741 pmol/L; reference range, 194 to 388 pmol/L). The cat was then referred to the **Veterinary Teaching Hospital (VTH)** at Michigan State University for further diagnostic evaluation and treatment.

On initial examination at the VTH, the presence of the systolic murmur as well as a mass in the left ventral aspect of the cervical region was confirmed. Results of a CBC indicated mild thrombocytosis (531,000 platelets/μL; reference range, 98,000 to 470,000 platelets/μL). A urinalysis was performed, and all variables were within reference limits; urine specific gravity was 1.022. Blood glucose concentration was 54 mg/dL (reference range, 74 to 152 mg/dL). Serum biochemical abnormalities included high total calcium concentration (11.7 mg/dL; reference range, 8.1 to 10.0 mg/dL) and low potassium concentration (2.56 mmol/L; reference range, 2.80 to 5.90 mmol/L). Serum sodium concentration was 153.7 mmol/L (reference range, 148.0 to 154.0 mmol/L).

A blood sample was analyzed to assess parathyroid gland function. Results confirmed high serum concentrations of ionized calcium (1.66 mmol/L; reference range, 1.0 to 1.4 mmol/L) and intact parathormone (8.5 pmol/L; reference range, 0 to 4 pmol/L). An assay for parathormone-related protein revealed a serum concentration of 0 pmol/L (reference limit, < 1.0 pmol/L). These data were consistent with a diagnosis of primary hyperparathyroidism.

Because of concern that oral administration of the potassium supplement may have potentially interfered with the original aldosterone assay, this assay was repeated after the supplementation was withheld from the cat for 1 week. The result of this assay confirmed the diagnosis of primary hyperaldosteronism (serum aldosterone concentration, 1,128 pmol/L; reference range, 194 to 388 pmol/L). Ultrasonographic examinations of the abdomen and neck were performed.

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A markedly enlarged left adrenal gland was observed in the abdomen. The ultrasonographic examination of the neck revealed a large cavitary mass located within the parenchyma of the left lobe of the thyroid gland. Because of the diagnosis of hyperaldosteronism, systolic blood pressure was measured and the value was high (185 mm Hg; reference limit, < 180 mm Hg).

An exploratory laparotomy was performed. Grossly, the liver appeared to be within normal limits; because of the potential concern that a neoplastic process was ongoing in the left adrenal gland, a biopsy specimen of the liver was obtained for routine tumor staging assessment. A 2 × 3-cm mass was identified in the right lobe of the pancreas (**Figure 1**). A partial pancreatectomy was performed to remove this mass. The right adrenal gland appeared to be within normal limits, and a left adrenalectomy was performed to remove the approximately 2.5 × 3.0-cm mass associated with the left adrenal gland. Findings of the remainder of the abdominal exploratory surgery were unremarkable, and routine closure of the abdominal approach was performed.

Because of concerns regarding the cat's ability to withstand prolonged anesthesia after the abdominal procedures, the decision was made to perform the cervical surgical procedure at a later date. A blood sample was collected immediately after the exploratory abdominal surgery; clinicopathologic analyses revealed hypoglycemia (53 mg/dL) as well as a hypokalemia (2.50 mmol/L). The cat received lactated Ringer's solution supplemented with potassium chloride (40 mEq/L) IV at a rate of 10 mL/h (ie, 2.2 mL/kg/h [1 mL/lb/h]). Dextrose was not included in the administered fluid mixture. Within 12 hours, the blood glucose concentration increased (157 mg/dL) and the serum potassium concentration was within reference limits. Fluid administration was halted, and blood glucose and serum potassium concentrations were within their respective reference ranges for the remainder of the hospitalization period. The cat was discharged 2 days after the abdominal exploratory surgery.

Histologic examinations of sections of the masses revealed a cortical adenoma in the adrenal gland and an undifferentiated neuroendocrine neoplasm of islet cell origin in the pancreatic tissue. Via immunohistochemical techniques, neoplastic cells of the cortical neoplasm of the adrenal gland were diffusely positive for melan A and focally positive for synaptophysin (which are markers that are used to identify adrenal gland cortical tissue) as well as positive for aldosterone but negative for protein gene product 9.5 and chromogranins A and B (which are markers that are used to identify neuroendocrine cells). Immunohistochemically, neoplastic cells of the pancreatic islet cell neoplasm were diffusely positive for insulin, protein gene product 9.5, chromogranins A and B, and synaptophysin and focally positive for glucagon but negative for gastrin and somatostatin. Insulin, glucagon, gastrin, and somatostatin are hormones produced by different subtypes of pancreatic islet cells. These findings are consistent with functional endocrine neoplasms of the adrenal gland (aldosterone-secreting neoplasm) and the pancreas (insulinoma). Histologic examination of the biopsy specimen of the liver revealed no evidence of metastatic disease.

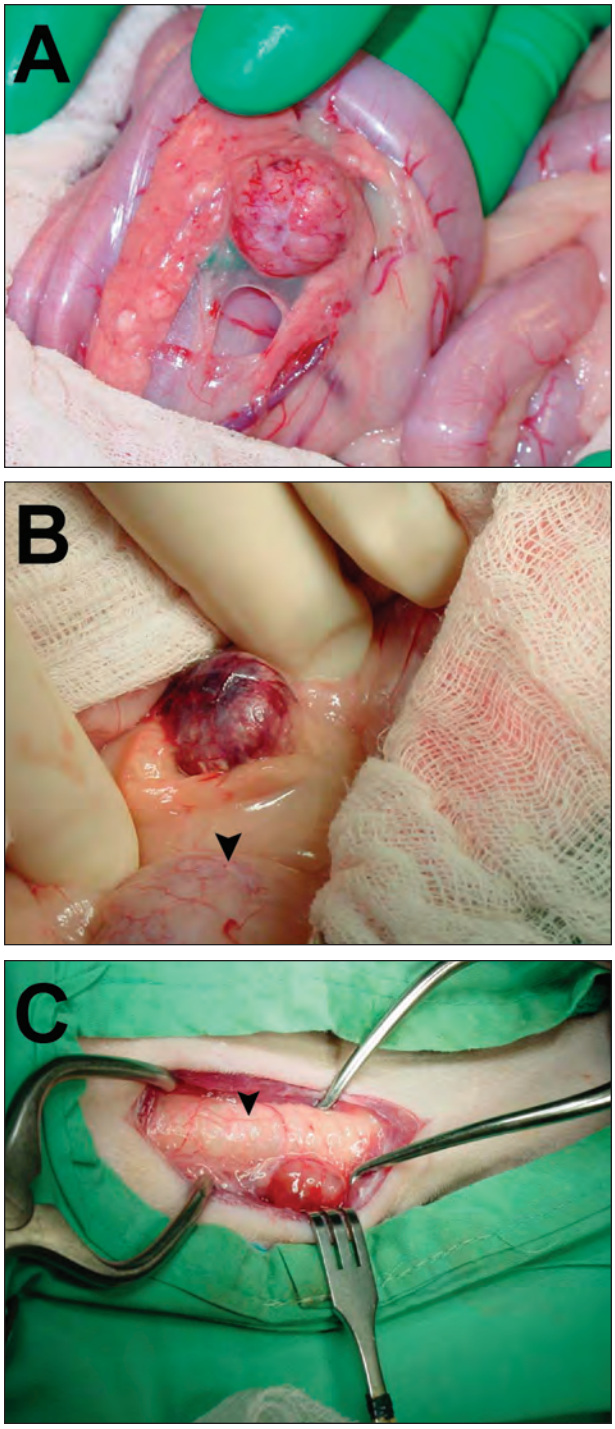

Figure 1—Photographs obtained during exploratory abdominal surgery and a later surgical procedure performed to remove a mass detected in the left ventral aspect of the cervical region of a cat. A—Exteriorized portion of the duodenum with the associated portion of the pancreas. Notice the 2 × 3-cm mass associated with the pancreas. B—Left lumbar region in which the left kidney (arrowhead) and a 2.5 × 3-cm mass associated with the left adrenal gland are observed. C—Ventral aspect of the cervical region in which the trachea (arrowhead) and a 1.2 × 0.8-cm mass associated with the left lobe of the thyroid gland are observed.

The owners reported that the cat's recovery from the abdominal surgery was uneventful and returned the cat to the VTH 6 days later for surgical removal of

the functional parathyroid gland mass. On admission, serum biochemical analyses revealed high ionized calcium concentration (5.90 mg/dL; reference range, 3.90 to 5.30 mg/dL). Surgical exploration of the cervical region revealed a pale yellow mass (approx 1.2 × 0.8 cm) associated with the caudal pole of the left lobe of the thyroid gland (Figure 1). Exploration of the cranial portion of this lobe of the thyroid gland failed to reveal any identifiable parathyroid gland tissue. The area where the right lobe of the thyroid gland and associated parathyroid glands would normally be located was explored and found to be devoid of any identifiable glandular tissue. Findings on exploration of the remainder of the cervical region were unremarkable. Because of the size of the mass within the parenchyma of the left lobe of the thyroid gland and the failure to identify any salvageable parathyroid gland tissue, an extracapsular thyroidectomy of the left lobe of the thyroid gland was performed.

Postoperatively, calcitriol[a] (0.05 µg/kg [0.023 µg/lb]) was administered orally every 24 hours in an effort to prevent development of hypocalcemia. The cat also received synthetic thyroxine (levothyroxine sodium,[b] 0.02 mg/kg [0.01 mg/lb]) orally every 24 hours as a thyroid gland hormone supplement. Recovery from anesthesia and surgery was without complications, and the cat's blood glucose and serum potassium concentrations remained within reference limits. During the 72-hour recovery period, serum ionized calcium concentration was slightly higher than the upper reference limit (ranging from 5.7 to 6.0 mg/dL); therefore, the dosage of calcitriol was reduced to 0.05 µg/kg administered orally every other day. The patient was discharged 3 days after surgery. Administration of calcitriol was discontinued 1 month after the extracapsular thyroidectomy of the left lobe of the thyroid gland. Serum ionized calcium concentrations were monitored for an additional 2 months and had remained within reference limits without further administration of calcitriol.

Histologic examination of sections of the left lobe of the thyroid gland and the associated parathyroid tissue revealed a parathyroid adenoma surrounded by normal thyroid gland tissue. There were no signs of atypia within the cells of the adenoma. Immunohistochemically, the neoplastic cells were positive for parathormone; however, the cells were negative for thyroglobulin and calcitonin (which are hormones expressed by the thyroid follicular epithelial cells and C cells, respectively).

Multiple endocrine neoplasia (MEN) is a well-recognized group of syndromes in humans.[1-3] These syndromes have been subdivided into MEN I, MEN IIa, and MEN IIb. The MEN I syndrome is most commonly characterized by abnormalities involving the pancreas, parathyroid glands, and pituitary gland.[3,4] Of these 3 endocrine organs, the pituitary gland is the gland least frequently affected with MEN I[3,5]; it is also the gland least frequently associated with clinical signs in MEN I-affected humans.[3] The MEN II syndromes classically involve neoplasms of the thyroid gland and the medulla of the adrenal glands as well as the variable presence of hyperplasia of the parathyroid glands and ganglioneuromas.[3,4]

The heritability of the MEN I syndrome has been documented.[1-3,6-8] In humans, the gene responsible for this syndrome has been isolated to a gene mutation present on chromosome 11[1,2,9] and the syndrome is associated with an autosomal dominant pattern of inheritance.[2,9,10] Cortical neoplasms of the adrenal glands are also quite commonly involved with the MEN I syndrome and have been reported to develop in 13% to 40% of MEN I-affected humans.[5,6] Other masses less commonly encountered with MEN I include gastrinomas, carcinoids, angiofibromas, collagenomas, and lipomas.[3,11]

Each of the 3 neoplastic conditions (parathyroid gland adenoma, adrenal gland cortical adenoma, and insulin-secreting tumor) identified in the cat of this report is quite rare in this species. To the authors' knowledge, insulin-secreting tumors have been described in only 4 cats[12-15] and primary hyperparathyroidism has been described in only 10 cats.[16-18] There are 4 clinical reports[19-21] of cats with hyperaldosteronism resulting from the presence of a functional adrenal gland cortical neoplasm. Therefore, the clinical signs, diagnosis, and treatment of each of these diseases are reported to date only in the form of single case reports or very small case series. In retrospect, assessment of the serum insulin concentration combined with a concurrent assessment of the blood glucose concentration would have assisted in the preoperative diagnosis of an insulin-secreting tumor in the cat of this report. The serum insulin concentration was not measured preoperatively because abdominal ultrasonography did not reveal any evidence of a pancreatic mass and the hypoglycemia was instead presumed to be a paraneoplastic effect of one of the masses that had been identified at the time.

Presently, the MEN syndromes have only rarely been described in veterinary patients. Some authors suggest that the incidence of MEN syndromes among cats, dogs, and horses may be considerably higher than realized and that MEN syndromes are underdiagnosed by veterinarians because of a failure to recognize the syndromes.[22,23] To the authors' knowledge, this syndrome has not previously been reported in cats and has been only sporadically reported in dogs[24-31]; there are isolated reports in sheep[32] as well as a horse.[23] Multiple endocrine neoplasia has been induced experimentally in mice and rats.[11,33,34]

In the cat of this report, the clinical signs of lethargy, exercise intolerance, and ventroflexion of the cervical portion of the vertebral column could certainly be attributed to the functional cortical adenoma of the adrenal gland and resultant hypokalemia. Alternately, the nonspecific clinical signs of lethargy and exercise intolerance could have been related to the hypercalcemia or hypoglycemia. In humans with MEN I, the initial clinical signs are most commonly attributable to hypercalcemia.[3] It is possible that the structure that was classified as a pericardial cyst was associated with a disease process unrelated to the MEN syndrome in the cat of this report; however, it is plausible that this finding may be linked to the development of MEN. Ganglioneuromas, which have been identified in humans with MEN, have also been identified in the

mediastina of humans[35,36] and can be cystic in nature.[36] In a case report[26] of a dog with MEN, the patient had a heart base tumor and resultant pericardial fluid; the mass was diagnosed as a paraganglioma. Although a mass was not detected via echocardiographic examination of the heart in the cat of this report, a small mass may have been present in this region and might have been the cause of accumulation of fluid within the pericardium.

In the cat of this report, resection of the 3 functional masses resulted in clinical recovery, and at 6 months postoperatively, the patient was free of clinical signs. The owners reported that the cat had no noticeable adverse disease-associated effects and its activity level and quality of life were considered excellent.

Multiple endocrine neoplasia is a rare but important clinical entity in human and veterinary medicine. In cats, the presence of a rare neuroendocrine neoplasm such as an insulinoma, functional adrenal gland cortical adenoma, or parathyroid gland adenoma may potentially be an indicator of MEN; in cats with 1 or more of these neoplasms, veterinarians should perform a thorough clinical assessment, including screening for other endocrine diseases, in an effort to rule out this syndrome. Resection of the affected glands may result in complete resolution of clinical signs and is suggested in the treatment of affected cats.

a. Rocaltrol, Roche Laboratories Inc, Nutley, NJ.
b. Soloxine, Daniels Pharmaceuticals, St Petersburg, Fla.

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