Cardiogenic hypertrophic osteopathy in a dog with a right-to-left shunting patent ductus arteriosus

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Hypertrophic osteopathy (HO) has been associated with a number of diseases in other humans and animals. In humans, congenital heart defects that cause cyanosis are among the most common causes of HO. Patent ductus arteriosus with right-to-left shunting may be associated with HO in dogs.

A 5-year-old castrated male Shetland Sheepdog that weighed 9.5 kg (20.8 lb) was examined because of progressive bilateral hind limb thickening over a 6-month period. The dog had indoor and outdoor access and traveled extensively in Georgia and Florida. Vaccinations were current, and heartworm preventative was administered monthly. The owner reported that the dog had experienced episodes of hind limb collapse during periods of excitement or strenuous activity since it had been a puppy, and cyanosis was evident when the dog was restrained for examination 2 months earlier.

Abnormalities detected during an initial physical examination included firm swelling and thickening of the distal portions of both hind limbs. The thickening extended from the metatarsal region to approximately the stifle region. The dog had a stiff hind limb gait, but there was no evidence of lameness or a neurologic abnormality. Cyanosis of the preputial mucous membranes was noticed, whereas the oral mucous membranes had a normal color.

Radiographs of both hind limbs were obtained (Fig 1). A well-structured, palisade-like periosteal reaction was seen. Articular surfaces were unaffected, and there was no underlying bone destruction. Severe soft tissue swelling was evident. On thoracic radiographs, severe right-sided cardiomegaly was seen (Fig 2). No abnormalities were seen on radiographs of the forelimbs and abdomen.

Blood samples were submitted for a CBC; serum biochemical analyses; a Coombs’ test; and serologic testing for heartworm antigen, antinuclear antibodies, and rheumatoid factor. Abnormalities included erythrocytosis (PCV, 73.7%; reference range, 36% to 60%), thrombocytopenia (106,000 platelets/µL; reference range, 170,000 to 400,000 platelets/µL), and azotemia (BUN, 48 mg/dL; reference range, 6 to 25 mg/dL). Macrothrombocytes were seen during cytologic evaluation of blood smears. Results of tests for antinuclear antibodies, rheumatoid factor, and heartworm antigen were negative. Results of a urinalysis and ACTH stimulation test were within reference limits. Serum erythropoietin (EPO) concentration was slightly high (28.2 mU/mL; reference range, 8.4 to 28 mU/mL), suggesting that the dog had secondary polycythemia.

Concentric hypertrophy of the right ventricle, flattening of the interventricular septum, dilatation of the pulmonary artery, and a sharply peaked velocity profile in the pulmonary artery were identified during echocardiography. There was no evidence of a ventricular septal defect, atrial septal defect, mitral regurgitation, tricuspid regurgitation, or pulmonic insufficiency. Electrocardiography revealed a heart rate of 98 beats/min and sinus arrhythmia. Deep Q or S waves were seen in leads I, II, and AvF and were considered a result of right axis deviation. Mean electrical axis was 120° (reference range, 40° to 100°). Results of abdominal ultrasonography were unremarkable.

In an attempt to identify a patent ductus arteriosus with right-to-left shunting, contrast echoangiography was performed. Briefly, 10 mL of agitated saline (0.9% NaCl) solution was injected rapidly into a cephalic vein while the heart was imaged from a right parasternal location. Echogenic bubbles were seen in the right but not the left ventricle. The injection was then repeated while the abdominal aorta was imaged medial to the right kidney. Echogenic bubbles were seen in the aorta with repeated injection. A diagnosis of patent ductus arteriosus with right-to-left shunting or reverse patent ductus arteriosus (rPDA) was made.

Clinical signs associated with rPDA in dogs include hind limb weakness, collapse, differential cyanosis, and seizures.2,3 These clinical signs are related to decreased delivery of oxygenated blood to the caudal part of the body. Renal hypoxia stimulates EPO expression and resultant polycythemia. Thus, treatment for rPDA is directed at decreasing the severity of the associated polycythemia.

Phlebotomy was initially attempted to decrease the polycythemia in the dog. Initial calculations suggested that 75 mL (7.9 mL/kg [3.6 mL/lb]) of blood would have to be removed and replaced with an equal volume of crystalloid fluids to decrease circulating blood volume by approximately 10%. After only half of this volume of blood had been removed, however, the dog became lethargic, mucous membrane color became dark red, and respiratory rate increased. Thus, the procedure was discontinued, and no further attempts at phlebotomy were made.

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Treatment with hydroxyurea (50 mg/kg [22.7 mg/lb], PO, q 48 h) was initiated to decrease the dog's PCV. Hydroxyurea causes bone marrow suppression by interfering with the action of the enzyme ribonucleoside diphosphate reductase, which is important in the synthesis of DNA, and has been recommended for the treatment of polycythemia. Two weeks after initiation of hydroxyurea treatment, the owner reported an increase in the dog's activity and appetite. Nevertheless, the dog still had episodes of hind limb collapse with excitement. A CBC performed 2 weeks after the initiation of hydroxyurea treatment revealed thrombocytopenia (51,000 platelets/µL; reference range, 150,000 to 700,000 platelets/µL) and a decrease in PCV to 55% (reference range, 37% to 55%). The dosage of hydroxyurea was decreased to prevent further decreases in PCV and platelet concentration (50 mg/kg, PO, q 72 h). Unfortunately, the dog was lost to further follow-up, and a CBC could not be performed after this change in dosage.

Hypertrophic osteopathy (HO) is characterized radiographically by periosteal proliferation beginning at the distal aspect of the affected limbs. The phenomenon has been associated with a number of diseases in animals and humans. In particular, in dogs, HO has been associated with primary and metastatic lung tumors, rhabdomyosarcoma of the urinary bladder, thoracic...
racic and abdominal mesotheliomas, a bronchial foreign body, an esophageal granuloma associated with Spirocerca lupi, bacterial endocarditis, Dirofilaria immitis infection, and pulmonary abscesses.

In humans, HO has been associated with a number of pathologic processes affecting the thorax and abdomen, but cyanotic congenital heart defects are among the most common causes of HO in humans. In a study of 32 human patients > 6 years old with cyanotic congenital heart disease, for instance, 10 (31%) had radiographic evidence of HO. Hypertrophic osteopathy in humans with cyanotic congenital heart defects is classified as cardiogenic HO, and lesions are seen in the cyanotic limbs. Affected limbs are typically not painful, in contrast to patients with HO secondary to pulmonary neoplasia. These features were all present in the dog described in the present report. Although the association between cyanotic congenital heart defects and HO in humans has been well documented, to our knowledge, HO secondary to cyanotic congenital heart defects in a dog has not been documented previously in the veterinary literature.

Several theories have been advanced to explain the pathogenesis of HO in humans, but most of these theories are based on clinical observations in a small number of patients. One theory suggests that vagal nerve stimulation by the diseased organ induces the periosteal changes via a neural reflex. This neurogenic theory was proposed after it was observed that human patients with nonresectable lung masses experienced a decrease in the severity of limb pain following vagotomy. However, this theory was based on observations in only 5 patients and does not readily explain the pathogenesis of HO associated with cyanotic congenital heart defects.

It has been speculated that cyanotic cardiac abnormalities may result in an abnormal platelet population characterized by an increase in mean platelet volume (macrothrombocytosis), and the platelet population in the dog described in the present report was abnormal. In human patients with right-to-left shunting circulatory defects, macrothrombocytes exist because the pulmonary microvasculature, which normally serves to fragment them, is bypassed. The macrothrombocytes circulate to the distal aspects of the affected limbs, where they fragment in the small vascular spaces. Fragmentation of these enlarged platelets causes the release of a number of growth factors into the systemic circulation, including vascular endothelial growth factor (VEGF). Vascular endothelial growth factor is an angiogenic factor that has been shown to be produced by neoplastic processes. Hypoxic induction of VEGF production and the constitutive production and release of VEGF by megakaryocytes and platelets have also been documented. Although a direct connection between VEGF and the development of HO has not been fully documented, VEGF induces several physiologic changes that could lead to HO, including promotion of osteoblast differentiation and angiogenesis.

References