Hypoadrenocorticism as the primary manifestation of lymphoma in two cats

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- Hypoadrenocorticism, a rare disease in cats resulting from inadequate glucocorticoid and mineralocorticoid production by the adrenal cortex, is characterized by vague clinical abnormalities, azotemia, hyperkalemia, and hyponatremia.
- Lymphoma is the most common neoplastic disease in cats and accounts for almost a third of all neoplasms in cats. Clinical abnormalities, which are often vague, are related to the organ system involved.
- Although most cats with naturally developing hypoadrenocorticism have idiopathic adrenocortical atrophy, cats can develop hypoadrenocorticism secondary to infiltration of the adrenal gland by lymphoma.

An 8-year-old 5.5-kg (12.1-lb), castrated domestic shorthair cat (cat 1) was examined at a university veterinary medical teaching hospital because of a 1-week history of lethargy, anorexia, and intermittent vomiting. The owner also reported that the cat had been losing weight (approx 1.5 kg [3.3 lb]) for the past 2 months. The cat did not have a history of previous medical problems. On physical examination, the cat was weak and had signs of severe depression. Other findings included dehydration (7%), hypothermia (37.5 C [99.4 F]), pale mucous membranes, cool extremities, delayed capillary refill time (3 seconds), and discomfort on palpation of the cranial portion of the abdomen. The cat was obese, but moderate wasting of the dorsal epaxial muscles was evident.

Results of hematologic testing revealed a PCV of 32%, considered a low-normal result (reference range, 30 to 45%). Results of serum biochemical analysis revealed mild azotemia (creatinine concentration, 2.6 mg/dl [reference range, 0.9 to 2.3 mg/dl]; serum urea nitrogen concentration, 33 mg/dl [reference range, 15 to 35 mg/dl]); hyponatremia (143 mmol/L; reference range, 148 to 157 mmol/L), hyperkalemia (6.0 mmol/L; reference range, 3.5 to 5.1 mmol/L), and mild hypoglycemia (71 mg/dl; reference range, 75 to 134 mg/dl). Specific gravity of urine was 1.018; other abnormalities were not found on urinalysis. Results of an ACTH stimulation test revealed a serum cortisol concentration that was low at baseline (< 25 nmol/L; reference range, 50 to 100 nmol/L) and did not increase 30 and 60 minutes (< 25 nmol/L for both samples; reference range, 100 to 292 nmol/L) after IM administration of 0.125 mg of synthetic ACTH (cosynthropin) 1This result was diagnostic for hypoadrenocorticism. 2,4 An electrocardiogram revealed normal sinus rhythm and a heart rate of 140 beats/min (reference range, 120 to 220 beats/min).

Initial treatment consisted of administration of saline (0.9% NaCl) solution (60 ml/kg [27.3 ml/lb] of body weight, IV) for the first hour, followed by administration of saline solution with 2.5% dextrose/L (4 ml/kg/h [1.8 ml/lb/h], IV). The cat was also treated with dexamethasone (1 mg/kg [0.45 mg/lb], IV q 12 h) and cinemidetine hydrochloride (5 mg/kg [2.3 mg/lb], IV q 12 h). A heating pad was used until the cat's rectal temperature returned to within the reference range.

On day 2, the cat could maintain its temperature without the heating pad, and the serum glucose concentration had returned to within the reference range. The cat was more alert but still extremely weak, and its mucous membranes were still pale. Results of a second serum biochemical analysis revealed resolution of the hyperkalemia (potassium concentration, 3.6 mmol/L) and azotemia (creatinine concentration, 1.2 mg/dl); serum urea nitrogen concentration, 13 mg/dl) and improvement of the hyponatremia (sodium concentration, 147 mmol/L), but the albumin concentration had decreased to 2.1 g/dl (reference range, 2.7 to 3.9 g/dl). Analysis of a second hemogram revealed severe microcytic normochromic nonregenerative anemia (PCV, 16.6%). Fifty milliliters of crossmatched, compatible, stored feline blood was administered IV during several hours. The PCV had increased to 26% when the cat was retested 1 hour after the transfusion.

On day 3, the cat was much stronger and was eating on its own. Treatment was initiated with fludrocortisone acetate (0.05 mg, PO, q 12 h) and prednisone (2.5 mg, PO, q 24 h). The rate of fluid administration was gradually decreased, and fluid administration was discontinued the next morning.

On day 4, anisocoria and ascites were evident on physical examination. The cat was still anemic (PCV, 22.6%), but the most important finding was a high total bilirubin concentration (1.2 mg/dl; reference range, 0.1 to 0.4 mg/dl) and persistent hypoalbuminemia (2.3 g/dl). Ophthalmologic examination revealed subretinal exudate in the right eye. Abdominal ultrasonography revealed mild peritoneal effusion and large, bilaterally hypoechogenic adrenal glands. Abdomi

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nocentesis and ultrasound-guided percutaneous needle biopsy of the left adrenal gland were performed, and the cat was released from the hospital pending results of analysis of the abdominal fluid and histologic examination of adrenal tissue.

Results for the abdominal fluid were consistent with chyle, and results of histologic examination of the adrenal tissue were diagnostic for lymphoma. An appointment was scheduled with an oncologist to enable clinicians to determine the stage of lymphoma and to begin chemotherapy, but the cat developed tachypnea the evening before the appointment (ie, 11 days after initial examination). The next morning, the cat was markedly icteric, dyspneic, and had extremely pale mucous membranes. The owners chose to have the cat euthanized because of the poor prognosis.

Necropsy revealed that the peritoneal cavity contained 20 to 30 ml of yellow-tinged serous fluid. The lungs were diffusely red and had multiple 1-mm white foci on the surface. The liver was large and friable. A multilobulated, soft tan mass encompassed the adrenal glands and adjacent midline. Results of histologic examination revealed lymphoma in the adrenal glands, lungs, liver, and mesenteric lymph nodes.

A 12-year-old 6-kg (13.2 lb), castrated domestic shorthair cat (cat 2) was admitted to a veterinary medical referral hospital because of acute onset of weakness and collapse. The cat had also been anorectic for 2 days. Cat 2 did not have a history of previous medical problems. Results of physical examination and laboratory tests were similar to those of cat 1.

Cat 2 responded to treatment, which included IV administration of fluids similar to those given to cat 1, and was discharged 4 days later. On day 7, the cat was reexamined because of recurrence of clinical signs. Laboratory test results revealed relapses of hyperkalemia, acidosis, and hypoglycemia. Treatment with intravenously administered fluids was repeated. Results of an ACTH stimulation test performed at this time revealed low-normal baseline serum cortisol concentration (28 nmol/L; reference range, 25 to 125 nmol/L) but without an increase in serum cortisol concentration 1 hour after IV administration of 0.125 mg cosynotropin (post-ACTH cortisol concentration, 28 nmol/L; reference range, 110 to 440 nmol/L). Analysis of these results confirmed a diagnosis of hypoadrenocorticism.24 The cat responded to treatment with prednisone (0.5 mg/kg, PO, q 24 h) and fluurocortisone (0.02 mg/kg, PO, q 24 h) and was discharged from the hospital on day 9. Vomiting and anorexia recurred on day 30. On physical examination, a mass was palpable in the caudal portion of the abdomen. Abnormal laboratory test results included neutrophilia (WBC, 47,500 cells/µl; reference range, 7,000 to 15,000 cells/µl) with a regenerative left shift (band neutrophils, 1,900 cells/µl; reference range, 0 to 450 cells/µl). Abdominal radiography (Fig 1) and ultrasonography revealed that the mass did not appear to originate from the liver, spleen, or stomach.

Exploratory laparotomy was performed, at which time a large mass was identified that appeared to originate from and encompass the mesenteric lymph nodes and adrenal glands. Results of histologic examination of a frozen section of the mass were consistent with lymphoma. The cat was euthanized because of the owner's unwillingness to treat lymphoma.

Necropsy of cat 2 revealed a soft grayish mass (6 ×
formed. In contrast, clinical findings for physical examination of the cats reported here were consistent with a hypoadrenocortical crisis. Hypoadrenocorticism was documented by an ACTH stimulation test, and neoplastic infiltration and destruction of the adrenal glands were confirmed at necropsy.

Primary hypoadrenocorticism (ie, destruction or atrophy of the adrenal cortices) has been reported in only 10 cats. Primary hypoadrenocorticism developed in 1 cat as a result of abdominal trauma, but the cats reported here did not have a history of such trauma. Latrogenic secondary hypoadrenocorticism (ie, deficient pituitary ACTH with secondary adrenal atrophy) can be induced in cats by administration of large doses of repositol glucocorticoids or use of recommended doses of megestrol acetate. The cats of this report had not been treated with glucocorticoids or progestagens (eg, megestrol acetate). In addition, the cats in the other reports did not have evidence of lymphoma.

The cats of this report had clinical signs typical of naturally developing primary hypoadrenocorticism, including lethargy, anorexia, weight loss, and severe weakness; however, these signs are also characteristic of lymphoma. The clinicopathologic findings (eg, hyperkalemia, hyponatremia, and azotemia) were similar to those reported in cats with naturally developing hypoadrenocorticism. Anemia, found in 30% of cats and 10 to 25% of dogs with primary hypoadrenocorticism, was evident in cat 1. It is not completely understood why this cat became severely anemic. It is possible that cat 1 was anemic at the time of the initial examination, but that anemia was masked by severe dehydration. Dehydration alone, however, is an unlikely explanation. Most dogs with severe anemia have signs of melena or hematemesis, which were not evident in cat 1 during physical examination or necropsy. Nevertheless, there may have been hemorrhage from the gastrointestinal tract that subsequently resolved during the 10-day period between the development of anemia and necropsy.

Lymphoma is the most common neoplasm in cats and accounts for approximately one third of all tumors in cats. Multicentric lymphoma, diagnosed in the cats reported here, is the most common anatomic form of lymphoma and is characterized by localization of tumor cells in the abdominal organs and lymph nodes. The high incidence of lymphoproliferative disease in cats has been attributed to infection with FeLV or feline immunodeficiency virus, although such viral infections did not appear to play a role in the development of lymphoma in the cats of this report.

The success rate is variable for treatment of humans with lymphomatous invasion of the adrenal glands. It is poor for those with concurrent tumor-induced adrenocortical insufficiency. Of 4 patients with non-Hodgkin's lymphoma who had signs of hypoadrenocorticism, all died of lymphoma within 6 months of commencing chemotherapy. Because neither cat reported here survived until they could receive chemotherapy, the authors do not know how successful chemotherapy would have been in cats with tumor-induced adrenal insufficiency.

Figure 2—Photomicrograph of a section of the abdominal mass obtained at necropsy from the cat in Figure 1. Notice the admixture of adrenal cortical cells (small arrow) and lymphoma cells (large arrow). H&E stain; bar = 30 μm.

4.5 × 4 cm) infiltrating the right adrenal gland, and a similar mass (4 × 2 × 2 cm) was infiltrating the left adrenal gland. Nodules of various sizes were seen in the omentum, liver, lungs, and kidneys. The spleen and visceral lymph nodes were moderately large. Results of histologic examination revealed effacement of adrenal tissue by the neoplasm, which also infiltrated the surrounding tissue (Fig 2). The neoplasm consisted of sheets of slightly pleomorphic, round to polygonal cells with little stroma. Similar populations of cells were also found in the mesenteric lymph nodes, spleen, pancreas, liver, kidney, peritoneum, and bone marrow. Multicentric lymphoma, possibly originating from the adrenal glands, was diagnosed.

Hypoadrenocorticism secondary to bilateral neoplastic invasion of adrenocortical tissue is a well-described syndrome in humans, but to the authors' knowledge, it has not been reported in cats. In humans, the adrenal glands are a common site for metastasis of neoplasms, such as mammary adenocarcinoma, bronchogenic carcinoma, gastric adenocarcinoma, and malignant melanoma. Of humans with non-Hodgkin's lymphoma, 25 to 35% have involvement of the adrenal glands; however, few have clinical signs of adrenal gland insufficiency on initial examination, most likely because clinical signs of adrenal insufficiency do not manifest until > 90% of the adrenal gland is destroyed. In a large study, only 4 of 127 (3.1%) people with non-Hodgkin's lymphoma had the characteristic clinical signs of hypoadrenocorticism.

Infiltration of the adrenal glands by lymphoma has been described as an incidental necropsy finding in 1 cat and 2 dogs with multicentric lymphoma; however, these animals did not have clinical signs consistent with hypoadrenocorticism on initial examination and, therefore, an ACTH stimulation test was not performed.
On the basis of the findings in the cats of this report, and because lymphoma is common in this species, neoplastic invasion of the adrenal glands should be suspected in any cat in which hypoadrenocorticism is diagnosed. Cats with lymphoma that respond poorly to chemotherapy or that have clinical signs suggestive of hypoadrenocorticism should undergo appropriate testing, such as biochemical analysis and ACTH stimulation tests, and abdominal ultrasonography should be performed to exclude concurrent adrenal insufficiency secondary to neoplastic infiltration of adrenal glands.

References


