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CASE REPORT

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Fatal hemoptysis after bronchoscopic biopsy in a dog

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Abstract

An 8-year-old 24.6 kg mixed breed dog underwent bronchoscopy for evaluation of a persistent progressive cough. Bronchoscopy documented a markedly thick and irregular, cobblestone appearance of the mucosa. A bronchoscopic biopsy was obtained; immediately after the biopsy, a large amount of hemorrhage poured from the endotracheal tube. Multiple efforts to control the hemorrhage were unsuccessful and the dog suffered a cardiopulmonary arrest and could not be revived. A necropsy was performed, which was significant for pallor, evidence of prior heartworm disease, prominent bronchial arteries, and erosion of the submucosal vessels at the site of the biopsy. The cause of death was hemorrhage associated with transbronchial biopsy of an enlarged bronchial artery associated with heartworm disease. This report describes a rare complication of a routine diagnostic procedure.

KEYWORDS

bronchoscopy, heartworm, hemoptysis, iatrogenic complication, massive transfusion

1 | CASE REPORT

An 8-year-old 24.6 kg male mixed breed dog presented for bronchoscopy for evaluation of a chronic gradually progressive cough. The dog had been treated for heartworm disease 7 years earlier before adoption. Annual heartworm antigen testing thereafter remained negative. Two years before presentation, the dog developed a nonproductive cough, occurring once a month. Laboratory testing, including heartworm testing, was normal. Thoracic radiographs and echocardiography were performed and documented changes resulting from previous heartworm disease, including mild right heart enlargement, and mild pulmonary artery enlargement with an estimated pulmonary artery pressure based upon calculation of the tricuspid regurgitant velocity via Doppler echocardiography of 47 mm Hg (reference range < 30 mm Hg). The dog was administered fenbendazole (50 mg/kg PO q24h × 14 days), doxycycline (5 mg/kg PO q12 × 21 days) and clopidogrel (1.7 mg/kg PO q24 indefinitely).

A month before presentation, the cough had progressed from once monthly to 2–3 times per month. This change had gradually occurred over approximately 2–3 months' time. Abnormalities were not detected on physical examination. Because of the subtle worsening of his respiratory signs, a bronchoscopy and an airway wash were planned in attempt to better define an etiology. Repeat thoracic radiographs documented a diffuse and patchy bronchointerstitial pattern with mild right-sided cardiomegaly. The pulmonary arteries were assessed as slightly enlarged and tortuous. The baseline PCV/TS was 44% and 6.7 g/dL. The last dose of clopidogrel was administered 24 hours before the procedure. The dog was premedicated with acepromazine (0.02 mg/kg) and butorphanol (0.15 mg/kg) IM, and propofol was administered to effect to allow for tracheal intubation. Bronchoscopy, using a 5.2 mm flexible bronchoscope (Karl Storz Endoscopy-America, Inc, El Segundo, California) was performed through the endotracheal tube while using an bronchoscopic adaptor. Bronchoscopy documented a cobblestone and irregular appearance to the mucosal region in the intra-thoracic trachea and mainstem bronchi

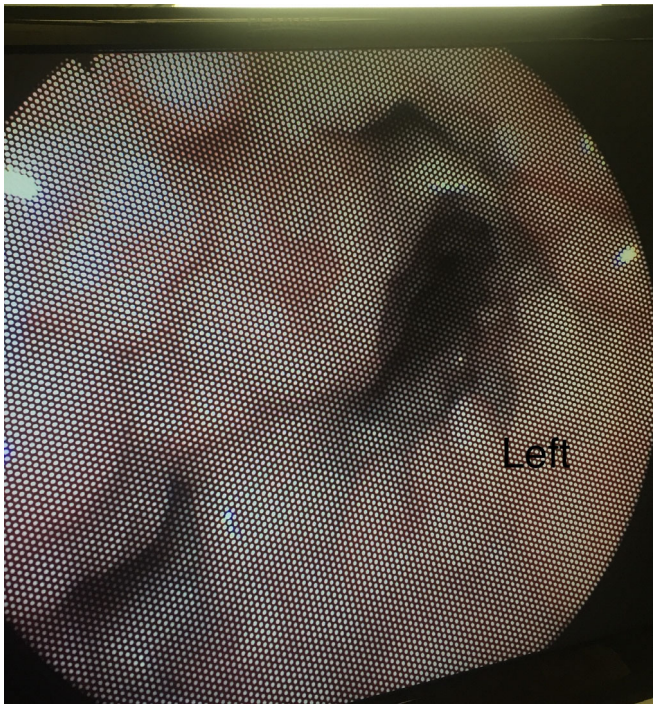

FIGURE 1 Bronchoscopic view of thickened and irregular mucosa and submucosa at the level of the carina. Right side of the image is the left side of the dog

(Figure 1). A bronchoalveolar lavage was performed, subsequently documenting limited cellularity, with only ciliated columnar epithelial cells, and a rare neutrophil observed. A biopsy, using 2 mm clamshell biopsy device, was obtained from an area of mucosal irregularity, near the junction of the left and right mainstem bronchi. Immediately after biopsy, a large volume of hemorrhage appeared, first visualized at the biopsy site, and subsequently grossly within the endotracheal tube.

Dilute (1:10) phenylephrine was applied to the region, and the endotracheal tube was replaced with a longer tube that would reach the level of the carina. The cuff was inflated in an attempt to provide direct pressure to the biopsy site. As the biopsy was in the middle of the carina, the tube was advanced as far as possible with the intent of being able to apply pressure. However, blood continued to pour from the endotracheal tube. A recheck PCV/TS 10 minutes after hemorrhage began showed a decrease to 35% and 5.2 g/dL, with a lactate of 2.0 mmol/L. A fluid bolus (25 mL/kg lactated ringers solution) was provided, and a type-specific transfusion (15 mL/kg) of packed red blood cells and 10 mL/kg of fresh frozen plasma was started. The dog continued to hemorrhage, and despite rapid transfusion, the PCV/TS fell to 32%/4.8 g/dL over the next 60 minutes.

Without recovering the dog from anesthesia, a multiphase thoracic CT angiogram (Toshiba Aquilon 16 CT; Canon Medical Systems, Glen Mills, Pennsylvania) was performed to attempt to clarify any specific abnormalities. The angiogram was performed using a power injector, using 2.2 mL/kg of contrast (Iohexol 300, GE Healthcare, Marlborough, Massachusetts) diluted to 96 mL, at a rate of 3 mL/s. The region of interest was the main pulmonary artery, and the threshold HU was 150. Slices were 3 mm. Apnea was induced with hyperventilation; 5 cmH_2O positive end expiratory pressure was applied. The CT scan did not identify a clear source of hemorrhage, but did identify enlarged and tortuous arteries, suspected to be the bronchial and possibly pulmonary arteries; intraluminal noncontrast enhancing amorphous material (30-35HU) within bronchi, consistent with clot; and evidence of prior heartworm infection, including main pulmonary artery enlargement, enlarged, tortuous and blunted pulmonary arteries, and mineral foci within vessels (Figure 2). Kaolin-activated thromboelastography to evaluate global coagulation status was unremarkable, and TEG platelet mapping was not performed.

Over the next hour, the dog continued to hemorrhage. The volume of hemorrhage was not able to be precisely quantified, but filled several anesthesia circuits, was well as about 500 mL into a suction canister, and about a 3 m radius of the floor. Surgical exploration was elected, and the dog was placed in dorsal recumbency to prepare for a median sternotomy. At this point, the hemorrhage suddenly ceased, and surgical exploration was canceled. The dog was placed in the intensive care unit, with the goal of keeping the dog sedated and intubated so clot formation could mature. Overnight, the dog was hemodynamically stable. No additional hemorrhage was evident either grossly and serial laboratory evaluations supported that that PCV/TS/lactate were stable. Sedation was maintained with fentanyl and midazolam. Supplemental humidified oxygen was provided. After 19 hours of intubation, sedation was slowly weaned and the dog was extubated and placed into a run.

Approximately 20 minutes after extubation, the dog coughed twice, and a large volume of hemorrhage was noted from the mouth. The dog was promptly induced and re-intubated; however, the hemorrhage continued at a high rate. The dog was positioned in dorsal recumbency. Crystalloid treatment (30 mL/kg IV) was administered, as was 3 whole units of pBRCs, 1 unit of fresh whole blood, and 2 units of fresh frozen plasma, for a total volume of 1650 mL (67 mL/kg) within 2 hours, and 95 mL/kg over 12 hours. One unit of commercially available cryoprecipitate (Cryoprecipitate, Hemopet, Garden Grove, California) reconstituted with 60 mL 0.9% NaCl was administered via the endotracheal tube with an attempt to provide topical clotting factors. Emergent surgical intervention was again planned, but the dog died before completing presurgical preparation.

A necropsy was performed. Cause of death was confirmed to be exsanguination (Figures 3 and 4). Extensively throughout the trachea and bronchi were mucosal ulcerations along with prominent submucosal vessels. The biopsy site was identified histopathologically and was consistent with mechanical removal of tissue over a submucosal vessel, suspected to be a branch of a bronchial artery. The adjacent tracheal mucosa had multifocal regions of tracheal necrosis and ulceration with submucosal edema and infiltration of neutrophils. Histopathology of the main pulmonary artery showed a long-standing proliferative arteritis from previous heartworm infection and enlargement of the pulmonary arteries (Figure 5). Bacterial and mycoplasma cultures were negative.

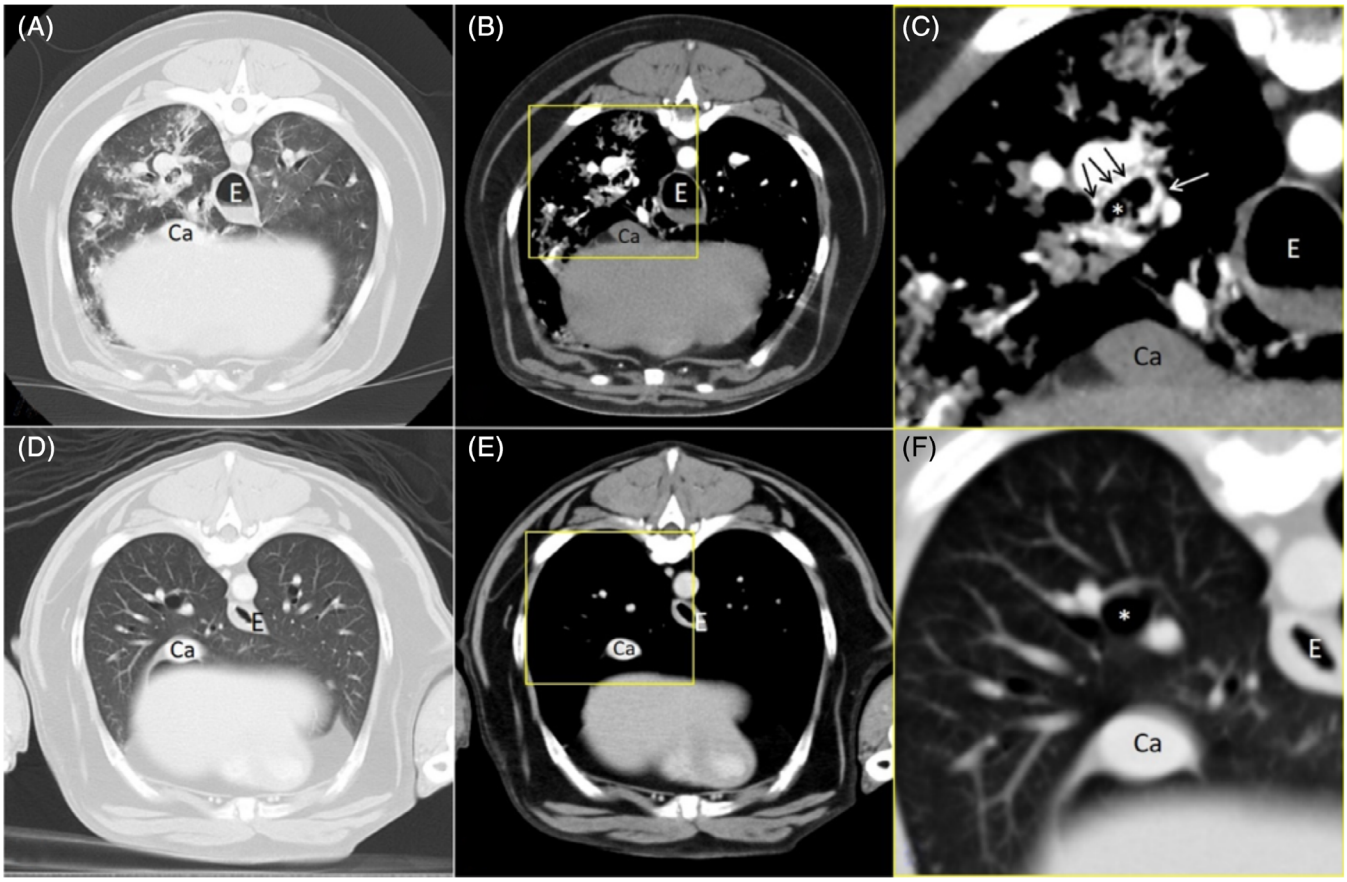

FIGURE 2 Transverse arterial phase slices of thoracic CT-angiogram in lung and soft tissue windows. A-C, Our patient; D-F, comparative images of a dog presented for reasons unrelated to the cardiopulmonary system. C and F are magnifications of the inset in B and E, respectively. Note the tortuous and ramified pulmonary arteries in A-C. The right caudal pulmonary bronchus is lined with distended arteries in C, visible as end-on contrast-filled foci (arrows), which are not present in the normal dog in F. There is intraluminal material within this same bronchus in C, consistent with clot from hemorrhage. Asterisk, bronchial lumen; Ca, caudal vena cava; E, esophagus

2 | DISCUSSION

Life-threatening hemoptysis has not previously been reported in conjunction with a bronchoscopic biopsy in a dog. Evaluation of severe hemoptysis centers on determining the origin as local to the lungs (eg, a bleeding bronchial mass) versus secondary to systemic coagulopathy.[1] In the dog of this report, the cause of the hemorrhage was the suspected inadvertent biopsy of a dilated bronchial artery. Although the bronchial arterial pressure in this dog was not known, it is considered equivalent to systemic arterial pressure, or 120 mm Hg in this dog as determined while under anesthesia before the biopsy. This systemic arterial pressure would be adequate to dislodge any forming clot.

While this dog received clopidogrel 24 hours before the biopsy, there was no support for primary coagulopathy on kaolin-activated TEG as the cause of the ongoing hemorrhage, although thrombocytopathy could have contributed to ongoing hemorrhage. TEG platelet mapping might have provided more useful information concerning any impact of clopidogrel. No prothrombin or activated partial thromboplastin time was performed. Current recommendations for discontinuation of a platelet inhibitor in a dog at low risk of thrombosis such as this dog include stopping the drug 5-7 days before the planned procedures.[2] These guidelines were not available at the time of this case; however, it is unclear how much role platelet inhibition played in resultant hemorrhage. Of interest, the periprocedural use of aspirin was not associated with an increased bleeding risk in people undergoing transbronchial biopsy.[3] Nevertheless, it is prudent to discontinue any anticoagulant/antiplatelet treatment before biopsy, as primary hemostasis is important in controlling hemorrhage.

Additionally, although histopathology documented erosion at the biopsy site, it was unclear why hemorrhage did not ultimately stop on its own from such a small wound, especially given the degree of intensive care provided to the dog in this report. Severe hemorrhage from focal palatine artery ulceration has been reported in cats.[4] A similar arterial ulceration was suspected to be present in the bronchial artery of dog of this report.

Blood supply to the canine lungs is twofold, consisting of the pulmonary circulation and the bronchial (systemic) circulation.[5-7] The pulmonary circulation, comprised of the pulmonary arteries, veins, and intervening capillary beds, participates in gas exchange and is a low-pressure system.[5-7] The bronchial circulation supplies the supporting structures of the lungs, including the *vasa vasorum* of the pulmonary arteries, and generally does not participate in gas exchange.[5-7] The

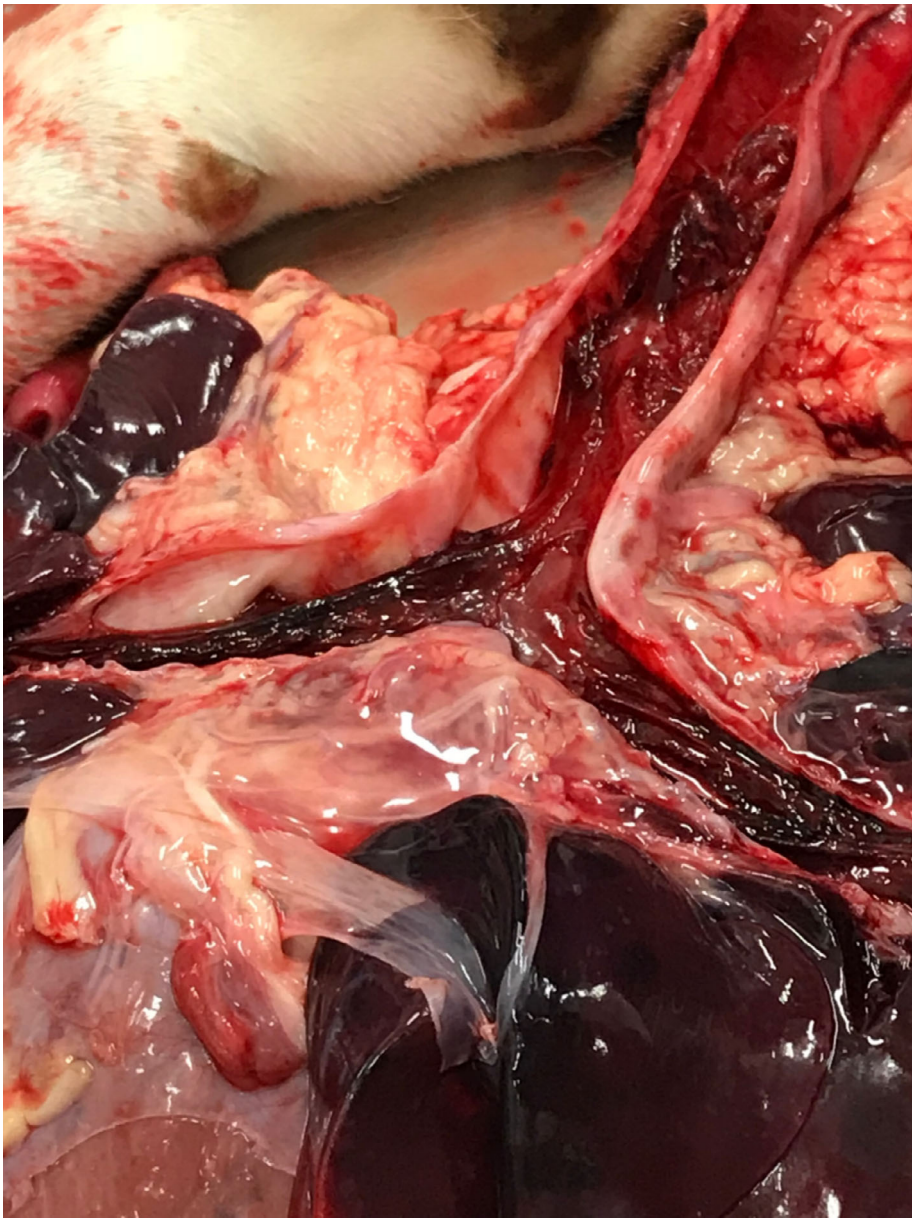

FIGURE 3 In situ appearance of clot in tracheal and main-stem bronchi at necropsy examination

bronchial and pulmonary systems are connected via microvascular anastomoses at the capillary level, connections which are minimally functional in a normal lung.[5-7] Although there is substantial variation in origin of the bronchial blood supply, the bronchial arteries all arise from branches of the bronchoesophageal and/or intercostal arteries, which themselves emerge directly from the aorta. Pressure in the bronchial circulation is therefore at systemic levels, and thus 4-6 times higher than that in the pulmonary circulation.[5-7] Disruption of a bronchial artery will leave little or no resistance to massive flow. This anatomy readily explains the sheer volume of hemorrhage that occurred in the dog of this report, although the reason for lack of clotting at the biopsy site remains unclear. In people, without successful arrest of bronchial artery hemorrhage, 50%-85% of massive hemorrhages are lethal.[8]

In a normal dog, this large volume of the bronchial blood supply is not accessible from the mucosal surface of the bronchi, as the bronchial arteries generally course parallel to bronchovascular bundles and ramify into capillary beds within the bronchial walls.[8] The dog of this report had a history of heartworm disease. Heartworm infection leads to multifocal constriction and obstruction of pulmonary arteries secondary to mechanical irritation, immunologic reaction, and thromboemboli, provoked by microfilaria.[9] The bronchial arteries may dilate and hypertrophy to provide compensatory circulation to the lung distal to pulmonary arterial obstructions,[9,10] reducing ischemia, but contributing to developing pulmonary hypertension. The thin-walled capillary communications between bronchial and pulmonary circulations might vasodilate and enlarge as well. This phenomenon is well described in people with chronic inflammatory lung conditions including bronchiectasis.[11-13] The dog in this case had evidence of bronchial and pulmonary arterial proliferation on thoracic CT. Such proliferation is visible along the mucosal surface on virtual endoscopy of the

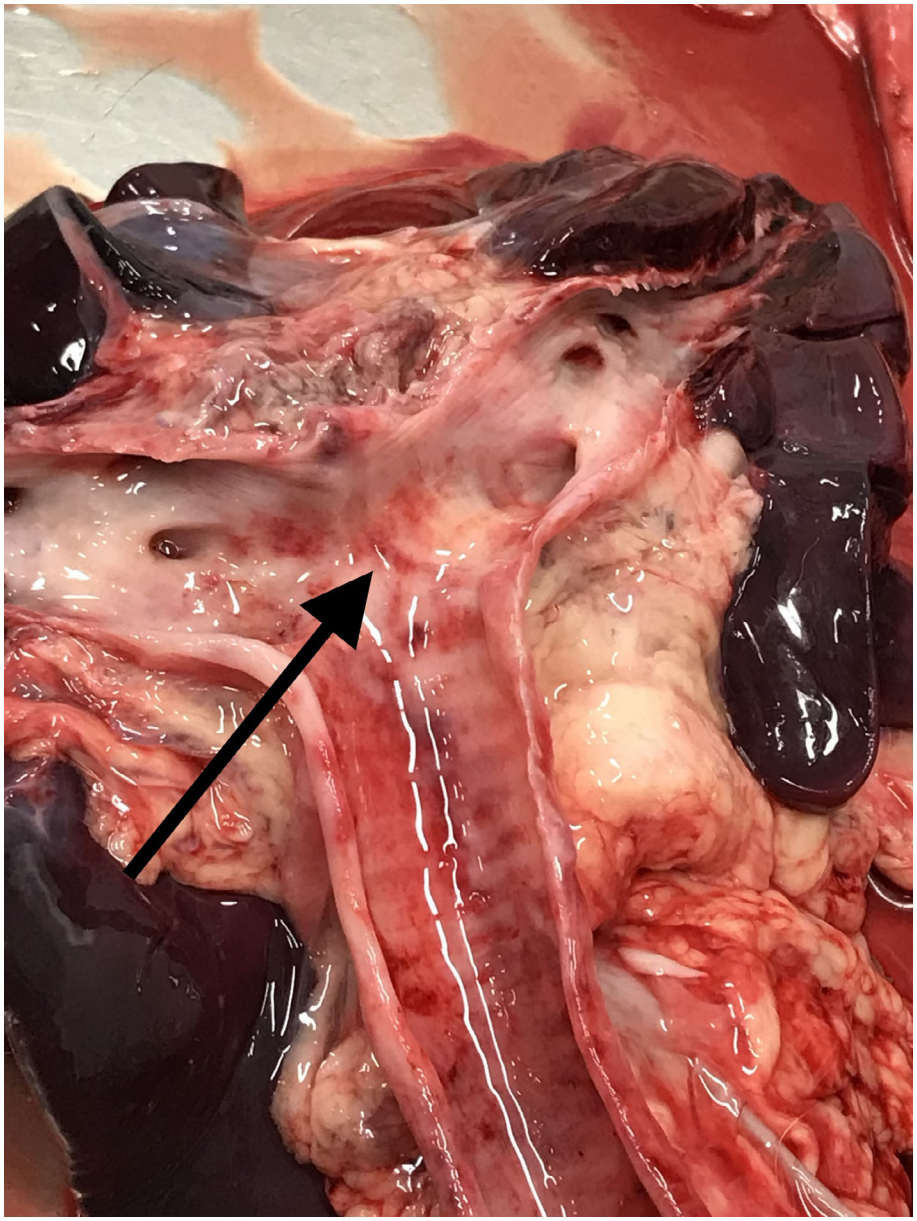

FIGURE 4 Gross view of the trachea and main-stem bronchi after removal of the clot. The suspected biopsy site is shown by an arrow; this was subsequently evaluated by histopathology

trachea and carina,[10] and has an irregular to cobblestone appearance, similar to that seen on bronchoscopy of our patient. The cobblestone appearance was not present during postmortem, supporting that the pattern was vascular engorgement. It was suspected that the prior heartworm infection induced bronchial artery hypertrophy, which was inadvertently biopsied when visualized on bronchoscopy.

Tracheal and bronchial mucosal abnormalities are not uncommon in dogs undergoing bronchoscopy, with eosinophilic bronchopneumopathy particularly likely to have abnormal mucosa.[14,15] It can be difficult to distinguish mucosal lesions from submucosal vasculature. However, nodules should not compress easily compared with submucosal vessels and will most commonly appear more irregularly spaced. Additionally, nodules are often seen more proximally in the airways, with tracheal blood supply being segmental in origin, and thus less likely to appear as a nodule. Bronchial biopsy can provide vital information concerning case management, such as the presence of eosinophilic infiltrates, or parasitic disease, or neoplasia.

In people, although severe hemoptysis can be associated with a bronchoscopic biopsy, it is most often spontaneous.[16-18] For hemorrhage associated with biopsy, management centers around patient stabilization and maintenance of a patent airway.[19] Coagulopathy should be excluded early and treated aggressively if present. Recommendations in people include application of a topical vasoconstrictor (phenylephrine or epinephrine) or cautery if the lesion can be directly visualized.[1,19] Because of the massive amount of hemorrhage, the actual site of the hemorrhage in this dog was not able to be visualized during premortem via the bronchoscope, but topical vasoconstrictors were unsuccessful in controlling hemorrhage.

The role of the mild pulmonary hypertension in contributing to this dog's hemorrhage is unknown. Certainly, higher pressures will

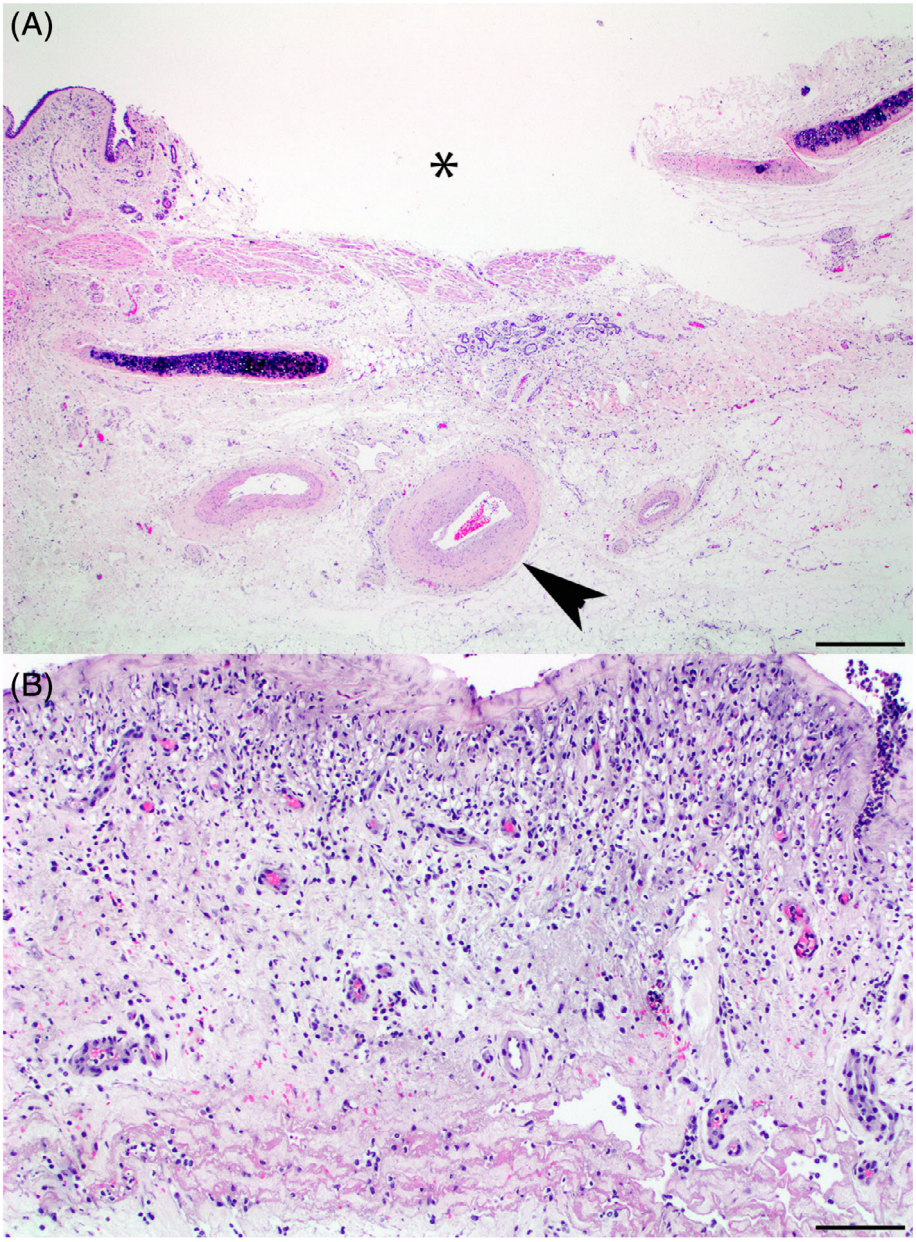

FIGURE 5 Tracheal biopsy site. A, The tissue disruption and deficit left by removing the biopsy (asterisk) shows a gap between the tracheal cartilage rings with the deepest aspect of the biopsy site overlaying a superficial artery (presumptive branch of the tracheal artery, arrowhead). H&E, bar = 500 μm. B, The tracheal mucosa adjacent to the biopsy site has multifocal regions of epithelial necrosis with underlying submucosal edema and infiltration of neutrophils. H&E, bar = 500 μm

result in a higher volume of shed blood. We believe the hemorrhage in this dog occurred from a bronchial artery, so it is suspected that the role of pulmonary hypertension is less clear.

Surgical management of severe hemorrhage remains a possibility, but much more likely to be successful given a mass lesion, rather than a small ulcerated lesion at the carina. However, it may have been more prudent to attempt earlier surgical exploration rather than wait for rebleeding to occur in this dog. For lesions localized to 1 lobe or side of the lungs, 1-lung intubation and ventilation may be considered. Unfortunately, the lesion in this dog was at the carina, meaning that any standard endotracheal tube, or endobronchial blocker set, would have impeded visualization of the surgical field and ventilation could not have been supported during median sternotomy.

Bronchial artery embolization or ligation is also pursued in people with life-threatening hemoptysis[8] but has not be described in dogs to the best of the authors' knowledge. This might have been a reasonable option to pursue in this dog, although access to the bronchial arteries may have been challenging. Bronchial artery embolization is reported to control life-threatening hemoptysis in people successfully in 90% of cases.[1] This has been accomplished through multiple means, including introduction of polyvinyl alcohol/trisacryl gelatin microspheres, gelatin sponge, or coils.[8]

In the authors' experience and those of others, bronchoscopy and bronchial biopsy are safe procedures that are useful in identifying the cause of a variety of pulmonary disease. Massive hemorrhage associated with biopsy appears rare, but this case highlights that a careful discussion of the benefits versus the risks of a specific procedure in an individual dog should be carefully considered. It is unclear how to prevent this negative outcome in the future. In the presence of an active interventional radiology department, embolization of a bronchial artery might be pursued. Repeat bronchoscopy before extubation may have

been useful to evaluate the site for ongoing bleeding or prolonged general anesthesia with intubation may have been useful to limit blood pressure changes, and intra-thoracic pressure triggered by coughing.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

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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