Canine Pheochromocytoma

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Introduction

Pheochromocytomas are rare neuroendocrine tumors of chromaffin cells. A portion of the sympathetic nervous system, chromaffin cells are located in the adrenal medulla, giving rise to pheochromocytomas. [6] Extra-adrenal chromaffin cells are also found in other locations throughout the body, potentially giving rise to paragangliomas or extradrenal pheochromocytomas. [7, 10] Chromaffin cells are responsible for production and release of catecholamines. When these cells become neoplastic, they may exhibit episodic release of catecholamine leading to paroxysmal clinical signs. [6, 10] Diagnosis can be difficult due to vague clinical signs and is usually based on clinical suspicion and presence of adrenal mass. [7] The preferred method of treatment is adrenalectomy. Medical therapy is utilized for pre-operative stabilization and management of metastatic disease or if the tumor in non-resectable. [6, 7]

History and Presentation

Most commonly diagnosed in older dogs with no sex or breed predilections, these patients can present in a multitude of different ways depending on functionality and invasiveness of the tumor. [6, 7, 10] Some breeds are over represented, including Golden Retrievers, Doberman Pinchers and Miniature Schnauzers. [8] Historical findings have a tendency to be subtle, vague and intermittent, making a diagnosis more challenging. [6] The most common historical findings are weakness, episodic collapse and panting, but may also include anxiety, restlessness, exercise intolerance, decreased appetite, weight loss, polyuria and polydipsia. [7, 10]

Physical examination can be completely normal due to the episodic release of catecholamines or may reveal tachypnea, panting, tachycardia, weakness, abdominal pain, hemoabdomen, palor, cardiac arrhythmias, hypertension or blindness. [7]

Pathophysiology

Neoplastic diseases can be divided in to the categories of epithelial, mesenchymal, discrete cell (round cell) or naked nuclei. Neoplasia of endocrine or neuroendocrine origin typically fall into the naked nuclei category.

Chromaffin cells are neuroendocrine cells of the adrenal medulla that produce, store and release catecholamines. [6] They are regarded as modified postganglionic sympathetic neurons lacking axons. [6, 11] Stimulation of the preganglionic fibers of the sympathetic nervous system lead to catecholamine secretion. [6] When these cells undergo malignant transformation, they disregard their normal function, secreting catecholamines inappropriately.

Typically, pheochromocytomas are considered malignant. [1] Local invasion can commonly occur to the adjacent lumen of the phrenicoabdominal vein and the caudal vena cava. [1, 6] These vessels may become entrapped as the mass grows and compresses the surrounding vasculature. [6, 7] Distant metastasis is not common, but can include regional lymph nodes, lungs and liver, as well as the CNS. [1, 6]

Differential Diagnosis

Careful consideration should utilized when an adrenal tumor is discovered. The clinician has to use their knowledge and the clinical picture to decide whether the tumor is associated with the cortex or medulla, if it is benign or metastatic, and whether it is function or not. [6,7] Differentials for nonfunctional masses can include cysts, abscess, hematoma or metastasis. [10] Functional adrenal tumors may include pheochromocytoma, cortisol and/or progesterone producing, or aldosteronoma. [7, 11]

Diagnostic Approach and Considerations

Since the clinical signs associated with pheochromocytomas are paroxysmal and vague, diagnosis can be difficult. [7] There are no pathognomonic abnormalities associated with clinical signs, blood work or diagnostic imaging. [10] Concurrent diseases are commonly associated with pheochomocytoma, further complicating diagnosis. [6, 10] No consistant abnormalities are noted on CBC, serum biochemistry and urinalysis and result may be completely normal. [6, 7]

Documentation of systemic hypertension is one of the hallmarks of a pheochromocytoma, but not pathognomonic. [7] It can vary from mild to severe. [10] A tentative diagnosis of pheochromocytoma can be made with suggestive clinical signs, hypertension and identification of an adrenal mass via ultrasound. [7]

Other possible adrenal masses can include cortical hyperplasia, cortical adenoma, cortical carcinoma and metastasis. [8] Pheochromocytomas can appear as an amorphous encapsulated mass, with irregular margins and loss of normal shape and parenchymal structure. [8] While some may be solitary or multiple nodules with normal adrenal shape. [8] Adrenal tumors can vary in size which can aid in diagnosis and predicting malignancy. [8] Tumors <20mm in diameter were found to be cortical hyperplastic nodules or adenomas, where as those >20mm were identified as malignant neoplasms. [8] The median diameter of pheochromocytomas was 13mm. [8] Ultrasound is also useful in aiding in clinical staging of the disease, along with thoracic radiographs and CT. Thoracic radiographs are helpful in identification for pulmonary metastasis, and CT helps to characterize local invasion. [9]

Hormonal testing is also being utilized support a diagnosis of pheochromocytoma. [7] Urinary catecholamine and its metabolites are typically higher in affected dogs than healthy dogs. [10] The most common metabolites tested are metanephrine and normetanephrine, with normetanephrine being more accurate. [6, 10] These can be falsely elevated with exercise or

excitement, contrast agents and some medications. [6] Another hormonal test used to differentiate pheochromocytoma from other endocrinopathies is serum inhibin concentrations. Only reliable in neutered dogs, inhibin concentrations were higher in those with adrenal cortical tumors and pituitary dependent hyperadrenocorticism than with pheochromocytomas. [3]

Definitive diagnosis is made histologically. The mitotic index is variable, but neoplastic chromaffin cells typically consist of packets separated by a fine fibrovascualr stroma. [10] They tend to be larger than nonneoplastic chromaffin cells with faintly granular pale amphophilic cytoplasm. [10] Special stains can be used to aid in diagnosis. Immunohistochemistry may be used to detect certain genetic neuroendocrine markers (protein gene product 9.5 or chromogranin) that are expressed by neoplastic chromaffin cells. 10

Treatment Options

The preferred method of treatment for a functional pheochromocytomy is unilateral adrenalectomy. [1, 5, 6, 7] Careful preoperative planning and management should be utilized to insure the best prognosis.

Prior to surgery, medical therapy is implemented to reverse the effects of excessive adrenergic stimulation. [7] The drug of choice to reduce the clinical signs associated with excessive catecholamine release is phenoxybenzamine, a noncompetitive alpha adrenergic antagonist. [6, 10] It should be administered for approximately two weeks prior to surgery. [6] If severe tachycardia persists after implementing an alpha adrenergic blocker, then a beta blocker can be used. It is imperative to start the beta blocker only after the alpha adrenergic blockade has been initiated. [6, 7] This is due to the severe hypertension that can result due to the beta receptor mediated vasodilation. [7]

Pheochromoctyoma patients are high anesthetic risk candidates and should be monitored closely during surgery and 1-2 days in the post-operative period. [10] Careful consideration must be given to preanesthetic, induction and maintenance agents. [6] Atropine and phenothiazines should be avoided due to profound tachycardia and unopposed vasodilation respectfully. [6] Propofol and etomidate have been shown to be effective and safe in these patients. [6]

Prior to surgical resection, advanced imaging should be utilized to determine the invasiveness of the tumor. Complete resection of tumors can often be achieved of tumors without extensive local invasion into the surrounding vasculature or tissues. [6] Those that are more invasive and too risky to attempt complete resection can be debulked as much as possible to decrease the concentration of circulating catecholamines. [5, 6] In about 10% of cases, pheochromocytomas can be bilateral. Complete abdominal exploration should be performed to observe the contralateral adrenal gland as well as to check for metastasis in surrounding organs. [6]

Intraoperative tumor manipulation can lead to some of the most serious complications. Severe hypertension, tachycardia and arrhythmias may result from excessive catecholamine secretion. They should be monitored closely during surgery as well in the postoperative period for approximately 1-2 days. [5, 6, 7] Some postoperative complications include arrhythmias, hypo or hypertension as well as hemorrhage. [9]

If surgery is not an option or if there is recurrence or incomplete resection of the tumor, medical management is an option. [10] The goal is control of the clinical signs associated with excessive catecholamine secretion with an alpha adrenergic blocker like phenoxybenzamine. There has been no success with use of radiation or chemotherapy for treatment of canine pheochromocytomas. [6, 7]

Prognosis

The overall prognosis is considered guarded to poor, but is variable and will depend on tumor size, presence of local invasion or metastasis, as well as perioperative complications and concurrent disease. [2, 9, 10] A median survival time of 15 months was reported for pheochromocytomas with adrenalectomy, and some as long as 2 to 3 years. [1] If complete surgical resection is achieved, long-term survival can be expected due to recurrence and late metastasis being rare. [2]

Signs of malignancy worsening the prognosis include a tumor that is 20mm or larger, early onset postoperative hypertension or high plasma or urine catecholamine metabolites, as well as multifocal and extra-adrenal tumors. [4]

Conclusion

A pheochromocytoma develops due to malignant transformation of the chromaffin cells of the adrenal medulla. [6] A presumptive diagnosis is typically made due to clinical suspicion and detection of an adrenal mass via ultrasound. [10] To help strengthen the tentative diagnosis, urinary catecholamine concentrations and their metabolites can be measured. [7] An adrenalectomy is the treatment of choice, but is preceded by medical management with an alpha adrenergic antagonist. [6, 7, 10] The prognosis is variable, and depends on several factors including invasiveness of the tumor and perioperative complications. [1, 9]

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