Case Description—An 8-year-old 38-kg (84-lb) castrated male German Shepherd Dog cross was referred to the Michigan State University Veterinary Teaching Hospital for evaluation of coughing and labored breathing of 2 days’ duration. Prior to this event, the dog had not had coughing or dyspnea, although its owners noted progressive exercise intolerance that they had attributed to orthopedic disease. A lateral thoracic radiographic view obtained prior to referral provided evidence of pneumothorax. The dog’s previous medical history included high serum liver enzyme activities of 1 year’s duration for which the dog had been fed a diet formulated to promote liver health and function. Seven years before this episode of respiratory distress, the dog underwent surgery for total hip joint replacement and lipoma removal. Except for administration of a glucosamine product daily and heartworm preventive monthly, the dog was not receiving any medications.

At the initial evaluation, the dog was bright, alert, and responsive. The dog was panting and was in mild respiratory distress, as evidenced by an extended neck and reluctance to lie down. Thoracic auscultation revealed muffled dorsal lung sounds bilaterally. Results of abdominal palpation were suggestive of generalized hepatomegaly. Other physical examination findings were unremarkable.

Clinical Findings—CT of the thorax confirmed the presence of pneumothorax and revealed pulmonary blebs without evidence of infiltrative pulmonary changes. A tentative diagnosis of primary spontaneous pneumothorax was made.

Treatment and Outcome—Exploratory median sternotomy revealed emphysematous changes along the margins of all lung lobes, with the ventral margins of the left cranial, right cranial, and right middle lung lobes most affected. Partial lobectomies of the ventral aspects of these lobes were performed. Histologic examination of tissue samples from the lung lobes revealed diffuse smooth muscle hypertrophy of the terminal and respiratory bronchioles with moderate numbers of peribronchiolar eosinophils. Mucus plugs and mucous cell metaplasia within the airway epithelium were also evident. After surgery, clinical signs resolved and the dog was discharged from the hospital 2 days later. Eight months after surgery, the dog developed a mild cough, and treatment with prednisolone (tapering dosage starting at 0.5 mg/kg [0.023 mg/lb], PO, q 12 h) was initiated. Dosage reduction resulted in recurrence of coughing; however, with continued prednisolone treatment at a dosage of 0.5 mg/kg, PO, once daily, the dog was not coughing at 10 months after surgery.

Clinical Relevance—Reactive bronchopneumopathy should be included as a differential diagnosis for spontaneous pneumothorax in dogs. (J Am Vet Med Assoc 2013;242:658–662)

Abbreviation

| EBP | Eosinophilic bronchopneumopathy |

Initial diagnostic tests included a CBC, serum biochemical analysis, coagulation profile, and thoracic radiography. The CBC revealed mild normocytic, normochromic anemia (Hct, 38.5%; reference interval, 41% to 55%). The leukocyte count, including circulating neutrophil count (7.15 × 10³ neutrophils/µL; reference interval, 3.80 × 10³ neutrophils/µL to 7.80 × 10³ neutrophils/µL) and eosinophil count (0.45 × 10³ eosinophils/µL; reference interval, 0.10 × 10³ eosinophils/µL to 1.90 × 10³ eosinophils/µL) was within reference limits. The serum biochemical analysis revealed hypoglycemia (67 mg/dL; reference interval, 80 to 120 mg/dL), high alkaline phosphatase activity (4,943 U/L; reference interval, 13 to 107 U/L) and mildly high alanine transaminase activity (192 U/L; reference interval, 14 to 102 U/L). Prothrombin and partial thromboplastin times were considered normal. Three-view thoracic radiography revealed moderate pneumothorax with generalized lung atelectasis that was more pronounced in the caudal lung lobes and no evidence of blebs or bullae. In the radiographic views, the liver was moderately enlarged, with rounded margins. A test for circulating heartworm antigen yielded negative results. Baermann testing of a fecal sample for intestinal parasites was also performed, and results were negative. Initial treatment of the pneumothorax consisted of needle thoracentesis, which yielded a total of 2 L of air (1 L from each hemithorax). Despite removal of a large...
amount of air, negative pressure within the thorax was not established. At this time, oxygen saturation as measured by pulse oximetry was 94%, and the dog’s increased respiratory effort continued. The dog was sedated with acepromazine maleate (0.01 mg/kg [0.0045 mg/lb], IV) and butorphanol tartrate (0.2 mg/kg [0.09 mg/lb], IV), and thoracostomy tubes were placed bilaterally; a thoracic drainage system was used to initiate continuous evacuation because of progressive labored breathing after thoracocentesis.

To further characterize the pneumothorax and hepatomegaly and to exclude primary or metastatic neoplasia from the differential diagnoses, the dog was anesthetized and underwent thoracic and abdominal CT. Anesthesia was induced with a combination of midazolam hydrochloride (0.3 mg/kg [0.14 mg/lb], IV) and methadone hydrochloride (0.3 mg/kg, IV) and maintained via inhalation of isoflurane (1% to 2%) in 100% oxygen. Computed tomographic images were acquired with a 16-slice helical scanner in the transverse plane (slice thickness, 2.5 mm) with and without contrast medium administration. Positive-pressure ventilation was maintained, and the thoracic cavity was emptied of air via suction through the thoracostomy tubes prior to scanning to prevent motion artifacts and improve evaluation of lung parenchyma. Multiple blebs and trapped gas bubbles were detected within the visceral pleura of the right cranial and middle lung lobes and left cranial lung lobe. Smaller blebs were also evident on the ventral aspect of the left caudal lung lobe and in the accessory lung lobe surrounding the caudal vena cava. Some persistent air was present in the pleural space, more prominently on the left side. Incidental single renal cysts were noted bilaterally as well as a small mineral focus in the cranial portion of the abdomen in the region of portal vein branching.

On the basis of the lack of infiltrative pulmonary changes evident via CT, primary spontaneous pneumothorax was suspected and surgical intervention was recommended. After routine preparation, draping, and administration of cefazolin (22 mg/kg [10 mg/lb], IV), a median sternotomy was performed to expose the thoracic cavity. Emphysematous changes consolidating into subpleural blebs were observed along the margins of all lung

Figure 1—Photomicrographs of representative sections of lung biopsy specimens obtained from a dog that was evaluated because of respiratory distress secondary to pneumothorax (detected radiographically prior to referral). A—In this section, the smooth muscle (arrowhead) of the terminal and respiratory bronchioles is thickened and prominent. H&E stain; bar = 50 µm. B—Eosinophils are present (arrow) within the lumens and epithelia of bronchi and bronchioles. H&E stain; bar = 50 µm. C—Mucus plugs (MP) are visible in a few airways. H&E stain; bar = 200 µm. D—The amount of collagen (stained blue) within the bronchial and bronchiolar lamina propria is increased, compared with that expected in tissues from a clinically normal dog. Masson trichrome stain; bar = 50 µm.
lobes, with the ventral margins of the left cranial, right cranial, and right middle lung lobes most affected. Partial lobectomies of the ventral aspects of these lobes were performed with a thoracoabdominal vascular stapler. Warm saline (0.9% NaCl) solution was instilled into the thoracic cavity and all lung lobes and partial lobectomy sites inspected for persistent air leakage. The position of the previously placed thoracostomy tubes was assessed and deemed adequate. Prior to closure, liver biopsy specimens were obtained with laparoscopic biopsy forceps by caudally extending the ventral midline incision to allow access to the cranial portion of the abdomen.

The dog’s recovery from anesthesia and surgery was uneventful. Intermittent aspiration of thoracostomy tubes was continued after surgery. A decreasing quantity of serosanguineous fluid and no air were withdrawn from the thoracostomy tubes, and they were removed at 36 hours after surgery. The dog was discharged from the hospital 2 days after surgery, and the owners were instructed to monitor for signs of respiratory distress.

All tissue samples collected during surgery were immersion-fixed in neutral-buffered 10% formalin. Sections of the fixed tissue were routinely processed and embedded in paraffin. Representative 6-µm sections were placed on glass slides and stained with H&E stain for routine microscopic evaluation. Additional 6-µm sections were stained with Masson trichrome or Alcian blue–periodic acid–Schiff stain to detect collagen and mucus, respectively. Within all lung sections examined, there was diffuse, marked hypertrophy of the smooth muscle of the terminal and respiratory bronchioles as well as moderate bronchial smooth muscle hypertrophy. Moderate numbers of eosinophils were present surrounding occasional bronchioles, with extension of the cells into the luminal epithelium of both bronchioles and small bronchi. There was mild mucous cell metaplasia within the corresponding airway epithelium, and small plugs of mucus were noted within a few small bronchi, with moderate fibrosis of the bronchial and bronchiolar mucosal lamina propria. Many of the alveoli were moderately dilated, particularly at the subpleural level. Alcian blue–periodic acid–Schiff staining of the lung sections confirmed the presence of the mucous cell metaplasia and mucus plugs; by use of Masson trichrome stain, the amount of airway collagen in the lung sections appeared greater than that expected in tissue from a clinically normal dog (Figure 1). These findings were consistent with chronic, reactive small airway disease and were typical of asthma syndromes in cats and humans. Results of histologic examination of the liver were consistent with a chronic active hepatitis (unrelated to the observed pulmonary changes).

Approximately 8 months after surgery, the dog developed a mild cough and excessive panting. At that time, thoracic radiography revealed no notable abnormalities. A tapering dose of prednisolone (initial dosage of 0.5 mg/kg [0.023 mg/lb], PO, q 12 h) was initiated. An update was obtained via telephone conversation with the owner 10 months after surgery; at that time, the dog was doing well and its activity level had returned to normal. Although a recurrence of clinical signs was associated with dosage reduction, the dog’s condition improved with continued prednisolone treatment at a dosage of 0.5 mg/kg, PO, once daily, and no further coughing episodes had been noted.

Discussion

Pneumothorax is a condition defined by the presence of free air in the pleural cavity. The causes of pneumothorax can be categorized as traumatic, spontaneous, or iatrogenic. Spontaneous pneumothorax can be further classified as either primary or secondary. Primary pneumothorax results from rupture of bullae or blebs that have formed in or adjacent to the lung parenchyma. Secondary pneumothorax results from leakage from lung tissue affected by infiltrative or inflammatory disease, including pneumonia, abscess, granuloma, migrating foreign body, primary or metastatic pulmonary neoplasia, and parasitic infection (eg, infection with Dirofilaria immitis, Paragonimus kellicotti, or Filarioidea osleri).1–3 In cats, asthma has also been reported as a cause of secondary spontaneous pneumothorax.1,4 In humans, asthma, chronic-obstructive pulmonary disease, cystic fibrosis, tuberculosis, and pregnancy are among the underlying causes of spontaneous pneumothorax.5–7 To our knowledge, reactive bronchopneumopathy with histologic features similar to those associated with asthma, as evident in the case described in the present report, has not been identified in dogs and presents an additional differential diagnosis to be considered in cases of spontaneous pneumothorax in that species.8

In humans, pneumothorax is an uncommon complication of asthma, affecting as few as 0.02% of individuals in 1 study.5–11 In the veterinary medical literature, there are few case reports1,5 of asthma-associated pneumothorax and all of those involved cats. Collectively, 7 cases of asthma-associated pneumothorax in cats have been described; those diagnoses were based largely on clinical signs and radiographic and cytologic findings. Histologic examination of lung tissue specimens was performed for only 1 cat, and findings included evidence of atelectasis, hyperinflation, and chronic bronchitis that confirmed the diagnosis of asthma.4

Asthma (allergic bronchitis) is characterized by a type 1 hypersensitivity reaction triggered by inhaled allergens in which inflammatory mediators are released by local mast cells and T-helper 2 lymphocytes; subsequently, the inflammatory mediators recruit eosinophils into the airways and lung parenchyma. Eosinophils, the primary effector cells in asthma, cause airway wall edema, metaplastic transformation of the airway epithelium, and hypertrophy and hyperplasia of the mucous glands and intraepithelial mucous cells.12 Chronic airway inflammation also causes airway smooth muscle hypertrophy and sensitization of airway sensory nerves, promoting bronchoconstriction. The resultant airway wall remodeling, distal airway mucus accumulation, and bronchoconstriction cause dynamic small airway obstruction.13,14 With each inspiration, air moves into the terminal airways, but increased intrapleural pressure combined with increased resistance to air flow caused by inflammation, mucus, and bronchospasm lead to air entrapment in the terminal airways.1,12 The inability to completely expel air on expiration leads to pulmonary hyperinflation and an increase in intrinsic positive-end expiratory pressure.13,15 Intrinsic positive-end expiratory pressure represents the difference between the pressure in the alveolus and the pressure during opening of the airways at the end of expiration and is...
therefore a reflection of an increase in alveolar pressure.\textsuperscript{10} This increase in alveolar pressure combined with chronic inflammation and airway obstruction can initiate rupture of the alveolar walls and progressive development of emphysematous lesions as well as blebs and bullae in the lung parenchyma. Pneumothorax occurs when the alveolar pressure becomes greater than the interstitial pressure, causing blebs or bullae to rupture and thereby allowing air to leak into the pleural cavity.\textsuperscript{10,13}

Typical histologic findings in the lungs of feline and human asthmatic patients include peribronchial epithelial infiltration of eosinophils and neutrophils, hyperplasia and hypertrophy of the goblet cells and submucosal glands, basement membrane thickening, bronchial smooth muscle hypertrophy, and accumulation of mucus and cellular debris within the bronchial lumens.\textsuperscript{1,16} Lobular and bullous emphysema and bronchiectasis have also been reported as morphological sequelae in humans and cats with asthma.\textsuperscript{1,16}

The syndrome of asthma has not been identified in dogs, to our knowledge. In cases of severe EPB and asthma, the lungs have some similar histologic features, including peribronchial eosinophilic infiltrates, epithelial ulceration, and mucosal infiltration with plasma cells, macrophages, lymphocytes, and mast cells. However, the presence of extensive peribronchial smooth muscle hypertrophy, a common finding in asthmatic lungs,\textsuperscript{13,17,18} has not been reported in association with EPB.\textsuperscript{19} Although some dogs with EPB can have bronchial hyperreactivity,\textsuperscript{7} this has not been associated with the smooth muscle remodeling observed in humans and cats with asthma.\textsuperscript{13,17,18} Furthermore, EPB has not been associated with the development of alveolar damage and pneumothorax, both of which can develop as sequelae to small airway obstruction in cases of asthma.\textsuperscript{1,16}

Histologic findings in the case described in the present report had more similarities with the reported histologic features associated with asthma in humans and cats than with the reported histologic features associated with EPB in dogs. Indeed, microscopic examination of specimens of excised lung from the dog of this report revealed marked bronchial and bronchiolar smooth muscle hypertrophy, a pathognomonic feature of asthma, as well as peribronchial clusters of eosinophils and intraluminal mucus. Hypertrophy of the intraepithelial and submucosal mucus secretory apparatus and peribronchial fibrosis were also detected in the sections of lung tissue. Although these latter features have also been associated with EPB, the constellation of the histologic findings and clinical signs for the dog of the present report are more consistent with asthma. Given that EPB is also believed to be the result of a type I hypersensitivity reaction mediated by exposure to aeroallergens,\textsuperscript{8} it is possible that the case described in the present report represents a more progressed form of EPB. However, the lack of smooth muscle remodeling, comorbid alveolar damage, and spontaneous pneumothorax described in previous reports\textsuperscript{10,19} of EPB suggests that the pathophysiologic processes in the present case may differ from those in typical cases of EPB. Further histologic and immunologic characterization of eosinophilic airway diseases in dogs is warranted.

Radiography is an excellent imaging technique for accurate diagnosis of pneumothorax but is less reliable for the identification and localization of bullae or blebs.\textsuperscript{10} The sensitivity of radiography for diagnosis of bullae or blebs ranges from 0% to 31%,\textsuperscript{20-22} and radiographic findings correlate with surgical findings in only 50% of dogs with pneumothorax.\textsuperscript{21} The superiority of CT in the characterization of bullous pulmonary disease and evaluation of surrounding pulmonary parenchyma has been determined in a study\textsuperscript{23} in dogs in which 2.5 times as many lesions were identified via CT as were identified via conventional radiography. Radiography is also commonly used in the diagnosis of asthma in humans and cats. However, thoracic radiographic views obtained from both asthmatic people and cats can appear normal.\textsuperscript{18,24} Furthermore, the presence of pneumothorax at the time of imaging can make interpretation of pulmonary parenchymal and bronchial alterations difficult. For this reason, maintaining continuous suction or performing thoracocentesis prior to thoracic imaging is recommended.\textsuperscript{23} Computed tomography has been used to evaluate the extent of airway remodeling in asthmatic humans by correlating indices of bronchial wall thickness and area and the ratio of total airway wall thickness to total airway diameter with measurements of airway epithelial membrane thickness in bronchial biopsy specimens.\textsuperscript{25,26} Parenchymal abnormalities such as centrilobular micronodules, mosaic perfusion, and air trapping can also be observed via CT.\textsuperscript{23}

In the dog of the present report, neither blebs nor bullae were identified on survey radiographic views, although radiography is recommended for evaluation of the thoracic cavity for obvious pulmonary abnormalities before anesthesia or surgery are pursued. In the case described in this report, CT was helpful in localizing the most affected lung tissue and assisted in surgical planning. Surgical findings were in agreement with CT findings regarding location and number of subpleural blebs, although CT failed to identify the extent of the emphysematous lesions at the periphery of all lung lobes.

Surgical management of spontaneous pneumothorax in dogs is associated with lower recurrence and mortality rates, compared with results of conservative management.\textsuperscript{21} As such, the standard of care in our hospital is for early surgical exploration and removal of bulla or blebs identified in dogs with spontaneous pneumothorax. In contrast, treatment of primary or secondary spontaneous pneumothorax in humans is usually conservative, involving rest, thoracocentesis, oxygen therapy, and thoracostomy tube placement.\textsuperscript{27,28} Medical management is also favored in cases of asthma-induced pneumothorax.\textsuperscript{9,10,27}

In the veterinary medical literature, cats that have asthma complicated with pneumothorax have been managed conservatively with thoracocentesis or thoracostomy tube placement and medical management for asthma (ie, administration of bronchodilators and corticosteroids).\textsuperscript{7,5} In 2 cases, mechanical ventilation was required, and one of those cats was euthanized. In 6 cats, pneumothorax resolved within 1 week after initial diagnosis.\textsuperscript{5} Long-term follow-up was only available in 1 case; for that cat, 2 episodes of recurrent pneumothorax causing respiratory distress 5 and 17 months after the initial evaluation were documented.\textsuperscript{5} The cat died before treatment could be initiated following the second recurrence.
In the dog described in the present report, thoracostomy tubes were placed during the initial evaluation because of the large amount of air obtained via thoracostentesis. Continuous suction via the tubes was started because of progressive labored breathing after thoracostentesis that was thought to be related to rapid accumulation of air within the pleural space. On the basis of the radiographic and CT findings, the need for continuous pleural suction, and the current recommendation for treatment of spontaneous pneumothorax, surgery was elected. Medical management may be acceptable in dogs with pneumothorax related to asthma but will be complicated in cases for which the diagnosis of asthma is made on the basis of histologic findings and not on the basis of a spectrum of known clinical signs and imaging findings. The recognition of asthma-like lung conditions in dogs may lead to increased differentiation of this syndrome from other diseases, the development of effective treatments, and further study of the optimal management of spontaneous pneumothorax related to asthma in dogs. The dog of the present report had secondary spontaneous pneumothorax resulting from reactive airway disease, which highlights the need to include reactive bronchopneumopathy among the differential diagnoses for spontaneous pneumothorax in dogs.

References