**Systemic hypertension in a dog with a functional thyroid gland adenocarcinoma**

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**Case Description**—A 12-year-old 21.9-kg (48.48-lb) spayed female Alaskan Malamute with a long-term history of panting, polydypsia and polyuria, weight loss, hind limb weakness, and a decrease in appetite was evaluated for hypertension.

**Clinical Findings**—Use of Doppler sphygmomanometry revealed a systolic blood pressure of 250 mm Hg (mean value for 5 consecutive measurements). Palpation of the ventral cervical region revealed a fixed asymmetric mass in the area of the lobes of the thyroid gland. The portion of the mass on the right side was approximately 2 × 2 cm, whereas the portion of the mass on the left side was approximately 1 × 1.5 cm. Hyperthyroidism was diagnosed on the basis of high serum thyroxine concentrations. Thyroidectomy of both lobes of the gland was performed. Histologic examination revealed a bilateral, multilobulated, and encapsulated thyroid gland adenocarcinoma.

**Treatment and Outcome**—Thyroidectomy of both lobes of the gland was performed with clinical resolution of hypertension. The dog was treated postoperatively with chemotherapeutics, including doxorubicin and carboplatin, and external beam radiation. Calcium and thyroxine homeostasis fluctuated; however, the dog finally achieved concentrations within the respective reference ranges through the administration of calcitriol, calcium carbonate, and levothyroxine.

**Clinical Relevance**—This report describes concurrent hypertension in a dog with a functional thyroid gland adenocarcinoma with subsequent return of blood pressure values to within reference ranges after thyroidectomy. (J Am Vet Med Assoc 2009;235:1474–1479)

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A 12-year-old 21.9-kg (48.48-lb) spayed female Alaskan Malamute was admitted to the University of Florida Veterinary Medical Center because of hypertension. The dog had a lengthy history that included uncontrolled glaucoma in the right eye treated with ciliary body ablation, urinary tract infections, intermittent vomiting, mammary gland tumors, and chronic polyuria and polydypsia of unknown cause.

Four months prior to evaluation for hypertension, abdominal ultrasonography revealed multiple hypoechoic nodules of various sizes throughout the spleen, in addition to a focal hypoechoic region (diameter, 2.5 cm) in the right lateral lobe of the liver. Subsequently, fine-needle aspirates were obtained from the nodules. Cytologic evaluation of the aspirates revealed a reactive lymphoid population; extramedullary hemopoiesis; well-differentiated, normally appearing mast cells in the splenic nodules; and hepatocellular hyperplasia, mild vacuolar degeneration, and an increase in lymphocytes in the focal hepatic nodule. The number and appearance of the well-differentiated mast cells were not sufficient to warrant a diagnosis of a type 1 mast cell tumor.

Two months prior to the evaluation for hypertension, the dog was examined at our facility because of a 1-month history of polydypsia and polyuria, weight loss, panting, mild tremors, and restlessness at night. Results of a CBC were within reference limits. Serum biochemical analysis revealed a severely high in alkaline phosphatase activity (2,142 U/L; reference range, 16 to 111 U/L), a mildly high alanine aminotransferase activity (153 U/L; reference range, 16 to 77 U/L), low creatinine concentration (0.6 mg/dL; reference range, 0.8 to 1.7 mg/dL), and low BUN concentration (6 mg/dL; reference range, 16 to 77 mg/dL), and low creatinine concentration (0.6 mg/dL; reference range, 0.8 to 1.7 mg/dL), and low BUN concentration (6 mg/dL; reference range, 16 to 77 mg/dL). Urinalysis revealed a specific gravity of 1.007, with all variables within reference limits. At approximately that same time (ie, 2 months prior to evaluation for hypertension), the referring veterinarian suspected the dog had hyperadrenocorticism and performed a low-dose dexamethasone suppression test and ACTH stimulation test; results of both were within reference limits.

One month prior to evaluation for hypertension, another ACTH stimulation test (including concentrations of sex hormones and aldosterone) was performed at our facility to evaluate the dog for atypical hyperadrenocorticism.4 Androstenedione concentrations before ACTH administration were slightly high (8.5 ng/mL; reference

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**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Explanation</th>
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<tr>
<td>ACE</td>
<td>Angiotensin-converting enzyme</td>
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<td>ACTH</td>
<td>Adrenocorticotropic hormone</td>
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<td>T₄</td>
<td>Thyroxine</td>
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range, 0.1 to 5.7 ng/mL), but they were within reference limits after ACTH administration. Progesterone (1.73 ng/mL; reference range, 0.1 to 1.5 ng/mL) and aldosterone (458 pg/mL; reference range, 72.9 to 398.5 pg/mL) were slightly increased after ACTH administration. The results indicated an increase in adrenal gland activity; however, it was equivocal as to whether it was the underlying cause of the clinical signs in the dog. The dog was treated by administration of an antigonadotropic compound (melatonin\(^{\ast}\) [0.2 mg/kg [0.09 mg/lb], PO, q 12 h]).

At that same time (ie, 1 month prior to evaluation for hypertension), iohexol clearance was also determined at our facility. The value was within reference limits (4.11 mL/min/kg; reference range, 2.89 to 8.07 mL/min/kg) and was only 25% below the expected mean of 5.48 mL/min/kg.\(^{7}\) The results suggested that renal disease was not a cause of isosthenuria in the dog. No additional diagnostic procedures were pursued at that time. One month later, the dog was referred to our facility because of hypertension detected by the referring veterinarian.

During the month preceding the evaluation for hypertension, the dog had persistent panting, polydypsia and polyuria, hind limb weakness, and a decrease in appetite. The dog also had lost weight (2 kg [4.4 lb] during the past 6 months). At the time of evaluation for hypertension, the dog was receiving enrofloxacin\(^{\ast}\) (6.2 mg/kg [2.8 mg/lb], PO, q 12 h) prescribed by the referring veterinarian for treatment of a suspected urinary tract infection. In addition, the dog was receiving the previously prescribed melatonin.

Physical examination at our facility revealed an area of erythematous crusting alopecia on the lateral aspect of the right hind limb. Palpation of the lumbar area elicited signs of pain. The dog was then allowed 15 minutes to acclimate to the examination room before a noninvasive systolic blood pressure measurement was obtained by use of Doppler sphygmomanometry\(^{\ast}\) and a No. 5 blood pressure cuff placed over the median artery of the right forelimb. The cuff width was 40% of the circumference of the limb, and a systolic blood pressure of 250 mm Hg was obtained (mean of 5 consecutive measurements). Thoracic auscultation revealed no abnormal sounds in all lung and cardiac fields. In addition, results of abdominal palpation were unremarkable. A fundic examination was performed; there was no evidence of retinal hemorrhage or detachment or tortuous vessels. A CBC, serum biochemical analysis, and urinalysis were performed, all of which yielded results similar to those obtained 2 months previously. Neurologic examination revealed discomfort on palpation of the lumbar region and a decrease in postural reactions of the pelvic limbs, especially the right hind limb.

Abdominal ultrasonography revealed that both adrenal glands and both kidneys had a normal ultrasonographic appearance. Ultrasonographic appearance of the spleen and liver was unchanged from that of 4 months previously.

Palpation of the ventral aspect of the neck revealed a fixed asymmetric mass in the area of the lobes of the thyroid gland that was not apparent by visual inspection alone because of the long, dense coat of the dog. The portion of the mass on the right side was larger (approx 2 × 2 cm) than the portion of the mass on the left side (1 × 1.5 cm).

Ultrasonographic evaluation of the ventral aspect of the neck revealed a 1.9 × 2.4-cm mass with multiple cavitations in the region of the right lobe of the thyroid gland (Figure 1). Multiple areas of distal acoustic shadowing were identified, which was consistent with mineralization. The mass was heterogeneous in appearance with irregular but encapsulated borders and abundant vasculature. The left lobe of the thyroid gland measured 1.5 × 3.0 cm, consisted of 2 rounded segments, and was hyperechoic with no evidence of mineralization (Figure 2). A central cavity was detected within the caudal portion of the mass on the left side. Thoracic radiography revealed normal-appearing cardiopulmonary structures and no evidence of pulmonary metastasis. There was ankylosing spondylitis between T9 and T10 and irregular bony proliferation at the joint between the fifth and sixth sternebrae. Cytologic examination of fine-needle aspirates obtained from the left prescapular lymph node revealed reactive lymphoid hyperplasia with low cellularity. There were no neoplastic cells or infectious organisms identified.
Serum total T₄ concentrations were diagnostic of hyperthyroidism (7.11 µg/dL; reference range, 0.66 to 3.50 µg/dL). The dog was discharged to the owners with instructions for administration of an antihypertensive agent (enalapril⁶ [0.5 mg/kg [0.23 mg/lb], PO, q 12 h]).

At a follow-up appointment 3 days later, imaging of the thyroid gland by use of technetium pertechnetate revealed an increase in isotope uptake in both lobes of the thyroid gland, with the right side markedly enlarged, compared with the left (Figure 3). Uptake was uneven with a relative photopenic area in the midportion of both the left and right lobes of the thyroid gland. There was no evidence of thyroid tissue invasion into surrounding tissue, and there was no evidence of ectopic tissue or isotope uptake by metastatic tumors.

Thyroidectomy of both lobes was performed 1 week later. A routine approach (ventral midline caudal to the larynx) was used. Cefazolin⁷ (22 mg/kg [10 mg/lb], IV, once) was administered perioperatively as prophylaxis in case of inadvertent bacterial contamination of the surgery site. Evaluation during surgery revealed that the right lobe of the thyroid gland was nodular and 3 cm in diameter and 5 cm in length. The left lobe of the thyroid gland was multinodular and tan to red, and it measured 3.0 × 2.5 × 0.5 cm. Dissection of the margins of each lobe of the thyroid gland, including muscle when possible, was performed. The surgeon attempted to save the parathyroid gland at the cranial pole of each lobe. It was unclear whether this was achieved because blood in the field obscured visual observation of the parathyroid glands.

The resected thyroid gland was fixed in neutral-buffered 10% formalin and submitted for histologic examination. Histopathologic findings were of a multilobulated, encapsulated, and moderately cellular neoplasm of the right and left lobes of the thyroid gland. The cells had moderate anisocytosis and anisokaryosis, and a few had megalocytosis. There was also scattered patchy hemorrhage and hematoidin in addition to variably sized areas of mineralization. The neoplastic cells invaded the fibrous capsule and extended to the sub-
rate infusion of 10% calcium gluconate solution2 (10 mg/kg/h [4.5 mg/lb/h], IV) was administered if the ionized calcium concentration decreased to < 1.0 mmol/L (reference range, 1.12 to 1.40 mmol/L), and infusion of the calcium gluconate solution was stopped if the value was > 1.0 mmol/L and no clinical signs of hypocalcemia were observed. On the third day after surgery, treatment involving administration of calcium carbonate (47 mg/kg [21.4 mg/lb], PO, q 8 h) and calcitriol (0.03 µg/kg [0.014 mg/lb], PO, q 24 h) was initiated. The dog was discharged from the hospital after it was able to maintain a consistent ionized calcium concentration between 0.91 and 1.06 mmol/L over a 40-hour period during oral administration of calcium carbonate and calcitriol without IV administration of calcium gluconate solution.

One week after discharge, the dog was reevaluated at our facility. Blood pressures, serum T₄ concentrations, and ionized calcium concentration were all within reference limits. The owners were no longer observing polydipsia and polyuria, and there was no evidence of retinal hemorrhage or detachment. Discomfort in the lumbar region and the decrease in postural reactions of the pelvic limbs detected during the initial examination for hypertension did not resolve after thyroidectomy. However, the owners chose not to pursue additional diagnostic testing for these issues.

The oncology service at our facility administered chemotherapeutics (doxorubicin [30 mg/m², IV, q 21 d] and carboplatin [300 mg/m², IV, q 21 d]) on an alternating schedule at 3-week intervals for a combined total of 6 doses. In addition, radiation treatment was administered at another facility by use of a linear accelerator with a bilaterally opposed field setup. The dog received a total dose of 48 Gy (16 fractions at 3 Gy/fraction).

Several emergency visits were made after thyroidectomy because of signs of hypocalcemia (eg, seizures or twitching), which resulted in alteration of the doses of the calcium supplementation. Four months after thyroidectomy, the ionized calcium concentration of the dog remained within the reference range. Calcium carbonate was discontinued, and a reduced dose of calcitriol (0.01 µg/kg [0.005 mg/lb], PO, q 48 h) was prescribed.

Also during the 4 months after thyroidectomy, total T₄ concentrations waxed and waned despite efforts to adjust the levothyroxine dose. The final adjustment of the levothyroxine dose was made after total T₄ concentrations were within reference limits at an evaluation conducted 4 months after the thyroidectomy. The dog was maintained by administration of the original dose of levothyroxine (0.02 mg/kg, PO, q 12 h).

**Discussion**

To the authors’ knowledge, there has been only 1 other report1 of concurrent hypertension in a dog with a functional thyroid gland adenocarcinoma. The author of that report did not mention resolution of hypertension after surgical management as was detected in the dog of our report. In addition, there have been other experiments conducted to evaluate the cardiovascular effects of experimentally induced hyperthyroidism in dogs; however, this is the first report of systemic hypertension in a dog attributable to naturally developing hyperthyroidism with resolution after thyroidectomy. The lack of clinical reports describing these 2 concurrent disease processes could be the result of the low prevalence of hyperthyroidism in dogs or attributable to the fact that routine blood pressure evaluation is not consistently performed when warranted. Although the prevalence of hyperthyroidism is much higher in cats than in dogs, a recent study4 on hypertensive cats revealed a relatively low prevalence of hyperthyroidism. This is in contrast to another study5 in which hypertension was prominent in hyperthyroid cats and did resolve with treatment. Nevertheless, the number of cats evaluated in that study was relatively low, compared with the number for the more recent study. This stresses the importance of routine blood pressure evaluation in animals with clinical disease, in addition to consideration of thyroid gland palpation during a routine physical examination. Careful palpation of the thyroid gland should be performed during the physical examination.

In cats, it has been proposed that hyperthyroidism causes an increase in β-adrenergic activity, which leads to tachycardia, increased myocardial contractility, and activation of the renin-angiotensin-aldosterone system, all of which lead to hypertension. The most common diseases that lead to secondary hypertension in dogs are renal disease, hyperadrenocorticism, pheochromocytoma, and diabetes mellitus. Less commonly associated diseases include primary hyperaldosteronism, obesity, hyperthyroidism, and idiopathic hypertension. For these conditions, specifically renal disease, hyperadrenocorticism, pheochromocytoma, and, rarely, hyperaldosteronism, an abdominal ultrasonographic evaluation was indicated in the dog of our report at the time the adrenal gland hormone panel and iohexol clearance test were performed.

Hypertension in dogs typically develops in older patients, with males more commonly affected than females. In a study6 of 5 hypertensive dogs, investigators reported a mean age of 8.6 years, with 3 of those dogs being > 10 years old. Although not performed in the dog of our report, a blood pressure measurement was indicated at the initial evaluation of polydipsia and polyuria. These clinical signs along with blindness or visual disturbances are common problems in the medical history of hypertensive dogs. Because many hypertensive dogs have underlying renal disease, it can be difficult to determine the factor that is the initial cause. Thus, a blood pressure measurement, although not performed, was also indicated in the dog of our report at the time renal insufficiency was evaluated by use of the iohexol clearance test. Other manifestations of hypertension include neurologic signs (such as seizures), cardiac complications attributable to left ventricular hypertrophy, and epistaxis. In terms of indirect blood pressure measurement, a substantially higher pulse pressure would indicate the need to isolate systolic and diastolic pressures. For this reason, a diastolic pressure should also have been measured in the dog of our report.

Dogs with hyperthyroidism may have signs of thyrotoxicosis (eg, polydipsia and polyuria, polyphagia, weight loss, hyperactivity, anxiousness, panting, tachycardia, voluminous feces, weakness, shivering,
In addition to signs of thyrotoxicosis, dogs with an enlarged thyroid gland may also have signs (such as coughing, dysphagia, dyspnea, dysphagia, and facial edema) attributable to a cervical mass. Thyroidectomy is the criterion-referenced standard for treatment of hyperthyroidism in dogs, assuming there is no evidence of metastasis to the lungs or lymph nodes and there is no invasion into adjacent blood vessels or nerves. At the time of initial diagnosis, it is estimated that only 25% to 50% of thyroid gland adenocarcinomas can be surgically resected. Prognosis is guarded with a median survival time after thyroidectomy of approximately 3 years when the tumor is freely moveable and 6 to 12 months when the tumor is more invasive. Subsequent radiation and chemotherapeutic treatments may be warranted, depending on the margins of surgical resection and invasiveness of the tumor. Postoperative monitoring of T3 and calcium concentrations is also necessary to determine the need for possible supplementation.

With a history of chronic polydipsia and polyuria associated with weight loss, panting, and restlessness (clinical signs of thyrotoxicosis), a serum T3 concentration would have been beneficial for use in diagnosing hyperthyroidism early on. At surgical excision, the thyroid gland mass had already become highly vascularized and invasive. An earlier diagnosis of hyperthyroidism could have potentially allowed for complete excision with margins free of tumor cells. In a study involving 146 dogs with thyroid gland tumors, 126 (86%) dogs had a visible mass on the neck, and this was the most common reason for owners to bring their dog for examination. The thyroid gland mass was not visible in the dog of our report because of the long and dense coat; however, the mass was detected during palpation of the neck. The metastatic potential for thyroid gland masses increases substantially as the volume of those masses approaches 27 cm3. Despite the fact the thyroid gland tumor in the dog of our report was < 27 cm3, metastasis was still a concern. Bilaterally manifested thyroid gland tumors are 16 times as likely to metastasize to the lungs and regional lymph nodes. The current recommendation for thyroid gland tumors with an increased risk of metastasis is systemically administered chemotherapy by use of a combination of doxorubicin and carboplatin, even if surgery or radiation therapy (or both) has been performed to control the primary tumor.

Sodium iodide I 131 treatment is another possible consideration for dogs with nonresectable thyroid gland tumors. In a retrospective study that involved use of sodium iodide I 131 treatment in 39 dogs with nonresectable tumors, there was a mean survival time of 839 days; however, 3 dogs died as a result of radioiodine-associated myelosuppression within 3 months after treatment. In addition, there are few facilities throughout the United States that offer this form of treatment.

In another retrospective study of 20 dogs with thyroid gland carcinomas treated by surgical resection alone, a median survival time of 20.5 months was reported. Because of the potential for fatal outcomes with sodium iodide I 131 treatment and the lack of resources to implement this treatment, surgical excision followed by chemotherapy and radiation therapy was elected for treatment of the dog of our report.

An ACE inhibitor, such as enalapril, is typically used as a first-line antihypertensive agent in dogs, whereas amiodipine, a calcium-channel blocker, is the treatment of choice in hypertensive cats. Although its use is not reported as commonly in dogs, amiodipine may be combined with an ACE inhibitor when the amiodipine does not effectively control hypertension. With respect to hyperthyroidism-related hypertension in cats, β-adrenoceptor blockers are the preferred choice because of the increased β-adrenergic activity associated with increased concentrations of thyroid gland hormones. Hyperthyroidism and the medical treatment of hyperthyroidism to control concurrent systemic hypertension are not commonly reported in dogs, and enalapril was selected as the first choice to control the hypertension in this dog. In addition, the hypertension in the dog was suspected to be a result of a functioning thyroid gland tumor; therefore, removal of the inciting cause was, in theory, likely to reduce blood pressure to within reference limits. After thyroidectomy, systolic blood pressures in the dog decreased to less than the values that are considered to cause end-organ damage, even after enalapril was discontinued.

After removal of both lobes of the thyroid gland, regulation of thyroid gland hormones and calcium concentrations proved challenging. Even though little is known regarding the effects of thyroid gland disorders on calcium hemostasis in dogs and cats, a study that involved the use of hypothyroid rats revealed an increase in renal excretion of calcium with a decrease in calcium absorption in the kidneys. In another study, increases in concentrations of thyroid gland hormones stimulated calcium uptake into intestinal brush-border membrane vesicles. Furthermore, it has been suggested that levothyroxine treatment in hypothyroid humans may cause an increase in bone turnover and a loss in bone mineral density. These findings regarding calcium homeostasis and thyroid gland hormones may explain why it was difficult to adjust the exogenous levothyroxine and calcium supplementation in the dog reported here.

a. Steroid profile for atypical Cushing's disease, Clinical Endocrine Service, College of Veterinary Medicine, University of Tennessee, Knoxville, Tenn.
b. Natrol, Chatsworth, Calif.
e. Doppler flow detector, Parks Medical Electronics Inc, Aloha, Ore.
f. Sphygmomanometer, Welch-Allyn, Skaneateles Falls, NY.
g. Sharn Veterinary Inc, Tampa, Fla.
h. IVAX Pharmaceuticals, Miami, Fla.
i. West Ward Pharmaceuticals, Eastontown, NJ.
j. Abbott, Chicago, Ill.
k. TEVA Pharmaceuticals, Petach Tikva, Israel.
l. i-Stat portable clinical analyzer, Heska Corp, Loveland, Colo.
m. Soloxine, Virbac, Fort Worth, Tex.
n. Datascope Passport XG, Soma Technology Inc, Cheshire, Conn.
References