The Adrenal Effect

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Introduction

Pheochromocytoma is a rare endocrine tumor that is derived from chromaffin cells in the adrenal medulla (2). Chromaffin cells synthesize and secrete catecholamines, epinephrine and norepinephrine (6). Catecholamine release in functional pheochromocytomas is usually paroxysmal. This may be attributed to changes in blood flow, chemicals, or drugs, or direct pressures on the tumor (abdominal palpation) since the tumors have no innervation. It is the most common adrenal medulla neoplasm in dogs, horses and cattle, but is rarely seen in cats (1). These tumors usually appear unilateral in older animals (mean age of 11 years). In dogs, pheochromocytomas are usually benign but have the potential of metastasis to local structures (1) . The tumor is considered malignant when it metastasizes to distant organs (liver, regional lymph nodes or lungs) or non-chromaffin cells. The clinical signs with pheochromocytomas are often vague, intermittent and can mimic other common disorders such as hyperadrenocorticism, diabetes mellitus, hepatic or renal disease, or other neoplasms. Clinical signs usually include weakness, collapse, lethargy, anorexia, vomiting, panting, weight loss, anxiety, restlessness, polyuria, polydipsia, diarrhea, abdominal distention, hind limb edema, epistaxis, seizures or acute blindness (1). These specific clinical signs are associated with catecholamine excess and systemic hypertension.

History and presentation

Dakota was an 11-year old, female spayed Boxer who presented to the MSU-CVM Internal Medicine service on June 10, 2019, for panting, pancreatitis and abnormal abdominal radiographs. On June 8, 2019, she started to have loose stools but no vomiting. On June 9, 2019, her stools were more loose with yellow-green mucus but no vomiting. In addition, she began panting that same day, so the owner gave her tramadol and methocarbamol, but her panting

became worse. That evening, the owner took Dakota to the emergency clinic and was diagnosed with pancreatitis via the PLI snap test. In addition, bloodwork revealed a stress leukogram, elevated liver enzymes and hyperglycemia. She was administered Norm-R + B12 + 1 g Cefazolin at 120 ml/hour, metronidazole, gabapentin, maropitant citrate, proviable and buprenorphine. The emergency veterinarian recommended the patient to stay overnight on IV fluids and transfer to her primary veterinarian the next day. Radiographs were performed at the owner's primary veterinarian clinic and revealed lungs that were within normal limits and loss of detail in the cranial abdomen. The referring veterinarian had a questionable diagnosis of pancreatitis and had splenic enlargement, neoplasia, peritonitis, and liver disease as differential diagnoses. Therefore, they referred Dakota to the MSU-AHC for further evaluation. Dakota had a previous history of being shot in the face before she was a year old, back pain that was medically managed with methocarbamol, tramadol and deracoxib. She previously had an oral melanoma removed and healing ulcer in the left eye. Dakota was up to date on vaccination and was on Advantage Multi.

On presentation, Dakota was non-ambulatory, quiet, alert and responsive and in respiratory distress. Her temperature was 102.1° F, heart rate of 130 and respiratory rate of 172. She weighed 29.6 kg with a body condition score of 7/9 (ideal being 4-5/9). Her mucous membranes were pink and she a capillary refill time of 2 seconds. Her left mandible was removed, and the left lateral aspect of the tongue was split due to a previous gunshot wound to the face and several teeth were absent due to previous oral melanoma surgical excision. Lymph nodes palpated normally. Rectal palpation revealed no apparent abnormalities and soft appearing stool. Auscultation of the heart revealed no murmurs and there were no crackles or wheezes heard on auscultation of the lungs. The abdomen was soft and nonpainful on palpation. Dakota was

painful upon flexion of the neck and palpation between T11-L1. Oscillometric blood pressure readings were taken and revealed that she was severely hypertensive at 182 mmHg/97 mmHg (126 mmHg), 266 mmHg/100 mmHg (155 mmHg), and 211 mmHg/88 mmHg (129 mmHg). She was given 90 mcg of fentanyl IV for pain and discomfort. The remainder of the physical exam and triage exam was within normal limits.

Diagnostic Approach/Considerations

Further diagnostics were performed to determine a diagnosis and rule-out any other underlying diseases. On the day of presentation, thoracic radiographs were performed and appeared within normal limits. An abdominal ultrasound was performed which revealed a right adrenal mass and a suspected caudal abdominal mass. Later, cytology of the caudal abdominal mass revealed inflammation and no evidence of neoplasia. After discussion with the owner about our concern for a pheochromocytoma, the owner elected to pursue an abdominal CT for surgical planning. Dakota was sedated with dexmedetomidine and butorphanol for an abdominal CT with contrast with no complications. Radiologists confirmed the right adrenal mass invading the phrenicoabdominal vein and caudal vena cava and a caudal abdominal mass. Urine was collected and submitted for a urine metanephrine test, which confirmed a diagnosis of pheochromocytoma with metanephrine/creatinine levels greater than 4 times the upper reference range. While hospitalized, Dakota was administered intravenous fluids, phenoxybenzamine, gabapentin and Tylenol 4. By her third day of hospitalization, she was resting comfortably and no longer constantly panting. Her blood pressures were evaluated every 12 hours and remained within normal limits. Dakota was discharged with an increased dose of phenoxybenzamine at 10 mg (0.3 mg/kg) and recommended to have Dakota's blood pressure checked at her local veterinarian

on 6/14/19. If her blood pressures remain controlled, she would remain on the prescribed dose for two weeks' time for her scheduled right adrenalectomy surgery.

The antemortem diagnosis of pheochromocytoma is difficult due to the vague and intermittent signs and physical examination findings. Patients usually have concurrent disease that complicates the diagnosis. Therefore, it is important to have pheochromocytoma as a differential or high index of suspicion (5).

Routine laboratory tests are usually nonspecific and rarely helpful. Also, there no consistent abnormalities on bloodwork that is specific to canine pheochromocytoma (8). However, it is important to perform these diagnostics to diagnose any concurrent disease. Complete blood count (CBC) is usually normal. Serum biochemistry panel is usually unremarkable. In Barthez' study, elevations in serum alkaline phosphatase (ALP) and alanine aminotransferase (ALT) concentrations were reported in approximately three-fourths of the dogs. However, there was no correlation between elevated liver enzymes and metastatic disease of the liver. Also, one-third of the dogs were diagnosed with hyperadrenocorticism (5). Other biochemical abnormalities were azotemia, hypercholesterolemia, hypoalbuminemia and hypocalcemia (7). High-normal blood glucose have been reported in dogs with pheochromocytomas. In urinalysis, proteinuria and hematuria are consistent abnormalities due to glomerulopathies secondary to hypertension. Hypertension is the most common finding in patients with pheochromocytomas. It should be expected in patients with systolic pressure greater than 160 mmHg or diastolic pressure greater than 95 mmHg. However, many dogs are normotensive at the time of evaluation due to the episodic secretion of catecholamines (6). Patients with pheochromocytomas usually have concurrent diseases such as hyperadrenocorticism, diabetes mellitus and chronic renal failure.

Diagnostic imaging is indicated to reveal a perirenal mass or signs of metastasis. In 26% to 56% of cases, abdominal radiography reveals a perirenal mass. Other abnormalities may include hepatomegaly, renal displacement, abnormal renal contour, ascites and enlargement or displacement of the caudal vena cava. On thoracic radiographs, cardiomegaly, right or left ventricular enlargement and pulmonary congestion or edema may be present due to systemic hypertension (7). Not only that, but pulmonary nodules may be a sign of metastasis disease in 8% to 11% of cases. Abdominal ultrasound is effective in evaluating the adrenal area and detecting adrenal masses. An adrenal mass can be detected by ultrasonography in 50% to 83% of cases. Common ultrasonographic characteristics of pheochromocytoma include multicystic and/or multilobular architecture, a mass causing displacement of the kidney(s) and involvement of other structures (6).

Urinary catecholamines and their metabolites are the most widely used tool for diagnosing pheochromocytomas in humans. A diagnosis is based on the increased excretion of these compounds. However, the use in dogs with pheochromocytomas has not been evaluated. The urinary assays are more specific but less than sensitive than plasma assays (10). Metanephrine/normetanephrine assays are more sensitive than epinephrine/norepinephrine assays because the metabolites are more stable. A four-fold increase in metanephrine/normetanephrine levels above the reference range supports a diagnosis of pheochromocytoma. Serial assessment of urinary catecholamines may be beneficial to rule out the presence of the tumor (10). False positives can result from exercise, excitement, radiographic contrast agents, and certain medications. Reduced renal function and intermittent secretion of catecholamines can result in lower values (6). A definitive diagnosis of pheochromocytoma is based on histopathology tissue (10).

Pathophysiology

In the normal adrenal medulla, epinephrine and norepinephrine are secreted (12). Most human pheochromocytomas secrete predominantly norepinephrine or a mixture of norepinephrine and epinephrine. However, it has not been reported in canine pheochromocytomas the typical excretion pattern. Catecholamine synthesis in normal and neoplastic adrenal medulla cells is initiated when tyrosine is hydroxylated by dopa. Then, dopa is decarboxylated to dopamine and transported to the intracellular granules of chromaffin cells. In turn, dopamine is hydroxylated to norepinephrine and further broken down to epinephrine. In pheochromocytomas, tyrosine hydroxylase is the rate limiting step in catecholamine synthesis. Norepinephrine usually suppresses catecholamine production by inhibiting tyrosine hydroxylase, but this feedback response is nonfunctional in pheochromocytomas. This could be due to there being increased tyrosine hydroxylase activity or rapid degradation of norepinephrine that the feedback does not occur (10). Episodic release of catecholamines from the tumor, called catecholamine surges, are responsible for the clinical signs of panting, tachycardia, hypertension and weakness commonly observed in patients with pheochromocytomas. Most canine pheochromocytomas appear unilateral in older dogs (median age of 11 years) (1). A majority of pheochromocytomas are malignant; mostly affecting the adjacent vasculature (phrenicoabdominal vein and/or caudal vena cava). Metastasis is less common accounting for a mere 20-30% of cases (12). The most common metastatic sites include the liver, spleen, regional lymph nodes, lungs and non-chromaffin cells (1). Less common sites include kidneys, bone, pancreas, peritoneum, brain, spinal cord and heart (11). However, the timeframe of metastasis is unknown.

Treatment and Management

Surgery is the treatment of choice for dogs that are good anesthetic candidates for pheochromocytomas. Medical therapy is used to treat intraoperative arrhythmias and hypertension. Also, it plays a role in long-term management of patients with nonresectable or metastatic disease (11).

Administration of alpha- and beta-adrenergic blocking agents are recommended preoperatively to decrease surgical morbidity and mortality (5). The goals of preoperative management are to control blood pressure and expand plasma volume. Alpha adrenergic blocking agents correct chronic vasoconstriction and allow plasma volume expansion to decrease the number of hypertensive responses during induction, intubation, and surgical manipulation of the tumor. Phenoxybenzamine is the preoperative alpha blockade drug of choice. The drug causes a long-acting, noncompetitive alpha-adrenergic blockade. Therefore, when a surge a catecholamine release cannot override the inhibition. The initial dose of phenoxybenzamine is 0.25 mg/kg PO bid, with a range of 0.2-1.5 mg/kg. It is recommended to use a low dose and gradually increase until the patient is normotensive. Therapy should be initiated two weeks before surgery; however, the optimal duration of treatment is unknown. Beta-blocking agents are indicated for patients with arrhythmias or severe tachycardia, only after alpha blockade has been achieved. Therefore, propranolol can be administered at a dose of 0.15 – 0.5 mg/kg PO tid in dogs (9).

The most serious intraoperatively considerations are severe hypertension, severe tachycardia, arrhythmias, and hemorrhage. Episodes of hypertension can be treated by administering phentolamine or sodium nitroprusside. Treatment of malignant pheochromocytoma with chemotherapy has not been reported. However, it is used from treatment in humans. The combination of cyclophosphamide, vincristine and dacarbazine resulted in a complete and partial response rate of 57% (median duration, 21 months; range, 7 to more than 34) (5).

The prognosis for dogs with pheochromocytomas depends on the presence of concurrent disease, metastasis, local invasion or perioperative complications. Pheochromocytomas have a guarded prognosis; however, a worsened prognosis is seen when there is caudal vena cava invasion that extends cranial to the hepatic veins. One study found that neurologic signs, abdominal distention and weight loss were frequently associated with more advanced tumors and a poorer prognosis. If the adrenal mass can be excised and metastasis is not present, the mean survival time from months to years is possible (10).

Case Outcome

On 6/25/19, Dakota presented to the MSU-CVM Small Animal Surgery service for a right adrenalectomy. On the day of presentation, a small animal anesthesia profile was performed. The results were unremarkable except for ALT which was elevated at 256 U/L (10-90). Dakota was blood typed in preparation for surgery revealing that she was DEA 1.1 negative.

On 6/26/19, Dakota underwent a right adrenalectomy. The mass measured approximately 4 x 6 cm and was intimately associated with the caudal vena cava especially dorsally. The tumor was bluntly dissected away from the dorsal vena cava. The mass had slightly invaded the caudal vena cava via invasion of the right phrenicoabdominal vein; however, direct invasion of the tumor through the wall of the vena cava was not seen. The adrenal mass was also adhered to the craniomedial pole of the right renal capsule, and had invaded into the epaxial musculature dorsal to the caudal vena cava and aorta. A right nephrectomy was performed in order to visualize and fully remove the tumor. Significant blood loss occurred during surgery from a friable kidney with tumor attachment and tributaries to the tumor from the caudal vena cava, and Dakota received 1 L of blood to replace her losses. The right adrenal gland and kidney were submitted for histopathology. Dakota survived surgery and recovered in ICU. She was kept on fentanyl,

lidocaine, norepinephrine, and enoxaparin. However, at approximately midnight the same day, Dakota passed away, from a suspected pulmonary thromboembolism.

The histopathology of the right adrenal gland revealed a severely expanded gland effaced by an endocrine neoplasm with marked periglandular fibrosis, thrombosis, hemorrhage and inflammation. The cytoplasm was large and polygonal with finely granular pale grey/blue cytoplasm and large ovoid nuclei. The medullary neoplastic cells were infiltrating the cortex and present throughout the vasculature surrounding the gland. The neoplastic cells stained strongly positive for chromogranin suggesting a neuroendocrine tumor, such as a pheochromocytoma. In the kidney, the arcuate artery, venous and stromal architecture were effaced with a round cell neoplasm. The glomeruli and a minority of the tubules exhibited diffuse fibrotic changes and hyaline material. The neoplastic cells in the kidney stained weakly for chromogranin and not for CD3 and CD79. The findings of the kidney suggested metastasis of the pheochromocytoma, leading to the diagnosis of a malignant pheochromocytoma.

Conclusion

Pheochromocytoma is a rare endocrine tumor derived from chromaffin in the adrenal medulla (1). A paroxysmal history is characteristic of pheochromocytomas due to the intermittent secretion of catecholamines. The clinical signs are often vague, so a thorough history and physical exam is important (2). Systemic hypertension is the hallmark sign of a pheochromocytoma. When performing diagnostics, bloodwork is usually unremarkable (6). However, diagnostic imaging is a useful tool for localizing and/or ruling out pheochromocytomas. Even though hormonal testing has limited application in dogs, the urine metaneprhine fraction test is a useful diagnostic step in diagnosing pheochromocytomas. Surgery

is the treatment of choice for canine pheochromocytoma. Medical therapy is reserved for stabilization and long-term management of nonresectable or metastatic disease (4).

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