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Authors

Raleigh, Joseph S
Culp, William TN
Brady, Rachel
et al.

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CASE REPORT

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Biopsy of an intracardiac paraganglioma in a dog using a fluoroscopically guided endovascular technique

Joseph S. Raleigh[1] | William T. N. Culp[2] | Rachel Brady[1] | Sami Al-Nadaf[2] |
Michael S. Kent[2] | Joanna L. Kaplan[1] | Joshua A. Stern[3] | Lance C. Visser[3] |
Kevin D. Niedringhaus[1] | Tatiana G. Wolf[1] | Eunju Choi[4] | Verena K. Affolter[4]

[1]Veterinary Medical Teaching Hospital, University of California-Davis, Davis, California

[2]Department of Surgical and Radiological Sciences, University of California-Davis, Davis, California

[3]Department of Medicine and Epidemiology, University of California-Davis, Davis, California

[4]Department of Pathology, Microbiology, and Immunology, University of California-Davis, Davis, California

Correspondence
William T. N. Culp, University of California-Davis, School of Veterinary Medicine, One Garrod Drive, Davis, CA 95616.
Email: wculp@ucdavis.edu

Abstract

A 10-year-old female spayed mixed breed dog was evaluated for diarrhea and vomiting. Diagnostic imaging demonstrated the presence of an intracardiac mass. A modified Seldinger technique was used to access the right jugular vein, and an endomyocardial biopsy forceps was introduced through a sheath to obtain several biopsies. Histopathology and immunohistochemistry demonstrated a paraganglioma. The dog underwent 1 fraction of radiotherapy and L-asparaginase chemotherapy and was discharged. The dog developed a pulmonary thromboembolism 2 days after radiotherapy and chemotherapy, and the owner elected humane euthanasia. Although long-term assessment of treatment response was unable to be performed, this novel diagnostic option could be considered for similar cases due to success in obtaining a histopathologic diagnosis, which is essential in developing a disease-specific treatment plan. This report also describes the use of radiotherapy for primary treatment of an intracardiac neoplasm, which can be a consideration in the future.

KEYWORDS
atrium, cardiac, chromaffin, endomyocardial, neoplasia, reproductive tract, surgery, theriogenology

1 | CASE DESCRIPTION

A 10-year-old female spayed mixed breed dog, weighing 24.5 kg was evaluated at the University of California-Davis, Veterinary Medical Teaching Hospital (UCD-VMTH) for acute diarrhea and vomiting of less than 1-day duration. The only additional clinical sign reported by the owners was an intermittent dry and nonproductive cough that had been present for 4 days before evaluation. The dog had a history

of bilateral elbow osteoarthritis and was receiving gabapentin 12.2 mg/kg (5.6 mg/lb) PO q8h and amantadine 12.2 mg/kg (5.6 mg/lb) PO q24h.

On physical examination, the dog was bright, alert, and responsive. Temperature [102.4 °F (38.6°C); reference range, 100.5 °F-102.5 °F] and pulse rate (120 bpm; reference range, 80-120 bpm) were within normal limits and the dog was panting. No murmurs or respiratory abnormalities were noted upon thoracic auscultation. The cardiac rhythm was regular. Femoral pulses were considered weak.

The abdomen was soft and nonpainful on palpation. The body condition score was 5/9.

Clinical laboratory testing included CBC, biochemistry panel, and urinalysis. The CBC demonstrated a leukocytosis of 14 800 cells/μL (reference range, 6000-13 000 cells/μL) and neutrophilia of 12 580 cells/μL (reference range, 3000-10 500 cells/μL). The biochemistry panel revealed multiple abnormalities including hypernatremia (154 mmol/L; reference range, 143-151 mmol/L), hyperkalemia (5.1 mmol/L; reference range, 3.6-4.8 mmol/L), hyperphosphatemia (5.7 mg/dL; reference range, 2.6-5.2 mg/dL), low bicarbonate (19 mmol/L; reference range, 20-29 mmol/L), increased ALT (84 IU/L; reference range, 21-72 IU/L), and increased alkaline phosphatase (153 IU/L; reference range, 14-91 IU/L). A blood test for vector-borne diseases was negative. The urine specific gravity was 1.015.

Thoracic radiographs revealed a roughly normal cardiac silhouette, normal in height but largely obscured by pleural fluid. No definitive pulmonary soft tissue nodules were noted. A moderate volume of peritoneal effusion and decreased serosal detail were noted.

An abdominal ultrasound (Philips iE 33 Ultrasound, Philips Healthcare Solutions, Andover, MA) identified a markedly enlarged liver, rounded, and hyperechoic with innumerable hypoechoic nodules and masses throughout all lobes. There was a heterogeneous splenic mass measuring ~5 cm in diameter. Moderate peritoneal and mild pleural effusion were confirmed. The hepatic veins were distended and the caudal vena cava did not change size significantly with respiration. Fine-needle aspiration of the liver and spleen was performed and no cytologic abnormalities were noted. Fine-needle aspiration and analysis of abdominal fluid revealed a total nucleated cell count of 3160/μL and a total protein of 5.3 g/dL, consistent with a low cellularity suppurative (predominantly nondegenerate neutrophils) exudate; no microorganisms were noted.

Based on the abovementioned imaging findings, an echocardiogram (Philips iE 33 Ultrasound, Philips Healthcare Solutions, Andover, MA) was recommended (Figure 1). An approximately 4.44 cm × 4.10 cm mass lesion extending from the atrial side of the tricuspid valve and expanding predominantly into the right atrium was noted. There was aliasing on color Doppler across the tricuspid valve both because of obstruction of inflow into the right ventricle and tricuspid regurgitation. Interventricular septal flattening was noted predominantly in diastole consistent with right-sided volume overload likely due to the obstructive mass and resultant tricuspid regurgitation. Treatment with furosemide 1 mg/kg (0.45 mg/lb) PO q12h and pimobendan 0.3 mg/kg (0.14 mg/lb) PO q12h was initiated. Gabapentin and amantadine were continued as previously prescribed.

The following day, the dog underwent surgery for splenectomy, liver, and lymph node biopsies, and to obtain fluoroscopically guided endovascular biopsies of the intracardiac mass. The dog was administered pre-anesthetic medications of hydromorphone 0.05 mg/kg (0.02 mg/lb) IV and maropitant 1 mg/kg (0.45 mg/lb) IV. The dog was induced with etomidate 0.65 mg/kg (0.30 mg/lb) and diazepam 0.5 mg/kg (0.23 mg/lb) administered IV. A standard midline celiotomy and abdominal exploration were performed. A hilar splenectomy was performed with a vessel-sealing device (LigaSure, Medtronic,
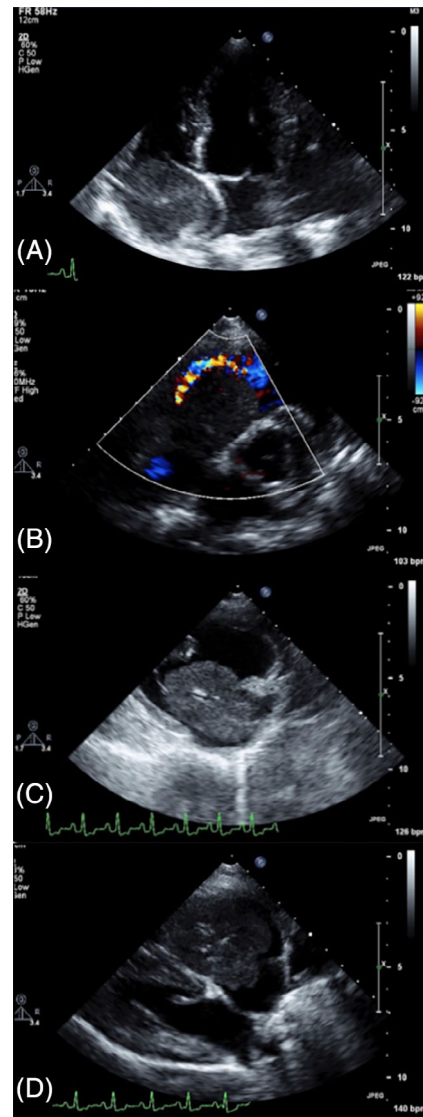

FIGURE 1 Transthoracic echocardiographic images of the right atrial mass. A, A 2-dimensional (2D) left apical 4-chamber view showing a mass expanding from the tricuspid valve to the roof of the right atrium. B, A 2D right parasternal short axis view at the level of the heart base with color Doppler shows turbulent flow along the margins of the obstructive mass. C, A 2D left cranial view of the right auricle showing the mass expanding into the right auricle. (D), A 2D right parasternal long-axis 4-chamber view showing the right atrial mass occupying the majority of the right atrium

Minneapolis, MN), and biopsies of the liver and a mesenteric lymph node were obtained routinely.

A stab incision was made into the skin overlying the right jugular vein. Using a modified Seldinger technique, an 18-gauge over-the-needle catheter (Becton, Dickinson and Company, Franklin Lakes, NJ) was introduced into the jugular vein and the needle was removed. A 0.035 in. × 150-cm long hydrophilic guidewire (Weasel Wire, Infiniti Medical, Redwood City, CA) was introduced into the catheter. A 7 Fr. dilator (Dilator, Infiniti Medical, Redwood City, CA) was placed over the 0.035 in. hydrophilic guidewire and then

removed. A 9 Fr. vascular access sheath with dilator (Introducer Sheath and Dilator, Cordis Medical, Santa Clara, CA) was introduced into the jugular vein over the guidewire. The dilator was removed, and the sheath was sutured to the skin with 3-0 nylon (Ethilon, Ethicon US, LLC, Bridgewater, NJ). The guidewire was passed beyond the heart into the caudal vena cava, and a 5 Fr. pigtail catheter (Cook Medical, Bloomington, IN) was introduced to the level of the cranial vena cava and used to measure central venous pressures; the pressure immediately cranial to the atrium was 17 mmHg. An angiogram was then subsequently performed through the pigtail catheter by injecting a mixture of 50% saline/50% contrast medium (Isovue-370, Bracco Diagnostics Inc., Princeton, NJ) to identify the mass and evaluate blood flow through the heart. Blood flow was clearly attenuated through the atrium, and an extended period of time (significantly longer than expected) was noted for the contrast medium to pass through the right heart to the pulmonary vasculature. The azygos vein was also notably dilated. The pigtail catheter was then removed, and the guidewire was manipulated into the right atrium. A 6 Fr. × 55 cm long sheath/dilator (Flexor Ansel Guiding Sheath, Cook Medical, Bloomington, IN) was introduced over the guidewire and into the right atrium. The dilator was removed, and a 5.5 Fr. endomyocardial biopsy forceps (Biopsy Forceps, Cordis Medical, Santa Clara, CA) was introduced into the right atrium through the sheath and directed toward the location of the intracardiac mass (Figure 2). Once engaged, 3 separate samples were collected for histopathology, culture, and an impression smear. Fluoroscopy during and after biopsy collection showed no evidence of hemorrhage (no contrast extravasation before or after biopsy). Intermittent, transient ventricular tachycardia resulted when the guidewire and sheath combination were in contact with the mass, or introduced into the right ventricle, particularly when the caudal wall was engaged. After biopsy collection, the sheath was removed over the guidewire and a 7 Fr. × 20 cm long triple-lumen catheter (MILACATH, MILA International, Inc., Florence, KY) was introduced into the cranial vena cava over the guidewire. After placement, the guidewire was removed. The triple-lumen catheter was sutured to the skin. Total anesthesia time was 278 minutes, and surgical time was 180 minutes with endovascular biopsy time approximating 45 minutes.

Expedited cytology was inconclusive and consistent with lymphoid hyperplasia. Aerobic/anaerobic culture results were negative. Histopathology revealed that the splenic mass was consistent with extramedullary hematopoiesis and venous congestion, liver parenchyma was consistent with severe subcapsular and centrilobular lymphatic dilation, and acute sinusoidal congestion with hepatocellular atrophy, and mesenteric lymph node findings were indicative of reactive hyperplasia. Two 2-mm-diameter tissue fragments of the cardiac mass were composed of small clusters of round cells separated by bland, acellular, vascular stroma (Figure 3A). Most cells had oval nuclei with stippled chromatin and a moderate amount of variably lacy cytoplasm. Mild anisocytosis and anisokaryosis and no mitotic figures were observed in ten 2.37 mm^2 fields. Immunohistochemistry revealed CD45-negative, CD18-negative, strongly synaptophysin positive tumor cells most suggestive of a diagnosis of paraganglioma (Figure 3B).
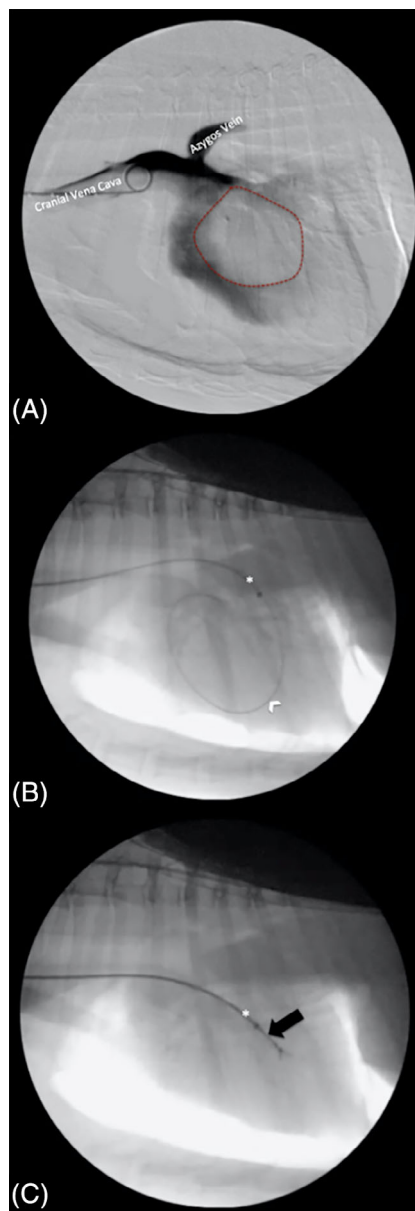

FIGURE 2 Fluoroscopic images obtained during a procedure to obtain a transvenous biopsy of an intracardiac mass. A, The dog is in right lateral recumbency, and a digitally subtracted image has been obtained during an angiogram. The contrast medium has been injected through a pigtail catheter placed in the cranial vena cava, and a filling defect in the right atrium because of a mass (marked by dashed line) can be seen. B, An endovascular sheath (*) has been introduced into the cranial vena cava and the right atrium over a guidewire (white arrow) through an access point in the right jugular vein. C, The guidewire has been removed, and an endomyocardial biopsy device (black arrow) has been introduced through the sheath (*) and is being pushed into the tumor. The jaws of the biopsy device will be compressed and a sample will be obtained and extracted

Postoperatively, the dog developed aspiration pneumonia and remained in the hospital for 4 days. She improved when administered ampicillin/sulbactam 50 mg/kg (22.7 mg/lb) IV q8h, ondansetron 0.5 mg/kg (0.23 mg/lb) IV q8h, maropitant 1 mg/kg (0.45 mg/lb) IV
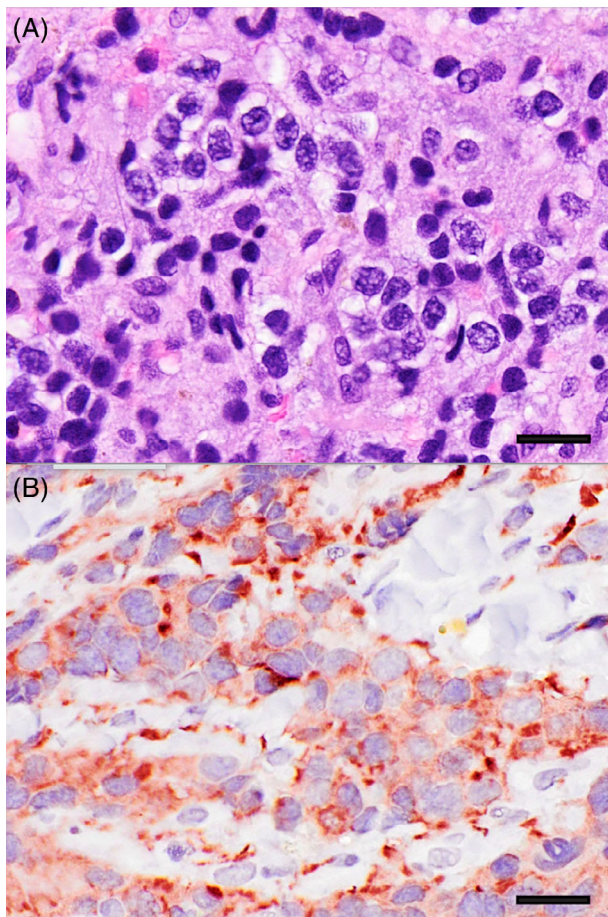
RALEIGH ET AL.

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1539

FIGURE 3 Histopathology of biopsy sample. A, Small clusters of round cells surrounded by eosinophilic stroma (×400; bar 20 μm). B, Packets of neoplastic cells with moderate to strong cytoplasmic immunoreactivity against synaptophysin suggestive of a paraganglioma (×400; bar 20 μm)

FIGURE 4 Gross and histopathology of intracardiac mass. A, A large, pedunculated mass arises from the right atrial wall. B, Histopathology of the mass is composed of packets of round cells with granular cytoplasm confirming the diagnosis of paraganglioma (×200; bar 20 μm)

q24h, trazodone 4.1 mg/kg (1.9 mg/lb) PO q12h, and continued furosemide and pimobendan at the previously prescribed dose and frequency. Three days after the biopsy was performed, the dog underwent radiotherapy because of the critical nature of the disease secondary to the intracardiac mass. The dog was anesthetized and placed in lateral recumbency. The radiation plan was to deliver 8 Gy in 2 5 × 5 cm parallel opposed fields with manual planning using 6 megavolt photons with a source-to-axis distance technique. Four days after the biopsy was obtained, the dog received L-asparaginase 400 IU/kg (181 IU/lb) SC, dexamethasone SP 0.2 mg/kg (0.09 mg/lb) SC, diphenhydramine 2 mg/kg (0.9 mg/lb) SC, and capromorelin 3 mg/kg (1.4 mg/lb) PO q24h. The dog was able to be discharged the same day after chemotherapy treatment.

The dog was clinically well over the next 2 days, at which point, the dog had acute respiratory difficulty and was reevaluated through the Emergency Service at the UCD-VMTH. After examination and because of the acute respiratory difficulty, a presumptive diagnosis of a pulmonary thromboembolism was made. The owners elected euthanasia.
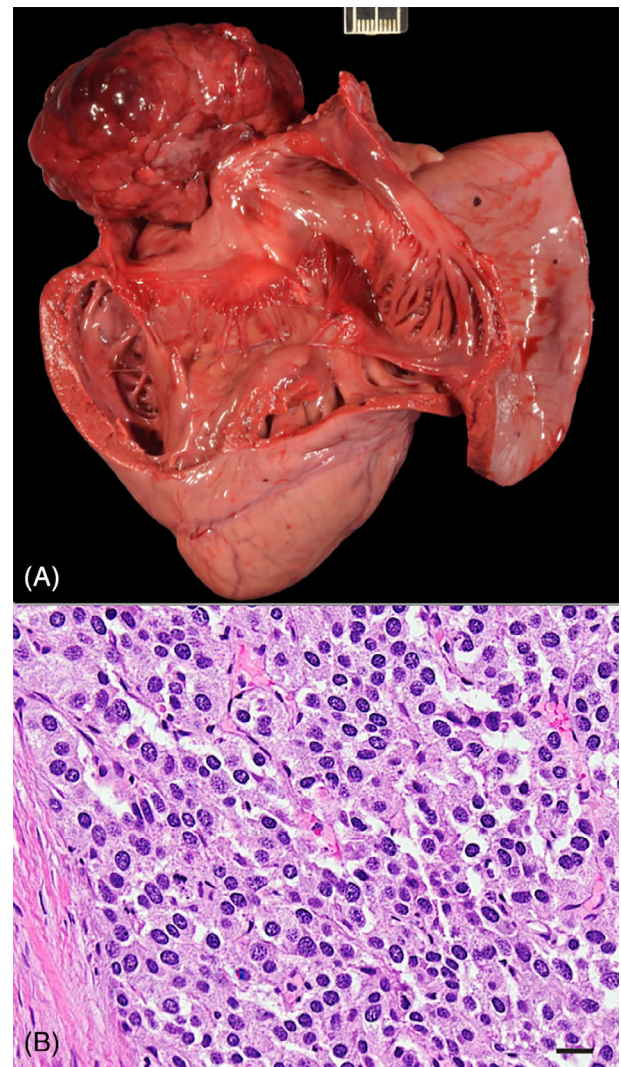
Necropsy revealed a 4.5 × 5.5 × 8 cm, red, firm, pedunculated mass with an irregularly smooth surface arising from the right atrial wall that filled approximately 30% to 50% of the right atrium (Figure 4A). Histopathologically, the mass was composed of packets of round neoplastic cells supported by a fine fibrovascular stroma (Figure 4B). Similar to the biopsy, the neoplastic cells expressed synaptophysin and chromogranin A and contained Grimelius-positive cytoplasmic granules, confirming the diagnosis of paraganglioma. In addition, a right atrial thrombus was closely associated with the neoplasm and fibrin thrombi were also observed in the lung (pulmonary thromboembolism) and liver. Moderate serosanguineous effusion was present in the thoracic and abdominal cavities. The liver had severe centrilobular sinusoidal congestion and hepatocellular loss and atrophy because of passive congestion, and acquired shunts were observed suggestive of portal hypertension (no thrombosis was noted in the portal vein). The hepatic lymph nodes were severely enlarged with edema.

2 | DISCUSSION

The endovascular biopsy technique utilized in this study enabled diagnostic histopathologic samples to be obtained, allowing for a disease-specific treatment plan. Although technically challenging, the procedure was performed without major intraprocedural complications, and the dog recovered uneventfully. Unfortunately, despite early initiation of treatment with radiotherapy and chemotherapy, the dog developed pulmonary thromboembolism and quickly decompensated; long-term assessment of treatment response was unable to be performed.

Endovascular techniques are regularly employed in human patients for both diagnostic and treatment purposes. In dogs, endovascular techniques are gaining popularity, and descriptions of intrahepatic portosystemic shunt coil embolization,[1,2] treatment of Budd-Chiari syndrome,[3] vascular foreign body removal,[4] heartworm extraction,[5] and transvenous pacemaker lead placement[6,7] have all been described. However, this case represents the first description of an intracardiac mass diagnosis obtained using modified Seldinger technique with fluoroscopic-guided endovascular (transvenous) biopsy in a dog. One other case utilizing a transvenous technique to obtain a biopsy sample after a venotomy has been reported; however, jugular ligation or repair was necessary in that case.[8]

Paragangliomas are tumors of sympathetic and parasympathetic paraganglia.[9,10] In general, extra-adrenal forms of these tumors are often considered "biochemically silent"; however, this phenomenon has not been well characterized as these tumors are rarely diagnosed in dogs.[9] Both functional and nonfunctional intracardiac paragangliomas have been reported in veterinary medicine; however, the literature available is scarce and limited to isolated case reports.[8,11,12] One study describes a functional right atrial paraganglioma in a dog that was presumed to be responsible for transient hypertension and atrial fibrillation that was observed under anesthesia. The cardiovascular changes occurred as biopsy samples were being collected and were hypothesized to result from tumor manipulation causing catecholamine release.[5] A similar consideration might explain the ventricular arrhythmias observed in the current case, although tumor function was not established as electron microscopy was not performed and chromaffin staining results were equivocal. As such, the observed ECG changes might have resulted from an instrument contacting the myocardium or from functional tumor cells.

The combination of clinical signs described in this case report is consistent with right-sided heart failure occurring secondary to an obstructive process within the heart. The fluoroscopic findings further support this in that the flow of contrast medium after injection into the cranial vena cava was clearly slowed through the right heart, specifically as blood flowed from the atrium to the ventricle. Additionally, the venous pressures recorded in the cranial vena cava were increased at 17 mmHg, and the azygos vein was visibly dilated intraprocedurally. Finally, a bicavitary effusion was noted in this dog, and histopathologic evaluation of both the liver and spleen biopsies suggested congestion secondary to impaired venous return. Similar clinical signs were reported in a dog diagnosed with right atrial paraganglioma.[5]

Treatment of intracardiac masses is based on the tumor type. For paragangliomas, surgical removal would be ideal when possible; however, this procedure inherently has massive risks and requires cardiopulmonary bypass, which is uncommonly available in veterinary medicine. The successful removal of a left atrial paraganglioma has been described in a single dog.[13] Recurrence of paraganglioma was noted in that case; however, this was 2 years after the initial resection.[13] In the current case, radiotherapy was elected as a treatment for the primary tumor. Radiotherapy is commonly utilized for canine heart-based masses[14]; however, descriptions of the use of radiotherapy for the treatment of intracardiac masses are lacking. This case describes the use of radiotherapy for local treatment of an intracardiac tumor. Radiotherapy will continue to be considered in future cases as it provides a less invasive treatment alternative to surgery, which carries a high rate of complications. Chemotherapy was also initiated in this dog with the goal of achieving gross tumor shrinkage to improve the clinical signs resulting from impaired blood flow through the heart. The biological behavior of intracardiac paragangliomas has not been thoroughly described but is thought to be similar to other aortic body tumors. Overall, while this group of neoplasms has demonstrated metastatic potential,[9] this is generally considered an uncommon sequela.[3]

Limitations of this report include the short follow-up time period preventing a more thorough understanding of the dog's response to radiotherapy and chemotherapy. Additionally, the procedure for obtaining an endovascular biopsy described here is technically challenging and requires a strong understanding of interventional radiology techniques, equipment, and associated imaging. Furthermore, as fluoroscopy is necessary for this procedure, both the dog and the operator/s are exposed to ionizing radiation. Finally, it should also be considered that the pulmonary thromboembolic event could have been induced by numerous causes, including the diagnostic and treatment options that were pursued. While obtaining the biopsy endovascularly, bleeding could have occurred, leading to the development of a thrombus and subsequent movement of that thrombus to the pulmonary vasculature. Alternatively, treatment with chemotherapy or radiotherapy could have generated a tumor thrombus, again leading to the pulmonary thromboembolic event.

The described fluoroscopically guided endovascular biopsy technique could be considered as a diagnostic option for dogs with cardiac masses. Although these tumors are rare, the location and limited options for obtaining a diagnosis make a minimally invasive procedure particularly attractive. Evaluation of this technique and other fluoroscopically guided procedures for similar scenarios should be further investigated to allow for a thorough understanding of the best intervention(s) available.

CONFLICT OF INTEREST DECLARATION

Dr. William Culp has taught laboratories focused on the use of some of the instrumentation utilized in this report. Dr. Josh Stern serves as Associate Editor for the Journal of Veterinary Internal Medicine. He was not involved in review of this manuscript.

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.

ORCID

William T. N. Culp https://orcid.org/0000-0001-6132-156X
Lance C. Visser https://orcid.org/0000-0002-3563-0737

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