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UNMASKING PHEOCHROMOCYTOMA IN DOGS

Pheochromocytoma is a catecholamine-producing neuroendocrine tumor arising from chromaffin cells of the adrenal medulla [1]. It is considered to be malignant. The manifestations are diverse and can mimic those of various conditions, which often results in erroneous and delayed diagnosis. Not surprisingly, pheochromocytoma has therefore earned the title "*great mimic*". The clinician's awareness of pheochromocytoma represents a crucial initial step in making a diagnosis, but for confirmation, biochemical evidence of excessive catecholamine production and diagnostic imaging are needed [1,2]. Most pheochromocytomas are unilateral, but occasionally both adrenals are affected. Pheochromocytoma may coexist with other endocrine neoplasms, such as cortisol-secreting adrenocortical tumor, ACTH-secreting pituitary tumor, thyroid tumor, insulinoma, or parathyroid tumor or hyperplasia. The etiology of pheochromocytoma in dogs is largely unknown. Recently, mutation analysis demonstrated for the first time a missense mutation of succinate dehydrogenase subunit D (SDHD) [3].

Clinical manifestation

Pheochromocytomas occur most often in older dogs, with an average age of 11 years [1]. Clinical signs associated with pheochromocytoma are related to the direct actions of secreted catecholamines and/or the space-occupying or invasive nature of the adrenal mass. Hormone secretion from the tumor is sporadic and unpredictable and clinical manifestations of the circulating catecholamine vary considerably. Dogs with pheochromocytoma present most often with intermitting episodes of collapse, weakness, and panting. The episodes are paroxysmal and may occur several times per day or per week, or only at intervals of weeks to months. They can be mild or life-threatening and may progress in time.

The clinical manifestation related to the catecholamine excess can be categorized as follows: cardiorespiratory system and/or hypertension: tachypnea, panting, tachycardia, arrhythmias, collapse, pale mucous membranes, nasal-, gingival-, or ocular hemorrhage, acute blindness:

- neuromuscular system: weakness, anxiety, pacing, muscle tremors, seizures
- nonspecific: anorexia, weight loss, lethargy
- miscellaneous: polyuria/polydipsia, vomiting, diarrhea, abdominal pain

Large pheochromocytomas are characterized by invasive growth and a heterogeneous structure and are predisposed to episodes of bleeding and necrosis. The clinical manifestation of a space-occupying adrenal mass underlying pheochromocytoma may be related to:

- invasion by the tumor of the vena cava: ascites, hind limb edema, distension of the caudal epigastric veins
- invasion by the tumor of the aorta (aortic thromboembolism): painful and weak hind limbs, paraparesis, absence of the femoral pulse, cold distal extremities
- spontaneous tumor rupture: retroperitoneal hemorrhage (lethargy, tachypnea, tachycardia, weakness, pale mucous membranes, abdominal pain)

Diagnostic evaluation

The initial step could be the fortuitous finding of an adrenal mass during diagnostic imaging for a problem for which pheochromocytoma was not even being considered in differential diagnosis. Nevertheless, a confirmed diagnosis requires biochemical evidence of excessive catecholamine production [1,4]. In clinical pathology, no consistent abnormalities in the CBC, serum biochemical panel, or urinalysis would raise suspicion of pheochromocytoma. Although arterial hypertension is one of the hallmarks of the disease, it is present in only about 50% of dogs with a pheochromocytoma at the time of examination.

Diagnostic imaging

Diagnostic imaging provides important information about adrenal size and structure, unilateral or bilateral involvement, and contact with or invasion of neighboring organs and blood vessels [5]. Based on selective criteria, it can provide an estimate of potential malignancy and is extremely helpful in selecting the best therapeutic approach, but it cannot predict the histological type of the adrenal mass.

Pheochromocytomas may present as nodules a few millimeters in diameter or as heterogeneous masses of 10 cm or more. The echogenicity pattern may be hypoechoic or heterogeneous, and large masses may include multilobular and/or multicystic architecture with anechoic foci of necrosis and hemorrhage. There is no sonographic appearance that is pathognomonic for pheochromocytoma. Most pheochromocytomas

are unilateral and present as an enlarged adrenal gland, with a contralateral adrenal gland of normal size and shape. However, bilateral pheochromocytomas do occur and make the differentiation from adrenocortical hyperplasia very challenging. Pheochromocytomas are reported to invade the surrounding structures and blood vessels more often than do other types of adrenal tumor. Invasion of the caudal vena cava occurs in 15 to 55% of pheochromocytomas and is more common in those on the right side [4]. Invasive behavior does not necessarily indicate malignancy, for it can instead represent mass expansion into structures with minimal resistance.[2]

Biochemical testing

Biochemical demonstration of excessive production of catecholamines is an essential step for the diagnosis of pheochromocytoma [1,4]. Biochemical evaluations typically include measurement of plasma and urinary catecholamines and their metabolites, MN and NMN.[3] The principle of measuring NMN and MN is based on the intramedullary metabolism of catecholamines. The production of catecholamine metabolites in tumor cells is continuous and more accurately reflects tumor mass than does release of catecholamines, which can occur episodically. Measurement of urinary catecholamines in dogs is performed in a single voided sample and their concentrations are expressed as ratios to the creatinine concentration in the same urine sample [6, 7]. The urinary NMN-to-creatinine ratio has a higher sensitivity than the MN-, epinephrine-, and norepinephrine-to-creatinine ratios. Corresponding to urinary measurements of NMN, measurement of plasma free NMN was superior to measurement of free MN in the diagnosis of pheochromocytoma [7, 8]. There is no consensus at present on the preference for plasma or urinary testing, however, the urinary NMN measurement seems to be the most reliable in making a diagnosis. In addition to availability and personal experience, the availability of reference ranges may influence the choice.

Treatment

Adrenalectomy is the optimal treatment for a dog with pheochromocytoma [9]. Removal of the adrenal tumor will reverse the clinical signs and symptoms associated with catecholamine release and avoid the complications of uncontrolled growth of the tumor. Complications occurring during and after surgery are catecholamine-induced effects, which are serious and potentially life-threatening. Prerequisites for success are preoperative medical treatment, an experienced anesthetist, and intensive postoperative care. If the tumor is inoperable or surgery is prevented by concurrent disorders or for other reasons, medical treatment is indicated. It will not affect the secretion or growth of the pheochromocytoma, but blocks the α-adrenergic response to circulating catecholamines.

In dogs with an unresectable pheochromocytoma, metastasis, serious concurrent disease, and/or owner constraints, medical treatment with phenoxybenzamine is used [10]. The preoperative management protocol is applied and if there are tachyarrhythmias, A selective β1 antagonist is added after an α-adrenergic blocker has been administered for at least a few days. There are as yet insufficient data for an appraisal of the survival of dogs receiving medical treatment alone.

Histopathology

The definitive diagnosis of pheochromocytoma rests upon histological examination. Pheochromocytomas consist of neoplastic cells arranged in lobules supported by a fine fibrovascular stoma. The neoplastic cells are round to polyhedral with eosinophilic to basophilic cytoplasm and hyperchromatic nuclei with variable mitotic activity [1]. Differentiation between cortical and medullary adrenal tumor is made by immunohistochemistry. Neuroendocrine markers are stained, chromogranin A being the most commonly used. It is normally present in chromatin granules in cells of the medulla but not in adrenal cortical cells, which renders it an ideal marker. Differentiation between benign and malignant pheochromocytoma based on histopathology is unreliable. The presence of metastasis is the only reliable indicator of malignancy, while the significance of capsular and vascular invasion with tumor thrombi remains controversial.

Prognosis

The size of the tumor, its endocrine activity, vascular invasion, and the presence of metastasis may affect the prognosis. With regard to surgical removal, both pretreatment with the α2-adrenergic blocker phenoxybenzamine and the extent of vascular invasion play a role. Additional prognostic factors are age, general well-being, and the presence of concurrent disease.

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