Pheochromocytoma

Carrie A. Palm, DVM
Resident, Small Animal Internal Medicine

Allyson C. Berent, DVM, DACVIM
Staff Veterinarian
Small Animal Internal Medicine and Interventional Radiology

Peter S. Chapman, BVetMed, DECVIM-CA, MRCVS
Assistant Professor, Small Animal Internal Medicine

Department of Clinical Studies
Matthew J. Ryan Veterinary Hospital
University of Pennsylvania

Pheochromocytomas are catecholamine-secreting neuroendocrine tumors that arise from the chromaffin cells of the adrenal medulla. These tumors are uncommon in dogs, humans, and rats and rare in cats. Antemortem diagnosis of these tumors is a challenge because the clinical signs seen in animals with pheochromocytomas are vague and often intermittent. In addition, affected animals frequently have concurrent diseases, such as hyperadrenocorticism, diabetes mellitus, and other neoplastic processes, which can further obscure a clear diagnosis. These tumors are typically solitary, slow-growing masses; however, bilateral adrenal pheochromocytomas and extra-adrenal pheochromocytomas have also been reported.

The adrenal glands are composed of two main divisions, the adrenal cortex and the adrenal medulla, which work in tight conjunction with one another. The adrenal cortex, which includes the zona glomerulosa, zona fasciculata, and zona reticularis, primarily secretes mineralocorticoids, glucocorticoids, and sex hormones. The adrenal medulla produces, stores, and secretes multiple substances, with catecholamines (norepinephrine, epinephrine, and, to a lesser extent, dopamine) being the primary products. In nonneoplastic adrenal medullary chromaffin cells, catecholamines are released via neural impulses that are stimulated secondary to physiologic stressors, such as hypotension, hypoglycemia, fear, and stress. Tight regulation of this release is lost in pheochromocytomas.

Some tumors release catecholamines constantly, whereas others secrete these products intermittently; diagnosis can be particularly challenging in the latter situation.

Clinical signs seen with pheochromocytomas are caused by excessive systemic release of catecholamines (by primary tumors and/or metastases), resulting in stimulation of α- and β-adrenergic receptors throughout the body (Table 1), or by local invasion of the tumor into nearby structures, primarily blood vessels (caudal vena cava, renal arteries and veins, and the phrenicoadominal artery).

As the use of ultrasonography has become more commonplace in veterinary medicine, adrenal tumors are being diagnosed more frequently. These tumors are often found incidentally during a workup for other disease processes. When evaluating an adrenal mass, several criteria should be considered. Diagnostic tests should be directed toward determining whether the tumor is of cortical or medullary origin and whether it is active or inactive. When evaluating the anesthetic risk in older patients, it is important to consider the potential for the presence of a pheochromocytoma; affected patients can lack symptoms of the primary disease. It is critical to conduct proper diagnostic testing and treatment planning to minimize the risk of anesthetic complications.
obvious clinical signs before anesthesia but can develop life-threatening complications, especially during induction of anesthesia.

**DIAGNOSTIC CRITERIA**

**Historical Information**

**Gender Predisposition**
- No known gender predispositions are reported in animals.

**Age Predisposition**
- Older dogs and cats, with a mean age of 10 to 11 years (range, 1–18 years) in dogs.
- Mean age in cats is unknown.

**Breed Predisposition**
- Pheochromocytomas have been reported more frequently in certain breeds, but this is more likely a reflection of the popularity of the dog breeds than a true genetic predisposition; no breed predisposition is proven.
- In humans, approximately 10% of pheochromocytomas are hereditary. This has been reported to be part of a syndrome known as multiple endocrine neoplasia (see box on page 3).

**Owner Observations**
- Episodic collapse/weakness.
- Episodic panting/tachypnea.
- Polyuria/polydipsia (seen more consistently in cats).
- Episodic anxiety.
- Anorexia.
- Weight loss.
- Abdominal distention from ascites (secondary to tumor thrombi).
- If severe hypertension develops, side effects that are more serious can be seen, such as acute onset blindness (due to retinal detachment), epistaxis, and signs associated with acute renal failure.

**KEY TO COSTS**

$ indicates relative costs of any diagnostic and treatment regimens listed.

$ costs less than $250

$$ costs between $250 and $500

$$ costs between $500 and $1,000

$$$$ costs more than $1,000
Other Historical Considerations/Predispositions

- Many pheochromocytomas are diagnosed incidentally during abdominal ultrasonography, laparotomy, or necropsy.
- Many animals with pheochromocytomas have concurrent disease processes, such as diabetes mellitus and hyperadrenocorticism. The high prevalence of concurrent disease is likely associated with the older age of affected animals but may also be associated with multiple endocrine neoplasia (see box).

Physical Examination Findings

- Physical examination is often unremarkable, and abnormalities are usually associated with concurrent disease processes.
- Detectable abnormalities caused directly by pheochromocytomas are often vague and nonspecific; such findings include tachycardia, cardiac arrhythmias, tachypnea, panting, weakness, epistaxis, and retinal hemorrhage, which occur secondary to excessive catecholamine secretion and resultant hypertension. In addition, tumor invasion into surrounding structures, such as the caudal vena cava, can lead to the development of ascites and abdominal distension.
- Clinical signs are often intermittent and can be absent if excessive catecholamine secretion is not occurring at the time of examination.

Laboratory Findings

- Patients should be fully evaluated for the presence of other underlying disease; many affected animals have concurrent disease.
- Complete blood count, serum biochemistry panel, and urinalysis are often unremarkable.
- Absence of abnormalities on routine hematology and biochemistry analysis can help to differentiate a functional adrenal cortical tumor from a pheochromocytoma.
- Despite the absence of specific changes on routine hematology and biochemistry analysis, a complete workup should be performed to screen for concurrent disease processes. Hyperadrenocorticism should be ruled out, but a positive diagnosis of hyperadrenocorticism does not rule out pheochromocytoma; these diseases have been reported simultaneously. The high-dose dexamethasone suppression test is more sensitive than the corticotropin stimulation test for diagnosing a functioning glucocorticoid-secreting tumor, and it is more specific than a low-dose dexamethasone suppression test or urinary cortisol:creatinine ratio. One approach is to determine the urinary cortisol:creatinine ratio (a simple, inexpensive test): If the ratio is

Multiple Endocrine Neoplasia (MEN)

- MEN is a group of heritable syndromes (autosomal dominant inheritance) of neoplasia in various endocrine tissues described in humans.
- Neoplasia can be functional or nonfunctional and benign or malignant.
- Three major syndromes are characterized by the location(s) of neoplasia:
  - MEN-1: Hyperparathyroidism, endocrine pancreatic tumors, pituitary adenomas, lipomas
  - MEN-2A: Hyperparathyroidism, thyroid carcinoma, pheochromocytoma
  - MEN-2B: Thyroid carcinoma, pheochromocytoma, intestinal ganglioneuromas
- A fourth subtype (mixed-type syndrome) has been described as a combination of the syndromes listed above.
- In a study of 277 dogs diagnosed with pheochromocytoma, 46% had other neoplasia, suggesting a possible hereditary predisposition.
- No genetic connection has been proven in dogs or cats; the multitude of neoplasias reported in these patients may be a true heritable syndrome or may simply represent unrelated disease processes.

Catecholamine production and metabolism. *Negative feedback on tyrosine hydroxylase (via norepinephrine) is lost in pheochromocytomas, resulting in excessive catecholamine production. (COMT = catechol-O-methyl transferase; MAO = monoamine oxidase; TH = tyrosine hydroxylase)
normal, a functional glucocorticoid-secreting tumor is unlikely; if the ratio is high, stress may be the culprit, and the high-dose dexamethasone suppression test should be performed to differentiate adrenal-dependent hyperadrenocorticism from a stress response.

**Phentolamine Suppression Testing**
- Phentolamine is an α-adrenergic antagonist that decreases blood pressure by blocking α-mediated vasoconstriction.
- Patient must be hypertensive for testing to be useful.
- If hypertension is due to excessive circulating catecholamine concentration, then administration of phentolamine should decrease blood pressure. Test result is considered positive if systolic blood pressure drops by 35 mm Hg for at least 5 minutes after administration.

**Stimulation Testing**
- Testing involves administration of agents known to stimulate release of catecholamines (e.g., glucagon, metoclopramide, drugs that cause histamine release).
- Use of stimulation tests is not recommended because of the potential for life-threatening complications.

### Diagnostic Testing

#### Clonidine Suppression Testing
- Clonidine is a centrally acting α-adrenergic agonist that decreases catecholamine release by normal adrenal medulla.
- Pheochromocytomas do not respond to clonidine, and catecholamine concentrations remain elevated after clonidine administration.

#### Phentolamine Suppression Testing
- Phentolamine is an α-adrenergic antagonist that decreases blood pressure by blocking α-mediated vasoconstriction.
- Patient must be hypertensive for testing to be useful.
- If hypertension is due to excessive circulating catecholamine concentration, then administration of phentolamine should decrease blood pressure. Test result is considered positive if systolic blood pressure drops by 35 mm Hg for at least 5 minutes after administration.

#### Stimulation Testing
- Testing involves administration of agents known to stimulate release of catecholamines (e.g., glucagon, metoclopramide, drugs that cause histamine release).
- Use of stimulation tests is not recommended because of the potential for life-threatening complications.

### Other Diagnostic Findings

**Blood pressure measurement:** Hypertension can be severe but also episodic. Documenting hypertension during an evaluation can therefore be difficult (25% to 86% of patients are hypertensive at evaluation).

**Plain thoracic radiography:** Pulmonary metastases have been reported in 8% to 11% of affected dogs. Cardiomegaly and/or pulmonary congestion can be seen secondary to severe hypertension. Pulmonary thromboembolism may also occur and may or may not be visualized on radiographs. Radiography can help rule out the presence of other disease.

**Abdominal radiography:** Identifiable perirenal mass reported in 26% to 56% of cases; 10% of pheochromocytomas are mineralized.

**Contrast radiography:** IV urography and vena caval venography have been used to evaluate for renal displacement, tumor thrombi, and tumor invasion into blood vessels (56% to 100% of patients are reported to have tumor thrombi).

**Abdominal ultrasonography:** Visualization of an adrenal mass has been reported in 50% to 83% of affected animals during ultrasonographic examination. The absence of a mass does not rule out pheochromocytoma.

- Can be used to evaluate for kidney displacement, local tumor invasion, and signs of metastasis.
- Tumor thrombi are present in 56% to 100% of all patients with pheochromocytomas. Visualization during ultrasonography is dependent on multiple factors, including the extent of metastatic tumor thrombi and ultrasonographer skill.
- The contralateral adrenal gland should be atrophied in adrenal-dependent hyperadrenocorticism, unless bilateral adrenal tumors or concurrent pituitary-dependent hyperadrenocorticism is present.

**Computed tomography:** Used for surgical planning to evaluate the extent of tumor invasion. This is the most commonly used modality in human medicine and has an accuracy of 85% to 95% for detecting adrenal tumors that are 1 cm or larger.

**Magnetic resonance imaging:** Used in human medicine to help differentiate between adrenal cortical and medullary tumors; may also be useful in differentiating between benign and malignant hepatic nodules.

**Metaiodobenzylguanidine (MIBG) scanning:** MIBG is a substance similar in structure to norepinephrine. MIBG is taken up into catecholamine-storing vessels and can help to differentiate pheochromocytomas from other causes of hypertension.

---

*Not evaluated in dogs or cats.*
cytomas from other adrenal tumors. This modality has also been used to identify metastatic disease and extra-adrenal pheochromocytomas. $$$$

**Summary of Diagnostic Criteria**
- Older dog or cat.
- Presence of vague clinical signs.
- Identification of an adrenal mass.
- Rule-out of adrenal-dependent hyperadrenocorticism.
- Antemortem diagnosis is difficult. Definitive diagnosis is based on histopathology of the tumor (with special stains) and signs suggesting catecholamine release during manipulation of tumor at surgery.

**Diagnostic Differentials**
- Adrenal medullary tumor: Nonfunctional.
  - Nonfunctional.
  - Cortisol-secreting tumor most common.
  - Aldosterone-, deoxycorticosterone-, progesterone-, and 17-OH-hydroxyprogesterone-secreting tumors have also been reported. With aldosterone-secreting tumors, animals present with clinical signs of weakness and lethargy and often have significant hypertension. Hypokalemia and hypernatremia are common findings, and diagnosis of hyperaldosteronism is confirmed with findings of elevated aldosterone levels both before and after administration of corticotropin. Plasma progesterone levels are increased with progesterone-secreting tumors. A corticotropin stimulation test should be performed to rule out the presence of 17-OH-hydroxyprogesterone-secreting tumors. Affected animals typically have elevated 17-OH-hydroxyprogesterone levels both before and after administration of corticotropin.

**ON THE NEWS FRONT**
- Percutaneous embolization and radiofrequency ablation have been described for both nonresectable adrenal and renal tumors in human medicine.

- Treatment of hypertension: Phenoxybenzamine is a nonselective, noncompetitive $\alpha$-adrenergic blocker. It can be initiated at a dose of 0.25 mg/kg PO bid (dogs and cats), and the dose can be increased gradually every few days until stabilization of blood pressure is achieved (maximum dosage, 2.5 mg/kg PO bid). NOTE: Because hypertension is often episodic, one must be careful not to induce hypotension.

- Treatment of tachycardia and arrhythmias: Propranolol is a nonspecific $\beta$-adrenergic antagonist that has been shown to be effective at controlling catecholamine-induced arrhythmias as well as tachycardia. $\beta$-Adrenergic antagonists should never be used without $\alpha$-adrenergic blockade in animals with pheochromocytomas because severe hypertension can occur secondary to blockade of $\beta$-receptor-mediated vasodilation. NOTE: Because tachycardia can be intermittent, one must be careful not to induce bradycardia.
  - Dogs: 0.15–1.0 mg/kg PO tid.
  - Cats: 2.5–5 mg/CAT PO bid–tid.

- Monitoring of plasma volume status: Patients can develop a relative hypovolemia once hypertension and sustained catecholamine-induced vasoconstriction are treated. Clinical findings seen with hypovolemia include tachycardia, hypotension, and signs of poor perfusion (e.g., decreased mentation, poor pulse quality, pale mucous membranes).

**TREATMENT RECOMMENDATIONS**

**Initial Treatment**

**Preoperative Medical Management**
- It is important to identify and treat other underlying disease processes.
- Medical management is indicated before and after surgery and in patients in which surgery is not feasible.
- Goals of medical management include stabilization of blood pressure, restoration of plasma volume (which is decreased secondary to chronic adrenergic stimulation), and control of cardiac arrhythmias/tachycardia. Appropriate therapy should be initiated 2 to 4 weeks before surgery.

**Anesthetic Considerations**
- Careful anesthetic planning is crucial.
- Life-threatening hypertension and cardiac arrhythmias occur frequently during anesthetic induction.
- Direct monitoring of arterial blood pressure and continuous electrocardiography must be performed.
- Measurement of central venous pressure allows for appropriate IV fluid administration. Severe hypovolemia can occur after tumor resection and subsequent decrease in circulating catecholamines.
- Because of the high risk of hemorrhage, blood typing and/or crossmatching must be performed before surgery.
- Many different anesthetic protocols have been used. Vagolytic drugs (e.g., atropine, glycopyrrolate), drugs that can cause histamine release (e.g.,...
Nests of polyhedral cells with lightly eosinophilic, granular cytoplasm. Adrenal cortical tumors from pheochromocytomas:

- Chromogranin A is found in secretory granules of endocrine cells but not in adrenocortical cells.
- Synaptophysin is a membrane component of synaptic vesicles in neuronal and neuroendocrine cells; it is present in adrenal medullary cells but not in adrenocortical cells.

**Intraoperative Considerations**

- Communication (e.g., regarding manipulation of the tumor, bleeding) between the surgical and anesthesia teams is critical.
- IV phentolamine, a short-acting competitive α-adrenergic blocker, can be used to control severe intraoperative hypertension in dogs. Careful monitoring is necessary to prevent development of hypotension. **Dose (dogs and cats):** 0.1 mg/kg IV loading dose, followed by constant rate infusion of 1–2 µg/kg/min. There are no established doses for phentolamine in cats.
- If IV phentolamine does not adequately control hypertension or if tachycardia and/or arrhythmias are present, IV esmolol can be used. Esmolol is a short-acting β₁-adrenergic blocker that has negative inotropic and chronotropic activities and thereby reduces myocardial oxygen demand. **Dose (dogs and cats):** 0.05–0.1 mg/kg IV loading dose, followed by constant rate infusion of 50–200 µg/kg/min.
- Stabilization of blood pressure, heart rate, and heart rhythm should occur with removal of the tumor. Failure of this to occur likely indicates incomplete removal of the primary tumor, presence of metastasis, and/or extra-adrenal pheochromocytomas. Again, one must monitor for onset of hypotension, which can occur if antihypertensive drugs are still circulating after tumor removal has been accomplished.

**Histopathology**

- Nests of polyhedral cells with lightly eosinophilic, granular cytoplasm.
- Difficult to distinguish between benign and malignant tumors.
- Special stains can be used to differentiate adrenocortical tumors from pheochromocytomas:
  - Chromogranin A is found in secretory granules of endocrine cells but not in adrenocortical cells.
  - Synaptophysin is a membrane component of synaptic vesicles in neuronal and neuroendocrine cells; it is present in adrenal medullary cells but not in adrenocortical cells.

**Alternative/Optional Treatments/Therapy**

- Radiation and chemotherapy have shown limited success in humans.
- Combination chemotherapy consisting of cyclophosphamide, vincristine, and dacarbazine has had some success in humans.
- Radiation and chemotherapeutic protocols for pheochromocytomas have not been evaluated in dogs.
- Targeted therapy with radiolabeled MIBG has been used in humans but has not been evaluated in dogs. Although pheochromocytomas are usually solitary, bilateral involvement may necessitate bilateral surgery.
adrenalectomy. If so, supplemental corticosteroids and mineralocorticoids will be necessary, but catecholamine supplementation has not been required in these patients.

- Nonresectable tumors have been embolized using interventional radiologic procedures.

### Supportive Treatment/Long-Term Treatment

- The goal of long-term therapy is to control the effects of excessive catecholamine release. Administration of medical therapy (as described in Preoperative Medical Management) is necessary for treatment of nonresectable tumors and in patients with metastatic disease. Treatment for hypertension, tachycardia, and cardiac arrhythmias should be continued and tapered based on individual patient factors following successful surgical resection. Care should be taken to avoid inducing hypotension and bradycardia in patients with a low postoperative tumor burden, where excessive catecholamine secretion is no longer present.
- Active suppression of catecholamine production with α-methylmetatyrosine (via inhibition of tyrosine hydroxylase [Figure 1]) has been attempted in humans. Renal and neurologic side effects have limited the use of this drug.

### Patient Monitoring

- Recheck examinations, abdominal ultrasonography, and blood pressure monitoring should be performed 1 week after surgery and then every 1 to 2 months or as needed on an individual patient basis.
- Careful evaluation of patients is necessary after surgery because adrenergic blockade will need to be altered based on the success of surgery and the presence of metastasis.

### Home Management

- Owner education should include advising owners on how to monitor for clinical signs associated with tumor progression and/or metastasis; these signs are listed under Owner Observations.
- Administration of phenoxybenzamine with or without β-blockade, as described above.
- Exercise restriction.
- Minimization of stressful events (which can induce catecholamine secretion).

### Milestones/Recovery Time Frames

- If complete tumor resection is achieved, clinical signs may no longer be present.
- In patients with metastatic disease, clinical signs may continue following complete resection of the primary tumor or may return as metastasis progress.

### PROGNOSIS

- For patients surviving the perioperative period, survival times have ranged from 2 months to more than 3 years.
- If complete surgical resection of a solitary pheochromocytoma is performed, a cure can be achieved.
- With a solitary, small (<3 cm) pheochromocytoma without vascular invasion, medical management alone has been associated with survival times of up to 1 year.
- Prognosis in cats is likely similar to that in dogs, but no established survival times have been reported.

#### Favorable Criteria
- Absence of concurrent disease.
- Absence of local invasion of tumor into surrounding structures.
- Absence of metastasis (can be difficult to determine).
- Tumor smaller than 3 cm.
- Patient survives beyond the perioperative period.

#### Unfavorable Criteria
- Presence of concurrent disease.
- Invasion of tumor into local structures: Guarded prognosis. Tumor invasion is not necessarily a contraindication to surgery, as debulking can increase success of medical management.
- Presence of tumor metastasis.
- The presence of neurologic signs, abdominal distention, and weight loss at the time of diagnosis has been associated with more aggressive tumors and poor prognosis.

### RECOMMENDED READING