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Clinical features of canine pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis

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Background: Histologic features of pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) have been described in dogs but without a thorough clinical description.

Objectives: To report the clinical features, diagnostics, treatment, and outcome of dogs with histologic evidence of PVOD and PCH.

Animals: Fifteen pet dogs meeting histopathologic criteria of PVOD (occlusive remodeling of small-sized to medium-sized pulmonary veins) or PCH (alveolar capillary proliferation and congestion), or both.

Methods: Medical records of dogs with PVOD and PCH identified based on histopathologic features between 2003 and 2017 were retrospectively reviewed.

Results: Fifteen dogs met inclusion criteria of a histologic diagnosis of PVOD or PCH or both. Dogs were older (median 11 years) with no apparent breed or sex predisposition. Dogs presented with acute clinical signs (median 3 days), usually respiratory distress. Thoracic radiography (available in 10 dogs) revealed right cardiomegaly and patchy or diffuse interstitial to alveolar patterns, with 9 dogs having a normal left cardiac silhouette. In 5 dogs tested, pulmonary arterial hypertension (PAH) was documented. In all 3 dogs, thoracic computed tomography scans showed pulmonary arterial enlargement and perivascular diffuse nodular ground-glass opacities. Ten of 15 dogs died within 1 day; median survival was 3 days.

Conclusions and Clinical Importance: In dogs with PAH, the inability to document left-sided congestive heart failure and failure to identify another cause of signs of respiratory disease should increase suspicion for PVOD and PCH. With increased awareness of PVOD and PCH by clinicians and pathologists, dogs with compatible clinicopathologic features should be evaluated for these pulmonary vascular disorders.

KEYWORDS

capillary proliferation, computed tomography, nodular ground-glass opacities, occlusive vascular remodeling

1 | INTRODUCTION

Canine pulmonary hypertension (PH) is a complex, poorly understood multifactorial group of disorders manifesting with increased pulmonary arterial pressures (PAP) greater than approximately 30 mm Hg.[1]

The current human clinical classification scheme for PH groups disorders with related pathologic and hemodynamic findings and similar therapeutic responses.[2] Broadly, there are 5 major categories: Group I, pulmonary arterial hypertension (PAH); Group 2, PH caused by left-sided heart disease; Group 3, PH caused by chronic lung disease or hypoxemia; Group 4, chronic thromboembolic PH; and Group 5, PH with unclear multifactorial mechanisms.[2] Although these categories of PH have been adapted for use in dogs,[1] the number of diseases within each category is much smaller, either because the parallel condition does not occur in dogs or because it has not yet been recognized. Recently, pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) in dogs were recognized, and histologic features detailed;[3] both of these conditions are considered a subset of Group I disorders leading to PH in humans.

The hallmark feature of PVOD is occlusive remodeling of small and medium pulmonary veins, leading to upstream congestion of alveolar capillaries and pulmonary arterial remodeling.[3,4] PCH is an angioproliferative disorder characterized by proliferation of alveolar capillaries, which may infiltrate into pulmonary veins and arteries as well as bronchioles.[5] In humans with PVOD, 75% have concurrent lesions of PCH, leading to speculation that they may be part of the same disease spectrum.[6-8] Regardless, both are rare causes of PAH that can be challenging to discriminate from other causes of PH. However, in humans, this discrimination is important as PVOD and PCH carry a grave prognosis and treatment for PAH with vasodilators can lead to acute deterioration and death from severe pulmonary edema.[9,10]

Given the paucity of veterinary literature on occlusive vascular diseases leading to PH, the main objective of our study was to report the clinical characteristics (signalment, historical clinical signs, physical examination findings, and diagnostic testing), treatments, and outcome of dogs with a histologic diagnosis of PVOD or PCH. Although a detailed histologic description of 11 of the dogs in our study has been previously published,[3] knowledge of the clinical presentation of PVOD and PCH in dogs will help increase suspicion for these syndromes, improve diagnosis and prognostication, and ultimately could promote future studies evaluating treatment interventions and investigation of underlying genetic or environmental triggers.

2 | MATERIALS AND METHODS

For our retrospective study, the sole inclusion criterion was histologic features of PVOD or PCH in canine lung tissue. A single author (K.W.) reviewed histopathology of lungs from 15 dogs with occlusive remodeling changes of the small-sized to medium-sized pulmonary veins (PVOD), alveolar capillary proliferation and congestion (PCH), or both from 2003 to 2017.[3] All lung tissues were evaluated by light microscopy after formalin-fixation, routine processing, and hematoxylin and eosin and Verhoeff-Van Gieson staining. In the current study, clinical case material includes 11 dogs from the previously published pathology study and 4 additional dogs. Dogs were evaluated at Michigan State University Veterinary Teaching Hospital (n = 5), primary care veterinary hospitals in Michigan (n = 3), University of Missouri-

Columbia Veterinary Health Center (n = 3), University of California-Davis Veterinary Medical Teaching Hospital (n = 2), Cummings School of Veterinary Medicine at Tufts University (n = 1), and The Royal Veterinary College, University of London (n = 1).

An attempt was made to review comprehensive medical records in each dog; however, some dogs had limited to no evaluation performed because of severity of clinical signs and perceived instability or sudden death. Clinical information gathered, when available, included signalment, body weight, types of respiratory and nonrespiratory clinical signs reported (acute and chronic), duration of respiratory distress when present, body temperature, results of thoracic auscultation, systolic blood pressure, hematologic and urine testing, coagulation testing, arterial blood gas and oxygen-hemoglobin saturation, thoracic imaging (radiography, echocardiography, and computed tomography [CT]), other ancillary testing, treatments, outcome, and survival time. When available, thoracic images were reviewed by board-certified radiologists (radiographs [N.N.] and thoracic CT images [I.M.]).

Thoracic radiographic evaluation was based on previously described methods.[11,12] When radiographs from multiple time points were available for a patient, the last set of radiographs were used for scoring evaluation. Briefly, increased pulmonary opacity was classified as unstructured interstitial, alveolar, or mixed interstitial/alveolar pattern. Distribution of pulmonary changes was classified as diffuse when all lungs were involved, focal when a single area of lung was involved or multifocal if multiple areas of lung were involved. Localization of focal or multifocal pulmonary patterns was determined as craniodorsal, cranioventral, caudodorsal, or caudoventral depending on the quadrant of lung involved on lateral projections. Pulmonary pattern was considered symmetric if the left and right lungs were equally affected, asymmetric otherwise. Size of the cardiac silhouette was evaluated subjectively. Blood vessel diameters were evaluated. Cranial lung lobe pulmonary vessels were considered normal if diameters were less than the width of the proximal one-third of the 4th rib.[11,13] Caudal pulmonary vessels were normal if diameters were less than the width of the 9th rib where they crossed.[11,13] Blood vessels were considered tortuous if any deviation from their expected course was identified. The presence of pleural fissures was recorded.

Thoracic CT images obtained from all 3 dogs at the University of Missouri were performed using a standardized protocol of inspiratory and expiratory breath holds with the assistance of a mechanical ventilator (Engstrom Carestation ventilator; GE Healthcare, Fairfield, CT). The volume-controlled ventilation setting was used, and tidal volume was set to 10 mL/kg, inspired oxygen at 40% and positive end-expiratory pressure at 5 cm H_2O. The positive end-expiration pressure was set to 0 cm H_2O for the expiratory scan. CT images were acquired with a 64-detector row Toshiba Aquilion scanner (Toshiba, America Medical Systems, Tustin, California) using 512 × 512 matrix, 120 kV, 500 mA, rotation time of 0.5/0.75 seconds, and either displayed at 0.5 mm (n = 2) or reconstructed to 3 mm (n = 1) slice thickness. Images were transferred to a PACS and viewed with Horos software, version v.1.0.7 (The Horos Project, Horosproject.org; sponsored by Nimble Co LLC d/b/a Purview, Annapolis, MD).

2.1 | Statistical methods

Because of the retrospective nature of our study and small sample size, data were analyzed descriptively, and when appropriate, the median and range were reported.

3 | RESULTS

3.1 | Signalment, historical signs, and physical examination findings

Fifteen dogs met the inclusion criterion. Dogs were of older age with a median of 11 years and a range from 8 to 16 years. Breeds included Australian Shepherd (n = 2), Golden Retriever (n = 2), German Shepherd/German Shepherd cross (n = 2), mixed breeds (n = 2), Labrador Retriever (n = 1), Goldendoodle (n = 1), Border Collie (n = 1), Greyhound (n = 1), Cairn Terrier (n = 1), Pomeranian (n = 1), and Beagle (n = 1). Nine dogs were female (8 spayed) and 6 dogs were male (all castrated). The median body weight was 25.4 kg (range, 4.6-37.5 kg). Of unknown clinical significance, one 9-year-old Australian Shepherd had 5 littermates that acutely died from respiratory disease, with 1 necropsy (unavailable for review) documenting pulmonary edema.

Clinical signs were reported to be present for a median of 3 days (range, 1-60 days). The most common presenting complaints associated with the respiratory tract included respiratory distress (n = 10), cough (n = 7), exercise intolerance (n = 3), and collapse (n = 2), serosanguinous nasal discharge (n = 1), increased respiratory effort (n = 1), and panting (n = 1). Of the 10 dogs with respiratory distress, all had an acute onset with a median of 1 day (range 0.5-3 days). Other historical clinical signs included anorexia (n = 5), lethargy (n = 3), weight loss (n = 2), an enlarged abdomen because of ascites (n = 1), and progressive pelvic limb lameness and pain (n = 1).

Results of physical examinations were not available in 4 dogs. Of the remaining dogs, normothermia was reported in 8, hypothermia (98.5 °F) in 1, and no recorded temperature in 2 dogs. Heart murmurs (grade II, n = 2; grade III, n = 5; grade IV, n = 1) were ausculted in 7 dogs, with 1 dog having both a grade II right-sided murmur and a grade III left-sided murmur. Auscultation of 1 dog with loud lung sounds did not allow determination of the presence of a heart murmur. Lung sounds were described as diffusely harsh or increased (n = 6) or as crackles (n = 3; diffuse in 2 and left cranioventral and right caudodorsal in 1). Systolic blood pressure measured in 5 dogs ranged from 100 to 168 mm Hg with a median of 136 mm Hg.

3.2 | Diagnostic testing

Limited hematologic data were available in a subpopulation of dogs using a variety of analyzers. Hematocrit was above the reference range in 3 of 11 dogs (56%, 60%, and 69%) for which values were recorded. The median hematocrit in 11 dogs was 52%, range 32%-69%, and in 7 dogs, the median neutrophil count was 11 900/μL (range 6200-16 080/μL). Hypoalbuminemia was reported in 9 dogs with a median of 2.5 g/dL (range 1.8-2.6 g/dL). Other abnormalities included increased (n = 3) or decreased (n = 1) blood urea nitrogen, decreased globulins (n = 3), increased creatinine (n = 2), increased

alanine aminotransferase (n = 2), increased alkaline phosphatase (n = 2), and increased total bilirubin (n = 1). Urine specific gravity was 1.015 in a single dog that had a concurrent urine protein to creatinine ratio of 2.4. Four dogs had coagulation profiles performed with no abnormalities in 3 dogs and increased fibrinogen, FDPs, D-dimers, and low antithrombin in 1 dog. Arterial blood gases were performed in 6 dogs, with a median PaO_2 of 47 and range of 33-71 mm Hg and a median $PaCO_2$ of 30 and range of 20-37 mmHg. In 6 dogs, pulse oximetry obtained while breathing room air showed a median hemoglobin saturation of 74% and ranged from 65% to 80%; 1 dog receiving supplemental oxygen (40%) had a hemoglobin saturation of 93%.

Thoracic radiographs were available in 10 dogs. Nine dogs had at least 1 lateral and orthogonal radiograph available; 1 dog had only lateral projections available. Right cardiomegaly was identified in all dogs. Four dogs had a prominent bulge in the cardiac silhouette corresponding to main pulmonary arterial enlargement. One dog had a mildly enlarged left atrium; however, in other dogs, the left cardiac silhouette was considered normal. Pulmonary vascular size, including the size of the pulmonary veins, was considered normal in 6 dogs. The remaining 4 dogs had mild enlargement of at least 1 peripheral pulmonary artery. One dog had a single, mildly tortuous pulmonary artery, and in all other dogs, the course of the pulmonary arteries was normal. All dogs had an abnormal pulmonary pattern (Figure 1). Four dogs had only a diffuse unstructured interstitial pattern, and 6 dogs had a mixed interstitial/alveolar pattern. In those 6 dogs with a mixed pattern, the unstructured interstitial pattern was diffuse and the alveolar component was either focal or multifocal over certain areas of the lung. The alveolar pattern affected the caudodorsal lung alone in 2 dogs, the caudodorsal/caudoventral lung in 1 dog, caudodorsal/cranioventral lung in 1 dog, caudoventral alone in 1 dog, and the cranioventral lung alone in 1 dog. The pulmonary pattern was symmetric between left and right lungs in 6 dogs and asymmetric in 3 dogs (symmetry could not be assessed in the dog with only lateral projections). Six dogs had multiple, thin pleural fissures noted between the peripheral aspects of the lungs.

Echocardiography performed in 7 dogs (abbreviated in 2 because of patient instability) most commonly revealed multiple abnormalities including evidence of right atrial enlargement (n = 6), right ventricular enlargement (n = 6), decreased chamber dimensions of the left ventricle (n = 4), dilated pulmonary arteries (n = 3), and distension of the caudal vena cava and hepatic vasculature with concurrent ascites (n = 1). There was no evidence to support left-sided heart disease as a cause of PH or pulmonary parenchymal changes in any of these dogs. PAPs in 5 dogs were estimated using continuous-wave Doppler assessment of peak tricuspid regurgitation, which in turn was used to calculate the pressure gradient between the right atrium and right ventricle using the modified Bernoulli equation. These estimated PAPs were 52, 84, 88, 117, and 150 mm Hg.

Paired inspiratory and expiratory thoracic CT images were interpreted in 3 dogs. Having both inspiratory and expiratory phases of respiration captured on CT scans allows for documentation of airway collapse (tracheal collapse, main stem or lobar bronchial collapse, bronchomalacia) and determination of the cause of a mosaic attenuation pattern (narrowing of distal airways with air trapping shows an accentuation of the mosaic pattern on expiratory scans). Nodular to
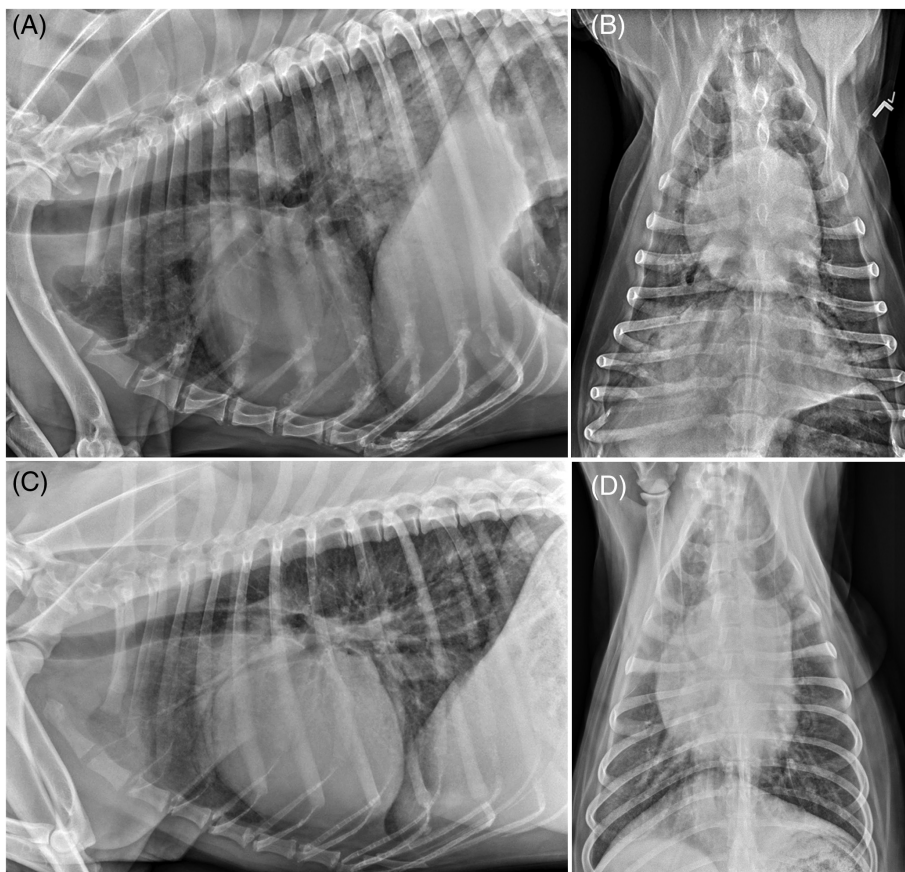
FIGURE 1   Lateral thoracic and dorsoventral radiographs of 2 dogs with pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis demonstrating abnormal pulmonary parenchymal patterns. (A, B) Twelve-year-old female-spayed Labrador displaying a diffuse-unstructured interstitial component with an alveolar pattern caudodorsally. (C, D) Nine-year-old female-spayed Goldendoodle demonstrating a diffuse-unstructured interstitial pattern only

ill-defined patchy ground-glass opacities (GGO) were seen in all lung lobes, the accessory lung lobe being the least severely affected lobe in 2 dogs (dogs 1 and 2; Figures 2A,B, 3A,B, and 4). The distribution of GGO lesions varied throughout the length and height of the thorax without any site of predilection in the 3 dogs. All 3 dogs also showed multifocal areas of complete opacification (Figures 2B, 3A, and 4) compatible with atelectasis or alveolar filling because of edema, hemorrhage, inflammatory cells, and so forth, and not limited to the dependent aspects of the lungs. Dog 1 had the most extensive GGO lesions varying in distribution from multifocal to diffuse, sparing only the cranial aspect of the cranial lung lobes and the accessory lung lobe being less affected. Both dog 1 and dog 2 had thickened pleural fissure lines, whereas all 3 dogs had subpleural interstitial thickening (Figure 2B). Irregular and nodular appearance of several bronchovascular bundles and dilatation of small airways (diameter <1 mm) were seen in dog 1 (Figure 2A) and dog 2. These 2 dogs also demonstrated corkscrew-like pulmonary arteries that were partially obscured by the severe GGO surrounding them (Figure 2C); in humans, corkscrew-like pulmonary arteries suggest plexogenic arteriopathy and have been associated with PH.[14] All 3 dogs had increased pulmonary trunk to aorta (both descending or ascending) ratio (>1.6 pulmonary trunk/ascending aorta; >2.0 pulmonary trunk/descending aorta), dog 3 having the smallest ratios (Figure 2D,E).[15] Dog 1 and dog 3 had normal pulmonary

artery to vertebral body height ratios, whereas dog 2 had an increased ratio of 0.87; although this has not yet been established in dogs, the normal ratio in cats is 0.57 ± 0.09.[16] Dog 2 also demonstrated occlusion of the right caudal lobar artery with a thromboembolus at the level of T8-T9 (Figure 3C,D) and distally and 2 incidental thin-walled cystic airspace lesions less than 7 mm in diameter. Both were considered comorbid conditions with a comparatively smaller impact on the clinical picture than PVOD/PCH. Dog 1 and dog 3 had reduction of lung volume and increased lung attenuation during exhalation suggesting normal air flow movement out of the airways and airway spaces during exhalation. Dog 2 had minimal change in lung volume and lung attenuation on the images taken at expiration compared to inspiratory images.

Other diagnostics included airway lavage (n = 4), testing for heartworm (n = 2), and in 1 dog each, fecal Baermann, screening for *Borrelia/Ehrlichia/Anaplasma*, abdominal radiography, abdominal ultrasonography, pro-BNP, urine culture, urine blastomyces antigen, lung fine-needle aspiration cytology, and culture and fluoroscopy. Results of aforementioned infectious disease testing were negative, abdominal imaging was unremarkable, Pro-BNP was increased at 1210 (reference range, 0-900 pmol/L), lung fine-needle aspiration cytology showed mixed inflammation with a small population of abnormal epithelial cells with some criteria of malignancy, and fluoroscopy revealed near complete main stem bronchial collapse during cough.
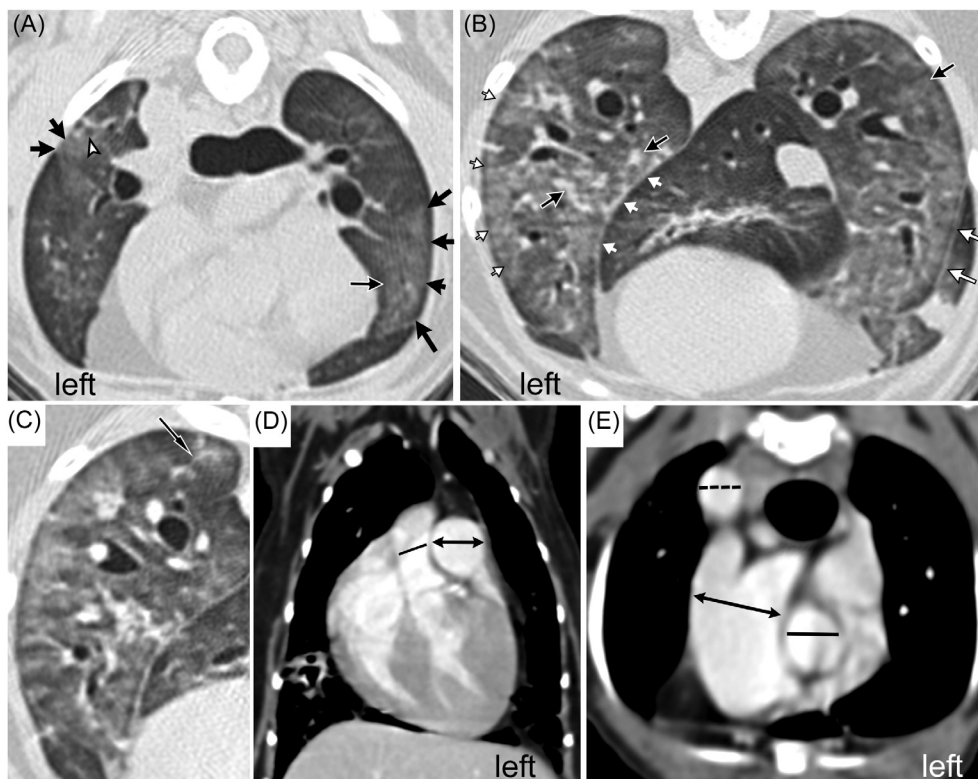
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FIGURE 2 Sixteen-year-old female-spayed Cairn Terrier with pulmonary capillary hemangiomatosis. Computed tomography (CT) transverse images at the level of the mid (A) and caudal (B) thorax demonstrating marked multifocal ground-glass opacification (GGO) characterized by nodular opacities (small white arrows) to patchy ill-defined areas (black arrows) affecting most lung lobes. Small airways (<1 mm) were occasionally dilated (arrowhead) as shown in the dorsal aspect of the cranial subsegment of the left cranial lung lobe. Several small areas of complete opacification (small black arrows with white outline) were also observed in the mid-level to ventral aspect of the caudal lung lobes. Pleural fissure lines were also mildly thickened (large white arrows). (C) Transverse CT image demonstrating a corkscrew-like pulmonary artery (black arrow) surrounded by GGO. Horizontal (D) and transverse (E) post-contrast images displayed in a soft tissue window and level highlighting the pulmonary trunk (double extremity arrow) in relation to the aorta (ascending: plain line; descending: dotted line). Measurements were made at the level of these lines where applicable

Airway lavage in 2 dogs showed hemosiderophages and nondegenerative neutrophils; in 1 dog, a light growth of *Rothia mucilaginosa* was noted and was negative in the other culture. In a 3rd dog, cytology showed low number of yeast and intracellular and extracellular cocci with pyogranulomatous inflammation and a small amount of blood. Bacterial culture revealed mixed growth of *Moraxella* sp., *Pasteurella* sp., nonhemolytic *Streptococcus* and *Mycoplasma canis* with no growth on fungal culture. In the final dog, results showed mild neutrophilic inflammation and a negative culture.

3.3 | Treatment and outcome

Treatment was attempted in 12 dogs with dogs receiving between 1 and 7 simultaneous or sequential treatments. Treatment included supplemental oxygen (n = 10), sildenafil (n = 6), furosemide (n = 3), antibiotics (n = 3), bronchodilators (n = 3), intravenous fluids (n = 2), glucocorticoids (n = 2), and in 1 dog each, nitroglycerin paste, pimobendan, itraconazole, butorphanol, tramadol, maropitant, hydrocodone, and carprofen. Three dogs had repeat measures of their PAPs using echocardiography after administration of a vasodilator with or without miscellaneous treatments. Two dogs had decreased PAPs: 1 dog treated with sildenafil had a decrease from 88 mm Hg to 40-50 mm Hg and lived 42 days, and the other dog treated with

sildenafil and pimobendan had a decrease from 117 to 66 mm Hg and lived 150 days. The 3rd dog treated with sildenafil had an increase from 150 to 155 mm Hg and was euthanized within a day. Three other dogs treated with sildenafil did not have repeat measures of PAPs; the outcome was euthanasia within hours, 2 days, and after 32 days, respectively. Overall prognosis was grave with a median survival time of 3 days. Most dogs died or were euthanized less than 1 day after presentation (n = 10), with the remaining dogs living 2, 3, 32, 42, and 150 days. Euthanasia was performed in 10 dogs, and spontaneous death occurred in 5 dogs.

Histopathologic specimens were procured after complete necropsy or postmortem lung sampling (n = 14) or antemortem lung biopsy (n = 1). Grossly, affected lungs were diffusely edematous and showed numerous, coalescing, pinpoint to several millimeters, typically sharply demarcated, red foci scattered throughout the parenchyma that correlated histologically with foci of PCH, congestion, and/or alveolar hemorrhage (Figure 5). Primary histologic lesions included remodeling of small-sized to medium-sized veins with luminal occlusion by endothelial cells, smooth muscle cells, and/or fibrous connective tissue (PVOD) (Figure 6) and foci of dilated, proliferative capillaries that expanded alveolar septa and occasionally infiltrated pulmonary vessels or airways (PCH). The remodeling of PVOD was more readily apparent with Verhoeff-Van Gieson staining (Figure 6B),
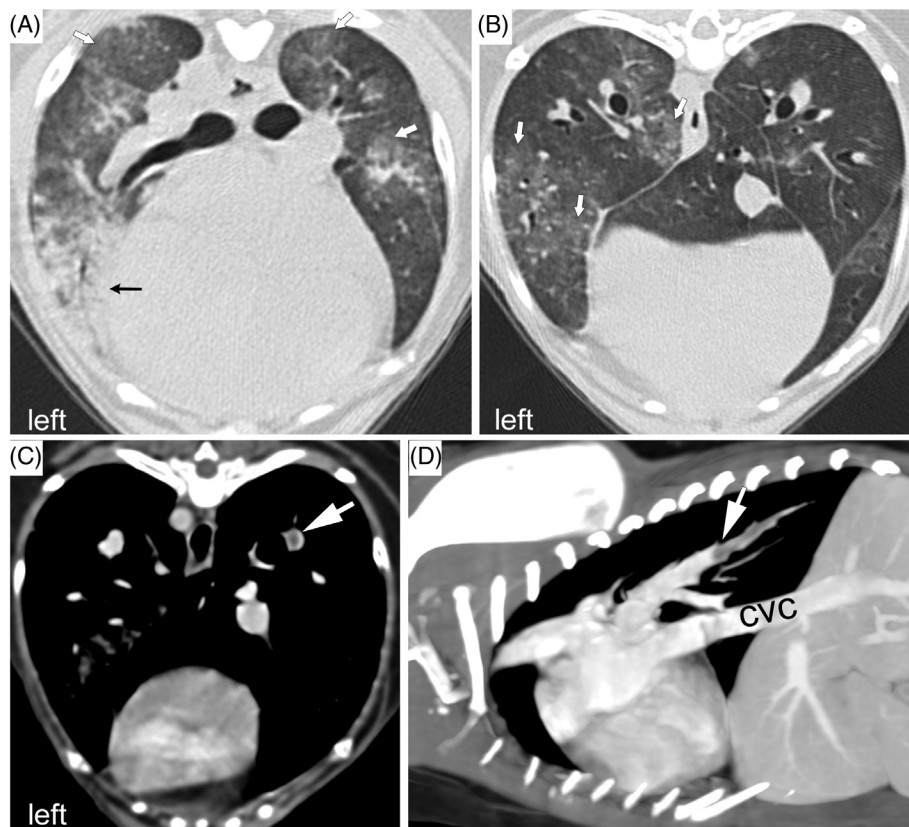
FIGURE 3   Ten-year-old female-spayed Pomeranian with pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis, and pulmonary thromboembolic disease. Computed tomography (CT) transverse images at the level of the mid (A) and caudal (B) thorax demonstrating moderate multifocal ground-glass opacification mostly characterized by nodular opacities and occasional patchy ill-defined areas affecting most lung lobes (white arrows). Several small areas of complete opacification were also observed in the mid-level to ventral aspect of the caudal lung lobes as shown in the caudal subsegment of the left cranial lung lobe (black arrow). Transverse (C) and maximal intensity projection sagittal post-contrast CT images (D) displayed in a soft tissue window illustrating a pulmonary thromboembolus in the right caudal lobar pulmonary artery (white arrow). Abbreviation: CVC, caudal vena cava

which highlighted the elastin fibers of the external elastic lamina of pulmonary veins, both demarcating the borders of the occlusive lesions and aiding in differentiating pulmonary veins from pulmonary arteries, the latter of which possess external and internal elastic laminae. Secondary histologic lesions included pulmonary edema, alveolar hemorrhage, hemosiderophages, and pulmonary arterial intimal and medial thickening. The final pathologic diagnosis was PVOD in 14 dogs (all with at least some degree of PCH) and PCH alone in 1 dog.

4 | DISCUSSION

In the dog, PVOD and PCH represent 2 newly described vaso-occlusive disorders leading to severe PH, respiratory compromise, and ultimately, death. An acute onset of respiratory distress is a sequel to many disorders of the cardiopulmonary system; however, in the context of thoracic radiographic evidence of enlarged pulmonary arteries and an interstitial or alveolar pattern, PVOD and PCH should be differentials. The cases represented herein had a rapid progression with a median survival of 3 days after presentation, likely corresponding to advanced remodeling lesions of the pulmonary vasculature. In human medicine, PVOD and PCH generally have a more insidious onset with progressive disease, although sudden death has been reported.[17]

Although 1 study of 35 humans documented a mean duration of clinical signs before diagnosis of 49 months (range, 0-480 months) for PVOD and 71 months (range, 0-168 months) for PCH,[17] most studies describe survival after onset of clinical signs of 2-3 years.[18,19] With increased recognition of canine PVOD and PCH as causes for PAH, discrimination from other causes of PH and ultimately earlier diagnosis may be possible in the future. Whether this will be possible using the collective clinicopathologic picture in conjunction with the unique CT scan features, or whether an invasive but definitive lung biopsy would be required, remains to be seen.

Classification schemes for PH based on clinical features, hemodynamic characteristics, and other pathologic findings are important not only in understanding pathophysiology and in potential underlying causes but also in prognostication and investigating optimal management strategies. A classification scheme for PH in the dog has been previously proposed with 5 categories: PAH, PH with left-sided heart disease, PH with pulmonary disease or hypoxia, PH due to thrombi or emboli, and PH due to miscellaneous disorders.[1] The 1st category, PAH, includes idiopathic PAH (pulmonary arteriopathy), acute necrotizing pulmonary arteritis, PAH secondary to heartworm disease (exclusive of effects from thromboemboli or eosinophilic pneumonia), PAH secondary to congenital systemic-to-pulmonary vascular shunts, and, in parallel with the human classification scheme,[2] should now
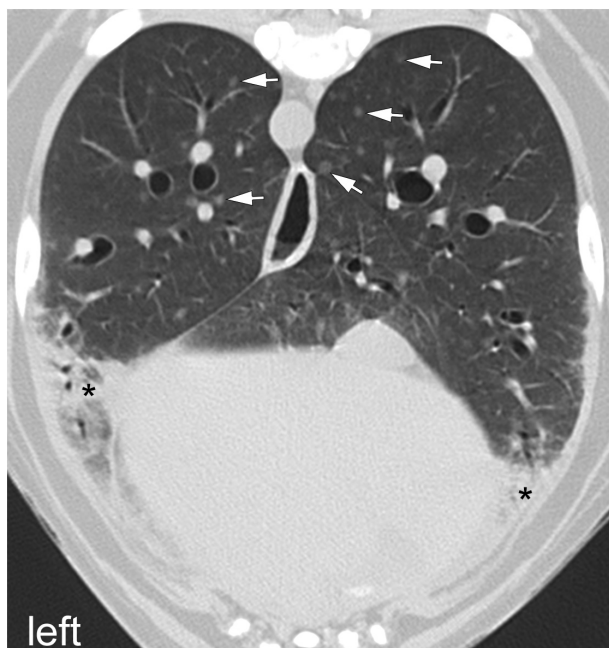
FIGURE 4 Nine-year-old female-spayed Goldendoodle with pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis. Computed tomography transverse image displayed in a lung window taken at the level of the caudal thorax demonstrating marked multifocal ground-glass opacification characterized nodular opacities (white arrows) of variable size and located in a random fashion throughout the parenchyma. Complete opacification suggesting atelectasis, consolidation or hemorrhage was consistently visible in the dependent aspect of the lungs in this dog (asterisk)

include PVOD and PCH.[1,20–25] Although PVOD and PCH primarily affect veins and capillaries, respectively, they are also associated with pulmonary arterial lesions (eg, intimal fibrosis and medial hypertrophy) and clinically manifest as PAH in both humans and dogs.[6] Diagnosis of PAH initially relies on ruling out disease mimics and confirming PH. Thoracic radiography can confirm pulmonary arterial enlargement and right-sided cardiac changes and help rule out left-sided cardiac disease. The type of lung pattern and appearance of the pulmonary vessels can tailor the differential list and guide additional testing (eg, serology for relevant infectious agents, targeted diagnostics for hypercoagulability). Inspiratory and expiratory cervical and thoracic views can be used to assess large airway collapse that may contribute to hypoxia. Alternatively, fluoroscopy can be a useful modality for dynamic upper and lower airway caliber changes. Echocardiography is required to document and when possible, estimate PH; is more definitive to show the presence or absence of left-sided heart disease contributing to PH; and could show thrombi or emboli. Arterial blood gas provides information on lung function including oxygenation and ventilation; a widely available, less invasive surrogate, pulse oximetry, provides a measure of hemoglobin oxygen saturation. Thoracic CT scans, especially if inspiratory and expiratory, can document airway caliber changes; determine the pattern, distribution, and location of lesions; and help determine if mosaic attenuation is due to air trapping versus primary lung or vascular disease causing increased opacity. Standard contrast may highlight areas of increased vascular permeability (eg, neoplasia, inflammation), whereas triphasic angiography can be used to detect PTE. Airway

cytology (fine-needle aspiration or bronchoalveolar lavage) could reveal evidence of infection or neoplasia or have nonspecific findings. Anesthetized airway examinations may provide complimentary data for obstructive airway disorders (eg, functional laryngeal/upper airway exam; tracheobronchoscopy). Lung biopsy is currently the only definitive means to diagnose PVOD and PCH and many interstitial lung diseases; it is also useful when the other aforementioned less invasive diagnostics have failed to reveal a definitive answer. Importantly, the risk of thoracotomy and biopsy needs to be carefully weighed against benefit of definitive diagnosis, and the goal is to identify a treatable underlying lung disease, so that it can be effectively managed.

One of the most common causes of PH in dogs is left-sided heart failure, generally caused by myxomatous mitral valve disease (MMVD).[26–28] This disorder predominantly occurs in small breed dogs, with PH developing as a continuum of heart disease progressing to heart failure.[26] An emergent presentation of a small breed dog in respiratory distress, with a left-sided systolic heart murmur, radiographic evidence of cardiac enlargement and pulmonary edema, and increased PAP would almost certainly be caused by MMVD. However, increased PAP in the absence of left-sided heart failure requires consideration of other differential diagnoses, including canine PVOD and PCH. Although to a certain degree all diseases associated with PH in dogs are generally considered to have a poor prognosis,[1] there is still marked variation in outcomes and survival. For example, one study in dogs with MMVD with PH documented a median survival time of 456 days.[26] In contrast, 10 of 15 (66%) dogs in our study survived less than 1 day.

All the dogs in our study were adults older than 8 years of age (median 11 years), which is in contrast to humans with PVOD who are predominantly young to middle-aged, although affected ages range from infancy to older than 70 years old.[6,7,17,19] Failure to identify PVOD and PCH in puppies and young to middle-aged dogs may be due to the lack of recognition, not the lack of the absence of these conditions, and deserves further study. There was no sex or breed predilection identified, perhaps, because of the small number of dogs

FIGURE 5 Postmortem image of the lungs from the 9-year-old female-spayed Goldendoodle with pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis (PCH). The lungs failed to fully collapse upon loss of negative intrathoracic pressure and contain numerous, often coalescing superficial red foci that correspond to histologic evidence of the angiomatous lesions of PCH. These foci also corresponded to ground glass opacity nodules on the computed tomography scan
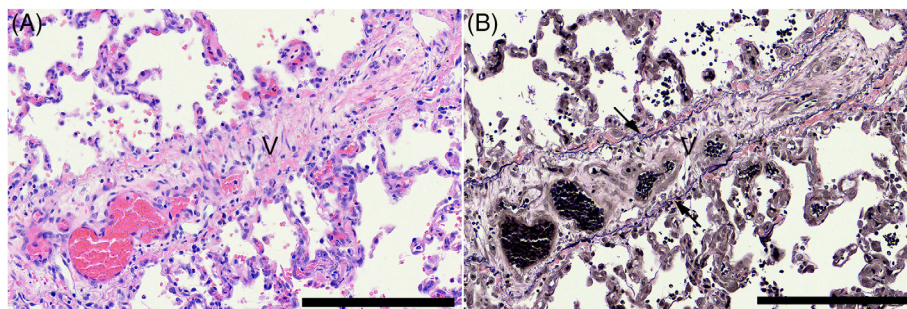
FIGURE 6 (A, B) Serial sections of a remodeled pulmonary vein from a 12-year-old male-castrated Golden Retriever with pulmonary veno-occlusive disease using hematoxylin and eosin (A) and Verhoeff-Van Gieson staining (B). The lumen of the vein (v) is markedly filled with tortuous vascular profiles and spindle cells in both images. The purple-black staining (black arrows) of the external elastic lamina in (B) confirms that this is a pulmonary vein and highlights the luminal orientation of the remodeling. Bar in both images = 200 μm

in our study. Most dogs were of larger body size with multiple breeds affected. In humans, a genetic risk for PVOD and PCH has been documented.[29–32] Aside from heritable genetic mutations, known predisposing factors for PVOD in humans include chemotherapeutics, exposure to organic solvents, bone marrow or stem cell transplants, neoplasia, connective tissue disorders/autoimmune diseases, sarcoidosis, HIV infection, and pulmonary Langerhans cell histiocytosis (reviewed in References 6, 7, and 10). In comparison, there are no clear-cut risk factors for PCH aside from genetic factors.[6] Because of the retrospective and multi-institutional nature of our study, putative exposures leading to canine PVOD or PCH were not assessed.

Results of complete blood counts, serum biochemical profiles, and urinalyses were generally nonspecific, and abnormalities could have been due to comorbid conditions. Development of polycythemia (27%; 3/11 dogs) is considered a chronic change and might suggest a more protracted clinical course than was suggested by their owners. Hypoxemia was noted in all dogs in which it was measured, consistent with reports in humans.[6,19] Echocardiography frequently revealed evidence of changes to the right side of the heart, consistent with increased workload caused by remodeled and occluded pulmonary vessels. Although not all dogs received an echocardiographic examination, for the 7 dogs that did, there was direct or indirect evidence of PH. Ancillary testing aimed at identifying underlying cardiac and respiratory disorders failed to reveal an antemortem diagnosis. Airway lavage was misleading in 1 dog with evidence of a yeast and bacterial infection that ultimately led to lung biopsy. In 2 other dogs, hemosiderosis was a notable finding. Chronic alveolar hemorrhage from engorgement of fragile pulmonary capillaries leads to hemosiderin-laden macrophages in airway lavage and sputum of humans with PVOD and PCH.[8,18,33,34] Congestive heart failure is another differential for hemosiderin-containing pulmonary macrophages[35] potentially adding confusion to the diagnostic evaluation of a dog with acute onset of respiratory distress, PAH, and radiographic changes supportive of pulmonary edema. Of note, based on histopathologic examination of the lung, several of the dogs in this report were initially diagnosed with congestive heart failure; use of special stains to highlight and differentiate pulmonary arteries and pulmonary veins was required for definitive diagnosis.[3]

Antemortem diagnosis of canine PVOD or PCH will need to start with an awareness of the existence of these syndromes. Most dogs presented for an acute onset of respiratory distress (with or without concurrent cough, exercise intolerance or collapse). Harsh lung sounds and, in particular, crackles may lead to a suspicion of pulmonary edema; heart murmurs were noted in most dogs for which physical examination results were available. Thoracic radiography is a critical initial diagnostic test to try to discriminate between cardiac and respiratory causes of the clinical signs. The most common radiographic findings included the presence of an interstitial or alveolar pattern often caudodorsal in distribution and enlargement of the pulmonary arteries with right cardiomegaly. Although left-sided cardiac disease was present in 1 dog, it was disproportionate to the clinical signs and ultimately failed to respond to treatment for congestive heart failure. Despite clear-cut evidence of a lack of left cardiomegaly in nearly all dogs, the other clinical and radiographic features were commonly but incorrectly initially interpreted as left-sided congestive heart failure. PTE would be a more viable differential diagnosis amenable to testing for hypercoagulability and use of advanced imaging. The use of Doppler echocardiography, a noninvasive surrogate for the gold standard diagnostic test of cardiac catheterization for direct measurement of PAP indicated moderate to severe PAH in all dogs tested. The absence of echocardiographic indicators of severe enough changes of left-sided heart disease to explain PAH (noted in all dogs tested) should increase suspicion for PVOD and PCH. The major echocardiographic findings in the dogs of this report aside from PAH supported decreased right-sided cardiac output and reduced left-sided preload secondary to PAH.

High-resolution CT in humans correlates well with histopathologic features of pulmonary vascular disease and serves as a noninvasive surrogate for lung biopsy that is particularly important in fragile patients.[14] Although lung biopsy could be considered, it would be risky in these unstable patients. From a veterinary perspective, CT may provide valuable information in dogs with an acute onset of respiratory distress, interstitial or alveolar patterns on thoracic radiography, and evidence of PAH without substantial left-sided cardiac disease evaluated using echocardiography. Major differentials for canine PH in this scenario would include PTE (because of a variety of causes, including but not limited to hypercoagulable states and neoplastic or parasitic emboli), interstitial lung disease, non-cardiogenic pulmonary edema, and causes of PAH (idiopathic PAH, PVOD, and PCH).[36,37] The authors are unaware of any studies to date evaluating the CT characteristics of dogs with spontaneous idiopathic PAH, PVOD, or PCH, and only a single case report describes CT features in a cat with a vasoproliferative disorder resembling PCH.[38]

In humans with idiopathic PAH, in addition to dilatation of the central, right, and left main pulmonary arteries and right-sided cardiac changes, the presence of tortuous corkscrew-like peripheral pulmonary arteries reflects the hallmark plexogenic arteriopathy lesions.[14] While sharing dilatation of the pulmonary arteries and pathology of the right chambers of the heart, CT lesions of PVOD and PCH have other unique features including centrilobular GGO.[39] Centrilobular GGO reflect increased capillary blood volume, thickening of interstitial tissues, airspace fluid accumulation, and alveolar collapse.[40,41] In humans with PVOD, widespread smooth thickening of interlobular septa in combination with centrilobular GGO helps to discriminate these conditions from other causes of PH.[42] On a microscopic level in human PVOD, occluded interlobular septal veins are reflected by CT evidence of interlobular septal thickening; centrilobular GGO are caused by upstream congestion of capillaries, concurrent lesions of PCH, or both.[8] In PCH, discrete areas of capillary proliferation can cause widespread poorly circumscribed centrilobular GGO; typically, this occurs without interlobular septal thickening, as the interlobular septal veins are unaffected.[8] In humans, larger centrilobular GGO nodules are seen with PCH compared with PVOD.[39] As dogs lack interlobular septa and secondary pulmonary lobules, interlobular pathology as seen in humans is not noted and the term "centrilobular" is not an appropriate descriptor. However, 2 dogs in our study having CT scans had GGO in a location analogous to the centrilobular position, which were similarly sized and equally distant from each other. The 3rd dog had more random distribution of GGO nodules.

The value of thoracic CT in dogs with suspect PVOD or PCH is not only to rule out other diseases with similar clinical presentations but also, as is critical in humans, to help guide the treatment. Although treatment with pulmonary vasodilators can improve the survival times of humans with idiopathic PAH and dogs with other forms of PH,[1,36,43,44] fatal or life-threatening pulmonary edema may result in cases of PVOD or PCH when there is relative vasodilatation of the precapillary resistance vessels with fixed resistance at the level of the capillaries or venules.[8,34] Oral administration of sildenafil to a cat with PCH-like disease was speculated to cause acute massive pulmonary edema that ultimately contributed to death.[38] Adverse response to vasodilators is not always immediate, with one study of 24 human cases of PVOD showing 9 days as the median time from the start of treatment to development of pulmonary edema (range, 1-240 days).[19] Of interest, a retrospective study using sildenafil for 13 dogs with PH (of which an underlying cause of PH was not determined in 5 cases and was deemed "idiopathic"), 3 dogs were euthanized with a day of initiating treatment because of severe respiratory distress.[43] It would be tempting to speculate that these dogs could have had PVOD or PCH. Although in the current study PAPs decreased in the 2 dogs treated with pulmonary vasodilators with the longest survivals, there were 3 dogs treated with sildenafil that were euthanized within 1-2 days. Thus it may be inappropriate to assume that vasodilators are harmful in these dogs as they are in humans, and further studies will be needed to draw conclusions about the role of vasodilators in management of canine PVOD or PCH.

The only definitive treatment for PVOD or PCH in humans is lung transplantation. Otherwise, as in dogs, these are fatal diseases. A presumptive diagnosis of PVOD or PCH based on clinical presentation, echocardiography, imaging (in particular CT scans), and other ancillary tests as deemed relevant provides important prognostic information about this grave condition, with most dogs dying within days of presentation regardless of attempted treatment. It is presently unknown if pulmonary vasodilators are harmful or helpful in these dogs, in contrast to the use of these medications for canine PH secondary to MMVD, non-cardiogenic pulmonary edema, and chronic respiratory diseases.[26,36,43,44] In conclusion, awareness of PVOD and PCH in dogs as newly described vaso-occlusive disorders causing severe PAH will be required for future investigation of genetic or environmental triggers and optimal treatment strategies. Given the striking similarities in clinicopathologic features, histologic characteristics, and grave outcome shared with human PVOD and PCH, these disorders have relevance for one health.

CONFLICT OF INTEREST DECLARATION

The histopathologic features of some of the dogs in this report were previously published: Williams K, et al. *Veterinary Pathology*. 2016;53 (4):813-822.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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