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Aortakroppstumörer på hund

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SAMMANFATTNING

Syftet med denna uppsats var att göra en litteraturstudie på aortakroppstumörer på hund. Tumörernas patofysiologi, diagnostiska metoder, makroskopiskt och mikroskopiskt utseende beskrivs. Aortakroppstumörer utgår från kemoreceptorerna belägna vid hjärtbasen och tillhör gruppen kemodektom. Kemoreceptorerna är neuroendokrina celler vars uppgift är att bland annat övervaka ändringar i pH i blodet.

Tumörerna utgör endast 7 % av alla hjärttumörer på hund men trots den låga prevalensen är dessa tumörer den näst vanligaste typen av primär hjärttumör. Tumörerna är kliniskt viktiga då de kan ge upphov till bland annat hjärtsvikt och hjärttamponad. Bland brachycephala raser såsom Boxer, Boston bullterrier och Engelsk bulldog är prevalensen högre. Det finns dock brachycephala raser t.ex. Mops där prevalensen inte är högre än genomsnittet bland alla raser. Etiologin är till stor del okänd, dock finns det teorier om en genetisk och/eller raspredisposition. Kronisk hypoxi och ”Brachycephalic airway syndrome” tros vara möjliga orsaker till att aortakroppstumörer uppstår.

Tumörerna mäter 0,5 – 12,5 cm i diameter och komplikationer uppkommer allt eftersom tumören ökar i storlek. Aortakroppstumörer kan upptäckas med hjälp av ultraljud eller röntgen. Tumörerna är oftast benigna men är expansiva vilket orsakar många av symptomen. Symptom kan även orsakas av infiltration av tumören. Diagnosen kan fastställas med histologisk färgning, hematoxylin- och eosinfärgning, i kombination med immunohistokemiska metoder såsom märkning med antikroppar t.ex. chromogranin A.

SUMMARY

The purpose of this essay was to review the literature and describe the patophysiology, diagnosis, microscopic and macroscopic appearance of aortic body tumors in dogs. The tumors originate from the chemoreceptor organs situated at the base of the heart. The chemoreceptor organs are neuroendocrine cells responsible for surveillance of changes in e.g. the blood pH.

Aortic body tumors are rare and represent 7 % of the total cases of primary cardiac tumors in canines. Despite their low prevalence the tumors are the second most common cardiac tumor. However, they are of clinical importance because they can cause cardiac failure and cardiac tamponade among other symptoms. Brachycephalic breeds such as Boxers, Boston bull terriers and English bulldogs have a high prevalence. However, there are other brachycephalic breeds e.g. Pugs where the prevalence is not higher than the average among all breeds. The etiology is not fully known but reports indicate a genetic and/or breed predisposition. Theories suggest that chronic hypoxia and "Brachycephalic airway syndrome" serves as contributing factors.

The tumors measure 0,5 – 12,5 cm in diameter and the size of the tumor determines the symptoms including cardiac failure and cardiac tamponade. A benignant behavior is mostly seen and the tumors are expansive which causes many of the symptoms. There are also infiltrative tumors and they cause symptoms as well though they are less common. Tumors can be discovered by ultrasonography or radiography and diagnosis can be confirmed with histological stains such as hematoxylin and eosin staining together with immunohistochemistry by labeling the tumor with a neuroendocrine marker e.g. chromogranin A.

INTRODUCTION

The aortic body tumor is the second most common cardiac tumor after hemangiosarcoma. The tumor arises from the chemoreceptor organs in the aorta and is sometimes called chemodectoma. Cardiac tumors are not by far as common as mammary tumors and aortic body tumors are rare. However, they are of great clinical importance because of the lesions they give rise to. As a practicing veterinarian it is important to be aware of their existence and the symptoms of an aortic body tumor. Aortic body tumors can cause life threatening symptoms such as congestive heart failure, sudden death and pericardial effusion. The purpose of this essay is to describe the patophysiology of aortic body tumors in dogs. The macroscopic and microscopic appearance will be described together with diagnosis, etiology and prognosis.

MATERIALS AND METHODS

Most of the articles were found in PubMed where following search terms were used for searching articles; "Chemodectoma AND dog OR canine", ""heart base tumor" AND dog OR canine" and ""aortic body tumor" AND dog OR canine". Google scholar and Science direct were also used for finding articles and with the same phrases as written above.

Through the articles found, their sources were traced and used in this essay if relevant. Since the subject is not fully explored scientifically further demarcation was not necessary except for the one already made through the "search terms".

REVIEW OF THE LITERATURE

Chemodectoma represents both aortic body tumors and carotid body tumors (Ehrhart et al., 2002). An aortic body tumor arises from the chemoreceptor organs that are localized in the tunica adventitia of the aortic arch. The carotid body tumor arises from the chemoreceptor organs in the carotid artery. The chemoreceptor organs are clusters of neuroendocrine cells that detect changes in blood pH, oxygen and carbon dioxide pressure and temperature (McGavin & Zachary, 2007). Aortic body tumors are four to five times more common than carotid body tumors in dogs (Deim et al., 2007). The tumors are rare in other domestic animals but have been reported in cats (Yates et al., 1980). Synonyms include cardiac paraganglioma, heart base tumor, APUDoma and glomus body tumor (Ehrhart et al., 2002).

Aortic body tumors are non-functional but can create lesions when they increase in size and exert pressure on surrounding organs i.e. the trachea or cardiac atria (Withrow & Veil, 2007). The tumors are of clinical relevance because they can cause hemorrhages and cardiac failure. The tumors are mostly benign but 22 % will eventually metastasize (Yates et al., 1980). In addition to Yates; Atasever & Çam (2003) states that the aortic body tumors seldom metastases; instead they have a tendency of being infiltrative. But when found, the metastases are mostly in the lungs and liver but can also be found in the brain, the mediastinum, the bones, the kidney, the adrenal cortex, the spleen, mediastinal lymph nodes, the dura mater in the cerebellum and in the myocardium (Noszczyk-Nowak et al., 2010; Atasever & Çam, 2003; Yates et al., 1980).

Malignant aortic body tumors are larger and less common than benign forms. The malignant tumors are primarily locally invasive and can infiltrate the wall of the pulmonary artery, the epicardium, pericardium, lymph nodes, lungs and the wall of the atria (DiFruscia et al., 1989; Withrow & Veil, 2007). However, they seldom metastases to the liver or lungs (McGavin & Zachary, 2007)

The aortic body tumor is the second most common cardiac tumor, after hemangiosarcoma, and represents 7 % of all primary cardiac tumors in dogs (Ware & Hopper, 1999). But primary cardiac tumors are rare (Aupperlea et al., 2007) and aortic body tumors are incidentally found at necropsy without having caused clinical symptoms while the dog was alive (Atasever & Çam, 2003). According to Yates et al. (1980) the tumors might be more prevalent than believed because small tumors might be overlooked during necropsy because of their location and size.

Etiology

Aortic body tumors are most common in brachycephalic breeds where Boxers, Boston bull terriers and English bulldogs are considered predisposed. However, German shepherds, a non-brachycephalic breed, have a higher incidence of the tumors. One theory suggests that chronic hypoxia causes the chemoreceptor cell hyperplasia (Withrow & Veil, 2007) which can result in neoplasia of the chemoreceptor cells (Noszczyk-Nowak et al., 2010). The incidence of aortic body tumors is higher in dogs aged 6 years or older but the incidence is lower in dogs aged 15 or older (Atasever & Çam, 2003; Ware & Hopper, 1999). Yates et al. (1980) reported tumors in dogs aged 2-15 years, medium age 10 years and that Boxer and Boston bull terriers were predisposed breeds. Ware & Hopper (1999) reported a 3,8 times higher relative risk for spayed females than for intact females. But there were no significant difference in incidence between castrated and non-castrated males. Neither, there was a significant difference between spayed females and castrated males. However, the relative risk of aortic body tumors for intact males was 3,52 times higher than for intact females.

The etiology is not fully known. Noszczyk-Nowak et al. (2010) describe, in their article, a theory about why Boxers are predisposed of aortic body tumors. The predisposition may be a result of chronic hypoxia due to the fact that they are brachycephalic and thereby suffer from "Brachycephalic airway syndrome" (BAS). The characteristics of BAS are elongated soft palate, stenotic nostrils, and lesions in the soft tissue of the pharynx due to a rostral shortage of the skull. The lesions cause a resistance of the airflow in the upper respiratory tract and give a higher negative pressure during inspiration which can result in secondary lesions such as collapse of the larynx. The soft tissue lesions result in chronic hypoxia which is suspected to cause hyperplasia of the chemoreceptor cells. The hyperplasia can transform into chemoreceptor cell neoplasia.

Hayes (1975) performed an etiological study from which he drew the conclusion that breeds from Bulldog ancestry are at risk for aortic body tumors. Bulldog breeds consist of individuals distantly related to each other. The genetic predisposition together with aggravation by the stimulation of high pCO_2 and low pO_2 resulted in the high frequency of chemodectomas within these breeds.

In a study performed by Noszczyk-Nowak et al. (2010) a blood gas measurement was done on dogs with aortic body tumors. The dogs showed symptoms of a compensated respiratory acidosis with low pO_2, high pCO_2, normal pH and less base excess. A big aortic body tumor can cause respiratory acidosis but in the study even dogs with small tumors suffered from respiratory acidosis. But the theory does not include all brachycephalic breed e.g. Pugs does not have a higher prevalence than other non-brachycephalic breeds (Noszczyk-Nowak et al., 2010).

Macroscopic appearance

Tumors range in size from 0,5 – 12,5 cm and appear as a grey single mass or multiple nodules with a mosaic pattern. The tumors have smooth external surface and have a spongy consistency (DiFruscia et al., 1989; Arlington- Headley et al., 2009; Noszczyk-Nowak et al., 2010). The cross section is white and mottled with areas shifting from brown to red (Arlington- Headley et al., 2009). The tumors have a rich blood supply and contain necrotic and hemorrhagic areas and areas with severe inflammation (Balaguer et al., 1990).

Malignant forms have a network of capillaries, muscular arterioles and thin walled veins. Focal hemorrhages and a necrotic center can be observed within tumors greater that 8 cm. They can infiltrate the walls of the surrounding vessels and atrium (Noszczyk-Nowak et al., 2010).

Histological appearance

The tumor is divided into lobules by a connective tissue stroma and these are further divided into smaller lobules by collagen and reticulin (Atasever & Çam, 2003). The cells are pleomorphic and surrounded by a fibrous capsule infiltrated with neoplastic cells (Balaguer et al., 1990). Two different cell types are most abundant, the neuroendocrine type I cells and the sustentacular or supporting type II cells. The type I cells are big, cubical to polyhedral with a small amount of lightly eosinophilic, granular cytoplasm containing vacuoles. The nucleus is big, round to oval or deranged/ deformed and contains nucleoli. The nucleus lacks chromatin and few mitoses are present (Aresu et al. 2006; Yates et al. 1980; Atasever & Çam, 2003; Balaguer et al., 1990). The type II cells are spindle-shaped and distributed in the periphery of the tumor (Atasever et al., 2006).

The tumor also contains giant mononuclear cells scattered around with hyperchromatic nuclei (Balaguer et al., 1990). Around the border of the tumor a lymphohistiocytic inflammatory infiltrate can be observed (Noszczyk-Nowak et. al., 2010). Scattered in the neoplasm; there is another cell type that lies in clusters or one by one with indistinct boundaries. They have a sparse cytoplasm and are characterized by a tightly packed, small nucleus surrounded by a small amount of eosinophil cytoplasm (Balaguer et al., 1990).

Malignant forms have a rich blood supply and numerous mitoses can be observed locally within the tumor (Noszczyk-Nowak et al., 2010).

Symptoms

Clinical signs of an aortic body tumor are often diffuse and the size and localization of the tumor determines the symptoms and their severity (Nowakowski, H., DVM, PhD, pers. com., 2011).

Hemorrhages from the tumor and congestive heart failure are the most common clinical effects of the tumors (Yates et al., 1980). When they increase in size they create functional disturbances such as compression of the aorta and vena cava which causes cardiac decompensation (McGavin & Zachary, 2007). The tumors cause pericardial effusion, dyspnea, hydrothorax, hydropericardium, fatigue, edema, cough, weight loss, vomiting and Vena Cava syndrome (Withrow & Veil, 2007; Noszczyk-Nowak et al., 2010). Hydrothorax and the pressure the tumor exerts on the main bronchus cause the dyspnea (Noszczyk-Nowak et al., 2010). The pressure the tumors exert on the heart might lead to increased diastolic pressure which in turn leads to right cardiac atria failure which causes cardiac tamponade (Ehrhart et al., 2003). Cardiac tamponade can sometimes be mistaken for an epileptic seizure, by the owners, because it causes the animals to faint (Nowakowski, H., DVM, PhD, pers. com., 2011).

The most common symptom associated with aortic body tumor is cardiac failure but Yates et al. (1980) found that hemorrhages that caused acute respiratory or cardiac embarrassment were of equal importance. The tumors are locally expansive and may compress the esophagus, trachea, heart and major vessels. Some tumors are invasive and can invade vessels and thereby cause impeded flow of blood and lymph which can result in congestive heart failure and hydropericardium (Yates et al., 1980).

Pericardial effusion is a life threatening condition and dogs with pericardial effusion show signs of weakness, dyspnea, exercise intolerance, weight loss, abdominal distention and right sided congestive heart failure (Shaw & Rush, 2007). Prognosis is poor for dogs with pericardial effusion as a result of an aortic body tumor according to Fine et al., 2003 while Owen et al. (1996) states that the prognosis is fair. Because of their location; aortic body tumors are difficult to remove surgically (DiFruscia et al., 1989). Therefore DiFruscia recommends pericardiocentesis or in certain cases; subtotal pericardectomy as conservative therapy to ease the symptoms of pericardial effusion. Radiation therapy has not been used enough therefore it is hard to judge the efficiency of it (Owen et al., 1996). Without treatment the dogs will have resistant or progressive pericardial effusion causing cardiac tamponade and eventually death (Ehrhart et al., 2003).

Diagnosis

The aortic body tumor has previously been diagnosed at necropsy but nowadays the tumors can be found with echocardiography (Nowakowski, H., VMD, PhD, pers. com., 2011). With radiography, a dorsal elevation of the trachea near the heart base can be observed. Other lesions seen with radiography include a peri hilar mass, pleural effusion and pulmonary edema (Ehrhart et al., 2003). However, diagnosis can be confirmed by immunohistochemistry

on biopsy. Gasometric blood tests can be performed on Boxers to see if they are at risk for aortic body tumors (Noszczyk-Nowak et al., 2010).

The tumors express neuroendocrine markers that can be used for immunohistochemical labeling e.g. neuron specific enolase (NSE), synaptophysin and chromogranin A (CrA), and S-100 (Deim et al., 2007; Aresu et al., 2006). The immunohistochemical labeling should be combined with a standard hematoxylin and eosin staining to confirm the diagnosis (Noszczyk-Nowak et al., 2010). NSE is a monoclonal antibody that labels neoplastic and normal cells of neuroendocrine and neuronal origin. Synaptophysin is a monoclonal or polyclonal antibody used for detection of endogenous levels of total synaptophysin protein. It detects neuroendocrine neoplasms of neural origin by reacting with a hydrophilic sequence of synaptophysin. Chromogranin A is a polyclonal antibody that reacts with chromogranin A in neuroendocrine cells. Neuroendocrine tumors can contain chromogranin A and therefore the antibody can be used for detection of such tumors. S-100 is also a polyclonal antibody that labels ependynomas, astrogliomas, Schwannomas and also nearly all malignant and benign melanomas and their metastases (Abcam, 2011).

Aresu et al. (2006) performed a study to see if the malignancy of the tumors could be decided with immunohistochemical markers. NSE, CrA and S-100 were used as markers and detectors of malignancy. 17 canine aortic body tumors were used and divided into three separate groups; I, II and III. There were no tumors classified as group I in the study. See table 1 for details.

Table 1. Classification of aortic body tumors in the study (After Aresu et al., 2006)

Tumor group I	**Tumor group II**	**Tumor group III**
Benign	Malignant	Malignant
Low mitotic rate < 2 per high field	Low mitotic rate < 2 per high field	High mitotic rate > 4 per high field
Uniform cells	Less uniform cells	-
No evidence of locally infiltrative growth or metastasis	Evidence of locally infiltrative growth or metastasis	Evidence of locally infiltrative growth or metastasis
0 cases in the study	8 cases in the study	9 cases in the study

All 17 tumors were positive for NSE which was expected since the type I cells are positive for NSE. The group III tumors were negative for CrA whereas the group II tumors were positive for CrA. All grade II tumors and one grade III were positive for S-100. The nuclei of the sustentacular cells were positive for S-100. Chromogranin is specific for neuroendocrine tumors and negative or weak staining indicated lack of chromogranin granules. A negative staining with S-100 indicated an absence or reduced number of sustentacular cells. In conclusion; negatively staining for S-100 and CrA indicated a malignant behavior and can therefore be used as a criteria for determination of malignancy of an aortic body tumor.

DISCUSSION

The purpose of this essay was to describe the macroscopic and microscopic appearance of canine aortic body tumors along with the patophysiology, diagnosis and prognosis. Based on their size and location these tumors might be more common than previously believed. A 1 cm big tumor located in the adventitia of the aorta might be overlooked during necropsy and because of that the prevalence might be higher than reported.

Many of the authors states that the tumors are mostly benign but can infiltrate the surrounding organs and vessels causing dyspnea, cough, pulmonary edema, pericardial effusion, hydrothorax, hydropericardium, fatigue, edema, weight loss, vomiting and Vena Cava syndrome. On the other hand Yates et al. (1980) reports that 22 % of all tumors will eventually metastasize despite their benignant behavior. The different opinions might be based on how they categorize malignant and benign. Perhaps Yates considers infiltration as a malignant behavior and categorizes it as metastasizing. On the other hand the length of Yates study was 12 years and he followed all the cases and with time a benign tumor might metastasize and thereby convert into a malignant tumor. Many of the other studies are single case studies and maybe they did not have the opportunity to follow each case and see how the tumor might evolve. Another difference might be euthanasia; Yates cases lived between 1967 and 1979 and many of the other case studies are from the 1990's and 2000's and there might be a different opinion now about euthanasia than during the 1960's and 1970's. Perhaps nowadays the owners are keener of euthanizing if they feel their dog suffers and thereby the development of the tumors can not be followed.

More research has to be done on the etiology, at the moment the etiology is mainly based upon theories. Chronic hypoxia has been confirmed to cause hyperplasia of chemoreceptor organs and hyperplasia can result in neoplasia. Since BAS causes chronic hypoxia it seems like a possible causing factor except for the fact that not all of the brachycephalic dogs have a higher prevalence of aortic body tumors. Genetic predisposition among different breeds combined with BAS could be the reason why aortic body tumors are more common in certain breeds such as Boxer. Research should be done on whether a combination of genetic predisposition and BAS increases the incidence of aortic body tumors. If a connection can be made between the two theories there might be a way to control if certain individual are at risk. Noszczyk-Nowak et al. (2010) took gasometric blood tests on Boxers to see whether they were at risk or not. This technique might be performed on other breeds to be able to see if they are at risk.

A weakness in the literature is the almost non-existing distinction between malignant aortic body tumors and benign. Some authors made the distinction and some did not and as a reader it was hard to know whether the tumors discussed were malignant or benign. In most case reports the description of the tumors appeared to be general. In this essay a distinction between malignant and benign has been done when the literature made the distinction.

In conclusion; more research should be done considering etiology and the distinction between malignant and benign tumors. More clinical tests should be developed to be able to detect the tumors at an early state to enhance the prognosis. As a veterinarian it is important to be aware

of the existence of aortic body tumors. Although they are uncommon they do exist and should not be neglected when a dog with pericardial effusion, cough and dyspnea needs medical expertise.

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