Severe Pulmonary Hypertension and Pulmonary Thrombi in a Dog

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INTRODUCTION

Pulmonary hypertension (PH) is an increase in pressure within the pulmonary vasculature.[1] PH is uncommonly idiopathic in dogs and is more often a sequela secondary to pulmonary, cardiovascular, prothrombotic conditions resulting in pulmonary thrombus (PT) and infectious disease (i.e., heartworm). We describe an unusual presentation of severe PH secondary to severe pulmonary PT in a dog.

CASE PRESENTATION

A 24-kg, 9-year-old, male, castrated Husky was presented to the University of Wisconsin Cardiology Service as a referral for increasing frequency of cough over a 2-month period. Thoracic radiographs from the primary care veterinarian showed right-sided cardiomegaly with subjective dilation of the main pulmonary artery (MPA) and severe dilation and tortuous appearance of the branch pulmonary arteries (PAs). A moderate diffuse bronchointerstitial pattern was seen. Complete blood count and chemistry at the time were within normal limits. Results of a heartworm antigen test, with and without heat tests, were negative.

On presentation, the patient was reported to have a temperature of 102.5°F (39.2°C; normal range, 101.0°F-102.5°F). The heart rate was 160 beats/min (normal range, 60-140 beats/min) with a regular rhythm, and femoral pulses were synchronous and weak. A split second heart sound was appreciated. The patient was eupneic and coughed occasionally, and findings on pulmonary auscultation were normal.

A point-of-care ultrasound scan of the abdomen and thorax did not reveal any free fluid. Repeat thoracic radiography showed that the cardiac silhouette was subjectively moderately enlarged secondary to severe right-sided cardiomegaly. The MPA, right PA (RPA), and left PA were subjectively severely dilated (Figure 1). Pulmonary parenchyma was normal.

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Keywords: Embolism, Protein-losing nephropathy, Obstruction, Pulmonary artery, Pathology

Conflicts of interest: The authors reported no actual or potential conflicts of interest relative to this document.

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2468-6441
https://doi.org/10.1016/j.case.2023.11.003

An oscillometric blood pressure measurement revealed systemic hypertension (176/83 mm Hg). Electrocardiography showed sinus tachycardia (170-200 beats/min) with a right caudal axis deviation suspected to be secondary to right ventricular (RV) hypertrophy.

Transthoracic echocardiography (TTE) showed a heteroechoic, irregular, intraluminal obstructive lesion within the distal RPA (Figure 2A, Video 1). This structure was measured at 3.0 × 3.0 cm. Color flow Doppler revealed minimal flow around the structure (Video 2). The MPA and RPA were severely dilated, with very poor distensibility of the RPA (Figures 2B and 3), with an MPA/aorta ratio significantly >1.0, which is seen with at least moderate enlargement, and an RPA distensibility index of 7.7%, which is severely decreased (29.5% is seen in moderate PH vs 40.5% in normal dogs). The RPA distensibility index is defined as the largest dimension of the RPA that occurs in systole minus the smallest RPA dimension that occurs in diastole, divided by the largest dimension in systole, multiplied by 100%. The pulmonary valve was normal, with no evidence of pulmonary valve stenosis.

There was subjectively moderate pulmonic regurgitation, with a severe increase in peak velocity of 4.3 m/sec and a pressure gradient of 72.6 mm Hg (Figure 4A; normal mean PA pressure is 20 mm Hg). A type II PA flow profile was present. There was severe RV dilation, RV hypertrophy (on the basis of left ventricular thickness), and RV systolic dysfunction, as indicated by a reduced tricuspid annular plane systolic excursion of 2.2 mm (normal range, >11 mm). The right atrium was subjectively severely dilated, and the interatrial septum was bowed to the left. The tricuspid valve apparatus was normal. There was a subjectively moderate amount of tricuspid regurgitation, with a severely increased peak velocity of 4.6 m/sec and a pressure gradient of 86.1 mm Hg (severe PH, >75 mm Hg; Figure 4B).

There was subjective left-sided underfilling and severe septal flattening with electrical and mechanical dyssynchrony, as seen when the appropriate myocardial contractility (i.e., mechanical systole) does not occur during the coordinated timing on the electrocardiogram (i.e., electrical systole; Figure 5, Video 3).[2]

The left atrium was normal in size and appeared to be compressed by the severely dilated RPA (Video 4). The primary differential diagnosis on TTE was severe PH secondary to the presence of an intraluminal obstructive mass lesion within the RPA. The obstructive mass lesion was most suspicious for a PT, although neoplastic disease and infectious granuloma (blastomycosis) could not be definitively ruled out.

The patient was started on sildenafil 50 mg (2.1 mg/kg) orally every 8 hours for PH, clopidogrel 75 mg (3.1 mg/kg) orally every 24 hours for possible PT, and enalapril 10 mg (0.4 mg/kg) orally every 12 hours for systemic hypertension.

To determine the underlying etiology of the suspected PT, a urine protein-to-creatinine ratio was submitted and revealed that the patient was mildly proteinuric (1.6; normal range, <0.5; equivocal, 0.5-1.0).

VIDEO HIGHLIGHTS

Video 1: Two-dimensional TTE, right parasternal short-axis view of the RPA, demonstrating large thrombus in the distal RPA and severe dilation and poor distensibility of the RPA.

Video 2: TTE, right parasternal short-axis view of the RPA with color flow Doppler, demonstrating large thrombus in the distal RPA, severe dilation of and poor distensibility of the RPA, and almost complete obstruction of flow past the large thrombus.

Video 3: Two-dimensional TTE, right parasternal short-axis view at the level of the left ventricular papillary muscles, demonstrating severe interventricular septal flattening in both systole and diastole, with evidence of electrical and mechanical dyssynchrony.

Video 4: Two-dimensional TTE, left parasternal long-axis four-chamber view, left atrium and left ventricle on right side of image, right atrium and right ventricle on left side of image. Severely dilated and poorly distensible RPA, in the short-axis view, is seen adjacent to, ventral to, and in between the left and right atria. The thrombus can be seen to occupy most of the RPA lumen.

View the video content online at www.cvcasejournal.com.

The patient returned to the cardiology service 17 days later for continued cough and new onset of exercise-induced syncopal episodes. The patient was bright and alert and weighed 25 kg, the heart rate was 176 beats/min, and the blood pressure was 186/92 mm Hg. The patient was continued on sildenafil 50 mg (2 mg/kg) orally every 8 hours and clopidogrel 75 mg (3 mg/kg) orally every 24 hours. Enalapril was discontinued, and telmisartan 25 mg (1 mg/kg) orally every 24 hours for management of systemic hypertension and proteinuria was initiated. Pimobendan 7.5 mg (0.3 mg/kg) orally every 12 hours and an L-arginine supplement 2,500 mg (100 mg/kg) orally every 8 hours was added to promote PA vasodilation, thereby improving RV function.

Before starting the change in medications, the patient had an acute increase in syncopal and presyncopal episodes, which greatly affected its quality of life, and humane euthanasia and necropsy were elected.

Gross necropsy revealed PT of the RPA and left PA, consistent with previous clinical, radiographic, and transthoracic echocardiographic diagnosis (Figures 6-8).

The PTs were almost entirely occlusive and extended into the medium and smaller arteries within the lungs. The RPA PT was firm and lamellated, with organization and mineralization, suggesting chronicity. The majority of the left PA contained a postmortem clot but possessed a distal fragment similar to the RPA PT, which was proposed to be a thromboemboli from the RPA vs a more recently formed PT. This potentially caused the acute clinical decompensation of the patient. Cultures of these PTs disclosed no bacterial or fungal growth.

Collagen, fibroblasts, and recanalization within the PT on histopathology supported chronicity. Thrombi in the right cranial lung lobe lacked fibrosis on histopathology, which also may have coincided with the acute clinical decompensation of the patient. Other histologic PA and branches changes included medial hypertrophy, disruption of elastic laminae, intimal proliferation, and plexiform lesions. These changes were consistent with PH.[3]

Renal histology revealed bilateral glomerulosclerosis with rare glomerular fibrin thrombi and minimal membranous glomerulonephritis.

DISCUSSION

In humans, PH is defined by a mean PA pressure ≥20 mm Hg at rest, determined using right-heart catheterization.[4] As right-heart catheterization is often not a practical diagnostic test in veterinary medicine, TTE, along with clinical signs, is used to determine the probability of PH.[1] Estimated systolic PA pressure can be derived using the peak tricuspid regurgitation velocity and the simplified Bernoulli equation (pressure gradient = 4 × velocity [m/sec]^2) plus estimated right atrial pressure. In dogs, a peak tricuspid regurgitation velocity >3.0 to 3.4 m/sec increases the probability of clinically significant PH. The number of anatomic changes on echocardiogram has a positive correlation with the probability of PH. Sites of anatomic change include RV, PA, right atrial, and caudal vena caval changes.[1] In humans, an estimated RV systolic pressure of 35 mm Hg is used to diagnose PH on echocardiography, which is higher than the invasive mean PA pressure of 20 mm Hg. Clinical signs of PH include syncope, respiratory distress at rest or after activity, right-sided heart failure, prolonged

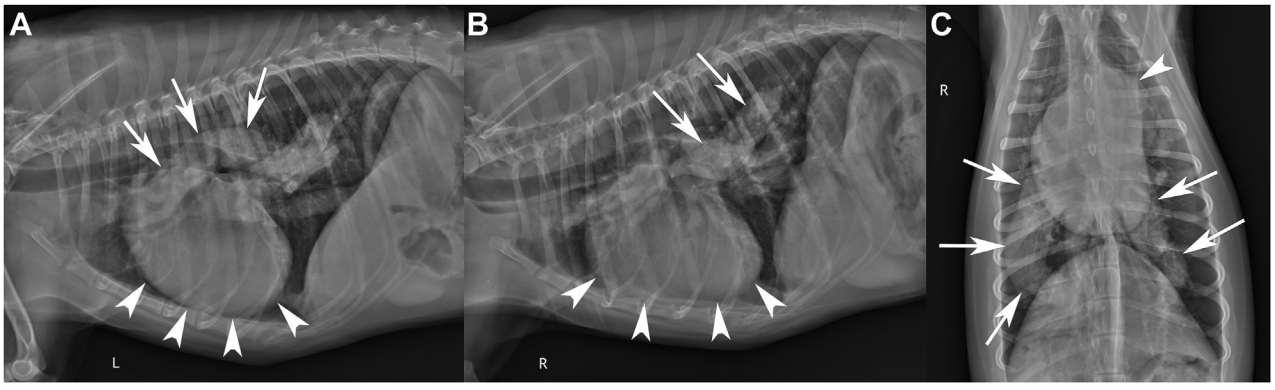

Figure 1 Thoracic radiographs. **(A)** Left lateral image. *White arrowheads* show RV enlargement. *White arrows* show the dorsal border of the left PA. **(B)** Right lateral image. *White arrowheads* show RV enlargement. *White arrows* show the dorsal border of the RPA. **(C)** Ventrodorsal image. *White arrows* show the lateral margins of the left PA and RPA. The *white arrowhead* shows the dilated pulmonary trunk.

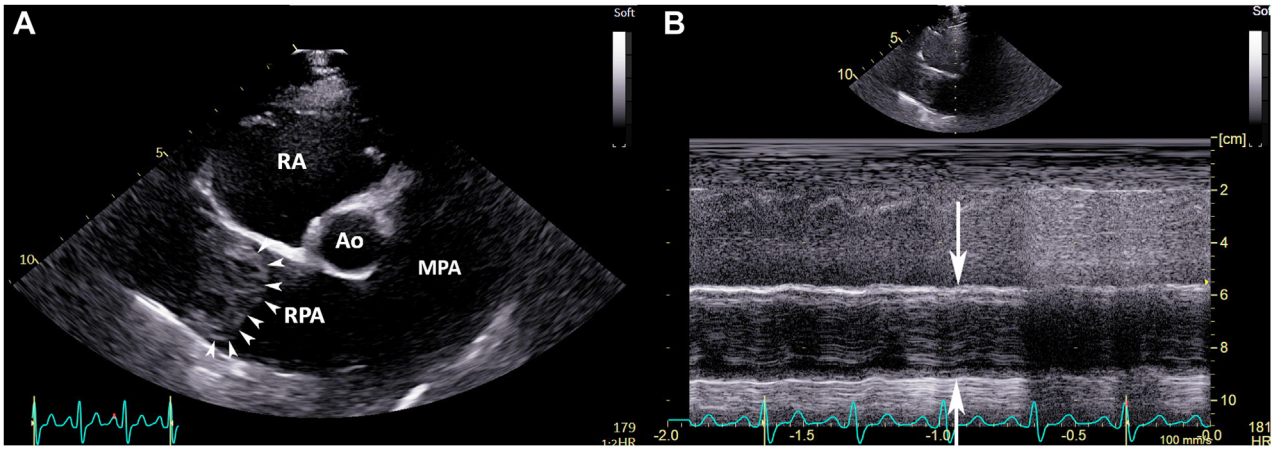

Figure 2 TTE, right parasternal short-axis view at the level of the heart base. **(A)** Two-dimensional image. A solid echogenic lesion can be seen in the distal RPA. **(B)** M-mode imaging perpendicular and through the severely dilated and nondistensible RPA. The *white arrowheads* outline the proximal border of the thrombus in the RPA. The *white arrows* outline the edges of the RPA. *Ao*, Aorta; *RA*, right atrium.

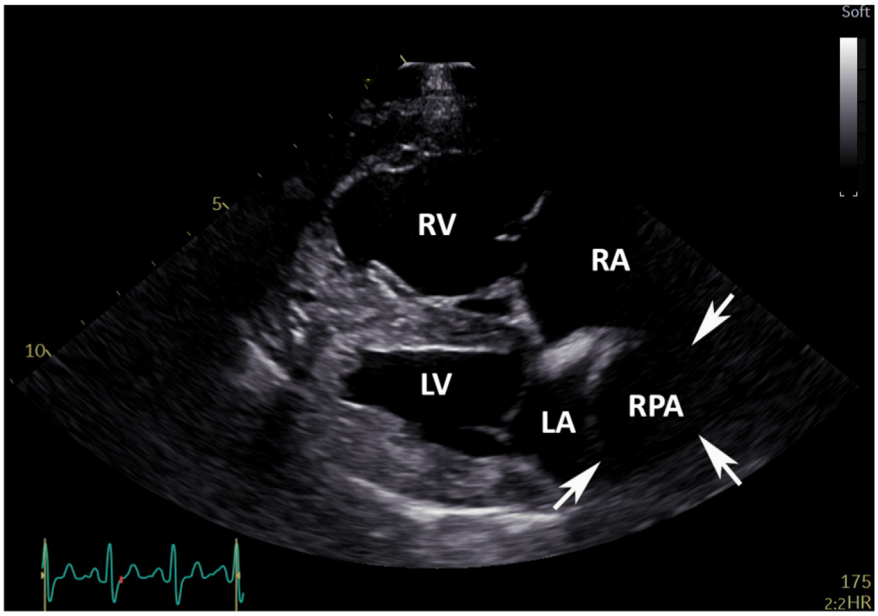

Figure 3 Two-dimensional TTE, right parasternal four-chamber view, demonstrates severe eccentric RV hypertrophy and moderate to severe RV eccentric hypertrophy, moderate right atrial enlargement, and severe dilation of the RPA (*white arrows*) in the short-axis view. *LA*, Left atrium.

respiratory recovery after activity, and cyanotic or pale mucous membranes.

There are six major groups of diseases that can cause PH in dogs: PA hypertension, left-sided heart disease, pulmonary disease or chronic hypoxia, PT, parasitic (heartworm) disease, and multifactorial disease.[1] Postmortem analysis confirmed the cause of this patient's PH to be PT. Risk factors for PT in dogs include protein-losing nephropathy, protein-losing enteropathy, hyperadrenocorticism, exogenous steroid administration, neoplasia, heartworm disease, sepsis, disseminated intravascular coagulation, trauma, blood transfusion, and cytotoxic agents.[4] Glomerular nephropathy, resulting in a prothrombotic state, was the suspected cause for this patient's PT.

Clinical signs of PT include dyspnea, tachypnea, altered oxygenation parameters, and lethargy.[5] Radiographic signs suggestive of PT include MPA enlargement, other pulmonary vessel changes, right-sided heart enlargement, pulmonary parenchymal changes, pleural effusion, and pulmonary volume loss. Radiographs of patients with PT may also appear normal. Thoracic radiography does not definitively diagnose PT, though it may provide supporting evidence that corresponds with other imaging modalities, such as TTE, which revealed an intravascular soft tissue mass in this patient. Other imaging modalities providing a more definitive diagnosis of PT include nuclear scintigraphy and pulmonary angiography with or without computed tomography.[6]

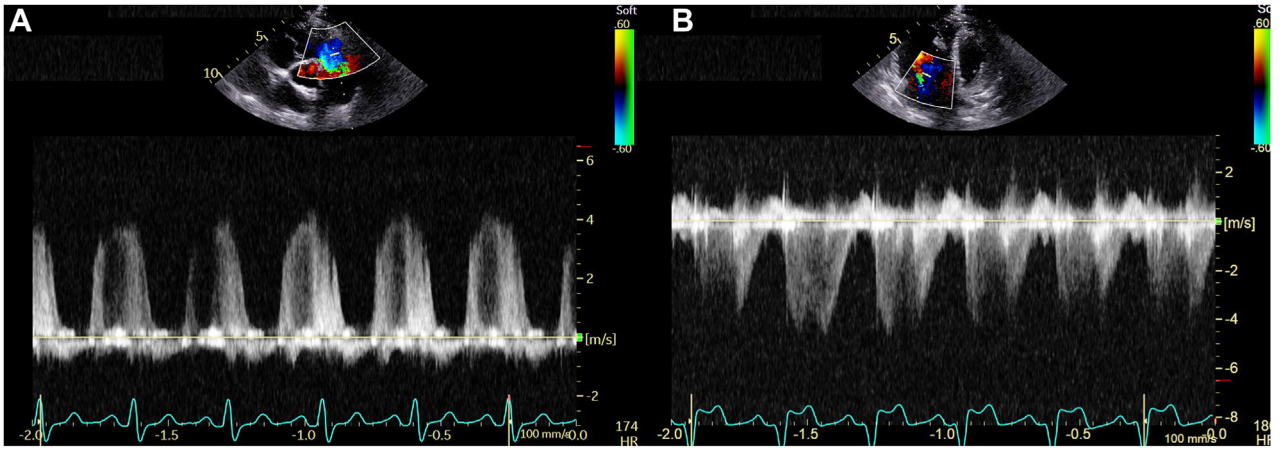

Figure 4 TTE, spectral Doppler of pulmonic regurgitation **(A)** and tricuspid regurgitation **(B)** consistent with severe pulmonary hypertension.

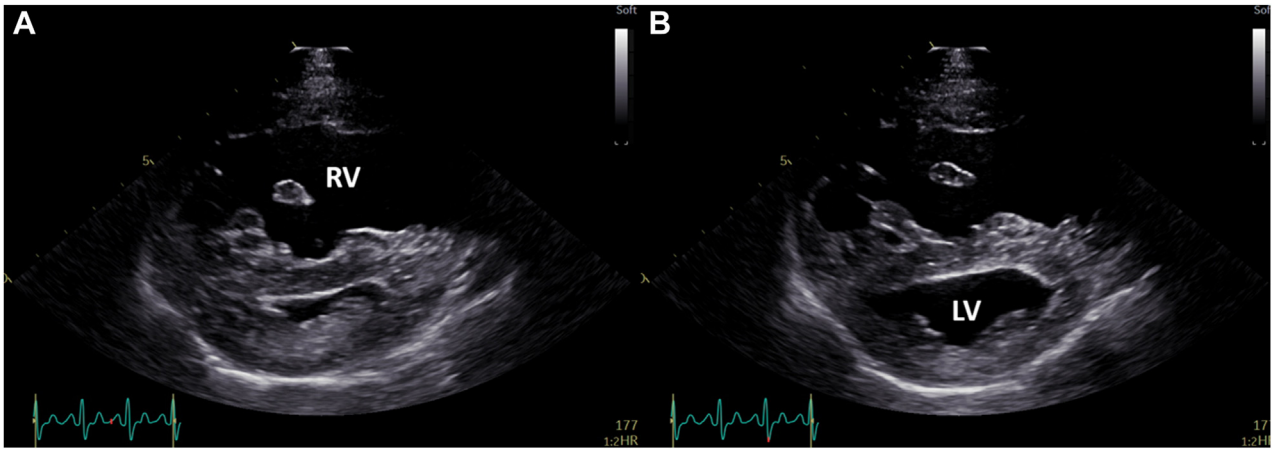

Figure 5 TTE, right parasternal short-axis view at the level of the papillary muscles, demonstrating severe septal flattening and severe eccentric and concentric RV hypertrophy in systole **(A)** and diastole **(B)**, with electrical and mechanical dyssynchrony.

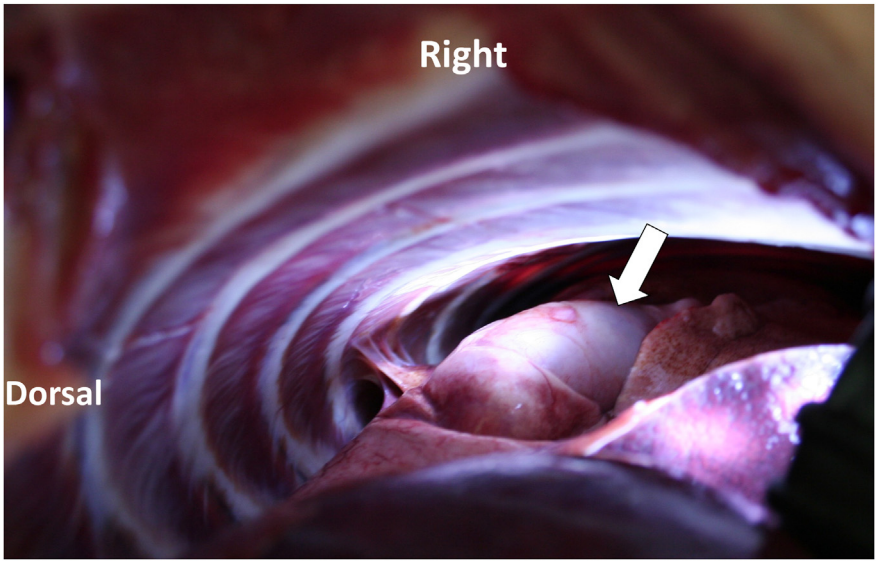

Figure 6 Necropsy image looking into the right side of the thorax, at the level of the diaphragm. The lungs are retracted away from the thoracic wall. The RPA (*white arrow*) is protruding from the lungs. Adjacent to the artery, multiple fibrous pleural adhesions extend from the right lungs to the thoracic wall.

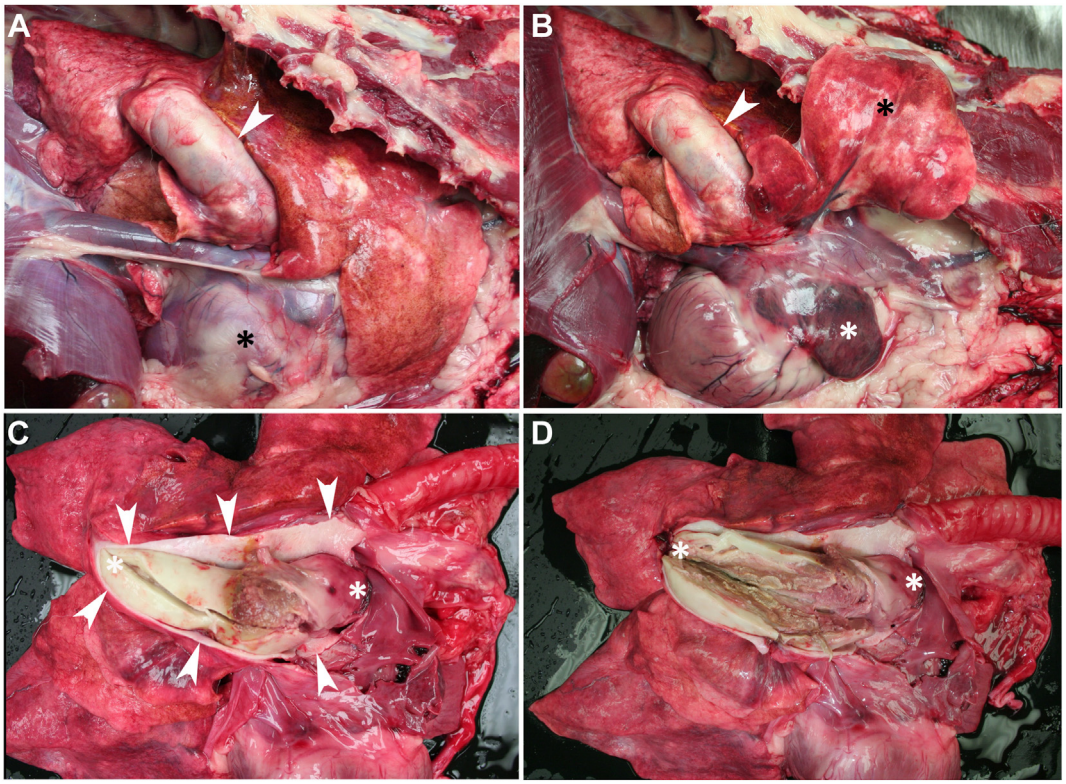

Figure 7 Necropsy images of the heart and lungs, as seen from the right side. Orientation in **(A)** to **(D)**: head to the right, dorsal on top, ventral on bottom, tail to the left. **(A)** In situ image of the heart and lungs. *White arrowhead* points to the protruding RPA. Black *asterisk* denotes the heart. **(B)** The right cranial lung lobe (*black asterisk*) has been retracted. The pericardium was removed, and the enlarged right atrium (*white asterisk*) can be seen. *White arrowhead* shows the RPA protruding from the lung. **(C)** *White arrowheads* outline the edges of the incised RPA. The *white asterisk* shows the length of the thrombus seen in the RPA. **(D)** The *white asterisk* shows the length of the incised thrombus in the RPA.

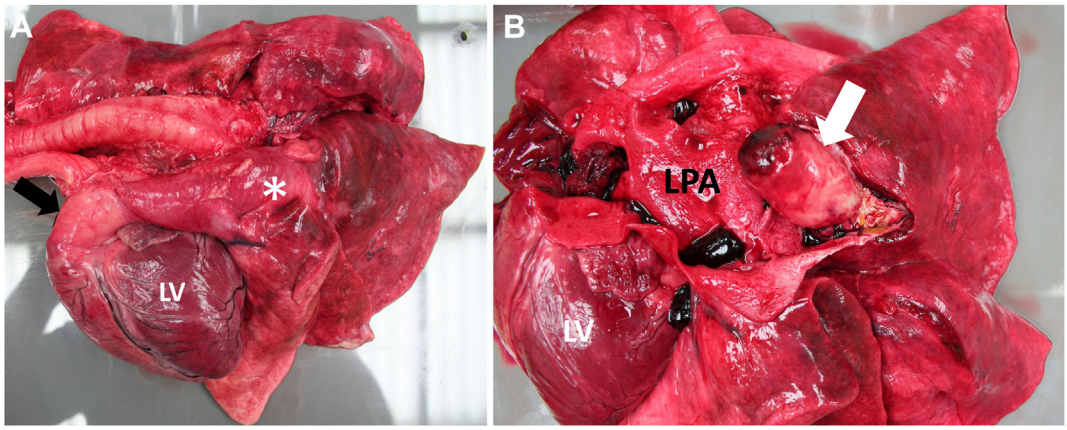

Figure 8 Necropsy images of the heart and lungs, as seen from the left side. Orientation in **(A)** and **(B)**: head to the left, dorsal on top, ventral on bottom, tail to the right. **(A)** *Black arrow* shows the severely dilated pulmonary trunk. *White asterisk* shows a large "bulge" in the lung, which overlies the thrombus in the left PA (LPA). **(B)** LPA is incised, showing the large thrombus in the more distal LPA (*white arrow*). *LV*, Left ventricle.

In humans, more aggressive approaches to remove PT would include surgical thrombectomy or catheter-delivered thrombolytics. These options are not typically feasible or pursued in veterinary medicine, and clopidogrel (as an antiplatelet mediation) was chosen as a therapy to prevent further thrombus formation.

As well as addressing underlying predisposing diseases, sildenafil has shown to be an effective treatment for PH secondary to PT.[7] Sildenafil has been shown to decrease mean PA pressure and blunt decreases in Pa_{O2}.[8] In chronic cases, an anticoagulant may be added. Although not yet proved, L-arginine, an amino acid that is necessary

for the production of nitric oxide, a vasodilator, may be considered an adjunct medication to sildenafil.[1,9,10]

This patient was started on sildenafil and L-arginine to promote PA vasodilation. The efficacy of this therapeutic plan was questioned because of the obstructive nature of the PT. The dog's changes on TTE could have been secondary to the obstructive lesion and less so to true PH. However, gross pathologic, histopathologic, and radiographic changes provided evidence supporting true PH in this patient. Unfortunately, the marked degree of PT obstruction in this case likely limited the potential therapeutic benefit gained though sildenafil and L-arginine therapy.

CONCLUSION

Although PT is not a new finding in dogs or people, this report offers a remarkable case of PT with concurrent severe PH including numerous supportive findings on TTE, radiography, gross pathology, and histopathologic changes. The present case provides specific value in the literature, as it demonstrates the correlation between diagnostic imaging (radiography and TTE) and pathologic findings (gross and histopathology). In addition, this dog lived with significant long-standing PH on the basis of the findings on pathology, implying that dogs, like humans, may modify lifestyle and are able to live with progressive PH.

ETHICS STATEMENT

The authors declare that the work described has been carried out in accordance with the following guidelines: research animal resources and compliance policy at the University of Wisconsin–Madison.

CONSENT STATEMENT

The authors declare that since this was a non-interventional, retrospective, observational study utilizing de-identified data, informed consent was not required from the patient under an IRB exemption status.

FUNDING STATEMENT

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

DISCLOSURE STATEMENT

The authors report no conflict of interest.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.case.2023.11.003.

REFERENCES

1. Reinero C, Visser LC, Kellihan HB, Masseau I, Rozanski E, Clercx C, et al. ACVIM consensus statement guidelines for the diagnosis, classification, treatment, and monitoring of pulmonary hypertension in dogs. J Vet Intern Med 2020;34:549-73.
2. Hill AC, Maxey DM, Rosenthal DN, Siehr SL, Hollander SA, Feinstein JA, et al. Electrical and mechanical dyssynchrony in pediatric pulmonary hypertension. J Heart Lung Transplant 2012;31:825-30.
3. Robinson WF, Robinson NA. Cardiovascular system. In Maxie MG, ed. Jubb, Kennedy, and Palmer's Pathology of Domestic Animals, Vol 3. 6th ed St. Louis, MO: Elsevier; 2016:66-7.
4. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53:1-13.
5. Johnson LR, Lappin MR, Baker DC. Pulmonary thromboembolism in 29 dogs: 1985–1995. J Vet Intern Med 1999;13:338-45.
6. Mitchell CW. The imaging diagnosis of pulmonary thromboembolism. Can Vet J 2009;50:199-202.
7. Ghofrani HA, Schermuly RT, Rose F, Wiedemann R, Kohstall MG, Kreckel A, et al. Sildenafil for lont-term treatment of nonoperable chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med 2003;167:1139-41.
8. Dias-Junior CA, Vieira TF, Moreno H, Evora PR, Tanus-Santos JE. Sildenafil selectively inhibits acute pulmonary embolism-induced pulmonary hypertension. Pulm Pharmacol Ther 2005;18:181-6.
9. Flynn KM, Kellihan HB, Trepanier LA. Plasma l-citrulline concentrations in l-arginine–supplemented healthy dogs. J Vet Cardiol 2017;19:376-83.
10. Souza-Silva AR, Dias-Junior CA, Uzuelli JA, Moreno H, Evora PR, Tanus-Santos JE. Hemodynamic effects of combined sildenafil and l-arginine during acute pulmonary embolism-induced pulmonary hypertension. Eur J Pharmacol 2005;524:126-31.