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Left Ventricular Outflow Tract Obstruction Secondary to Hemangiosarcoma in a Dog

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A 3-year-old, 8-kg male standard Schnauzer was referred to the Murcia University Veterinary Teaching Hospital with a history of exertional syncope over the preceding 2 days. No history of previous cardiac or systemic disease was reported by the owner except for a murmur detected when the dog was a puppy. On physical examination, the dog appeared bright and alert, with slightly pale mucous membranes and a capillary refill time of more than 2 seconds. Respiratory rate and heart rate were within the reference range and femoral pulses were unremarkable. Thoracic auscultation revealed a regular cardiac rhythm and a grade V/VI systolic murmur with the point of maximal intensity at the left heart base with radiation to the right cranial hemithorax. Systolic blood pressure (Doppler method) and ECG measurements were within reference limits. Thoracic radiographs revealed an elongated cardiac silhouette (12.0 vertebral heart size [VHS]; reference VHS, 9.7 ± 0.5)[1] with normal pulmonary parenchyma and pulmonary vasculature. Two-dimensional echocardiography showed an echodense mass located within the left ventricular outflow tract (LVOT), below the aortic valve. The mass was best seen using right parasternal long- and short-axis views and a subcostal view (Fig 1) and depending on the echocardiographic views, the mass appeared round or oval. M-mode measurements were compatible with left ventricular concentric hypertrophy. Color-flow mapping revealed an aliased color-flow pattern in the LVOT and ascending aorta (Fig 2). The pulmonic, mitral, and tricuspid color blood flow patterns and velocities (V) (pulsed-wave Doppler echocardiography), recorded from standard positions, were within the reference range. The aortic blood flow velocity (continuous-wave Doppler echocardiography) recorded from subcostal position was 5.05 m/s (reference range, 1.48 ± 0.03 m/s)[2] with a maximum instantaneous systolic Doppler pressure gradient (DPG) of 102.01 mm Hg (DPG = 4[V]^2). No cardiac arrhythmias were noted during the continuous ECG throughout the echocardiographic examination. Hematologic and biochemical values were unremarkable.

A tentative diagnosis of a cardiac tumor was made. Continuous ambulatory electrocardiography (24-hour Holter monitoring) was recommended to investigate the cause of the syncope, but the owner declined this. The dog was discharged and we recommended exercise restriction and 6.25 mg of atenolol PO q12h. The dog died suddenly 3 weeks later.

At postmortem examination, the gross appearance of the skin, head, abdominal organs, and lungs was unremarkable. The heart weight to body weight ratio was increased (15 g/kg; reference range, 5.5–10.5 g/kg).[3] The interventricular septum and left ventricular free wall appeared grossly hypertrophied. A solitary 1.5-cm, greenish brown firm round mass was present in the LVOT below the aortic valve, raised above the endocardium. One section of the mass showed this tissue extending into the myocardium of the interventricular septum. A whitish fibrous band also was present below the aortic valves, extending on both sides of the mass, compatible with a subvalvular aortic stenosis (SAS).

Samples of the heart and other organs were obtained. All samples were fixed in 10% buffered formalin, processed routinely in Poliwax,[a] and stained with hematoxylin and eosin, toluidine blue for metachromasia, Gallego's trichrome for collagen and muscle fibers, and an immunohistochemical technique using von Willebrand factor[b] for endothelial cells. On histologic examination, the greenish brown, firm, round mass was characterized by variably sized vascular spaces filled with erythrocytes and lined by cells ranging from spindle shaped to ovoid. Solid groups of poorly differentiated and vacuolated cells appeared between the vascular spaces (Fig 3A). Neoplastic cells were positive for von Willebrand factor (Fig 3B). Solid groups were infiltrated by numerous mast cells (Fig 3C). The whitish fibrous band present below the aortic valves consisted of connective tissue with abundant accumulation of mucinous ground substance below the endothelial layer of the endocardium and small areas of cartilage formation in the inner part (Fig 4). No lesions were seen in the other organs examined.

The most common form of left ventricular outflow tract obstruction (LVOTO) in dogs is SAS, which especially affects large breeds of dogs.[4–6] The lesion is due to a fibrous or fibromuscular ridge partially or totally encircling the LVOT at variable distances beneath the aortic valve.[4,5] The lesions have been classified as grades 1–3 depending on the severity of

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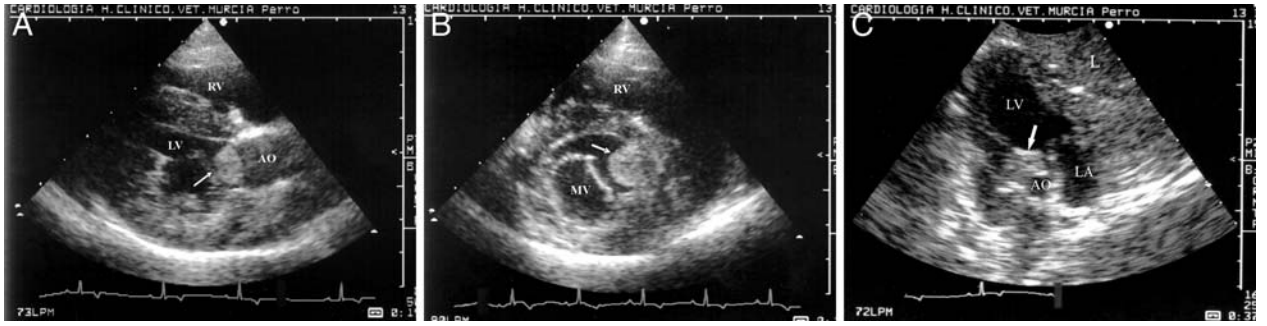

Fig 1. Two-dimensional echocardiograms recorded from right parasternal position, **(A)** long-axis view, **(B)** short axis view, and from **(C)** subcostal position disclosing a mass (arrows) in the left ventricular outflow tract, just below the aortic valve. LV, left ventricle; LA, left atrium; AO, ascending aorta; RV, right ventricle; MV, mitral valve; L, liver.

the obstruction.[4] In the present clinical case, the LVOTO was due both to a round mass located below the aortic valve and to a lesion of SAS grade 2 extending on both sides of the mass.

Tumors involving the heart occur infrequently in dogs,[7,8] accounting for an incidence of 0.19%.[8] The most common primary cardiac tumor in the dog is hemangiosarcoma, followed by aortic body tumors.[7–10] The most common metastatic cardiac tumors reported in dogs have been hemangiosarcoma, adenocarcinoma, osteosarcoma, mastocytoma, lymphoma, and various other sarcomas.[8] In this clinical case a mass outside the heart was not detected on gross or microscopic examination and, thus, a primary cardiac hemangiosarcoma could be considered. Cardiac tumors may occur in intracavitary, intramural, or pericardial locations.[7] In dogs, most primary intracavitary tumors are located in the right side of the heart, especially the right atrium[8–10]; those located in the left ventricle are very uncommon.[11] Several LVOT tumors have been reported in humans, causing LVOTO such as rhabdomyoma[12] and myxoma.[13] However, in the authors' knowledge only tumors involving the right ventricular outflow tract have been reported in dogs, such as an ectopic thyroid carcinoma and a myxoma.[14]

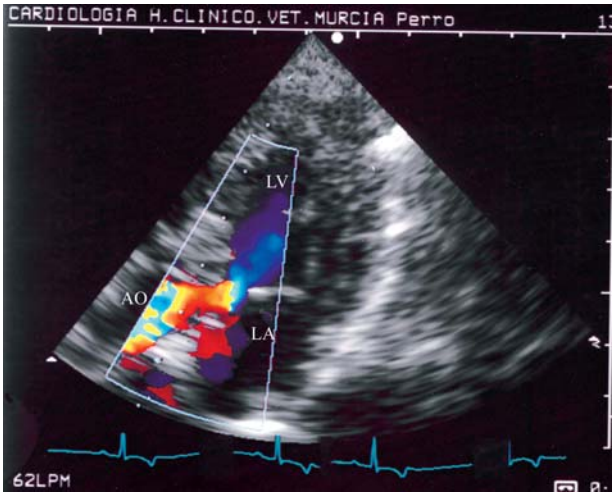

Fig 2. Color-flow Doppler echocardiogram recorded from left apical position showing an aliased color-flow pattern in the left ventricular outflow tract and ascending aorta (Ao). LV, left ventricle; LA, left atrium.

Because hemangiosarcoma (angiosarcoma or malignant hemangioendothelioma) arises from vascular endothelium it may occur at anywhere in the body, but the most frequent sites include the heart, spleen, liver, subcutaneous tissues, muscles, central nervous system, bones, and gastrointestinal tract.[9,15,16] Cardiac hemangiosarcomas have been reported in the right atrium and auricle, near the crista terminalis of the right atrium, and atrioventricular junction, but cardiac hemangiosarcomas located in the left-sided cardiac chambers are very uncommon.[9,15] The size of the largest cardiac hemangiosarcomas ranged from 0.5 to 13.0 cm, but most were approximately 2.0–4.0 cm.[9,10,17] These tumors often were spherical, as in this case, or botryoidal and typically soft and dark red or yellow with numerous fibrous strands on a cut section and a considerable amount of blood oozed from their cut surfaces.[9,15,16] Histologically, hemangiosarcoma is composed of immature endothelial cells that generally form vascular spaces, often as small clefts but sometimes as cavernous channels, in the tumor tissue.[16] In this clinical case the tumor was poorly differentiated and solid groups were infiltrated by numerous mast cells. The presence of mast cells surrounding tumor cells has been described in some angiosarcomas and has been related with tumor growth as well as host immunity and stromal reaction.[18] Accumulations of mast cells in the stroma of some tumors may cause a mistake in the histopathologic diagnosis and confuse the tumor with a mast cell tumor. In this dog an immunohistochemical stain using von Willebrand factor for endothelial cells identified the tumor.

The clinical signs caused by cardiac tumors are more closely related to their anatomic location and associated hemodynamic disturbances than to their histologic types.[10,12,14,19,20] When left ventricular tumors are predominantly intramural in location, they are often asymptomatic and can present as conduction disturbances or arrhythmias, or they can interfere with ventricular function.[11,19,20] However, when the tumor also has a significant intracavitary component, the LVOT can be obstructed, resulting in syncope and findings on physical examination simulating aortic or

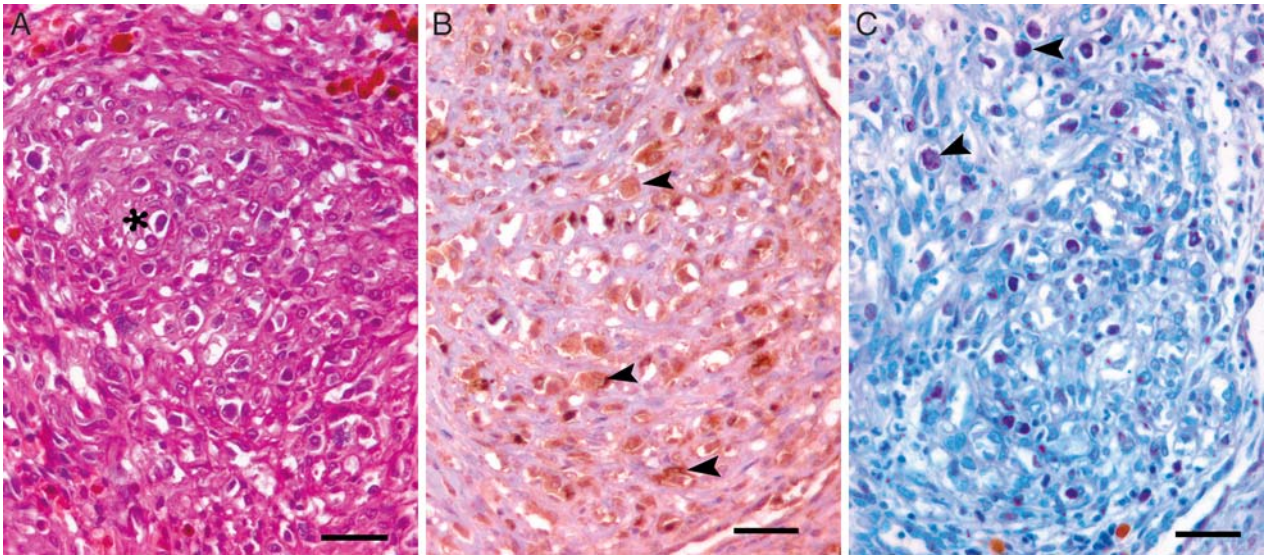

Fig 3. Photomicrographs of the left ventricular hemangiosarcoma of a dog. **(A)** Solid groups of poorly differentiated and vacuolated cells (*) located between the vascular spaces. Hematoxylin and eosin; bar = 38 μm. **(B)** Neoplastic positive cells to von Willebrand factor (arrows) by immunohistochemistry can be seen. Bar = 38 μm. **(C)** Mast cells (arrows) infiltrating the solid groups of neoplastic cells showing metachromasia with toloudine blue stain. Bar = 38 μm.

subaortic stenosis,[19,20] such as in this clinical case. In 2 dogs with right ventricular outflow obstruction, 1 had a systolic ejection cardiac murmur and exertional syncope and the other had findings of secondary to right heart failure and hypoxemia.[14] Mildly affected animals with SAS are clinically normal, with the exception of a soft, left-sided, localized systolic murmur. With severe obstruction, signs of low cardiac output may include exercise intolerance, syncope, or sudden death.[5,6] In this clinical case, history and characteristics of the murmur agree with those reported in dogs with severe SAS. The combination of SAS and tumor contributed to exertional syncope and sudden death in this dog. Although the cause of exertional syncope and sudden death associated with LVOTO has not been determined in dogs, likely mechanisms include ventricular arrhythmias secondary to myocardial ischemia and severe hypotension resulting from excercise-induced increases in left ventricular pressure, activation of ventricular mechanoreceptors, and inappropriate bradycardia or vasodilation.[19] Cardiac arrhythmias were not detected in the resting ECG in the dog of this case, nor in the continuous ECG during echocardiographic examination at the time of diagnosis. However, because continuous 24-hour Holter monitoring was not performed, a cardiac arrhythmia cannot be excluded as the cause of sudden death.

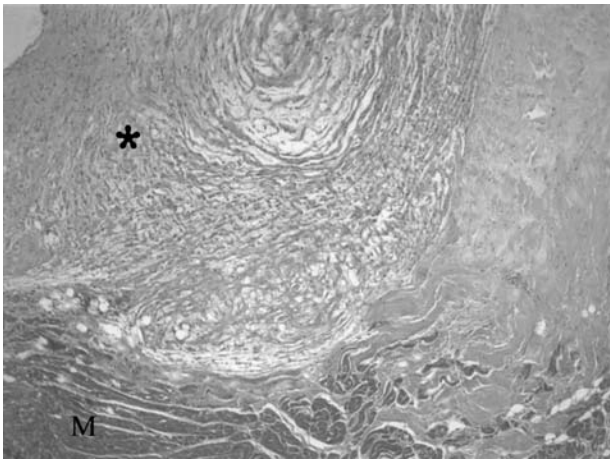

Fig 4. Section of myocardium (M) showing fibrous connective tissue and abundant mucinous substance (*) corresponding to the ring of subvalvular aortic stenosis. Hematoxylin and eosin; 33×.

The diagnosis of cardiac neoplasia is usually based on clinical history, physical examination, radiographic, and echocardiographic findings, and is confirmed with biopsy when indicated.[10,11,21] Two-dimensional echocardiography has became the most valuable diagnostic procedure for identifying tumors and masses of the heart,[10–14,17,19] providing information about tumor size, attachment, extension (superficial or invading myocardium), and mobility to guide endomyocardial biopsy and to allow operative resection without preoperative angiography.[19,20] Intracavitary tumors are recognized echocardiographically as clusters of echoes partially filling 1 or more cardiac chambers,[13,14,19] whereas intramural tumors most commonly cause localized thickening or nodularity of 1 or more heart walls.[11] In the dog of this clinical case, a raised and round or oval mass was well observed from several standard echocardiographic views involving the LVOT myocardium. Possible differentials other than a tumor could include thrombus (uncommon in dogs) and bacterial endocarditis (commonly associated with SAS).[6] The lesion of SAS was not seen on the echocardiographic examination. Doppler echocardiography is considered useful for evaluating the hemodynamic consequences of valvular

obstruction or incompetence caused by the cardiac tumors.[6] On the basis of a maximum instantaneous systolic DPG of 102 mm Hg recorded in this clinical case, the LVOTO can be classified as severe.[6] Endomyocardial biopsy was not considered in this dog because of tumor localization close to the aortic valve. Reported treatment of dogs with cardiac hemangiosarcoma have consisted of pericardectomy and tumor resection,[15,22] with or without adjuvant chemotherapy,[22] or administration of chemotherapy alone, such as doxorubicin, vincristine, and cyclophosphamide.[17] In dogs with right atrial hemangiosarcoma, surgical resection of the tumor was associated with low complications and use of adjuvant chemotherapy (different protocols including doxorubicin, cyclophosphamide, and vincristine) after resection of the tumor was associated with significantly longer survival times, compared with resection alone.[22] In this dog, only atenolol for treatment of LVOTO was considered. Beta-blockers are usually prescribed in dogs with SAS with a history of syncope or high gradients;[6] however, the long-term value of β-blockade on clinical signs or survival has not been demonstrated conclusively in dogs with LVOTO.[6]

Footnotes

[a] Poliwax, Medical & Veterinary Supplies, Buckingham, UK
[b] Polyclonal Rabbit Anti-Human VonWillebraud Factor Daxocytomation Dk-2600, Glostrup, Denmark

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