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PERSPECTIVE

Perspectives in veterinary medicine: Description and classification of bronchiolar disorders in cats

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Abstract

This Perspectives in Veterinary Medicine article seeks to define, describe putative causes, and discuss key diagnostic tests for primary and secondary bronchiolar disorders to propose a classification scheme in cats with support from a literature review and case examples. The small airways (bronchioles with inner diameters <2 mm), located at the transitional zone between larger conducting airways and the pulmonary acinus, have been overlooked as major contributors to clinical syndromes of respiratory disease in cats. Because the trigger for many bronchiolar disorders is environmental and humans live in a shared environment with similar susceptibility, understanding these diseases in pet cats has relevance to One Health. Thoracic radiography, the major imaging modality used in the diagnostic evaluation of respiratory disease in cats, has low utility in detection of bronchiolar disease. Computed tomography (CT) with paired inspiratory and expiratory scans can detect pathology centered on small airways. In humans, treatment of bronchiolar disorders is not well established because of heterogeneous presentations and often late definitive diagnosis. A review of the human and veterinary medical literature will serve as the basis for a proposed classification scheme in cats. A case series of cats with CT or histopathologic evidence of bronchiolar lesions or both, either as a primary disorder or secondary to extension from large airway disease or interstitial lung disease, will be presented. Future multi-institutional and multidisciplinary discussions among clinicians, radiologists, and pathologists will help refine and develop this classification scheme to promote early and specific recognition and optimize treatment.

KEYWORDS

asthma, bronchiolitis, chronic bronchitis, fibrotic lung disease, interstitial lung disease, tree-in-bud pattern

1 | WHAT ARE BRONCHIOLAR DISORDERS?

Abnormalities of the bronchioles, defined as small airways <2 mm in internal diameter and lacking cartilage in their walls, result from a variety of pathologic processes and lead to a wide spectrum of clinical

Abbreviations: BAL, bronchoalveolar lavage; CBO, constrictive bronchiolitis obliterans; CT, computed tomography; DAB, diffuse aspiration bronchiolitis; DSH, domestic shorthair; FeLV, feline leukemia virus; FIV, feline immunodeficiency virus; FS, female spayed; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; MC, male castrated; PBO, polyploid bronchiolitis obliterans.

disease. Advances in understanding bronchiolar disorders in humans have been hampered by lack of a widely accepted classification scheme because of different viewpoints of clinicians, radiologists, and pathologists. In humans, bronchiolar disorders are classified by inciting cause (eg, infection, drug related, immune-mediated, or occupational or environmental exposures), clinical sequelae (eg, restrictive, obstructive, or mixed disorders), imaging, histologic features, or some combination of these.[11,14,15] Bronchiolar disease can be focal or diffuse, acute, or chronic, inflammatory or fibrotic, and confined to the lungs or develop as part of a variety of systemic diseases.[8,9] In primary bronchiolar disorders, disease centers on bronchioles and spares other parts of the respiratory tract. In secondary bronchiolar disorders, disease extends to small airways from either the large airways or pulmonary parenchyma (eg, interstitial lung diseases [ILDs]).[10] Bronchiolar disorders, although recognized in humans, have not yet been described as distinct clinical entities in veterinary medicine.

Lower airway diseases of cats (eg, asthma, chronic bronchitis, parasitic bronchitis) are common, although lower airway disease has been considered a large (ie, "bronchial") airway disorder. Extension of inflammation into the bronchioles, although at times recognized histologically,[17] is not characterized clinically. Uncommonly recognized in cats, descriptions of ILDs infrequently mention bronchiolar involvement.[18,19] With increasing use of computed tomography (CT), abnormalities suggestive of bronchiolar disease are being identified in cats. Multidisciplinary input from clinicians providing detailed clinical descriptions, radiologists characterizing CT features, and pathologists documenting and describing bronchiolar lesions will be essential to develop a consensus classification.

2 | ETIOLOGY WITH AN EMPHASIS ON ENVIRONMENTAL TRIGGERS

Bronchiolar disorders may result from infection, environmental or occupational exposures, immunologically mediated disease, neoplasms, chronic aspiration, and drug-induced toxicity, among other causes.[20–23] Although a description of each is beyond the scope of this article, a discussion of environmental bronchiolar disorders in humans appears relevant because cats and humans share their environment and potential exposures. Known or suspected exposures causing bronchiolar disorders in humans have been reviewed[11] and include chemicals (eg, cleaning compounds, pesticides, artificial flavorings), inhalant particulates, animal or mineral dusts, and gas and smoke inhalation. Previously, environmental bronchiolar disorders were thought to be an acute sequela to a severe, overwhelming exposure, but more recently, disease with an insidious onset of clinical signs without a recognized overexposure event (perhaps representing cumulative smaller exposures) or a mild single exposure has been appreciated.[24] Injury to bronchiolar epithelial cells leads to inflammation and a fibroproliferative repair response, ultimately resulting in mural fibrosis (constrictive bronchiolitis) or intraluminal fibrosis (proliferative bronchiolitis).[25] Four histopathologic types of disease have been proposed: cellular bronchiolitis (inflammatory infiltrate of the bronchioles), constrictive bronchiolitis (concentric fibrosis of the wall leading to narrowed airway caliber), proliferative bronchiolitis (polyps of connective tissue within the bronchiolar lumen), and bronchiolitis obliterans organizing pneumonia (proliferative bronchiolitis with polyps extending into the alveolar ducts and alveoli).[11]

BOX 1 The importance of the secondary pulmonary lobule in humans and the lack of an analogous structure in cats

Superior imaging detail of computed tomography (CT) allows comparison with histologic features. In the human lung, an understanding of microscopic anatomy centering on the secondary pulmonary lobule is critical to make these correlations.

- The secondary pulmonary lobule consists of polyhedral regions approximately 2 cm in diameter bordered by interlobular septa
- Secondary pulmonary lobules have multiple pairs of lobular bronchioles and arterioles that accompany each other into the center of this anatomic unit (ie, the so called "centrilobular" location)
- Lobular bronchioles successively divide in the following manner: terminal bronchioles, respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli
- Blood flows from arterioles into sheets of capillaries in the walls of alveoli and finally are drained by venules located at the borders of the secondary pulmonary lobules (ie, in the interlobular septal regions)
- Lymphatics extend from respiratory bronchioles tracking back to the hilus of the lung in bronchovascular bundles and are present in the interlobular septa following venules back to the hilus; no lymphatics surround alveoli
- Collectively, the cross-sectional area of the bronchioles is larger than the proximal airways; although they provide little resistance to airflow in the normal lung, even mild disease of the small airways can have severe detrimental effects on lung function[8,9]

In cats, there is a lack of a structure analogous to the secondary pulmonary lobule seen in humans. This has important implications in use of the same CT descriptors and between-species comparative studies.

3 | LACK OF A SECONDARY PULMONARY LOBULE IN CATS AND IMPLICATIONS FOR CT DESCRIPTORS

Compared to humans, cats lack connective tissue septa in the lung outlining a secondary pulmonary lobule (Box 1). Furthermore, there is no distinctive recognizable pattern of analogous bordering venules and lymphatics arranged in discrete polyhedral shapes that might comprise this unit. Thus, even in disease, pathology on CT scans of cats would not reflect distribution around a pulmonary lobule. Terms used in imaging of human lung such as centrilobular, panlobular, interlobular, and intralobular are not appropriate descriptors in cats. Dogs are similar to cats and also lack secondary pulmonary lobules, and the pulmonary acinus has been suggested to be the important high-resolution CT (HRCT) unit of the canine lung.[26] The acinus is defined as the region of the lung supplied by a single terminal bronchiole, representing the smallest functional unit of the lung. Because it is smaller than the secondary pulmonary lobule that is the smallest visible structure on HRCT, we believe that the pulmonary acinus is not a replaceable term as the important HRCT unit of the feline (or canine) lung. Instead, descriptors of collective changes of multiple acini visible on HRCT will need to be developed and refined.

4 | IMAGING AND HISTOLOGY

Thoracic radiography is insensitive for diagnosis of small airway (bronchiolar) disease, likely contributing to the absence of its recognition in clinical practice. Thoracic radiographs in humans with bronchiolar disease may be normal or show nonspecific changes such as hyperinflation, nodules, and reticular to alveolar infiltates.[11,21] In our experience, thoracic radiographs in cats with histologic evidence of bronchiolar disease can have bronchial or bronchointerstitial patterns (with or without bronchiectasis), patchy alveolar patterns, ill-defined nodular opacities, and hyperinflation or hypoinflation. The radiographic appearance of histologically confirmed bronchiolar disease in cats does not present as a single pathognomonic radiographic pattern, but is highly variable, reflecting the different diseases encompassed in the spectrum of bronchiolar disorders. Importantly, without clinical recognition of these disorders, bronchiolar disease is not considered as a differential diagnosis. In humans, HRCT has been instrumental in improving diagnosis of bronchiolar disorders, establishing them as important disease entities in pulmonary medicine. With more commonplace use of CT in cats, we are recognizing some features similar to those described in humans. Paired inspiratory and expiratory scans and thin section reconstruction (0.625-2 mm slice thickness)[27] provide optimal detail.

Normal bronchioles in humans and cats are below the limits of resolution on HRCT, but with dilatation, mural thickening, and intraluminal plugging, small airways become visible.[8] Bronchiolar disorders have characteristic HRCT features, classified as direct or indirect signs.[8,28] Direct signs imply a change in the walls or lumens of bronchioles resulting in an ability to visualize them. These signs include centrilobular nodules (humans only), tree-in-bud pattern (nodular opacities connected to branching linear structures originating from a single stalk reflective of impacted debris, cells, or fluid within bronchioles), peribronchiolar ground glass opacity or consolidation, and dilatation (bronchiolectasis).[5,14,27] Indirect signs reflect changes to the pulmonary parenchyma distal to the diseased bronchiole and include mosaic attenuation (because of air trapping) or, in the setting of bronchiolar disorders, rarely mosaic perfusion.[27] Because air trapping may be imperceptible on inspiratory images, expiratory scans are crucial to accentuate air trapping.[8] Direct findings reflect inflammation or proliferative changes within the bronchiolar lumens, whereas indirect findings reflect fibrosis within the bronchiolar wall (eg, constrictive bronchiolitis).[8]

Definitive confirmation of bronchiolar involvement requires histopathology. The microscopic anatomy of bronchioles is similar between humans and cats. Distal bronchioles are lined by simple cuboidal epithelium supported on a thin lamina propria and surrounded by smooth muscle. Airways end as respiratory bronchioles before the alveolar parenchyma in the cat (Figure 1) and in humans. Microscopic morphology has been used to categorize lesions as inflammatory or fibrotic, recognizing there are a limited number of ways airways respond to injury.[9] Inflammatory or cellular lesions often are subcategorized as acute, chronic, acute on chronic, granulomatous, or eosinophilic. Fibrotic lesions reflect the site affected (intraluminal or intramural); overlap in inflammatory and fibrotic changes can be noted within the same patient.[9] Multiple wedge biopsy specimens are recommended to capture patchy and sometimes subtle lesions.[29] A particular histologic pattern of disease may have a wide variety of causes. For example, inflammatory bronchiolitis can be caused by infection, aspiration, transplant rejection, and extension from large airway disease or systemic collagen vascular disease, among other causes.[9] Fibrosis may be a sequela to chronic inflammation so that in end-stage disease, the inflammatory etiology can be missed. Thus, classification schemes based solely on histopathologic features are likely to be less clinically useful, and multidisciplinary

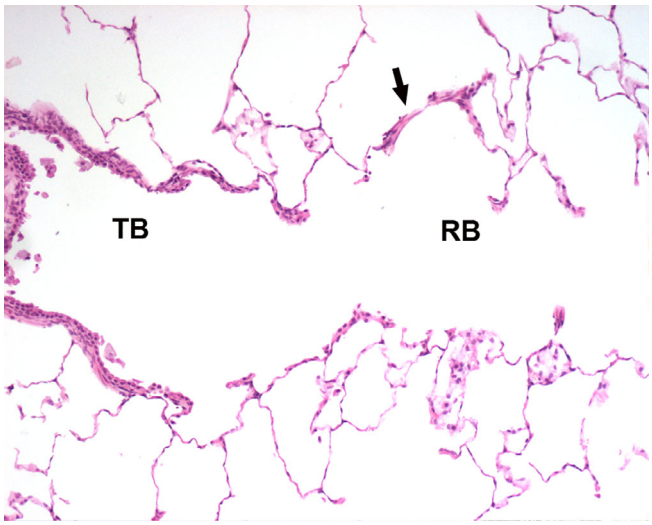

FIGURE 1 Normal cat lung histology (hematoxylin and eosin stain). Terminal bronchioles (TB) are lined by low cuboidal epithelium and surrounded by thin smooth muscle. The airway terminates as respiratory bronchiole (RB) before entering the alveoli

input should be sought to allow meaningful interpretation of histologic findings. This should not dampen enthusiasm for the central role of histopathology in an understanding of bronchiolar disorders. In fact, in humans, histopathology may be the only means to document bronchiolar disease in the subset of symptomatic patients with normal lung function (as assessed by spirometry, diffusion capacities, and cardiopulmonary exercise testing) and normal HRCT scans.[30]

5 | CLASSIFICATION OF BRONCHIOLAR DISORDERS

In humans, bronchiolar disorders often have distinct historical data, clinical presentations, CT findings, and histopathology. Our proposed scheme, adapted for cats, is based on a state-of-the-art review of bronchiolar disorders in humans that focuses on discrete clinical syndromes supported by distinct CT imaging patterns and histopathologic features.[10] Of note, this scheme is not universally accepted, and there are other proposed schemes biased by specialty, in particular pathology.[9]

Primary bronchiolar disorders in humans encompass disease in which the pathologic process is limited to bronchioles.[10] They are distinct from secondary disorders in which extension to bronchioles occurs from large airway disease or from ILD. Analogous disorders occur in cats and will require further efforts among veterinary clinicians, radiologists, and pathologists for full characterization. Herein, we describe a series of clinical cases in cats with small airway disease using a modification of the aforementioned classification scheme adopted from usage in humans (Table 1). Protocols for thoracic CT and histologic examination are provided in Supporting Information 1 and 2.

TABLE 1 Proposed classification scheme for bronchiolar disorders in the cat

Primary bronchiolar disorders[a]
- Constrictive/obliterative bronchiolitis (Case 1)
- Mineral dust airway disease (Case 2)
- Infectious bronchiolitis[b40-45] (Case 3)
- Other primary bronchiolar variants (Case 4, 5)[16]

Secondary bronchiolar disorders
- Extension of large airway disease
  - Asthma (Case 6, 7)
  - Chronic bronchitis (Case 8, 9)
  - Parasitic bronchitis (Case 10)
  - Bronchiectasis[17]
- Component of interstitial lung diseases[c]
  - Bronchiolitis obliterans with organizing pneumonia/cryptogenic organizing pneumonia[12]
  - Bronchiolocentric interstitial pneumonia/airway centered interstitial fibrosis (Case 11)

Adapted from Ryu et al. (2003).
[a]Excluded from the list of primary human bronchiolar disorders at this time are diffuse panbronchiolitis (described as predominantly occurring in humans of Asian descent with a genetic predisposition), respiratory bronchiolitis (a smoking-related airway disorder), and follicular bronchiolitis[59] (a lymphoproliferative pulmonary disease).
[b]In the human classification scheme, "acute bronchiolitis" is used. This is a common disorder almost always secondary to infection in the pediatric population. We have revised the feline classification scheme to include acute and chronic infectious diseases affecting the small airways.
[c]Excluded from the list of human bronchiolar disorders as a component of ILDs at this time are hypersensitivity pneumonitis (not yet recognized in cats), and respiratory bronchiolitis-associated ILD/desquamative interstitial pneumonia (smoking-related disorders).

Although this suggested classification scheme is a starting point for cats, it will need modification as awareness of bronchiolar disorders in cats increases and cases are investigated prospectively. Additionally, it is critical to realize that veterinarians are likely to detect bronchiolar disorders late in the disease course for several reasons: (i) cats hide respiratory disease well, (ii) aggressive diagnostic testing, including lung biopsy, is rarely advocated unless underlying disease is serious and there are potentially treatable differential diagnoses, (iii) serious disease is associated with anesthetic risk, and (iv) advanced diagnostic tests are expensive. Detection of end-stage lesions will not provide much needed clues about common underlying etiologies because the inciting factor may be gone, and there are likely many insults that share a final common pathway with similar clinical, physiological, and histologic appearances.[25] At the present, we believe that CT provides the best minimally invasive antemortem evidence of bronchiolar disease in cats. Importantly, histopathologic correlates will be required before CT alone can be considered a less invasive surrogate diagnostic test.

6 | PRIMARY BRONCHIOLAR DISORDERS

6.1 | Constrictive/obliterative bronchiolitis

Subepithelial and peribronchiolar fibrosis and inflammation that externally surrounds and narrows or obliterates the lumen of bronchioles is termed constrictive bronchiolitis obliterans (CBO).[10] In advanced stages, the bronchiolar lumen undergoes complete cicatrization and is replaced by collagenous tissue. This pattern of bronchiolar fibrosis is not to be confused with intraluminal polyps of connective tissue within the bronchiolar lumen as occur in polypoid bronchiolitis obliterans (PBO).[25] In cats, PBO previously has been described with associated pneumonia (ie, bronchiolitis obliterans with organizing pneumonia[12]) and is considered an ILD.

Disorders and exposures in humans leading to CBO include prior infection, inhalational injury (flavoring chemicals in microwave popcorn, e-cigarettes, coffee, and others[31–34]), ingested drugs or toxins, autoimmune disease, and connective tissue disorders.[25] Humans present with clinical signs of an obstructive lung disorder with an insidious onset of progressive dyspnea and cough.[25] Thoracic radiography may be normal or show hyperinflation from air trapping; airway wall thickening also may be appreciated.[25,35] High-resolution CT predominantly identifies mosaic attenuation, bronchiolectasis or bronchiectasis, and air trapping accentuated on expiratory views.[10,27] Most cases are progressive, poorly responsive to corticosteroids and result in respiratory failure and death.[36] One cat in a case series had suppurative bronchopneumonia, bronchiolitis obliterans, and pulmonary fibrosis; it is unclear if this cat had a primary bronchiolar disorder or an ILD with secondary bronchiolar involvement.[18] Another cat in a case series had "fibrosing bronchiolitis" and "pneumonia" as histologic descriptors but not as the clinical syndrome or final diagnosis.[37] Recently, a reversible form of acute fibrosing bronchiolitis has been

identified in humans.[38] Although this acute form has not yet been identified in cats, treating with immunosuppressive drugs to prevent permanent bronchiolar fibrosis has important implications.

6.1.1 | Case 1

A 7-year-old female spayed (FS) domestic shorthair (DSH) cat had been treated over a 10-month period by a primary veterinarian for intermittent and progressive labored respiration. The cat was 1 among 50 cats housed in a double-wide trailer. Potential inhalant exposures included particulates from clumping cat litter and concentrated bleach used for cleaning. The owner herself recently had been diagnosed with small airway disease. Thoracic radiographs showed hyperinflation, a diffuse bronchial pattern, a multifocal unstructured interstitial pattern with progression toward an alveolar pattern, lung atelectasis, subpleural thickening, and bronchiectasis and bronchiolectasis in peripheral opaque regions (Figure 2 A, B). The cat did not respond to multiple courses of antibiotics or antifungal drugs but had a partial clinical response to prednisolone. The cat died and was submitted for necropsy. Grossly, the lungs were hyperinflated. Histologically, mixed chronic inflammation involved the pulmonary interstitium and was especially prominent in subpleural areas (Figure 2 C). Respiratory bronchioles were obliterated by loose fibrous tissue (Figure 2 D). The lesions noted in this cat represented a spectrum of early (markedly inflammatory) and late (predominantly fibrosis) foci. Furthermore, although distribution was centered on small airways reflective of a primary bronchiolar disorder, there was extension into the interstitium with a subpleural distribution. Important considerations for discriminating primary bronchiolar disorders like CBO from secondary bronchiolar disorders are noted in Box 2.

6.2 | Mineral dust airway disease

Still considered a form of pneumoconiosis, mineral dust can deposit around and primarily cause disease of respiratory bronchioles and

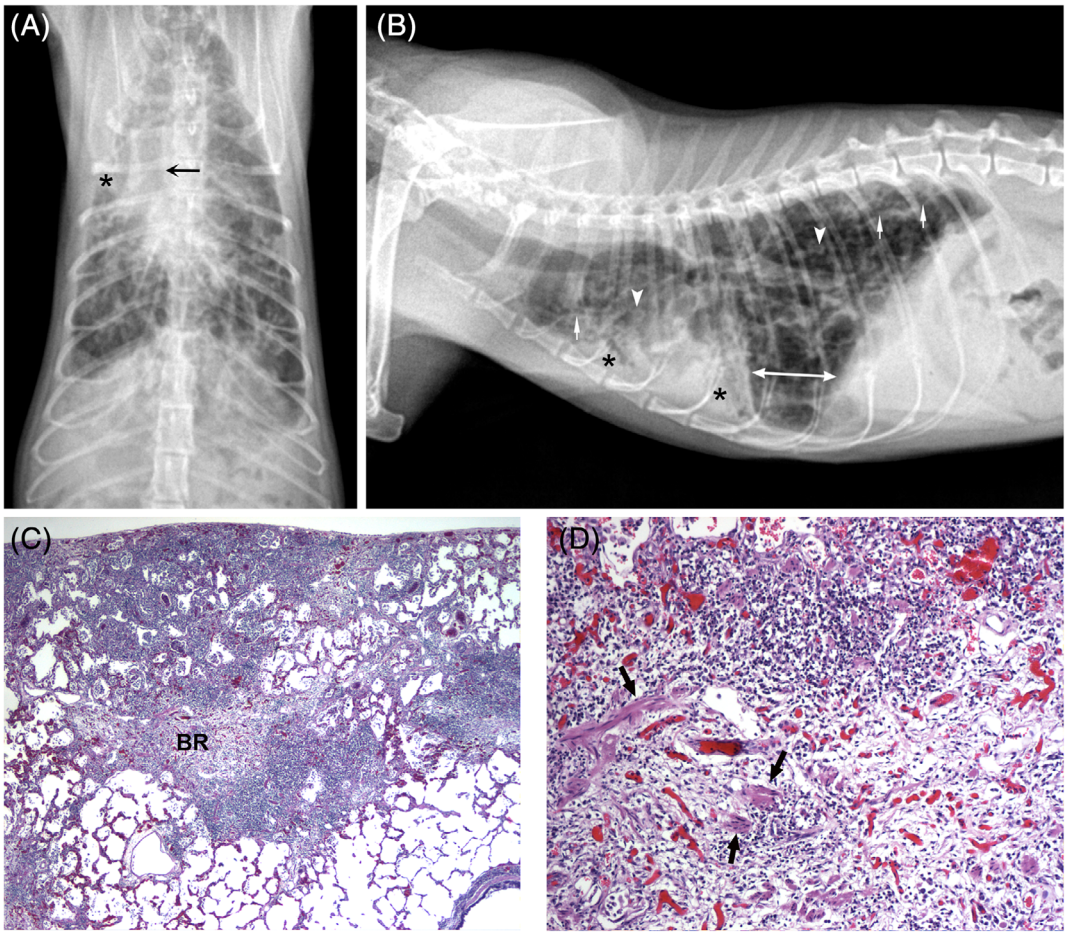

FIGURE 2 A 7-year-old domestic shorthair cat with constrictive bronchiolitis. (A) Ventrodorsal and (B) right lateral radiographs obtained at the referring veterinarian showing hyperinflation, as represented by an increased distance between the cardiac silhouette and the diaphragm (double-headed arrow). A severe bronchial pattern is seen throughout the lung field accompanied by severe peribronchial infiltrates (arrowhead). Consolidated/atelectatic areas (*) involving the cranioventral aspect of the lung, more severe on the right, and rightward deviation of the trachea (black arrow) are also present. Several bronchi (white arrows) do not taper as they extend to the periphery suggesting the presence of extensive bronchiectasis. (C) Severe mixed chronic inflammation is present involving the subpleural alveolar parenchyma and extending into the deeper lung. In the center of the figure, the remnants of a bronchiole (BR) can be seen among fibrosis and inflammation. Hematoxylin and eosin stain. (D) Smooth muscle (arrows) indicate the presence of the aforementioned disrupted bronchiole. Hematoxylin and eosin stain

BOX 2 Challenges in discriminating primary from secondary bronchiolar disorders

A diagnosis of feline asthma is frequently made based on thoracic radiography showing hyperinflation with a bronchial or bronchointerstitial pattern (with or without lobar atelectasis) and is the major obstructive airway disorder clinically described in cats.

- Constrictive/obliterative bronchiolitis represents an important "new" differential diagnosis, especially in cats with other unusual radiographic features, those who fail to respond to treatment with bronchodilators and glucocorticoids, or both. Thoracic computed tomography (CT) should be offered in these situations. Although a CT scan was not performed in case 1, presumptively there would have been lesions localized to small airways.

Pathology extending from bronchioles into the interstitium makes it tempting to speculate that primary bronchiolar diseases may in their end stages appear as an ILD, analogous to ILDs starting in the interstitium and progressing to a secondary bronchiolar disorder (see case 11).

- Lesions involving both bronchioles and interstitium are challenging to determine which region suffered the initial insult before progression to other local regions. This underscores the need to take adequately large specimens from multiple regions of the lung (more and less affected) when submitting for histopathologic examination.

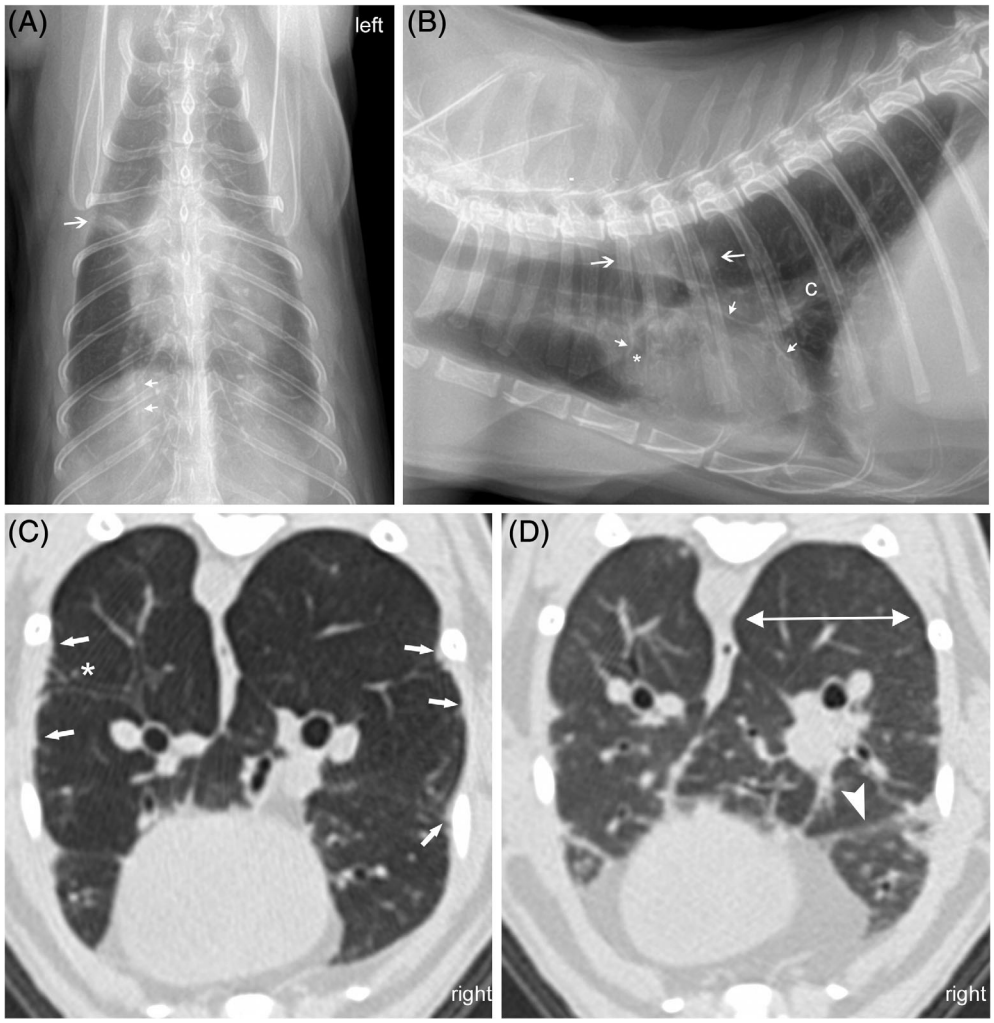

FIGURE 3 A 5-year-old domestic shorthair cat with mineral dust airway disease. (A) Ventrodorsal and (B) right lateral radiographs showing thickening of the bronchial walls (small white arrows), bronchiectasis (*) and unstructured interstitial pattern affecting the lungs more severely in the central aspect of the thorax particularly at the level of the lung lobe margins creating the impression of ill-defined nodule (wide arrows). The caudal vena cava (c) is not well demarcated. (C) Inspiratory and (D) expiratory computed tomography (CT) transverse images of the same cat acquired 2 weeks after the radiographs. Subpleural interstitial thickening (thick arrows) is visible at multiple locations along the costal aspect of the right and left lungs, and the lung fissures are thickened. Bronchiolectasis (*) is seen involving the subsegmental bronchus LB2D2. No air trapping is visualized on the expiratory CT image as illustrated by the reduced lung volume (double headed arrow), and homogenous diffuse increased lung attenuation. Pleural thickening is accentuated during exhalation (arrowhead). The right side of the patient is on the right of the CT images

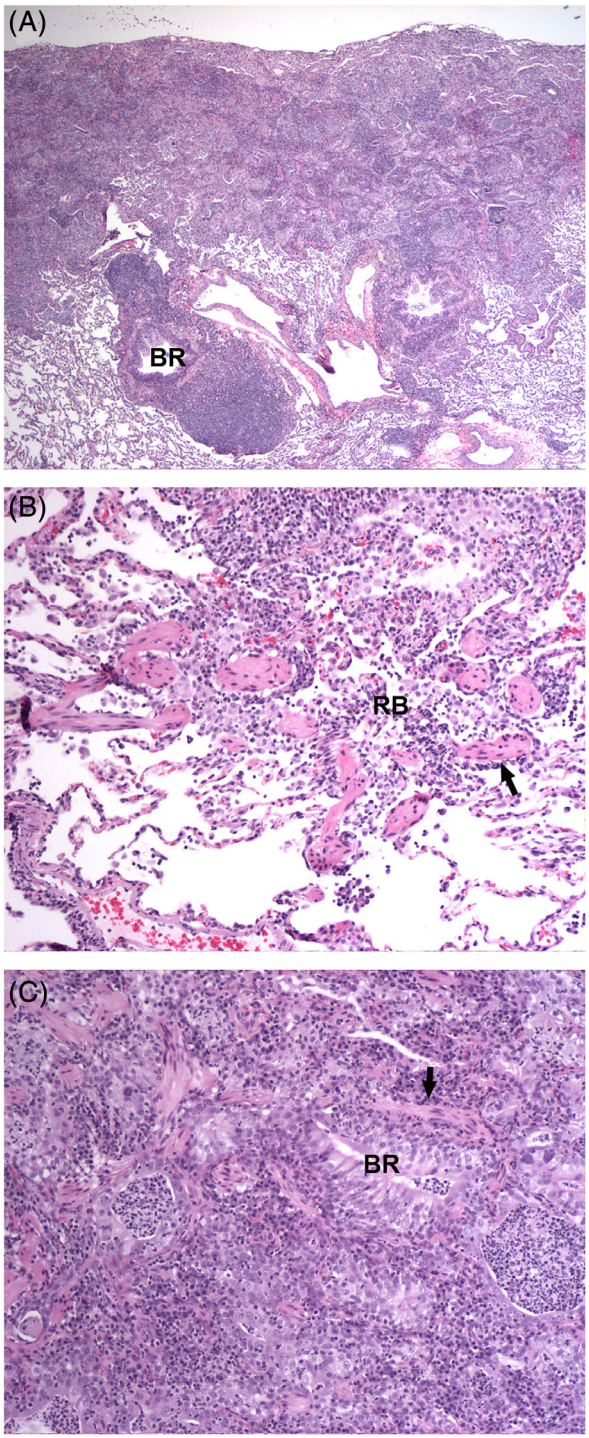

FIGURE 4 A 5-year-old domestic shorthair cat with suspect mineral dust airway disease. (A) Severe mixed chronic inflammation is present involving the subpleural alveolar parenchyma and extending into the deeper lung. Hematoxylin and eosin stain. (B) Bronchiole (BR) is surrounded by prominent hyperplasia of bronchiolar-associated lymphoid tissue. In areas of lung less severely affected, foci of inflammation are present centered on the respiratory bronchioles (RB); note the increased mass of bronchiolar smooth muscle (arrow). Hematoxylin and eosin stain. (C) In the subpleural lung, there is severe chronic inflammation and smooth muscle hyperplasia. Bronchioles (BR) are lined by hyperplastic epithelium and surrounded by enlarged smooth muscle (arrow). Hematoxylin and eosin stain

alveolar ducts. The pathologic response to inhalation of asbestos, silica or silicates, aluminum, and coal (among others) targeting small airways is mural fibrosis with mild chronic inflammation leading to luminal narrowing.[2,14] In humans, classic pneumoconiosis leading to pulmonary parenchymal fibrosis is considered a restrictive lung disorder, whereas mineral dust airway disease may present as an obstructive airway disorder.[10]

6.2.1 | Case 2

A 5-year-old male castrated (MC) DSH cat was presented for evaluation of chronic cough and 1 week of tachypnea. Its environment was exclusively indoors with clumping clay cat litter noted as a potential inhalant exposure. Physical examination identified increased bronchovesicular sounds with a respiratory rate of 70 breaths per minute. Thoracic radiographs disclosed a moderate diffuse bronchointerstitial pattern, patchy areas of unstructured to structured (with ill-defined contours) interstitial pattern, and repeatable hypoinflation on all views (Figure 3 A, B). On echocardiography, no evidence of pulmonary hypertension was found. On thoracic CT, multifocal subpleural linear opacities, parenchymal bands, and bronchiolectasis with no air trapping on expiratory breath-hold images were observed (Figure 3 C, D). Bronchoalveolar lavage (BAL) cytology identified 45% nondegenerate neutrophils, and aerobic and anaerobic cultures were negative. Lung biopsy (Figure 4 A-C) disclosed marked inflammation within and around terminal and respiratory bronchioles, with most severe inflammation in subpleural regions. Away from the severe fibrosis and inflammation, inflammation was centered upon respiratory bronchioles. Many of these bronchioles were lined by hyperplastic epithelium and surrounded by thickened smooth muscle. Rarely, small numbers of acicular particles suggestive of mineral origin were noted in macrophages and epithelial cells (not shown). Additional comments regarding mineral dust airway disease are presented in Box 3.

BOX 3 Mineral dust airway disease: additional considerations

Mineral dust airway disease is associated with the presence of foreign material (inhaled inorganic dusts) and an associated chronic bronchiolar inflammatory response with some degree of mural fibrosis.[1,2]

- Identification of mineral dusts can be challenging unless a careful search with polarized light is used; very small particulates will be difficult to visualize using routine microscopy.
- Owners should be questioned about specific environmental exposures and identified mineral dusts should be avoided.
- It is unclear in cats if mineral dust airway disease in its end stages can appear as a constrictive bronchiolitis or pulmonary fibrosis, and further study is needed.

6.3 | *Infectious bronchiolitis* (referred to as "acute bronchiolitis" in the human medical literature)

Acute bronchiolitis occurs most commonly in infants and children secondary to infection (especially respiratory syncytial virus, adenovirus, influenza, parainfluenza, mycoplasma, and chlamydia), and in adults from inhalation of toxins, after organ transplantation and in connective tissue disorders. [10,39] Confusingly, histologic descriptions of infectious bronchiolitis include both acute and chronic inflammation; fungal and mycobacterial infections are mentioned in the discussion of acute bronchiolitis despite the potential to be more chronic.[10] Direct signs of bronchiolitis in cats using CT imaging include tree-in-bud lesions noted with pulmonary fungal infection (see Case 3 below), and peribronchiolar ground-glass opacity and bronchiolectasis with mycobacteriosis (data not shown). Experimentally or spontaneously, influenza A viruses including H1N1, H5N1, and H5N2 as well as herpesvirus and *Mycoplasma* spp. have been associated with bronchiolar wall thickening on CT or histopathologic evidence of bronchiolar involvement in cats.[40–45]

In most cases, bronchiolar involvement was overshadowed by alveolar involvement, with pneumonia being the final diagnosis. To our knowledge, noninfectious causes of acute bronchiolitis recognized in adult humans have not been described in cats thus the proposal to rename this category "infectious bronchiolitis."

6.3.1 | Case 3

A 15-year-old FS DSH cat was presented for fever, anorexia, and lameness of 2 weeks' duration. Physical examination disclosed a respiratory rate of 120/min, increased bronchovesicular sounds, and thickened bowel loops. Diagnostic test results included pancytopenia, hyperbilirubinemia, and hypoalbuminemia, normal total T4 concentration, negative status for feline leukemia virus (FeLV) and heartworm antigen, but positive results for feline immunodeficiency virus (FIV), normal neurologic and ophthalmic examinations, and a diffuse bronchointerstitial pattern on thoracic radiography. A CT scan of the thorax showed a diffuse tree-in-bud pattern and mosaic attenuation (Figure 5A-C); abdominal

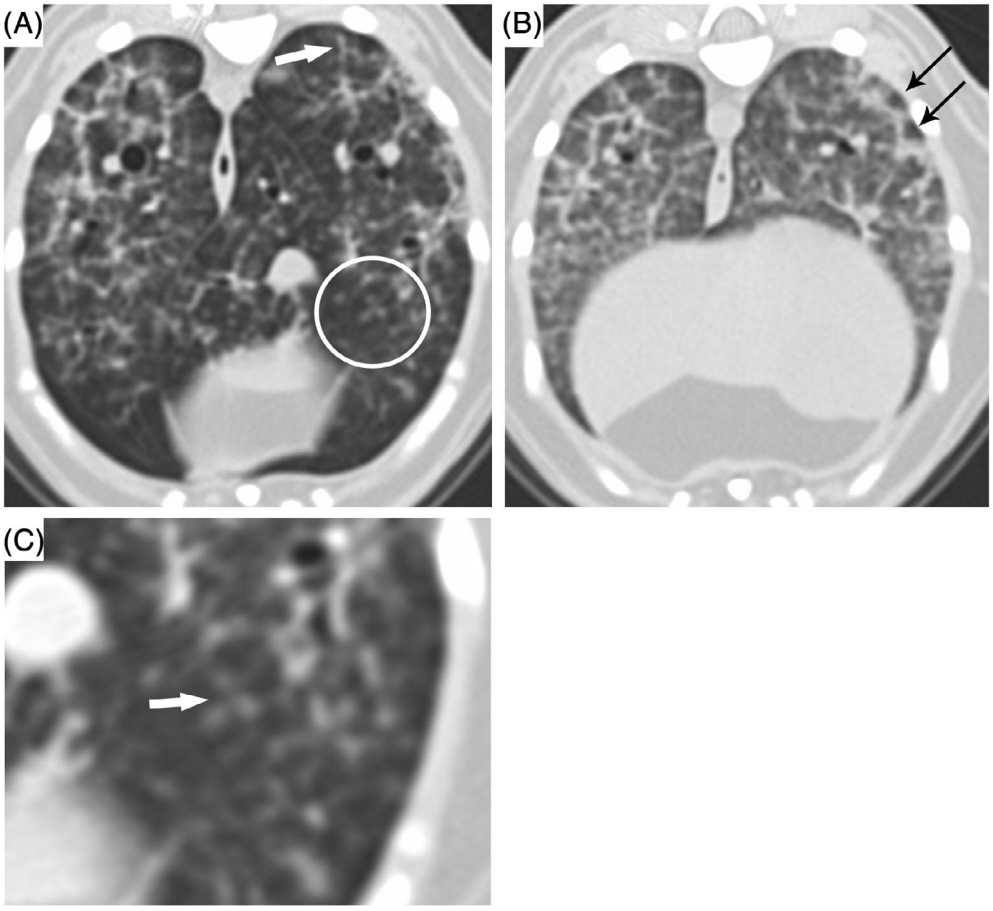

FIGURE 5 Infectious bronchiolitis in a cat with disseminated histoplasmosis. (A) On inspiratory images, there were extensive nodular and linear ground glass opacities as well as tree-in-bud pattern (white arrow) throughout the lungs, more severe at the dorsal aspect of the lungs with no preferential distribution toward the pleural surface. Several subpleural hypoattenuating areas (black arrows) are visible on the expiratory (B) computed tomography (CT) image in addition to an overall increased lung attenuation. It is unclear if the peripheral hypoattenuating areas correspond to paraseptal emphysema, loss of alveolated lung parenchyma distal to an ectatic terminal bronchiole or air trapping. (C) Close up of the image A centered over the region surrounded by the white circle showing a typical tree-in-bud pattern (arrow) in the right caudal lung lobe. Cytology confirmed the diagnosis of histoplasmosis and histopathologic examination was not performed in this cat. The right side of the patient is on the right of the CT images

BOX 4 Differential diagnoses for direct signs of bronchiolar disease on thoracic computed tomography scans

- When evaluating computed tomography (CT) scans, infection causing tree-in-bud or other direct signs of bronchiolar disease is an important mimic of noninfectious inflammatory and fibrotic disease.
  - Depending on the type and extent of infection, these cases may be treatable with a better prognosis and/or potential for cure.
  - Of interest, the thoracic CT scan in the cat described in case 3 was originally interpreted by the attending radiologist as consistent with usual interstitial pneumonia (ie, idiopathic pulmonary fibrosis), an as yet, untreatable disease with a grave prognosis.

CT was unremarkable. Cytology of BAL fluid indicated 66% nondegenerate neutrophils, 30% macrophages, and 4% lymphocytes. Many *Histoplasma capsulatum* organisms were observed within macrophages. Treatment was not pursued. Diseases with similar CT patterns are described in Box 4.

6.4 | Other primary bronchiolar variants

In humans, primary disorders of the bronchioles, not fitting into the aforementioned categories, currently are considered together as "other primary bronchiolar variants". Diffuse aspiration bronchiolitis (DAB), once thought to be a disease of the bed-ridden elderly with neurologic disorders predisposing to aspiration, is now recognized in young individuals with and without occult gastroesophageal reflux disease.[46–48] Typical histopathologic findings include a foreign body reaction with mural inflammation associated with bronchioles.[39] In cats, a presentation with CT evidence of a tree-in-bud pattern, using clinicopathologic data (including of an underlying condition predisposing to chronic aspiration) can increase the suspicion for bronchiolar disease occurring secondary to chronic small volume aspiration. [5]

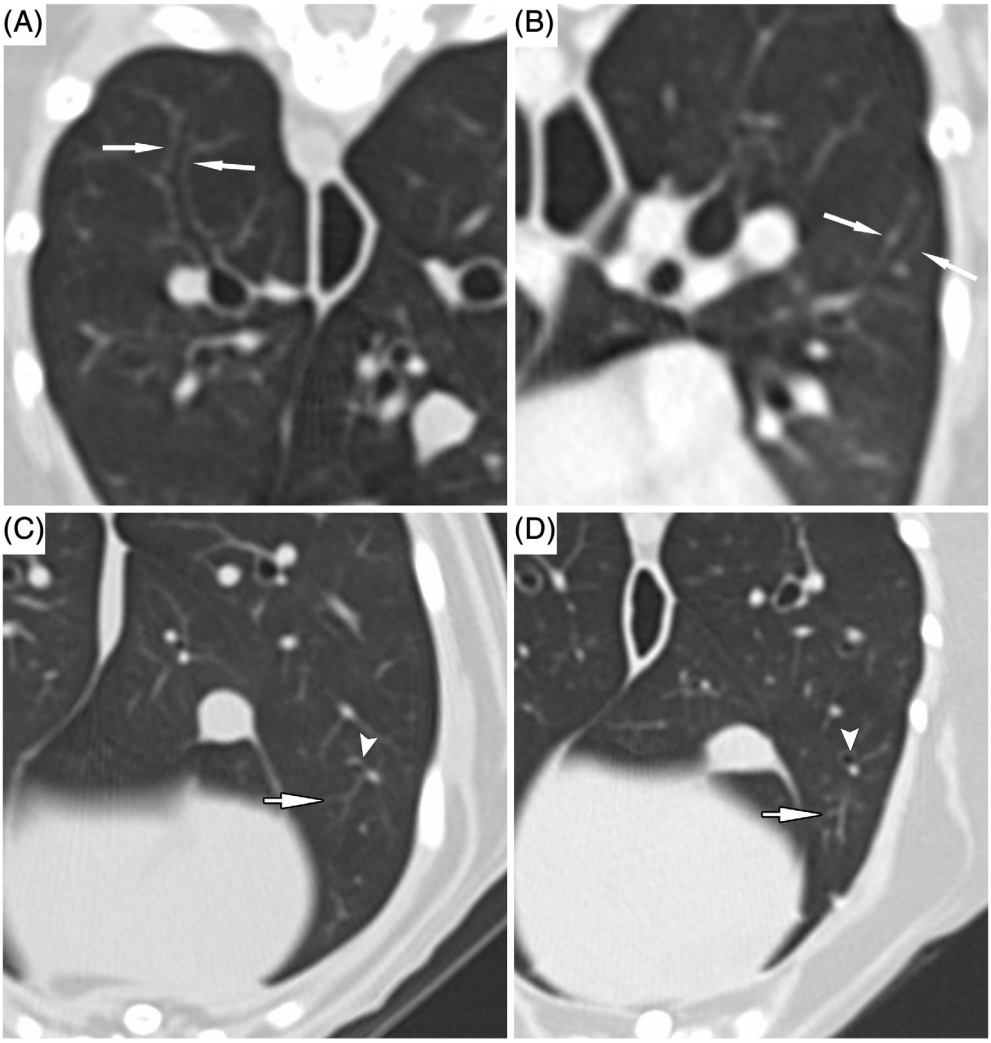

FIGURE 6 Presumptive diffuse aspiration bronchiolitis in a 13-year-old domestic long hair cat. (A, B) Inspiratory computed tomography (CT) images were characterized by multifocal bronchial wall thickening, absence of normal tapering of several bronchi (white plain arrows). (C, D) Transverse CT image of the right caudal lung lobe taken at the same level (arrowhead) showing various appearance of the bronchovascular bundle (arrow with black contour) in a normal cat (C) compared to the affected cat (D). In the affected cat, nodular opacities were seen involving the bronchial wall or peribronchiolar space (open arrow). The right side of the patient is on the right of the CT images

6.4.1 | Case 4

A 13-year-old FS domestic longhair cat was presented for chronic productive cough and gagging especially pronounced after eating and drinking, intermittent vomiting and anorexia, and regurgitation. On physical examination, a grade III/VI parasternal heart murmur was heard, respiratory rate was increased (60 breaths per minute), and body condition score was 3/9. A diffuse bronchointerstitial pattern was observed on thoracic radiography. Computed tomography was suggestive of DAB with a multifocal distribution of lesions (Figure 6 A-D). Specifically, nodules of similar size were equally spaced from each other and, when in the periphery, were at the same distance from the pleural surface, consistent with affected small airways. Bronchoalveolar lavage cytology was unremarkable. Cough improved after treatment with omeprazole. Histologic evaluation of tissue was not performed. However, the supportive clinical history, including conditions predisposing to repetitive microaspiration, the bronchiolocentric CT lesions, and subsequent improvement in clinical signs after a trial of omeprazole, supports presumptive DAB.

6.4.2 | Case 5

A 7-year-old FS DSH cat was presented for potential mammary tumors. The cat had lived in South Korea for 2.5 years until 9 months before presentation. The cat had been treated for psychogenic alopecia with megestrol and methylprednisolone acetate and subsequently developed mammary masses. Relevant history included exposure to "yellow dust" in South Korea, a serious environmental health threat affecting air quality and leading to respiratory disease in humans.

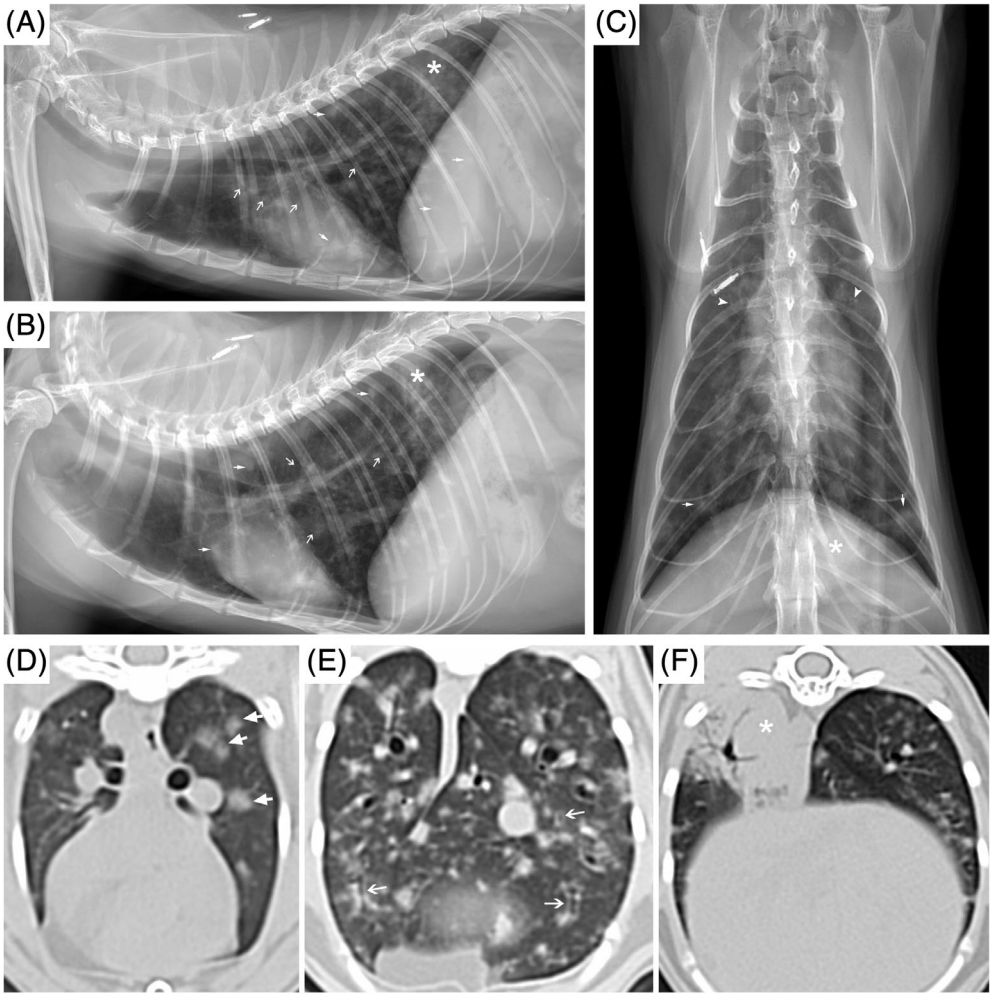

FIGURE 7 A 7-year-old female spayed domestic shorthair cat with cellular bronchiolitis attributed presumptively to environmental exposures. (A) Left lateral, (B) right lateral, and (C) ventrodorsal radiographs showing patchy ill-defined soft tissue nodules (closed arrows) and diffuse severe peribronchial infiltrates and wall thickening of small caliber bronchi (open arrows). The caudodorsal lung fields were more severely affected on the lateral projections demonstrating severe unstructured interstitial to alveolar pattern (*) corresponding to a focal area of increased opacity overlying the left medial aspect of the caudal lung lobe on the ventrodorsal projection (*). (D-F) Transverse computed tomography (CT) images taken at 3 different levels of the thorax highlighting the multifocal distribution of lesions affecting all lung lobes. Multiple solitary nodules of varying sizes were seen throughout the lungs (closed arrows). Wall thickening and peribronchial ground glass opacification of small caliber bronchi/bronchioles (open arrows) was seen throughout the lungs. A large area of complete opacification with air bronchograms occupied the mediocaudodorsal aspect of the left caudal lung lobe (*). The right side of the patient is on the right of the CT images

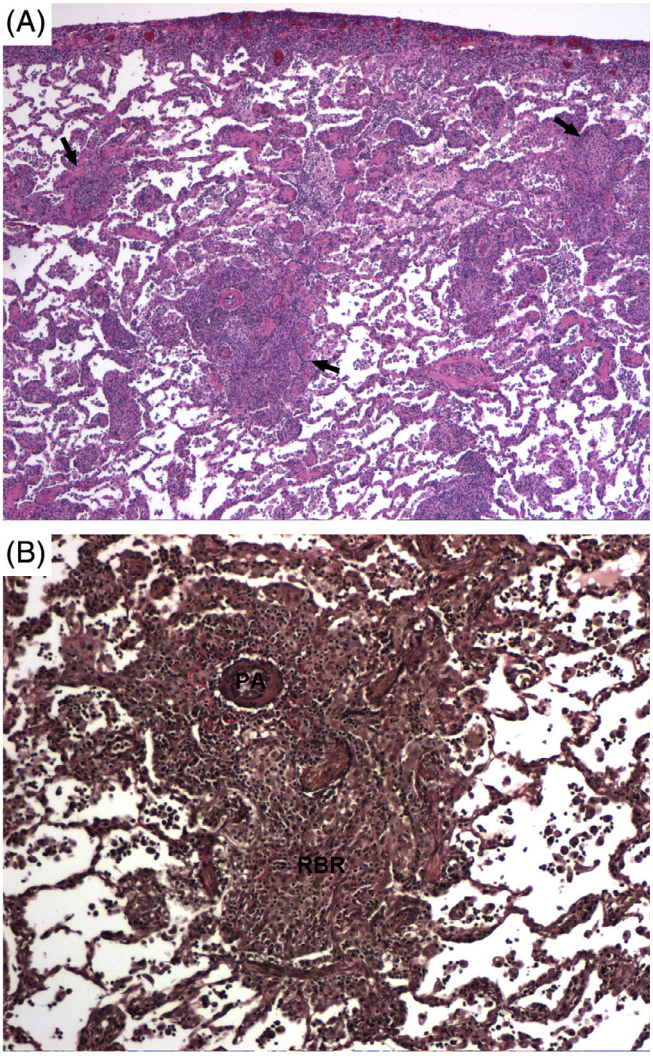

FIGURE 8 A 7-year-old female spayed domestic shorthair cat with cellular bronchiolitis attributed presumptively to environmental exposures. (A) Severe chronic inflammation is centered primarily on terminal and respiratory bronchioles and surrounds the associated pulmonary arteries (arrows). Hematoxylin and eosin stain. (B) Verhoeff van Gieson–stained lung highlights an affected respiratory bronchiole (RBR) and pulmonary artery (PA)

Additionally, 10 months prior, the cat sustained inhalational injuries from a house fire. No abnormalities were found on CBC, serum biochemical profile, and urinalysis, and the cat tested negative for FIV, FeLV, and heartworm. On thoracic radiography (Figure 7 A-C), a severe bronchial pattern leading to multifocal patchy areas of increased opacity was observed. In some areas, the soft tissue opacities appeared as nodules with ill-defined borders. Abdominal CT was unremarkable. On thoracic CT, randomly distributed soft tissue attenuating pulmonary nodules of variable sizes, bronchial wall thickening, and areas of complete opacification were identified (Figure 7 D-F). Bronchoalveolar lavage fluid cytology identified 1906 cells per microliter with 63% nondegenerative neutrophils, 23% small lymphocytes, 12% macrophages, and 2% eosinophils, and no neoplastic cells or organisms were seen. Aerobic and anaerobic cultures were negative. Histopathology of biopsy specimens of the mammary masses indicated mammary hyperplasia. Thoracotomy with left caudal lung lobectomy subsequently was performed. Histopathology (Figure 8 A,B) identified severe inflammation (lymphocytes, plasma cells, and histiocytes) within the terminal and respiratory bronchioles and surrounding alveoli, and large cuffs of perivascular inflammation. The large area of complete opacification on the CT scan comprised confluent inflammation, and the smaller nodules on CT corresponded to affected small airways on histopathology. Immunohistochemistry for coronavirus was negative. Trichrome staining identified minimal fibrosis of alveolar walls; periodic acid-Schiff staining was positive in smooth muscle of respiratory bronchioles. Immunohistochemistry performed to identify CD3+ T cells, CD80+ B cells, and E-cadherin showed a mixed population of cells consistent with inflammation. Polarized light failed to identify particulates. Owners were instructed to bring the cat back for baseline pretreatment thoracic radiographs after healing from the thoracotomy and before starting immunosuppressive doses of glucocorticoids. They were unable to do

BOX 5 Other primary bronchiolar disease variants

While not specifically mentioned in the state of the art review article on human bronchiolar disorders[10] from which we have adapted the feline classification scheme, "cellular bronchiolitis" is a term used to describe cellular inflammatory intraluminal infiltrates of the bronchioles secondary to occupational and environmental exposures.[11]

- Cellular bronchiolitis is discriminated from constrictive bronchiolitis in which there is concentric mural fibrosis and narrowing of small airways, and from polyploid bronchiolitis obliterans (PBO; sometimes called proliferative bronchiolitis)
  - To date PBO with organizing pneumonia has been reported in 1 cat and is classified as an interstitial lung disease.[12]
- Lymphocytic bronchiolitis and peribronchiolitis are thought to be caused by an immune response to specific inhalational triggers in humans.[13]
- Lymphoplasmacytic infiltration of the lamina propria and submucosa of bronchi and bronchioles of a cat after sudden anesthetic death were noted without histopathologic features supporting asthma or chronic bronchitis (ie, minimal smooth muscle hyperplasia/hypertrophy, airway eosinophils and bronchial gland hyperplasia).[16]
  - A cilia-associated respiratory bacillus-like organism was identified by light and electron microscopy; however, a review of lung tissue sections from other cats submitted for necropsy identified the same organisms that did not correlate with the presence of inflammation or lymphoid hyperplasia, thus casting doubt on a cause-and-effect relationship.
  - Environmental exposures were not described.

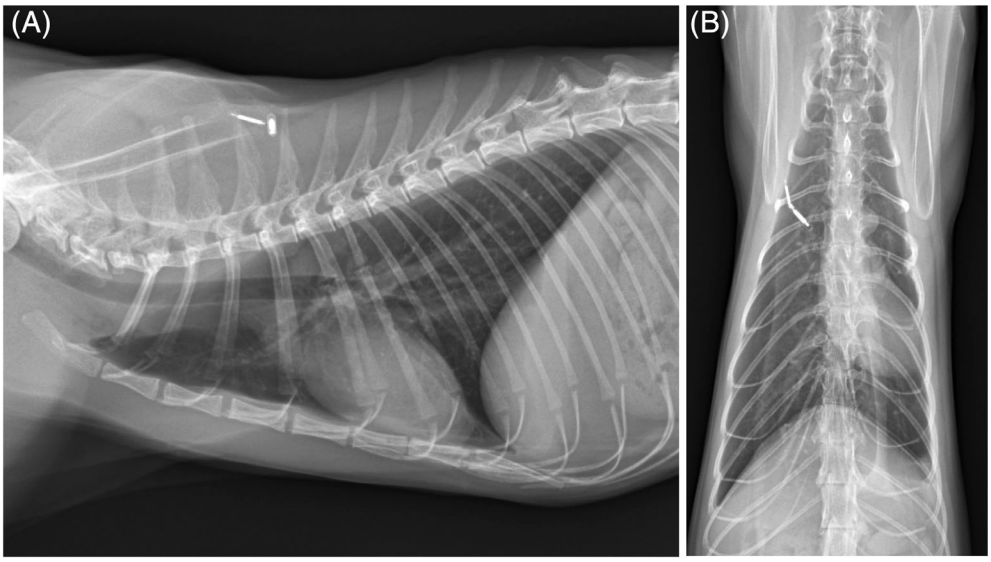

FIGURE 9 A 7-year-old female spayed domestic shorthair cat previously diagnosed with cellular bronchiolitis. Right lateral (A) and ventrodorsal thoracic projections (B) belonging to the same cat from Figure 7 . When compared to Figure 7 A-C, the lung fields are now exempt of pulmonary nodules, interstitial or alveolar pattern. Only a very mild bronchial pattern remains visible. On the ventrodorsal projection, the mediastinal shift to the left was attributed to the prior left caudal lung lobectomy

so until 10 weeks postoperatively. At that time, evaluation of thoracic radiographs indicated dramatic improvement of previously documented lesions in the absence of any treatment (Figure 9 A,B). It was unclear if this improvement was a result of spontaneous remission or waxing and waning disease. Other primary bronchiolar variants are described in Box 5.

7 | SECONDARY BRONCHIOLAR DISORDERS

7.1 | Extension of large airway disease

In humans, asthma, chronic bronchitis, cystic fibrosis, and bronchiectasis generally are considered disorders of the central (large) airways. Extension of disease to involve small airways may have important implications for clinical signs and treatment. Bronchiolar inflammation has been described in asthmatic cats[49] and in cats with concurrent chronic bronchitis and bronchiectasis.[17]

7.1.1 | Case 6

A 7-year-old FS Ocicat was presented with a 5-year history of asthma. Diagnosis was based on clinical signs (cough and wheeze), negative fecal and heartworm antigen and antibody testing, lack of response to doxycycline and fenbendazole, serial thoracic radiographs showing a moderate to severe diffuse bronchial pattern and collapse of the right middle lung lobe (Figure 10 A,B), and a BAL finding of eosinophilia. A CT scan performed under sedation 2 years previously was compatible with both large and small airway disease (Figure 10 C-E). The cat's clinical signs were managed with prednisolone and terbutaline until 6 years of age, at which time the cat was refractory to higher doses of glucocorticoids. The cat ultimately was euthanized and histopathology identified severe lymphocytic, plasmacytic, and eosinophilic bronchitis and bronchiolitis with bronchiectasia, goblet cell hyperplasia, severe peribronchitis, and arteriolar smooth muscle hypertrophy.

7.1.2 | Case 7

A 5-year-old FS DSH cat was presented for chronic cough. No abnormalities were noted on physical examination except obesity. Thoracic radiography disclosed a mild diffuse bronchointerstitial pattern. A trial of fenbendazole did not resolve the cough. Thoracic CT identified wall thickening of segmental and subsegmental bronchi, nodular appearance to the bronchovascular bundle with occasional tree-in-bud pattern, and partial or complete atelectasis of the caudal segment of the left cranial, right cranial, and right middle lung lobes. The central and dependent portions of the right cranial lung lobe were consolidated with visible air bronchograms (Figure 11 A-E). Cytology of BAL fluid identified 70% eosinophils. Serum allergen-specific IgE testing to aeroallergens identified multiple strong positive reactions. Given the severe changes noted in the right cranial lung lobe, which could not easily be ascribed to asthma, lobectomy was performed. Histology identified mild to moderate eosinophilic bronchitis and bronchiolitis with luminal mucus accumulation, moderate bronchial gland hyperplasia, mild subpleural air trapping consistent with asthma, but no evidence of an infiltrative disease was found (Figure 12). The cat initially was treated with PO, followed by inhaled, corticosteroids and a weight loss plan with marked clinical improvement.

7.1.3 | Case 8

A 10-year-old DSH female spayed cat was presented for acute labored respiration. Prior respiratory signs included wheezing, coughing, and sneezing for 4-5 months. On physical examination, a respiratory rate of 90/min, increased bronchovesicular sounds and morbid obesity were observed. An echocardiogram identified normal left atrial size; a pro-brain natriuretic peptide test was negative. On thoracic radiography, a mild to moderate bronchial pattern involving the caudal lung fields and right middle lung lobe atelectasis was observed. Thoracic CT with contrast identified a tree-in-bud pattern with regions of accentuation of mosaic attenuation on the expiratory series suggestive of air trapping (Figure 13 A,B). Bronchoalveolar lavage fluid cytology identified 36%

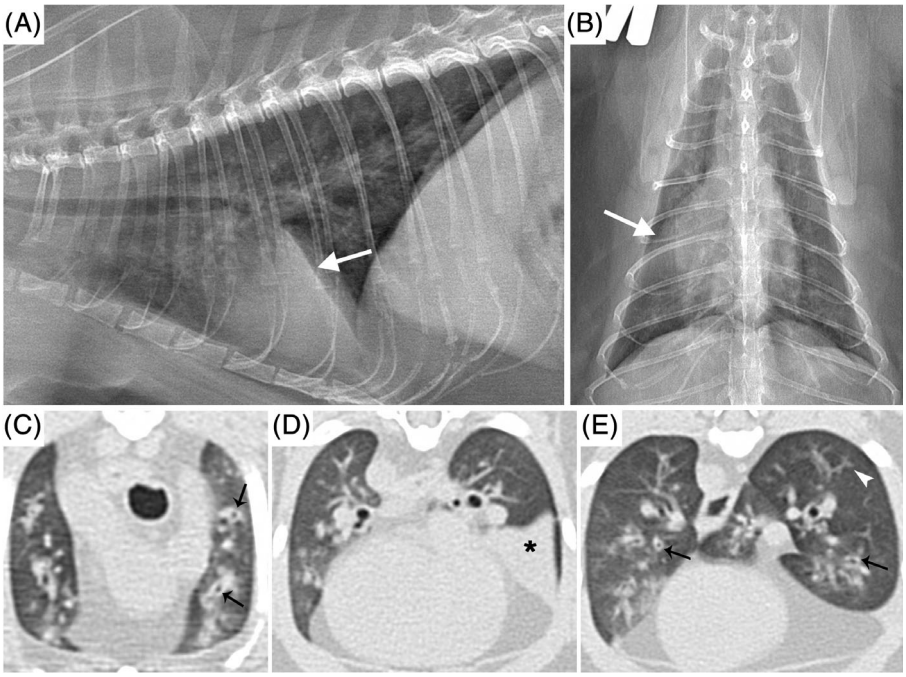

FIGURE 10 A 7-year-old Ocicat with bronchiolitis secondary to extension of large airway disease. (A) Left lateral and (B) ventrodorsal radiographs showing diffuse bronchial and unstructured interstitial pattern with atelectasis of the right middle lung lobe. Lobar margination is noted between the atelectatic right middle and right caudal lung lobes (white arrow). Computed tomography (CT) images taken at the level of the cranial (C), middle (D), and caudal (E) aspects of the lungs while the cat was awake and not chemically restrained. Diffuse bronchial wall thickening with irregular margination (black arrows), nodular opacities and tree-in-bud pattern (arrowhead) were seen throughout the lungs. The right middle lung lobe was completely opacified and decreased in size compatible with atelectasis (*). The right side of the patient is on the right of the CT images

nondegenerate neutrophils and 12% eosinophils, and aerobic and anaerobic cultures were negative. Because of a poor response to glucocorticoids, the owner elected euthanasia. Histopathology identified moderate to marked multifocal neutrophilic bronchial and bronchiolar inflammation (Figure 14A,B). Many neutrophils were present in the airway lumen, infiltrating the airway epithelium and extending beneath the submucosa to surround submucosal glands. There was moderate expansion of bronchial-associated lymphoid tissue with mild to moderate inflammation

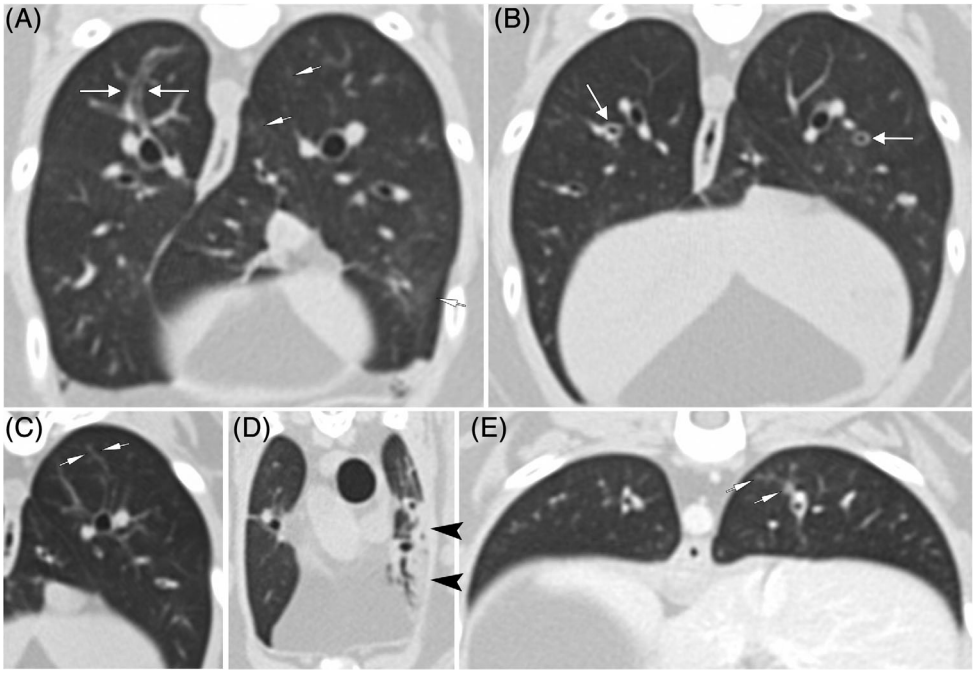

FIGURE 11 A 5-year-old female spayed domestic shorthair with bronchiolitis secondary to extension of large airway disease. Transverse computed tomography (CT) images taken at various levels along the cranial to caudal aspects of the thorax demonstrating multifocal lesions involving both large and small airways. (A and B) Thickened bronchial wall (white arrows) indicates large airway disease. (C) Nodular and thickened bronchovascular bundles (short white arrows) are more suggestive of bronchiolar disease. (D and E) In addition, increased opacification with air bronchograms of the ventral aspect of the right cranial lung lobe (arrowheads) was also identified. The right side of the patient is on the right of the CT images

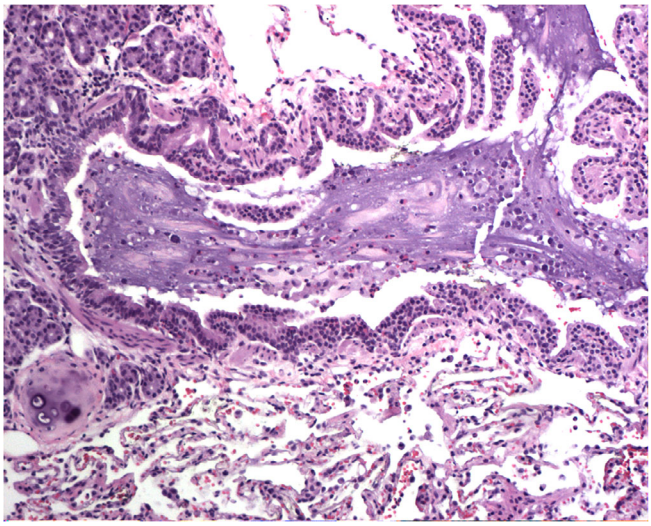

FIGURE 12 A 5-year old female spayed DSH with bronchiolitis secondary to extension of large airway disease. Abundant mucus and eosinophils are present within the lumen of a bronchiole. Hematoxylin and eosin stain

within the lumen of affected bronchioles with large numbers of neutrophils extending into alveoli in some areas. Small numbers of affected bronchioles were surrounded by abundant inflammation and were markedly and concentrically decreased in diameter. The luminal epithelium of the affected bronchioles exhibited mild hyperplasia to squamous metaplasia (Figure14B). The final diagnosis was chronic bronchitis and bronchiolitis.

7.1.4 | Case 9

A 17-year-old MC DSH cat was presented for chronic coughing and wheezing and chronic kidney disease. On physical examination, a body condition score of 3/9, grade II/VI parasternal systolic heart murmur, expiratory wheezes, and irregularly shaped kidneys were identified. Thoracic radiographs disclosed a severe diffuse bronchial pattern with subtle hyperinflation. Heartworm antibody and antigen testing was negative. There was no response to fenbendazole. Thoracic CT identified bronchial wall thickening and thickened bronchovascular bundles, bronchiolectasis, undulated pleural margins, right middle and accessory lung lobe atelectasis, and a tree-in-bud pattern (Figure 15 A-G). Bronchoalveolar lavage fluid cytology identified 660 nucleated cells per microliter with 62% nondegenerate neutrophils. Empirical treatment with azithromycin and prednisolone was started. Respiratory signs stabilized, but the cat subsequently progressed to stage IV renal disease and the owner elected euthanasia. Histopathology (Figure 16A,B) identified multiple large bronchi moderately to markedly dilated and filled with neutrophils, macrophages, mucus, and amorphous cellular debris. A rim of inflammatory cells surrounded these airways. Lesions extended into terminal bronchioles the lumens of which were nearly obliterated by concentric submucosal fibrosis; less commonly these airways were completely replaced by loose connective tissue (Figure 16B). The final diagnosis was chronic bronchitis and constrictive bronchiolitis.

7.1.5 | Case 10

A 1.5-year-old FS DSH cat was presented for chronic cough and increased respiratory effort. An inducible cough, increased bronchovesicular sounds, and respiratory rate of 64/min were noted on physical examination. Thoracic radiographs disclosed pulmonary nodules with cavitations and ill-defined margins in the right cranial and both caudal lung lobes over a background of a diffuse moderate unstructured interstitial pattern, moderate bronchial pattern, and a focal alveolar pattern involving the right cranial lung lobe associated with mild

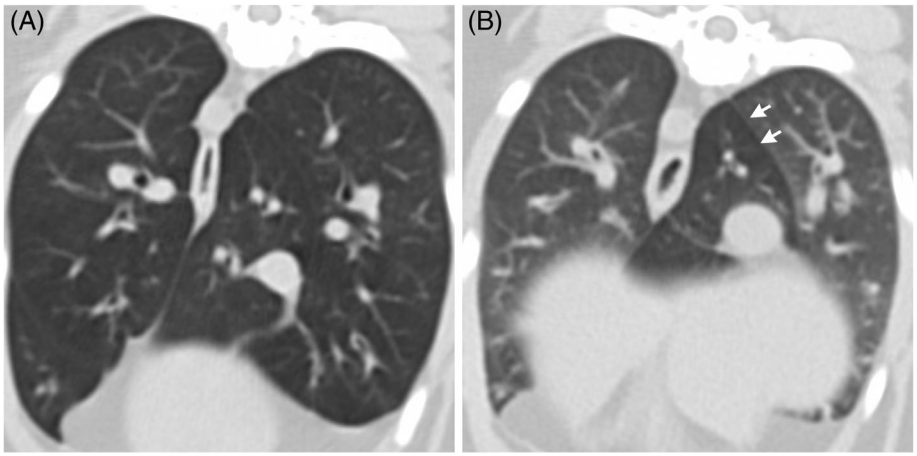

FIGURE 13 A 10-year-old domestic shorthair cat with chronic bronchitis and bronchiolitis. Inspiratory (A) and expiratory (B) computed tomography (CT) images taken at the level of the caudal and accessory lung lobes. On inspiratory images, the attenuation of the left caudal (−856 HU), right caudal (−852 HU), and accessory (−855 HU) lung lobes is homogenous and at the expected level of density.[60] On expiratory images taken at the same level, the attenuation of the accessory lung lobe remains hypoattenuating (−773 HU) in comparison to the surrounding pulmonary parenchyma of the right (−625 HU) (arrows) and left (−682 HU) caudal lung lobes, suggesting air trapping of the accessory lung lobe. The right side of the patient is on the right of the CT images

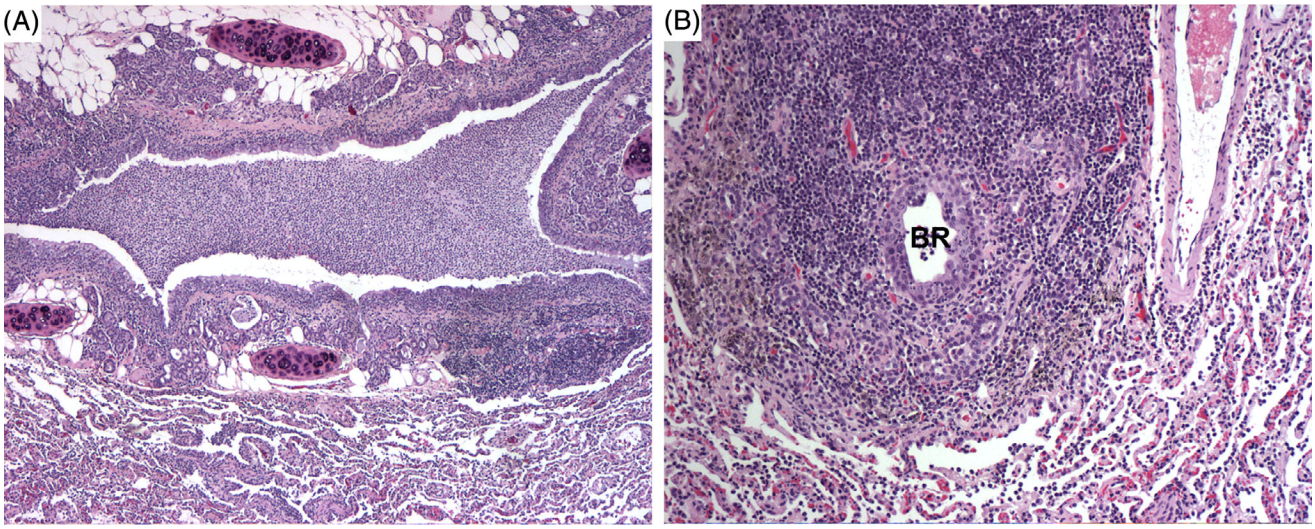

FIGURE 14 A 10-year-old domestic shorthair cat with chronic bronchitis and bronchiolitis. (A) Numerous neutrophils fill the lumen of a bronchus. Moderate epithelial hyperplasia lines the bronchus and there is moderate chronic inflammation within the wall of the affected bronchus. Hematoxylin and eosin stain. (B) Intense chronic inflammation surrounds and extends transmurally into a small bronchiole (BR); note the squamous metaplasia of the lumen epithelium. Hematoxylin and eosin stain

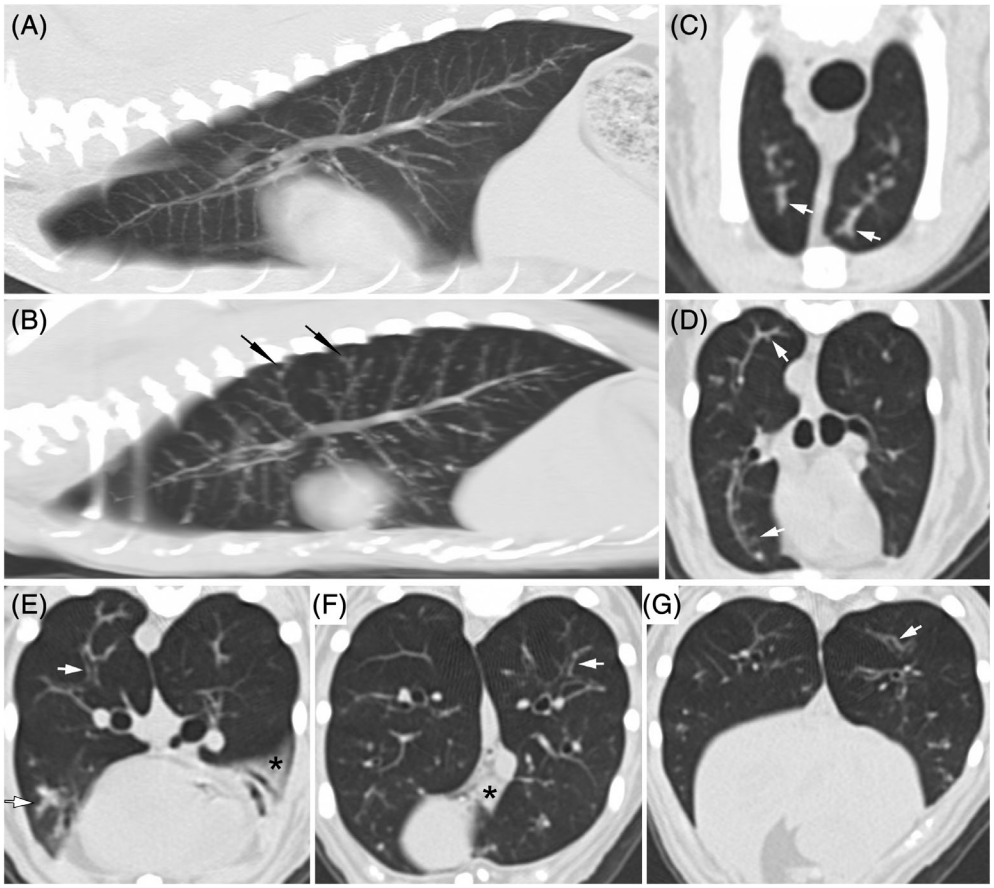

FIGURE 15 A 17-year-old domestic shorthair cat with chronic bronchitis and constrictive bronchiolitis and comparison to a normal cat. (A) 3D multi-planar reconstruction (MPR) image of the left lung of a normal cat depicting thin bronchovascular bundles and the absence of tree-in-bud patterns. (B) 3D MPR image of the left lung in a cat with secondary constrictive bronchiolitis showing tree-in-bud patterns (arrows) or multiple small ground glass opacities within the bronchovascular bundles. Transverse computed tomography (CT) images illustrating thickened bronchovascular bundles (arrows) within the dependent (C, D bottom arrow) and nondependent (D, top arrow) portions of the cranial lung lobes. (E) Transverse CT image at the level of the heart showing bronchial wall thickening (top white arrow), severely thickened bronchovascular bundle (bottom arrow) and atelectatic right middle lung lobe (*). (F-G) Bronchial wall thickening involved both lungs as seen on the right side on the last 2 images (white arrows). The accessory lung lobe was atelectatic (*). On all transverse images, the left side of the patient is to the left on the image

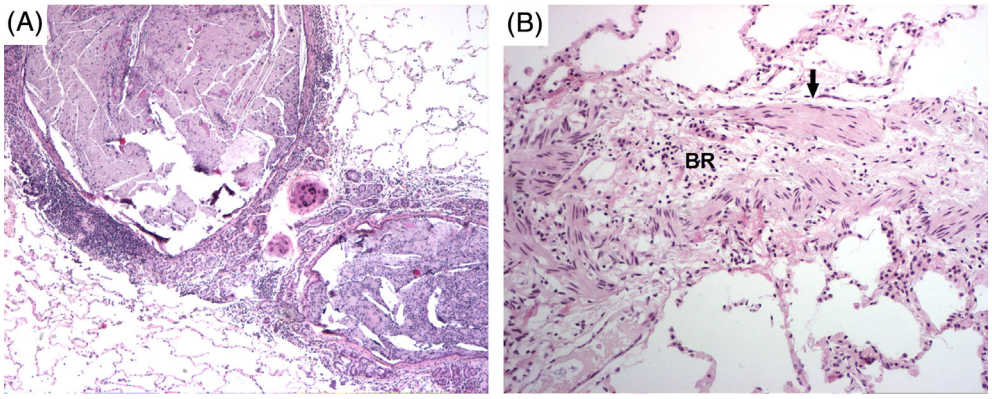

FIGURE 16 A 17-year-old domestic shorthair cat with chronic bronchitis and constrictive bronchiolitis. (A) Large bronchi are markedly dilated and filled with neutrophils, macrophages, mucus, and amorphous cellular debris. Hematoxylin and eosin stain (B) The lumen of small numbers of bronchioles (BR) distal to affected bronchi were obscured by loose fibrosis. Note the enlarged smooth muscle bundles (arrow) delimiting the bronchiolar wall. Hematoxylin and eosin stain

rightward mediastinal shift (Figure 17 A,B). Testing for FeLV, FIV, and heartworm antibody was negative; titers for Toxoplasma IgM were negative and for IgG were positive at >1 : 2560 consistent with prior exposure. Inadequate feces were available for examination. Thoracic CT identified a large number of variably sized pulmonary nodules (many more observed than on 3-view thoracic radiography) most having cavitations and with walls measuring 0.7-1.5 mm. Other lesions included bronchial wall thickening, thickened bronchovascular bundles, tree-in-bud pattern, mosaic perfusion, and bronchiectasis and bronchiolectasis among other findings (Figure 17 C-E). On BAL fluid

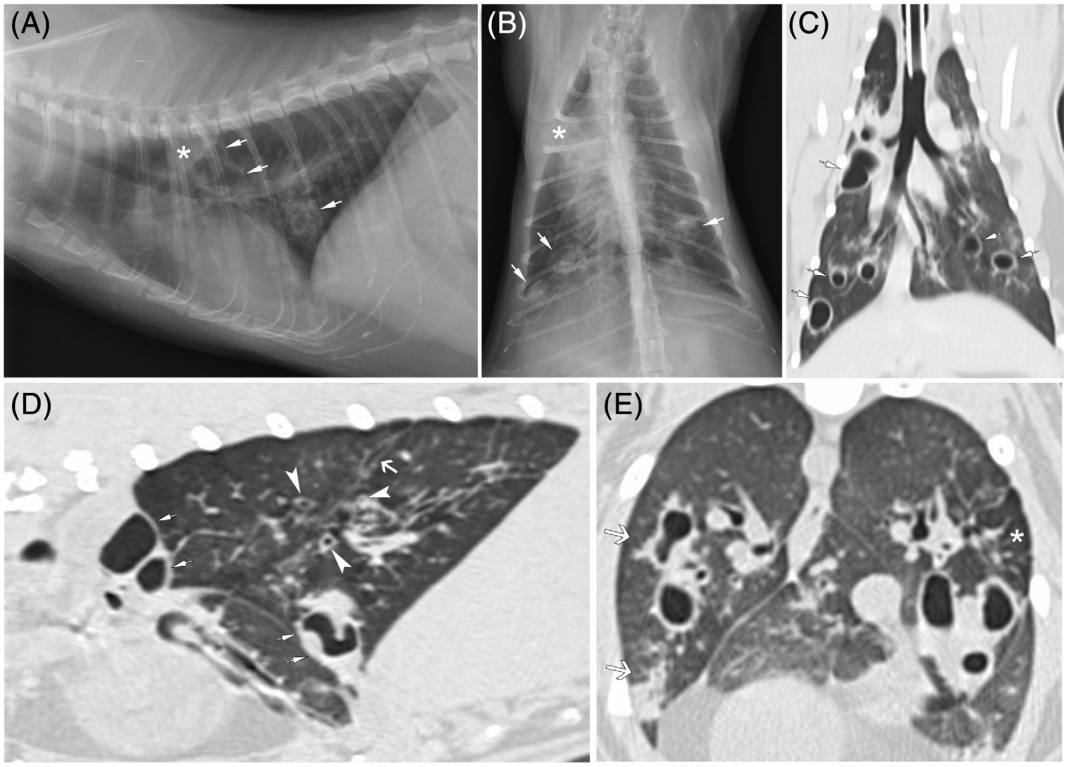

FIGURE 17 Parasitic bronchiolitis in a 1.5-year-old female domestic shorthair cat with disseminated paragonimiasis. (A) Left lateral and (B) ventrodorsal radiographs showing multifocal ill-defined nodules partially radiolucent (white arrows) and focal area of increased opacification (*) in the right cranial lung lobe creating border effacement with the cardiac silhouette and the thoracic wall. A diffuse unstructured interstitial pattern accompanied by mild bronchial pattern was also seen. Computed tomography (CT) horizontal (C), sagittal (D) and transverse (E) images of this cat depicting bronchial thickening (arrowheads), linear opacities (small open arrow), and several nodules with cavitations (small closed arrows) of varying sizes. The nodules were characterized by thick walls; they contained varying amounts of air and soft tissue attenuation and were occasionally multilobulated. A focal area (*) of decreased attenuation is seen at the costal aspect of the right caudal lung lobe resulting in mosaic perfusion

BOX 6 Additional considerations regarding large versus small airway disease

Feline large airway disease is common and is subdivided into asthma, chronic bronchitis, and parasitic bronchitis.

- The diagnostic evaluation of such cats rarely includes thoracic computed tomography (CT) or histopathologic evaluation, contributing to the lack of recognition of small airway disease secondary to extension from primary large airway disease

Small airway pathology secondary to large airway disease does not present uniformly and is often overlooked.

- Of interest, the 2 cats with chronic bronchitis (cases 8 and 9) had differing types of bronchiolar pathology: the first having inflammatory lesions and the second, fibrotic and obliterating lesions.
- Case 9 illustrates subtle but clear localization of lesions to the terminal bronchioles using histopathology, with CT providing evidence for discussion with pathologists to scrutinize for small airway involvement

On CT examination, feline inflammatory large airway disease appears to be a common cause of direct bronchiolar signs, especially tree-in-bud.[5]

- Computed tomography changes affecting larger airways such as increases in peribronchovascular density, peribronchial cuffing, and thickened airway walls support feline asthma, chronic bronchitis, or parasitic bronchitis as the primary lesion.

Cytology of BALF is key to classification of large airway disorders in cats.[6,7] Antemortem lung biopsy is rarely performed as less invasive diagnostics allow for reasonable classification and treatment.

- In case 8, lung biopsy was performed because of concern for a comorbid condition in addition to feline asthma; the lesions noted on CT were not explained by histopathologic examination.
- In case 9, chronic bronchitis was the antemortem clinical diagnosis; however, most cats with chronic bronchitis do not present in respiratory distress.
  - The more serious clinical signs and objective evidence of air trapping on CT scan is attributed to extension of involvement of inflammation to small airways.

Larger numbers of cases with large airway disease will be required to determine if cats with small airway involvement have more severe clinical signs, refractory responses to treatment, or a more guarded prognosis.

cytology, there were 1084 cells per microliter with 80% neutrophils. Culture was positive for 3 enteric bacteria. Pending test results, the cat was discharged on fenbendazole and praziquantel. Overnight, the cat's breathing was labored. The cat was re-presented and a pneumothorax was ruled out by thoracic radiography. The cat failed to respond to dexamethasone and terbutaline, and euthanasia was elected. Necropsy confirmed pulmonary paragonimiasis with numerous bronchi and bronchioles being dilated and filled with degenerate neutrophils, necrotic cellular debris, fibrin, and ova.

Additional considerations regarding large versus small airway disease are provided in Box 6.

7.2 | Extension of ILD

The ILDs encompass a spectrum of disorders with overlapping clinical and imaging features with inflammation, fibrosis, or both noted on histopathology.[50] Although >200 ILDs have been described in humans,[51] only a few have been recognized in cats.[12,19,52–56] A few ILDs are characterized by bronchiolocentricity, blurring the line between primary disease of the bronchioles extending into the interstitium and primary disease of the interstitium extending into the bronchioles.[4,57]

In humans, inhalational exposures may lead to hypersensitivity pneumonitis or pneumoconiosis; cigarette smoke is associated with respiratory bronchiolitis-ILD and desquamative interstitial pneumonia. A single case report described "desquamative interstitial pneumonia-like" histologic lesions in a cat with no mention of environmental exposure to tobacco smoke.[56] Idiopathic pulmonary fibrosis has been described in cats although the initial histopathologic characterization did not provide specific mention of lesions centered around small airways.[58]

7.2.1 | Case 11

A 6-year-old FS DSH cat was presented with chronic weight loss, cough, and respiratory distress. Thoracic radiography performed 6 months previously disclosed an unstructured interstitial pattern and a moderate bronchial pattern, more severe in the ventral thorax (Figure 18 A,B). Treatment for presumptive asthma with prednisolone and theophylline resulted in minimal response. On physical examination, respiratory rate was 128/minute and body condition score was 3/9. On thoracic CT, multifocal areas of consolidation with air bronchograms were observed, more severe in the ventral aspect of the thorax and at the periphery (Figure 18 C-F). In nonconsolidated areas, bronchial wall thickening, tree-in-bud (Figure 18 F), or bronchovascular thickening were marked, and traction bronchiectasis (Figure 18 D) was seen in numerous locations. The pleural margins had a scalloped appearance with pleural fissure thickening, multifocal subpleural thickening, or peripheral consolidation. Interestingly, in the areas least affected by fibrosis, evidence of bronchiolar pathology (bronchiolectasis) was noted. Cytology of BAL fluid identified 3969 cells per microliter with 72% degenerate neutrophils and 20% lymphocytes. Given the severity of CT changes, compromised clinical state, and a lack of an identifiable treatable disease, the owner elected

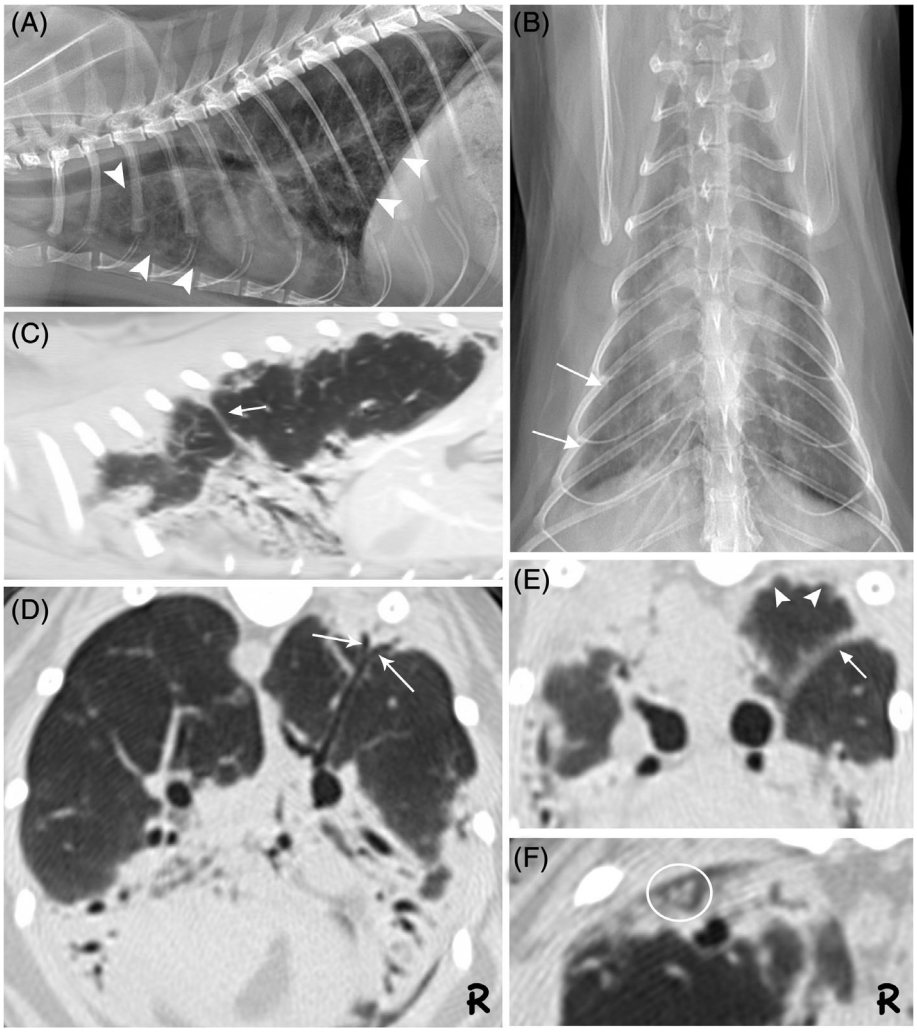

FIGURE 18 A 6-year-old domestic shorthair cat with bronchiolitis secondary to extension of interstitial lung disease. (A) Left lateral and (B) ventrodorsal radiographs showing diffuse moderate bronchial and unstructured interstitial pattern, more severe at the peripheral aspect of the thorax including the sternum and diaphragm (arrowheads) and the costal pleura (arrows). (C-F) Sagittal and transverse computed tomography (CT) images of this cat demonstrating pleural fissure thickening (straight closed arrow), bronchiectasis (curved arrows), subpleural thickening (arrowheads), and tree-in-bud (circle). R indicates the right side of the patient

euthanasia. On necropsy, severe multifocal chronic-active terminal and respiratory bronchiolitis with bronchiolar loss, parenchymal fibrosis, interstitial inflammation, and smooth muscle hyperplasia with marked locally extensive pleural fibrosis were observed (Figure 19 A, B). The continuum between primary bronchiolar disorders and end-stage fibrosis is discussed in Box 7.

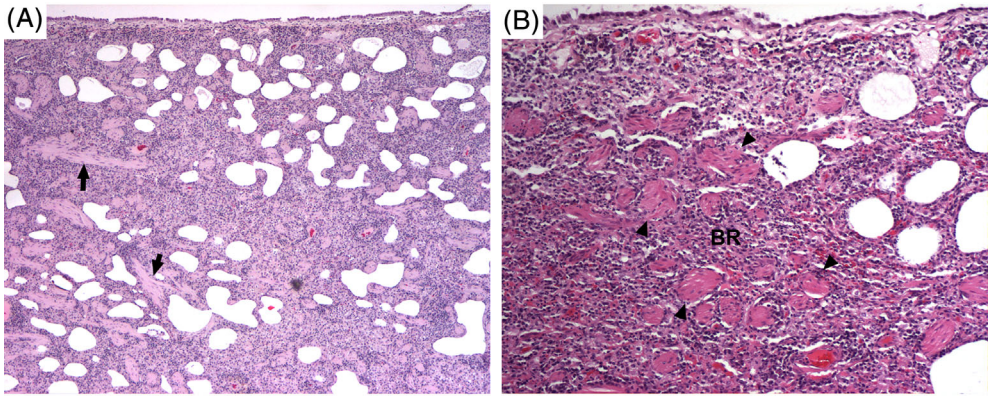

FIGURE 19 A 6-year-old domestic shorthair cat with bronchiolitis secondary to extension of interstitial lung disease. (A) Severe fibrosis and chronic inflammation extends from beneath the pleura into the underlying lung parenchyma. Large bundles of hyperplastic smooth muscle, likely arising from respiratory bronchioles (arrows) are interspersed with the fibrosis. Hematoxylin and eosin stain. (B) Severe respiratory bronchiolar fibrosis among the interstitial fibrosis. The outline of the respiratory bronchiole (RB) is indicated by the enlarged bundles of smooth muscle (arrowheads)

BOX 7 Pulmonary fibrosis is an end-stage lesion and can mask the primary disease process

Bronchiolocentric interstitial pneumonia or airway-centered interstitial fibrosis in humans can result from chronic small airway-terminal acinar disease with progression to encompass associated alveolar parenchyma with inflammation and fibrosis.[3,4]

- The striking amounts of fibrosis and clinical picture of a restrictive lung disease is the reason the authors categorized case 11 as an ILD; however, it is likely this case may represent an advanced primary bronchiolar disorder leading to an "end-stage" lung and what most veterinary clinicians, radiologists, and pathologists would call idiopathic pulmonary fibrosis
- The cat in case 11 illustrates the need for additional study and refinement of the classification scheme for bronchiolar disorders in the cat.

8 | CONCLUSIONS

Airway disorders in cats are not limited to large airway diseases such as asthma and chronic bronchitis. With more common use of CT, lesions suggestive of small airway (bronchiolar) disorders are being detected. Clinical signs and some features of thoracic radiographs can be identical for large and small airway disorders, making additional diagnostic testing necessary for definitive diagnosis. We used CT and histopathologic examinations in cats with a wide spectrum of clinicopathologic features allowing proposal of an initial classification scheme for bronchiolar disorders. Broadly, diseases of the bronchioles can be subdivided into primary bronchiolar disorders in which disease originates and is anatomically limited to small airways and secondary bronchiolar disorders at which disease in large airways or the interstitium extends to involve bronchioles. Multidisciplinary collaboration among clinicians, radiologists, and pathologists will allow further refinement of the proposed classification scheme. This review represents the first step toward recognizing and understanding a new clinically important category of respiratory disease in the cat. Future studies targeting early recognition and evaluation of therapeutic strategies for bronchiolar disorders in cats are warranted.

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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 APPROVED 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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Additional supporting information may be found online in the Supporting Information section at the end of this article.

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