Canine Pheochromocytoma

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Introduction

Pheocromocytomas are a rare neoplasm of the endocrine system with an unpredictable growth rate. They have been documented in humans, horses, cattle, dogs, cats, and laboratory rats (Barthez). Malignant forms are often characterized by invasion to the caudal vena cava. They may be unilateral or bilateral. They have the potential to become metastatic to distant organs such as the lungs, liver, and lymph nodes. Dogs affected by pheochromocytoma are typically older. No sex predilection has been documented. Pheocromocytomas are derived from chromatin cells, which are responsible for normal release of catecholamines. Clinical signs may be sporadic and vary in intensity due to the altering levels of catecholamines released.

History and presentation

Roxie was an older spayed female mixed breed large yellow dog with a history of flank alopecia. She was found Sunday morning 10/28/16 by her owner, a veterinarian, laterally recumbent in a puddle of urine and feces. A seizure of unknown time and duration was suspected. She was tachycardia with a weak pulse. Upon presentation to MSU, she was still laterally recumbent, her pupils were fixed and dilated, with Absent PLRs, menace, and dazzle response. Elevated intracranial pressure was suspected at this time. Roxie was in a state of hypovolemic shock, which was corrected with a 1 liter shock dose bolus of hypertonic saline. This fluid bolus was repeated twice. She also received three doses of lidocaine to stabilize the ventricular tachycardia. Roxie's mentation did not change and her pupils remained unresponsive. At this time, she was given a coma score of 8. No physiologic nystagmus was noted. She received methylprednisone via IM injection. Approximately an hour later Roxie had a brief

grand-mal seizure and was given midazolam IV for rescue. Approximately 30 minutes later Roxie began to vomit a large amount of malodorous food material. Soon after, Roxie developed agonal breathing patterns and was intubated and manually ventilated. Her mentation remained the same. Her coma state remained at an 8 which left her prognosis at grave. At this time, the owners elected to euthanize.

Common signs to pheochromocytoma are not specific and include; anorexia, lethargy, dyspnea, seizure, polyuria, diarrhea, and arrhythmia have been seen. It is not uncommon to see secondary endocrine disease along with this tumor. In the case of Roxie, she developed Cushing's disease. Cushing's disease is caused by an ACTH secreting pituitary tumor. It is also the most common form of hyeradrenocorticism in dogs. Most tumors of this nature arise in the pars distalis region of the pituitary gland. However, in 10-20% of cases, including the case of Roxie, they arise in the pars intermedia. The truncal alopecia was likely secondary to the hyeradrenocorticism. Hypertension is often seen with pheochromocytoma due to increased vascular resistance mediated by stimulation of alpha-1 receptors causing vasoconstriction (VSSO). Stimulation of Beta-1 receptors may contribute to hypotension via tachyarrhythmia. Acute attacks can be severe enough to cause sudden rapidly declining signs such as in the case of Roxie. The signs include; sudden collapse, cariogenic shock, pulmonary edema, ventricular fibrillation, cyanosis, epistaxis, cerebral hemorrhage and seizures.

Pathology

On gross necropsy, Roxie was in body condition (BCS 5/9). She had bilateral flank alopecia and epidermal atrophy. On Histopathology, the right adrenal gland was effaced and notably expanded by a cellular dense, un-encapsulated, multi-nodular one cell type neoplasm. Cells form tightly packed irregular cords in a fine elastic fibro-vascular stroma. They were large

and had ample finely granular amphophilic cytoplasm and large round nuclei. Neoplastic cells were stained diffusely and strongly for chromagranin. The zona fasciculata and reticularis of the left adrenal gland were diffusely and moderately hyperplastic, with mild nodular hyperplasia. Focally within the fasciculata there is an aggregate of several dozen neoplastic adrenal medullary cells (Baumgartner).

The pars intermedia of the pituitary is expanded by a densely cellular, roughly spherical, unencapsulated, well demarcated, infiltrative and expansile neoplasm composed of one cell type in fine fibrovascular stroma. Cells form irregular islands and thick cords with interspersed irregular small ducts and sinuses filled with mucinous content. They are large and polygonal with abundant finely granular pale amphophilic cytoplasm and large round centrocellular nuclei with a large central nucleolus. Anisocytosis and anisokaryosis are moderate. Mitoses are not seen. The small ducts are lined by a short ciliated columnar simple epithelium. (Baumgartner).

Upon examination of the abdominal cavity, the liver was noted to exhibit post mortem pseudomelanosis on the capsular surface. Multi focal masses, up to 7cm x 5cm x 4cm were also seen. On cut surface the masses were smooth, white and budged. Dark red infarts were also seen throughout. The liver was soft in texture. On histological exam multifocal areas of neoplastic cells, similar to those in the adrenal gland were seen. The portal triads were filled with fibrous storm, with mild bridging, duct reactions and lipo-granulomatous change. The central veins were fibrotic and sclerotic with siderophages. The lungs also contained approximately 30 firm neoplastic nodules 5-15mm in size randomly disbursed in a generalized nodularity pattern. The masses were umbilicated appearance on cut surface (often associated with carcinomas). Upon histopathology, the neoplastic nodules were similar to the masses described in the right adrenal gland (Baumgartner).

The caudal vena cava had a 7.5 cm x 4 cm lobulated marble red, white, gray mass growing into it at the level of the kidneys arising from the right adrenal gland. Upon cut surface, the mass was pink to dark purple and wart like with smooth lymph nodes and soft nodules within. The massively enlarged vessels feeding the tumor were traced to beyond the bladder towards the genitalia. The tracheobronchial lymph node was enlarged and on histological exam, it is effaced and expanded by a neoplasm similar to that described in the adrenal gland and lungs. Other lymph nodes exhibit mild to moderate atrophy. Many sinuses are filled with lymph, pink fluid or red cells and fibrin. (Baumgartner).

Pathophysiology

Pheocromocytomas are derived from chromatin cells. These cells are responsible for normal release of catecholamines including; epinephrine, norepinephrine, and dopamine. Chromaffin cells are capable of amine precursor uptake and decarboxylation (APUD). Pheochromocytoma is an example of APUDoma. The synthesis of epinephrine and norepinephrine begins with the hydroxylation of tyrosine by tyrosine hydroxylase. The product formed is dihydroxyphenylalanine. This is further converted to dihydroxyphenylethylalanine (dopamine). Dopamine is then transported into the intracellular vesicles or granules of the chromaffin cell where the enzyme dopamine 13-hydroxylase converts to norepinephrine. In adrenal medullary cells, norepinephrine can undertake methylation and be thus can be converted into epinephrine. In the normal adrenal cell, a rising level of cytoplasmic norepinephrine can suppress its own production via a negative feedback loop on the rate-limiting enzyme tyrosine hydroxylase. This normal feedback inhibition may uncouple in the pheochromocytoma patient. The tumor may metabolize norepinephrine at a rate too fast to prevent its accumulation thus resulting in feedback inhibition. Commonly secondary disease such as hyperadrenocortisism is

seen in conjunction with pheochromocytomas, as in the case of Roxie. Whether pheochromocytomas have the ability to produce ACTH or other hormones has yet to be determined (Maher).

Catecholamine receptors exist in two main categories, alpha and beta. These categories can be further broken down into which category acts most favorably on norepinephrine (a1,a2,b1) and epinephrine (b2). Hypertension is often seen in patients with pheochromocytoma, as a result of an increase in peripheral vascular resistance from stimulation of alpha-1 which cause vasoconstriction. Catecholamine activation of Beta-1 receptors are responsible for the tachyarrhythmia often seen with these patients. The majority of clinical signs associated with these tumors is a direct result of the tumor or the space occupying nature or the catecholamine release. Prolonged stimulation of catecholamine receptors can lead to progressive diminution in response by the tissue to subsequent stimulation (Maher).

In a functional pheochromocytoma, catecholamine release may be intensified both in amount and or frequency of release. The tumors can trigger a massive catecholamine release which can lead to collapse and sudden death. Pheochromocytomas are often associated with a local infiltration of the caudal vena cava which can result in a thrombus. In the literature, the metastatic rate of pheochromocytomas is listed between 25% and 50%. The neoplasm is considered malignant when metastasis is present in non-chromatin cells (Jun).

Diagnostic Approach and consideration

The problem with diagnosing pheochromocytoma is that often it is only discovered as an incidental finding or via necropsy. The symptoms are very nonspecific. Also, due to the correlation with secondary diseases such as Cushing's disease, clinicians can easily be misled. If pheochromocytoma is suspected, abdominal imaging may help determine the degree of

infiltration. Abdominal as well as thoracic radiographs are also crucial in determining metastatic spread. Abdominal ultrasound is a key diagnostic tool to view infiltration to adjacent organs or vessels. Medullary biopsies may also be performed to determine malignancy. CT and MRI imagine is the most sensitive yet most expensive method of viewing adrenal masses. You may determine the adrenal mass is functional capacity as well as the origin (cortex or medulla) via urinary normetanephine: creatinine ratio test. A functional cortical adrenal tumor should be confirmed with a low dose dexamethasone suppression test (Desmas). An echocardiogram may also be performed. Left ventricular hypertrophy consistent with hypertension is often seen with an echo.

A minimum database may be used. It is important to remember that pheochromocytoma alone would not cause blood work values to be abnormal. Urinalysis is also a limited diagnostic tool. However, you may see a decrease in urine specific gravity due to the PU/PD signs associated with the tumor.

Another diagnostic option is cytology. It is simple to distinguish adrenocorticale neoplasia and neuroendocrine tumors such as pheochromocytoma via cytology. Pheochromocytoma shows the similar cytological features as other neuroendocrine tumors. These include; naked uniform nuclei, nuclei aligned in rows and rosette-like structures, fine chromatin with inconsistent nucleoli. In contrast, aadrenocorticale tumors are characterized by aggregates of polygonal to round cells, with a low nuclear-cytoplasmic ratio, micro-vacuolated basophilic cytoplasm, and round eccentric nuclei with coarse chromatin and small nucleoli. Extramedullary hematopoiesis may be found in adrenocortical neoplasms. Thus, megakaryocytes, erythroid, and myeloid precursors may be observed in cytological samples (Bertazzolo).

Cytology should be used with caution. The risk of complications associated with FNA on adrenal tumors should be weighed heavily before performing such aspirates. If a catecholamine-producing tumor such as a pheochromocytoma were to be biopsied, side effects including pain, uncontrolled hemorrhage, and severe hypertensive crisis due to sudden release of catecholamine could be deadly (Bertazzolo).

Treatment and Management

Treatment for pheochromocytoma is primarily surgical with a low mortality rate of 6-15% when followed by medical management (Desmas). Alfa-antagonist may be used to control the hypertension seen secondary to the excessive release of catecholamines.

Surgical- Adrenalectomy

Two approaches have been described for an adrenalectomy, the midline and paralumbar approach. The adrenal glands lie at the cranial pole of each kidney. It is important for the caudal vena cava (CVC) to be protected as it lies in close proximity to the right adrenal gland. Making removal of the right adrenal gland more difficult than the left. If the tumor has invaded the CVC, surgical debulking is not expected to prevent metastasis. The phrenicoabdominal vein lays at the ventral aspect of each adrenal gland as it feeds to the CVC. This vein is typically double ligated. Surgeons must also identify and protect the ureters as they run in close proximity to the adrenal glands. When removing the adrenal gland, it is important not to disrupt the capsule as this can lead to a large release of catecholamines.

Medical

Medical management is often preoperative treatment aimed to control hypertension and arrhythmias. Alpha antagonist are used over a period of 2-3 weeks to normalize the blood pressure. The mainstay of medical management is phenoxybenzamine, which is often started at

lower doses and gradually increased until normotension is reached. This is useful in the manage the effects of the catecholamines. However, Prazosin has also been used to achieve the same goal. Beta blockers, such as propranolol can be used perioperatively to treat arrhythmias, but should be used in conjunction with alpha antagonist to avoid exacerbating the hypotension.

Post operatively, medical management may include adrenergic antagonist if there is incomplete resection or metastasis. Phenoxybenzamine or Prazosin and Propanolol are recommended for the lifespan of the animal. No treatment is without risk. If long term adverse effects of chronic alpha-blockade were a concern, alpha-methyltyrosin can be used to reduce the dose of phenoxybenzamine. Chemotherapy has been used in human cases and resulted in a complete and partial response rate of 57% (Kim). This protocol has not been reported in veterinary literature.

Prognosis/Outcome

The prognosis for Pheochromocytoma is guarded (Kim). The addition of concurrent disease, metastasis, and level of resection with surgical management all influence the prognosis. You may find in the literature that invasion of the caudal vena cava is a poor prognostic indicator. However, with medical and surgical treatment from a skilled surgeon can add 18-24 months to the life span of the dog. The metastatic rate to regional lymph nodes and distant sites has been reported to range from 11%-24% (VSSO).

Conclusion

While rare, pheochromocytomas are one of the more challenging neoplasms to diagnose. Once diagnosed as non-metastatic and localized to one tissue, the gold standard treatment is a combination of medical and surgical. Unfortunately, in Roxie's case the degree of metastasis left no option but euthanasia and a diagnosis was made upon necropsy. It is most likely that when

Roxie presented to MSU CVM over the weekend, she was experiencing a massive catecholamine release. Due to post mortem findings, the degree of infiltration and metastasis of the primary tumor, Roxie was not a surgical candidate.

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