

# Pheochromocytoma and hyperadrenocorticism in dogs: Six cases (1982–1992)

Benita J. von Dehn, DVM; Richard W. Nelson, DVM; Edward C. Feldman, DVM;  
Stephen M. Griffey, DVM

**Summary:** Pheochromocytoma was diagnosed in 4 dogs with pituitary-dependent hyperadrenocorticism and 2 dogs with hyperadrenocorticism caused by adrenocortical tumor. All dogs were examined initially because of clinical signs associated with hyperadrenocorticism. Pheochromocytoma was suspected in 2 dogs with pituitary-dependent hyperadrenocorticism that had ultrasonographic evidence of an adrenal gland mass, and in 1 dog suspected to have hyperadrenocorticism associated with an adrenocortical tumor after complications (systemic hypertension, cardiac arrhythmias) developed during induction of anesthesia. Pheochromocytoma was an unexpected finding at necropsy in the remaining 3 dogs. Two dogs collapsed suddenly and died before diagnostic tests could be performed; the other dog died during anesthesia for cobalt teletherapy of a pituitary macroadenoma. Hypertension, most notable during digital manipulation of the affected adrenal gland, developed during anesthesia and surgery in 3 dogs that underwent exploratory celiotomy.

In dogs, hyperadrenocorticism is usually diagnosed on the basis of history, physical examination findings, results of routine clinicopathologic tests (CBC, serum biochemical analysis, urinalysis), and results of endocrine function tests. Pituitary-dependent hyperadrenocorticism (PDH) is differentiated from hyperadrenocorticism caused by an adrenocortical tumor by measuring plasma-endogenous ACTH concentration or by performing a high-dose dexamethasone suppression test, abdominal radiography, abdominal ultrasonography, or exploratory celiotomy.<sup>1</sup> In most instances, results of these various discriminatory tests will agree. There is some confusion, however, when bilateral adrenal gland masses are identified in a dog suspected, on the basis of endocrine function tests, to have an adrenocortical tumor, or when a solitary adrenal gland mass is identified in a dog suspected, on the basis of endocrine function tests, to have PDH.

In some instances, this confusion is a result of unusual manifestations of hyperadrenocorticism. Bilateral adrenocortical tumors have been reported in 4 dogs with hyperadrenocorticism,<sup>2</sup> and nodular adrenal hyperplasia in a dog with PDH could give the appearance of an adrenal gland mass. In other instances, however, this confusion could be a result of a concurrent adrenal gland abnormality. Pheochromocytomas, for instance, originate from the chromaffin cells of the adrenal medulla and secrete excess catecholamines. Although these tumors are uncommon in dogs,<sup>3–5</sup> their presence in dogs

with hyperadrenocorticism can create discordance between results of endocrine function tests and results of abdominal ultrasonography and can affect the prevalence of perioperative complications in dogs undergoing exploratory celiotomy for suspected adrenocortical tumor. The purpose of the study reported here was to determine the prevalence of pheochromocytoma in dogs with hyperadrenocorticism and to determine the effect of pheochromocytoma in diagnosing and treating hyperadrenocorticism.

## Criteria for Selection of Cases

Medical records of all dogs in which hyperadrenocorticism was diagnosed between 1982 and 1992 were reviewed. Dogs with hyperadrenocorticism that also were found, on the basis of histologic examination of adrenal gland tissue, to have a pheochromocytoma were included in the study.

## Results

During the study period, 493 dogs were examined because of PDH, and 87 dogs were examined because of hyperadrenocorticism caused by an adrenocortical tumor. Six dogs, 4 with PDH and 2 with an adrenocortical tumor, also were found to have a pheochromocytoma. In all 6 dogs, clinical signs, physical examination abnormalities, results of clinicopathologic tests, and results of endocrine function tests were consistent with a diagnosis of hyperadrenocorticism.

In 4 dogs (1 sexually intact male, 1 neutered male, and 2 spayed females), a pheochromocytoma was identified within 6 weeks after hyperadrenocorticism was diagnosed. These dogs were between 7 and 13 years old (mean, 10.5 years) and represented 4 different breeds. In all 4 of these dogs, abdominal ultrasonography had been performed following diagnosis of hyperadrenocorticism to subjectively evaluate adrenal gland size.<sup>6</sup> Two dogs, both of which were suspected to have PDH on the basis of results of endocrine function testing, were found to have bilateral asymmetric adrenomegaly. The other 2 dogs, both of which were suspected, on the basis of results of endocrine function testing, to have an adrenocortical tumor, were found to have a unilateral adrenal gland mass. The contralateral adrenal gland could not be imaged in these dogs.

Mitotane<sup>a</sup> treatment (25 or 50 mg/kg of body weight, PO, q 24 h) was started in the 2 dogs with bilateral asymmetric adrenomegaly. In 1 dog, clinical signs improved, and 7 days after initiation of mitotane treatment, plasma cortisol concentration, measured 1 hour after administration of ACTH<sup>b</sup> (0.25 mg, IM), was less than 5 µg/dl. The dosage of mitotane was reduced to 50 mg/kg, given once weekly; however, 1 month later, the dog developed progressively worsening mental dullness. A large pitui-

From the Veterinary Medical Teaching Hospital (von Dehn) and the Departments of Medicine and Epidemiology (Nelson, Feldman) and Pathology (Griffey), School of Veterinary Medicine, University of California, Davis, CA 95616.

Address reprint requests to Dr. Nelson.

tary mass was identified by means of magnetic resonance imaging. Cobalt teletherapy was begun, and mitotane treatment was discontinued. During anesthetic recovery after the seventh cobalt treatment, acute gastric dilatation and cardiac arrest occurred, and the dog died. Pituitary adenoma and adrenal gland pheochromocytoma were identified at necropsy.

In the other dog, plasma cortisol concentration 1 hour after administration of ACTH was greater than 10  $\mu\text{g}/\text{dl}$ , despite treatment with mitotane (25 mg/kg, PO, q 24 h) for 2 months. Abdominal ultrasonography was repeated, and bilateral asymmetric adrenomegaly was still detected; however, there now appeared to be a mass involving the left adrenal gland. Exploratory celiotomy was performed, and the adrenal gland mass removed. Histologic evaluation of the mass and a biopsy specimen from the right adrenal gland revealed pheochromocytoma and adrenocortical destruction consistent with mitotane treatment. Recovery from anesthesia was uneventful; however, the dog developed respiratory distress 72 hours after surgery and died. On thoracic radiographs obtained prior to death, there were mild cardiomegaly and a bronchointerstitial pattern. Pulmonary thromboembolism was suspected; however, a complete necropsy was not performed.

Ketoconazole<sup>c</sup> (15 mg/kg, PO, q 12 h) was administered to 1 of the dogs suspected to have a unilateral adrenocortical mass. Clinical signs had improved within 3 weeks and the post-ACTH plasma cortisol concentration was 2.1  $\mu\text{g}/\text{dl}$ . Abdominal ultrasonography was repeated, and the adrenal gland mass appeared to be larger than before. Exploratory celiotomy was performed, and a left adrenal gland mass was removed. The right adrenal gland was normal on digital palpation. Histologic evaluation of the mass revealed adrenocortical adenoma. Recovery from anesthesia was uneventful, and the dog was discharged 7 days after surgery. One month later, the dog suddenly developed respiratory distress, collapsed, and died. A pheochromocytoma was found in the right adrenal gland at necropsy.

Adrenalectomy was attempted in the other dog suspected to have a unilateral adrenal gland mass. Severe systemic hypertension and cardiac arrest occurred during induction of anesthesia. The dog was resuscitated and stabilized, and adrenalectomy was postponed for 1 week. Two days prior to surgery, treatment with phenoxybenzamine (1.25 mg/kg, PO, q 12 h) and propranolol (0.3 mg/kg, PO, q 8 h) was initiated. The dog's arterial blood pressure fluctuated markedly when the left adrenal gland mass was digitally manipulated during surgery. Left adrenalectomy was performed; the right adrenal gland could not be evaluated because a flank approach to the left adrenal gland had been used. Histologic evaluation of the mass revealed pheochromocytoma. The dog developed acute pancreatitis and sepsis postoperatively and died 8 days after surgery. Necropsy revealed adrenocortical carcinoma of the right adrenal gland.

In the remaining 2 dogs in the study, pheochromocytoma was diagnosed 2 and 3 years after initiation of mitotane treatment for PDH. The dogs were 15 and 16 years old when pheochromocytoma was diagnosed. Both were male (1 neutered, 1 sexually intact), mixed-breed dogs. One dog developed acute retinal degeneration,

choroidal hemorrhage in the left eye, and cardiac arrhythmias after 2 years of mitotane treatment. The dog collapsed and died before diagnostic tests could be performed. A pheochromocytoma was found at necropsy. The other dog collapsed suddenly after 3 years of mitotane treatment. The dog's mucous membranes were pale, and it had bradycardia, third degree atrioventricular block, tachypnea, and mild abdominal distention. An adrenal gland mass that appeared to be invading the caudal vena cava was identified ultrasonographically.

Exploratory celiotomy was performed, and 2 masses (1 involving the right adrenal gland and extending into the caudal vena cava and 1 involving the liver) were found. The dog was euthanatized during surgery, and histologic evaluation of the masses revealed pheochromocytoma and hepatocellular carcinoma.

Systemic blood pressure was measured at rest, using an indirect method,<sup>d</sup> in 4 dogs. In all 4 dogs, systolic blood pressure (range, 120 to 138 mm of Hg; reference interval, < 160 mm of Hg), diastolic blood pressure (range, 80 to 93 mm of Hg; reference interval, < 95 mm of Hg), and mean systemic blood pressure (range, 100 to 108 mm of Hg; reference interval, 90 to 110 mm of Hg) were within the reference intervals. Three of the 4 dogs that underwent exploratory celiotomy and adrenalectomy developed hypertension (systolic blood pressure > 200 mm of Hg, diastolic blood pressure > 120 mm of Hg) during surgery. Hypertension was most noticeable during digital manipulation of the affected adrenal gland. Acepromazine (0.03 to 0.08 mg/kg, IV) given intraoperatively was effective in treating hypertension.

## Discussion

All 6 of these dogs were examined initially because of clinical signs associated with hyperadrenocorticism, and none of the dogs had historic, physical, clinicopathologic, or endocrinologic abnormalities that would lead us to suspect that the dogs had a pheochromocytoma. Three of the 6 dogs died suddenly, and pheochromocytoma was an unexpected finding at necropsy. In 1 of these dogs, the affected adrenal gland was considered normal by digital palpation during exploratory celiotomy 1 month prior to death. Pheochromocytoma was suspected prior to death in the remaining 3 dogs; in 2 dogs suspected to have PDH, an adrenal gland mass was seen during abdominal ultrasonography, and in 1 dog suspected to have an adrenocortical tumor, systemic hypertension and cardiac arrhythmias developed during induction of anesthesia.

Commonly reported clinical signs of pheochromocytoma in dogs include excessive panting and weakness,<sup>3,5</sup> and these signs were identified in all of these dogs. However, these clinical signs also are associated with hyperadrenocorticism. Acute collapse also is common in dogs with pheochromocytoma,<sup>3,5</sup> and both of the dogs in this study that had been receiving mitotane for an extended period were examined because of acute collapse. Potential causes for acute collapse of a dog with PDH that has been receiving mitotane include mitotane overdose, thromboembolism, CNS dysfunction resulting from a pituitary macroadenoma, and cardiac insuf-

iciency. Our results suggest that pheochromocytoma also should be considered.

Identification of pheochromocytoma in a dog with hyperadrenocorticism may be difficult. Biochemical and pharmacologic tests used to diagnose pheochromocytoma include measurement of plasma catecholamine concentration; measurement of systemic blood pressure prior to and after administration of histamine, glucagon, phenolamine, or clonidine; and measurement of 24-hour urinary excretion of catecholamines and their metabolites.<sup>3,5,7,8</sup> Unfortunately, these tests are available on a limited basis, difficult to perform, and expensive, and reference intervals for normal results have not been established. Computerized tomography and magnetic resonance imaging are the preferred techniques for examination of the adrenal glands in people,<sup>8</sup> but limited availability, expense, and the need for general anesthesia limit their use in dogs.

Abdominal ultrasonography was instrumental in establishing a diagnosis of pheochromocytoma in 2 of these dogs. Both of these were dogs with PDH that had ultrasonographic evidence of a unilateral adrenal gland mass. On the other hand, in 2 dogs with a pheochromocytoma and hyperadrenocorticism caused by an adrenocortical tumor, only a single adrenal gland mass was seen ultrasonographically, and we did not determine that these dogs had a pheochromocytoma until problems arose during anesthesia or until necropsy.

Sustained or intermittent systemic hypertension is a characteristic clinical manifestation of pheochromocytoma in human beings,<sup>7,8</sup> and has been reported in approximately 50% of dogs with pheochromocytoma.<sup>3,4,9</sup> However, systemic hypertension is not a reliable marker for pheochromocytoma in dogs with hyperadrenocorticism because hyperadrenocorticism itself can cause hypertension.<sup>6</sup> Interestingly, systemic hypertension was not documented in any of the 4 dogs in this study in which blood pressure was measured at rest. However, severe systemic hypertension developed during anesthesia and digital manipulation of the pheochromocytoma in 3 dogs, and was the primary reason for considering pheochromocytoma in 2 of these dogs. The sudden onset of severe systemic hypertension in these dogs was presumably a result of sudden release of catecholamines by the pheochromocytoma.<sup>3,5</sup>

The treatment of choice for pheochromocytoma is surgical excision. Unfortunately, perioperative complications developed in all 3 of the dogs in which pheochromocytoma was suspected prior to death and that underwent adrenalectomy. In human beings, medical

treatment to control systemic hypertension and reduce the prevalence of perioperative complications is typically initiated 14 days prior to surgical excision of a pheochromocytoma, and drugs that can potentiate the deleterious actions of catecholamines (eg, atropine and phenothiazines) are avoided during anesthesia.<sup>8</sup> Presurgical medical treatment was attempted in only 1 of these dogs, and, possibly because of inadequate dosage or duration of treatment, it did not prevent development of cardiac arrhythmias or systemic hypertension.

All 6 of the dogs in this study died, and the prognosis for dogs with pheochromocytoma and hyperadrenocorticism should be considered guarded or poor. Our results suggest that pheochromocytoma should be suspected when clinical signs of hyperadrenocorticism do not resolve with appropriate treatment, when results of endocrine function tests conflict with results of abdominal ultrasonography, and when systemic hypertension or cardiac arrhythmias develop during anesthesia or digital manipulation of an adrenal gland mass.

<sup>a</sup>Lysodren, Bristol Meyers Co, Evansville, Ind.

<sup>b</sup>Cortrosyn, Organon Inc, West Orange, NJ.

<sup>c</sup>Nizoral, Janssen Pharmaceutical Inc, Piscataway, NJ.

<sup>d</sup>Dinamap Vital Signs Monitor, Model 1846 SX, Critikon, Tampa, Fla.

<sup>e</sup>Kallet A, Cowgill LD. Hypertensive states in the dog (abstr), in *Proceedings. Am Coll Vet Intern Med Annu Meet* 1983;79.

## References

1. Feldman EC. Distinguishing dogs with functioning adrenocortical tumors from dogs with pituitary-dependent hyperadrenocorticism. *J Am Vet Med Assoc* 1983;183:195-200.
2. Ford SL, Feldman EC, Nelson RW. Hyperadrenocorticism caused by bilateral adrenocortical neoplasia in dogs: four cases (1983-1988). *J Am Vet Med Assoc* 1993;202:789-792.
3. Twedt D, Wheeler SL. Pheochromocytoma in the dog. *Vet Clin North Am Small Anim Pract* 1984;14:767-782.
4. Feldman EC, Nelson RW. *Canine and feline endocrinology and reproduction*. Philadelphia: WB Saunders Co, 1987;375-398.
5. Bouayad H, Feeney DA, Caywood DD, et al. Pheochromocytoma in dogs: 13 cases (1980-1985). *J Am Vet Med Assoc* 1987;191:1610-1615.
6. Kantrowitz BM, Nyland TG, and Feldman EC. Adrenal ultrasonography in the dog. Detection of tumors and hyperplasia in hyperadrenocorticism. *Vet Radiol* 1986;27:91-96.
7. Sheps SG, Jiang N, Klee G, et al. Recent developments in the diagnosis and treatment of pheochromocytoma. *Mayo Clin Proc* 1990; 65:88-95.
8. Landsberg L, Young JB. Catecholamines and the adrenal medulla. In: Wilson JD, Foster DW, eds. *Williams textbook of endocrinology*. 8th ed. Philadelphia: WB Saunders Co, 1992;621-705.
9. Howard EB, Nielsen SW. Pheochromocytomas associated with hypertensive lesions in dogs. *J Am Vet Med Assoc* 1965;147:245-252.