Severe bronchoconstriction after bronchoalveolar lavage in a dog with eosinophilic airway disease

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- Eosinophilic airway disease is associated with a variety of chronic inflammatory changes in the lower airways and is caused by antigenic stimulation that induces release of various mediators produced by eosinophils and mast cells in the small airways and the pulmonary interstitium.
- Inflammatory mediators, such as histamine, cytokines, prostaglandins, and leukotrienes, alter vascular permeability, leading to edema, and cause increased mucus production, damage to bronchiolar epithelium, and fibrosis, resulting in narrowing of the airways.
- An acute crisis, characterized by severe bronchoconstriction, can occur as a result of a type I hypersensitivity response (eg, asthma) or mechanical disruption (eg, bronchoscopy).
- Medical management of this disease process typically involves the use of anti-inflammatory, vagolytic, or bronchodilatory drugs.

A 27-kg (59.4-lb) 4-year-old male castrated mixed-breed dog was brought to The Ohio State University Cardiology Service for evaluation of a suddenly worsening cough the dog had since it was adopted at the age of 1 year. The dog had paroxysms of coughing, now productive, that lasted for almost 72 hours. The owner reported that the dog had occasional episodes of reverse sneezing but no evidence of exercise intolerance. The dog received heartworm preventative continuously but no other medications. Results of physical examination were unremarkable except for an easily elicited cough. A CBC was performed and revealed moderated eosinophilia (1,600 cells/µL; reference range, 0 to 1,300 cells/µL) and basophilia (900 cells/µL; reference value, 0 cells/µL) but no other abnormalities. Thoracic radiography revealed no abnormal findings. During coughing in the hospital, the dog expectorated a small amount of thick brownish fluid; cytologic examination revealed numerous eosinophils and eosinophilic granules. Bronchoscopy and airway cytologic examination were not performed. A heartworm antigen test was performed, and results were negative. A tentative diagnosis of eosinophilic bronchopneumonopathy was made, and the dog was sent home to be treated with an empirically chosen 10-day course of fenbendazole (50 mg/kg [22.7 mg/lb], PO, q 24 h) for possible respiratory parasitism. No other medications were administered at that time. Recommendations were made for follow-up examination and bronchoscopy with airway lavage if clinical signs did not improve.

Initially, the dog had considerable improvement after administration of the anthelmintic, and coughing did not occur for several weeks. However, 3 months after the first evaluation, coughing had resumed and become worse, so the dog was returned for further diagnostic testing. Physical examination results were normal except for a dry hacking cough. A CBC revealed mildly high eosinophil concentration (1,300 cells/µL) and basophil concentration (1,100 cells/µL). Thoracic radiography revealed evidence of lower airway disease (**Figure 1**). To further clarify the nature of the dog's cough, the decision was made to pursue bronchcoscopy and **bronchoalveolar lavage (BAL)** for airway cytologic examination and bacteriologic culture. These tests were performed 2 days later.

The dog received preanesthetic medication with acepromazine (0.05 mg/kg [0.023 mg/lb], IM) and butorphanol (0.2 mg/kg [0.09 mg/lb], IM). Anesthesia was induced with ketamine (6 mg/kg [2.73 mg/lb], IV) and diazepam (0.28 mg/kg [0.13 mg/lb], IV) and maintained with sevoflurane (2% to 4%). The dog was extubated to perform the bronchoscopy, and anesthesia was maintained with propofol boluses (1 mg/kg [0.45 mg/lb] and then 0.5 mg/kg [0.23 mg/lb], IV). Bronchoscopic examination[a] revealed a normal oral cavity, oropharynx, nasopharynx, and upper two thirds of the trachea. In the lower third of the trachea, there was accumulation of white mucus and the carina was mildly swollen. There was also mild red discoloration of the tracheal and bronchial mucosa and diffuse mucus accumulation in both mainstem bronchi (**Figure 2**). There was no evidence of the disease being worse in 1 lung versus the other. Given the diffuse nature of the disease, an arbitrary decision was made to obtain a brush sample[b] from the lower airways of the left lung for bacteriologic culture. The bronchoscope was advanced to the point at which it fit snugly, and the brush was extended from there to decrease the risk of contamination from the endoscope itself.

The dog received 100% oxygen for several minutes before the BAL. A flexible bronchoscope was passed into successively smaller airways of the right middle lung lobe until a snug fit between the endoscope and the airway was achieved. The right side was chosen for cytologic examination to decrease the risk of blood contamination from the brush sample performed on the left side. Two boluses (20 mL each) of room temperature (21°C), sterile, nonbacteriostatic saline (0.9% NaCl) solution were instilled through the biopsy port and immediately retrieved by use of suction. The recovered volume was 18 mL, and the fluid was mod-

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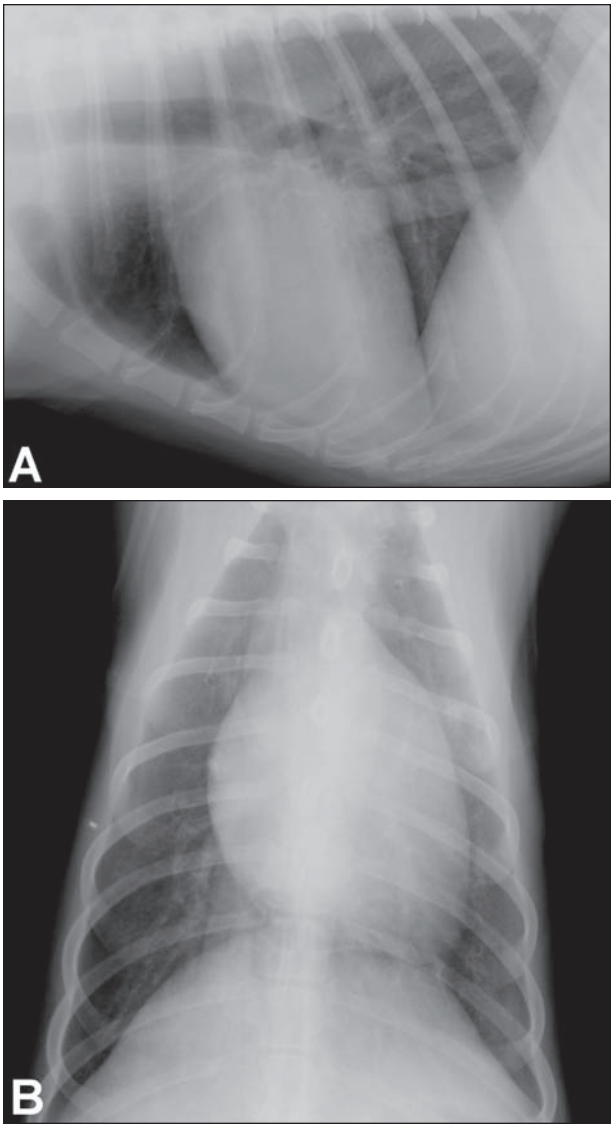

Figure 1—Right lateral (A) and dorsoventral (B) radiographic views obtained before bronchoalveolar lavage in a dog. Notice evidence of mild peribronchial thickening.

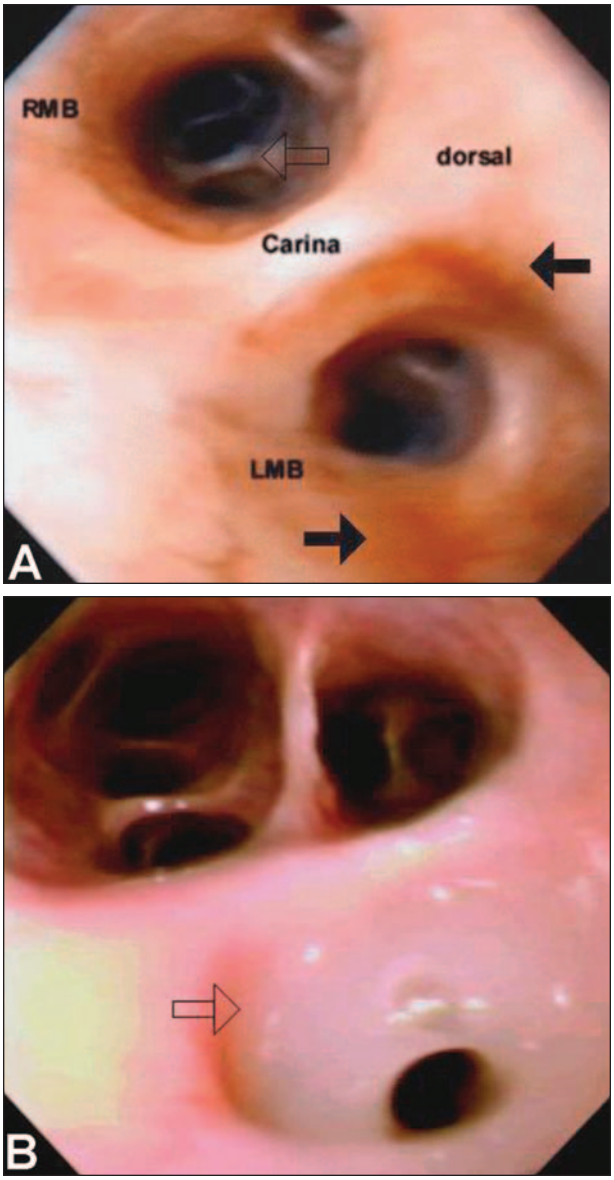

Figure 2—Endoscopic findings prior to bronchoalveolar lavage in a dog. (A) Notice mild mucus accumulation in the right mainstem bronchus (RMB, open arrow) and mild localized reddish discoloration of the epithelium of the left mainstem bronchus (LMB, solid arrows). The carina is mildly swollen. (B) Notice large amounts of white mucus obstructing the entrance into a segmental bronchus of the right caudal lung lobe (open arrow).

erately turbid. The sample was submitted for cytologic evaluation, which revealed severe mixed inflammation with 71% eosinophils, 19% neutrophils, 9% monocytes, and 1% lymphocytes. No etiologic agents were seen, and an interpretation of severe mixed inflammation with eosinophilic predominance was made. The dog was reintubated and taken to the intensive care unit to recover.

After the dog was extubated, approximately 15 minutes after the BAL, it rapidly became profoundly dyspneic and cyanotic. The dog was given propofol (1 mg/kg, IV) and reintubated and had breaths delivered via a handheld bag. Auscultation of the lungs did not reveal any abnormalities. The dog was given dexamethasone sodium phosphate (0.6 mg/kg [0.27 mg/lb, IV), aminophylline (3 mg/kg [1.4 mg/lb, IV), and atropine (0.02 mg/kg [0.01 mg/lb], IV) for suspected bronchoconstriction. Other differential diagnoses for the dog's dyspnea included intrapulmonary hemorrhage, exaggerated mucus production causing diffuse airway obstruction, tension pneumothorax, and acute respiratory distress syndrome. Initial arterial blood gas analysis after manual ventilation with 100% oxygen had been initiated revealed P_{O_2} of 65.3 mm Hg (reference range, 90 to 100 mm Hg), P_{CO_2} of 46.8 mm Hg (reference range, 35 to 45 mm Hg), and pH of 7.269 (reference range, 7.35 to 7.45). Manual ventilation was continued, and the dog required an additional dose of propofol (0.8 mg/kg [0.36 mg/lb], IV). An arterial catheter was placed to facilitate frequent sampling for blood gas analysis. Another arterial blood gas analysis was performed approximately 30 minutes after the first and revealed no substantial improvement (P_{O_2}, 64.6

mm Hg; P_{CO_2}, 39.2 mm Hg; pH, 7.335). The decision was made to provide mechanical ventilation for respiratory support and to perform further diagnostic tests.

The dog was extubated and reintubated with a sterile endotracheal tube. Although there would be some contamination from the oropharynx, this was done in the hope of decreasing the risk of nosocomial pneumonia in a patient receiving mechanical ventilation. A constant rate infusion of pentobarbital (2.5 mg/kg/h [1.14 mg/lb/h]) was initiated to maintain anesthetic plane after 2 initial boluses (0.2 mg/kg, IV). The dog was then connected to a mechanical ventilator system[c] with the spontaneous intermittent mandatory ventilation mode. The initial settings were as follows: **fractional inspired oxygen content (F_{IO_2})**, 80%; frequency, 20 breaths/min; pressure support, 5 cm H_2O; and positive end-expiratory pressure, 5 cm H_2O. Lower airway pressures were used because the cause of the dyspnea was still not known and there was risk of exacerbating the problems with overly aggressive positive-pressure ventilation. After the dog was connected to the ventilator, thoracic radiography was performed with a portable unit (**Figure 3**). The radiographs revealed complete collapse of all lung lobes in the right hemithorax. Despite positive-pressure ventilation, there still appeared to be minimal inflation of the right lung. At this time, the dog was given a dose of diphenhydramine (2 mg/kg [0.9 mg/lb], IV) in hopes of limiting any potential role of mast-cell degranulation and release of histamine. It was decided to repeat the bronchoscopic examination to determine whether there were any overt changes from the previous endoscopic findings.

The dog was disconnected from the ventilator and connected to an anesthesia machine for manual ventilation during the bronchoscopy. The endoscope was passed through the endotracheal tube and down to the level of the tracheal bifurcation. No substantial differences were seen between the first and second examinations. There was no evidence of intrapulmonary hemorrhage, bronchial obstruction by mucus, or constriction of airways, at least to the level the bronchoscope could reach (third-order bronchi). The endoscope was withdrawn, and the dog was returned to the intensive care unit and reconnected to the ventilator. The decision was made to obtain another airway sample. By use of the in-line sterile suction system connected to the endotracheal tube and ventilator circuit, a small amount of fluid was obtained and submitted for cytologic examination and bacteriologic culture and susceptibility testing. Because the sample was obtained without bronchoscopic viewing, the risk of contamination was increased. Cytologic examination revealed many eosinophils (84%); however, there was also a mixed population of heterogeneous extracellular bacteria (many large rods, a few small rods, and cocci). There were occasional degenerate neutrophils with intracellular bacteria. Occasional squamous epithelial cells with associated *Simonsiella* organisms were also seen, which suggested oropharyngeal contamination.

After most of the diagnostic tests were completed, the dog was connected to monitoring devices to determine continuous ECG, direct arterial blood pressures, end-tidal CO_2, and pulse oximetry. A urinary catheter was placed to monitor urine output, and serial arterial blood gas analyses were performed. Intravenous administration of fluids[d] (70 mL/h) was initiated. Largely on the basis of the belief that severe bronchoconstriction and airway inflammation were the primary causes of

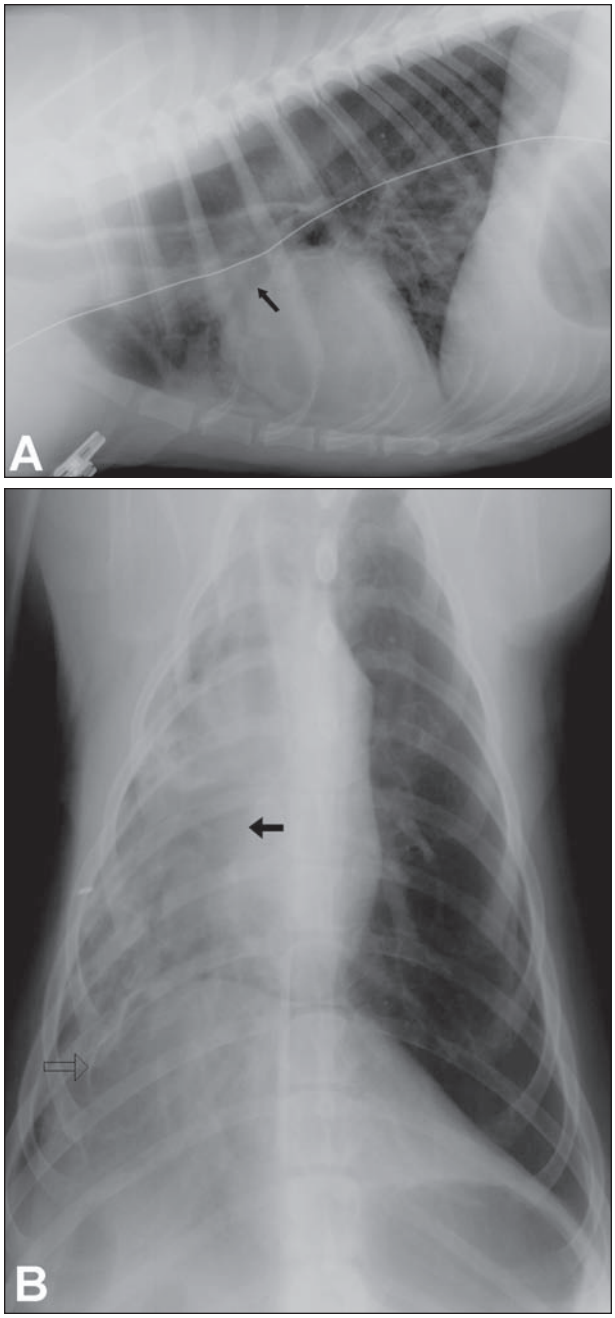

Figure 3—Left lateral (A) and dorsoventral (B) radiographic views obtained after bronchoalveolar lavage in a dog. The dog was intubated for mechanical ventilation. Notice air bronchograms, which indicate alveolar disease in the cranial portion of the right lung. An unstructured interstitial pattern is in the right middle and right caudal lung lobes. Rightward mediastinal shift and cranial displacement of the right crus of the diaphragm indicate severe atelectasis and collapse of the right lung lobes. The bronchi of the right cranial and middle lung lobes are dilated (solid arrows) with evidence of hyperinflation of the left lung lobes. A thin-walled, gas-filled bulla is in the right caudal lung lobe on the dorsoventral view (open arrow). Gas is present in the esophagus, and an ECG lead is superimposed on the lateral radiographic view.

the oxygenation impairment and radiographic changes, bronchodilator administration was continued through the first night. This included aminophylline (3 mg/kg, IV, q 12 h), albuterol (180 µg delivered via inhaler into the ventilatory circuit, q 8 h), and magnesium sulfate (30 mg/kg [13.6 mg/lb], IV, q 8 h). Although intracellular bacteria in the second airway cytologic sample were likely the result of airway contamination, administration of ampicillin potentiated with sulbactam[a] (30 mg/kg, IV, q 12 h) was initiated.

Through the first night, the dog did well with mechanical ventilation. Because only the left lung lobes were being ventilated, pressure support was used cautiously to limit the possibility of barotrauma. The P_{O_2} and S_{O_2} improved, so the FI_{O_2} was decreased in a stepwise fashion. The dog was moderately hypertensive through the night, with systolic blood pressure ranging from 160 to 180 mm Hg and diastolic pressure from 70 to 90 mm Hg. A normal sinus rhythm was maintained with a heart rate from 150 to 180 beats/min. These findings may have been the result of bronchodilator treatment with a β_2-receptor agonist or an indication that the level of anesthesia was too light or the dog felt discomfort. The urine output closely matched the IV fluid administration rate.

The next morning, the decision was made to start weaning the dog off of the ventilator because oxygenation was adequate at a low FI_{O_2}. The dog was extubated, and nasal prongs were placed for supplemental oxygen support. Thoracic radiography was repeated and revealed considerable improvement, although there was still evidence of moderate right-sided lung atelectasis. Administration of albuterol (5 µg/kg [2.27 µg/lb], via inhaler, q 8 h) and dexamethasone (0.1 mg/kg [0.045 mg/lb], IV, q 6 h) was continued. In the evening, the dog began to have ventricular arrhythmias, including monomorphic ventricular premature beats and episodes of ventricular tachycardia with a heart rate of approximately 200 beats/min. After an initial bolus of lidocaine (2 mg/kg, IV), a constant rate infusion (50 µg/kg/min) was begun and heart rhythm converted back to a normal sinus rhythm. The dog was slow to recover from the anesthetic agents received while on the ventilator, so close monitoring was continued through the second day.

By the third day, the dog had mostly recovered from anesthesia and was mentally more alert. Heart rate had decreased to a normal sinus rhythm of 70 beats/min, so the lidocaine infusion was discontinued. Administration of supplemental nasal oxygen was discontinued, and the dog remained eupneic. A CBC was repeated, and results were consistent with a stress leukogram, likely secondary to corticosteroid administration. The total WBC count was increased (25,000 cells/µL; reference range, 4,100 to 15,200 cells/µL) with a predominantly mature neutrophilia (22,500 cells/µL; reference range 3,000 to 10,400 cells/µL). There were no longer any eosinophils or basophils, and the lymphocyte count was decreased (800 cells/µL; reference range, 1,000 to 4,600 cells/µL). Serum biochemical analyses revealed moderately high activities of alanine transaminase (227 U/L; reference range, 10 to 55 U/L), aspartate transaminase (694 U/L; reference range, 15 to 120 U/L), and creatine kinase (5,526 U/L; reference range, 50 to 400 U/L). These changes were likely caused by hypoxic injury to the liver and muscle damage caused by recumbency. There were no other abnormalities. A fecal flotation and Baermann test were performed to rule out lungworms, and both results were negative. The dog continued to do well clinically throughout the day despite marginal oxygenation status (Pa_{O_2}, 70 mm Hg) and was discharged from the hospital the following morning. Prescribed medications included prednisone (1 mg/kg, PO, q 12 h), terbutaline (0.1 mg/kg, PO, q 8 h), amoxicillin-clavulanic acid (13.75 mg/kg [6.25 mg/lb], PO, q 12 h), omeprazole (1 mg/kg, PO, q 24 h), and fenbendazole (25 mg/kg [11.4 mg/lb], PO, q 12 h for 10 days).

The dog was returned for reexamination 5 days later and appeared to be doing well clinically at home. Because the dog had become polyuric and polydypsic, the owner had decreased the prednisone dosage to 0.5 mg/kg every 12 hours. The dog had also vomited 3 times, so the owner discontinued administration of omeprazole and terbutaline. Administration of prednisone was continued at the decreased dose, and the albuterol inhaler was added back into the treatment regimen. The dog was evaluated once again a month later and was still doing well with only an occasional cough. Follow-up radiographs revealed a mild bronchointerstitial pattern similar to radiographs prior to the BAL.

On the basis of history, clinical signs, results of blood analyses, and, especially, results of airway cytologic findings, we presumptively diagnosed reactive eosinophilic airway disease. Radiographs revealed evidence of mild, diffuse bronchial markings, which are consistent with lower airway disease.[1] The finding of predominantly eosinophils in the cytologic samples is uncommon, compared with finding neutrophils or lymphocytes in dogs with airway disease.[2] Presently, there is no well-defined classification system for the accumulation of eosinophils in the small airways or pulmonary interstitium in companion animals.[3] There are a number of potential underlying causes, however. Some possibilities include infectious organisms, such as fungal, parasitic, or bacterial organisms. Results of testing for all of these were negative. Neoplasia is another potential cause of eosinophilic airway disease, but no evidence of this was found via radiography or cytology. Eosinophils are also the predominant cell type in patients with other eosinophilic conditions, such as **pulmonary infiltrates with eosinophils (PIE)**.[4] However, the dog's clinical findings did not fit with the current description of PIE. Drug-induced eosinophilic pneumonia has been reported in humans, but there has been no clear evidence of causation in dogs and cats.[3] Several forms of idiopathic eosinophilic pneumonia have been reported in humans, but they are believed to occur rarely in other animals.[3] Because these other causes seemed unlikely, allergic bronchitis (asthma) or chronic eosinophilic bronchitis was the primary differential diagnosis for this patient.

Several recent studies[5-7] in humans have revealed a clear distinction between eosinophilic bronchitis and asthma or allergic bronchitis. Eosinophils are the pre-

dominant cell type with both diseases, but the pathophysiologic features of the diseases differ considerably. It is believed that asthma is associated with airway hypersensitivity and bronchoconstriction, whereas eosinophilic bronchitis causes chronic cough in the absence of airway hyperreactivity.[8] This is believed to occur because of increased mast cells in airway smooth muscle of patients with asthma.[9] Additionally, it has been determined that patients with asthma also have a significantly increased concentration of vascular endothelial growth factor in their sputum versus patients with eosinophilic bronchitis.[5] It is unclear at this time whether this type of distinction exists in other animals. Our dog's history and clinical signs would seem to fit better with eosinophilic bronchitis (chronic cough with no dyspnea), but the acute crisis that occurred after the BAL suggested there might also be a component of allergic or hypersensitivity disease. However, asthma has not been determined to occur naturally in dogs.

Eosinophilic airway disease is associated with a variety of chronic inflammatory changes in the lower airways. This inflammation is brought about by antigenic stimulation, which causes the release of various mediators produced by eosinophils and, to some extent, mast cells in the small airways and the pulmonary interstitium. These mediators (such as histamine, cytokines, prostaglandins, and leukotrienes) alter vascular permeability and lead to edema, increased mucus production, and bronchospasm.[10] Additionally, cytotoxic proteins can damage bronchiolar epithelium, leading to fibrosis and further narrowing of the airways.[7] These are all changes that occur over time. An acute crisis, most commonly seen in feline asthma, can occur as a result of a type I hypersensitivity response secondary to antigenic stimulation.[11] Theoretically, mechanical disruption of eosinophils (eg, from delivery of fluid to the lower airways or contact with the endoscope or brush) could also initiate this type of response. In this dog, we believe that lavage of the right hemithorax caused massive degranulation of inflammatory cells and subsequent release of inflammatory mediators. This resulted in severe bronchoconstriction, which then brought about the dog's clinical course and could explain the radiographic changes. Radiography revealed evidence of atelectasis with proximal bronchial dilatation, which is consistent with terminal airway collapse secondary to bronchoconstriction on the same side in which the BAL was performed. The alveoli in the affected lungs could not be ventilated, and a severe ventilation-perfusion mismatch developed. This led to severe dyspnea and hypoxemia. Dilation of the proximal portion of the airways likely occurred as the tidal volume, under positive-pressure ventilation, exceeded the capacity of the remaining functional lung.

Medical management of this type of reaction typically involves the use of anti-inflammatory, vagolytic, and bronchodilatory drugs. Corticosteroids are commonly used for long-term treatment but have questionable efficacy in an acute crisis. Several studies[12,13] in humans have revealed substantial improvement in clinical condition, whereas others[14,15] have revealed no clear benefit. Efficacy of corticosteroids in veterinary patients with acute bronchoconstriction has not been established, but dexamethasone was used in this dog. Bronchodilators, conversely, can have a more rapid onset of action and are generally the mainstay of treatment for acute episodes. β_2-Receptor agonists are the most commonly used bronchodilator, whether administered parenterally or via an inhaler. Along with relaxation of bronchial smooth muscle, β_2-receptor agonists can inhibit histamine release and cholinergic neurotransmission.[16] In humans, use of bronchodilators via inhalation is as effective as IV administration and has fewer systemic adverse effects.[17] Appropriate delivery of inhaled medications is challenging in animals, but inhalers have been modified and were used in the dog reported here, after an initial IV administration of aminophylline. Methylxanthine derivatives (such as aminophylline) are another class of bronchodilators that have been used to treat asthma in animals. They act by nonspecific inhibition of phosphodiesterase isoenzymes as well as by interfering with calcium mobilization, thereby causing bronchodilation.[10] Although aminophylline was used in this patient, β_2-receptor agonists are generally preferred in an acute setting, with methylxanthines reserved for chronic use.[10] Additionally, these drugs are no longer used for the treatment of asthma in humans because the risk of adverse effects outweighs the potential benefits.[18,19] Atropine was also given to this dog during the acute crisis. Anticholinergics can be used as bronchodilators, but they are less effective than β_2-receptor agonists and have a slower onset of action.[20] This, combined with inducing tachycardia (during hypoxemia) and drying of mucous secretions (potentially exacerbating airway obstruction), limits the value of anticholinergics in treating severe bronchoconstriction. Finally, IV administration of magnesium sulfate was also used as a bronchodilator in this dog. Magnesium can cause bronchodilation through several mechanisms including alteration of calcium influx and intracellular phosphorylation reactions.[21] Magnesium might also have some anti-inflammatory effects by inhibiting superoxide production and, thereby, neutrophilic burst in patients with asthma.[22] Reports[21,23] of efficacy in humans are mixed, but the consensus is that magnesium is primarily beneficial in cases of severe asthmatic-bronchoconstrictive crisis, which our dog also appeared to have.

The clinical condition and dyspnea were severe enough to warrant mechanical ventilation. However, whether the dog benefited from this intervention was unclear. Radiographs performed immediately after positive-pressure ventilation revealed little ventilation of the right hemithorax. Given the degree of hyperinflation on the left lung, it seems that the use of lower airway pressures was prudent. Higher pressures might have resulted in barotrauma to the left hemithorax because the right side was not being ventilated. Despite the lower pressure, there was a substantial improvement in arterial oxygenation. The improvement was likely attributable to increased oxygen delivery to the portions of the lungs that were functional. It is also possible that the improvement could have been the result of the various medications the dog received.

To our knowledge, this potential complication of bronchoalveolar lavage has not been reported in veterinary medicine. However, there has been documentation of this type of event in humans with reactive airway disease, with fairly low incidence. One large study[24] revealed evidence of bronchospasm or worsening of clinical signs in 5.1% (14/273) of humans with asthma that underwent a BAL. Another study[25] that involved 57 patients with chronic obstructive pulmonary disease revealed only 1 patient with severe bronchospasm after a BAL was performed. Other potential complications associated with BAL include hypoxia, coughing, hemoptysis, and fever or flulike signs.[24-26] In other animals, there are few references to adverse affects with the primary concern being transient hypoxia.[27,28] Instillation of excessive amounts of fluid or decreased fluid recovery could be a contributing factor in the hypoxia seen with BAL, especially in smaller animals.[29,30] In 1 retrospective study[31] of 101 dogs, 2 deaths were associated with BAL but the dogs were severely dyspneic prior to the procedure and had extensive pulmonary disease.

Generally speaking, bronchoalveolar lavage is considered to be a safe procedure in humans and veterinary species. Caution should be exercised, however, when there is suspicion of a reactive airway disease, such as asthma or other eosinophilic airway diseases; to avoid this potential complication, pretreatment with oxygen and β_2-receptor agonists should be considered. Use of short-acting corticosteroids immediately after the procedure might also be warranted. Owners should be made aware of this risk, however unlikely, given the potential severity of the consequences.

a. Video gastroscope, 8.7-mm outer diameter, Olympus, Melville, NY.
b. Gastrointestinal microbiology brush REF 4352, 2.0-mm diameter, Hobbs Medical Inc, Stafford Springs, Conn.
c. Nelcor Puritan-Bennet 800 Series Ventilator, Puritan-Bennet Corp, Carlsbad, Calif.
d. Plasmalyte 148, Baxter Health Corp, Deerfield, Ill.

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