

Clinical, computed tomographic and histopathological findings in two cats with pulmonary fibrosis of unknown aetiology

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Eleanor C Duffy¹, Sally Griffin², Erin M O'Connell¹  and Jeremy R Mortier¹

Abstract

Case series summary Two cats were presented for further investigation of respiratory signs. One cat had a history of a cough and the other, tachypnoea. In each case, thoracic CT was performed, which revealed a generalised marked reticular pattern in the first cat and focal consolidation of the right caudal lung lobe in the second cat. The first cat was euthanased following completion of the imaging study and a post-mortem examination was performed. The second cat underwent surgical excision of the abnormal lung lobe and survived for 4 years after diagnosis. Histopathology performed on lung tissue removed from each cat was consistent with pulmonary fibrosis.

Relevance and novel information This small case series adds to the existing literature and highlights the heterogeneous clinical course and variable appearance of pulmonary fibrosis on CT of affected cats. These cases provide evidence that pulmonary fibrosis in cats incorporates a wide spectrum of fibrotic lung disease and demonstrates the possibility for prolonged survival following diagnosis where disease is localised and amenable to surgical resection.

Keywords: CT; fibrotic lung disease; idiopathic interstitial pneumonia; idiopathic pulmonary fibrosis

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Introduction

In human medicine, interstitial lung disease (ILD) is an umbrella term for more than 200 distinct diseases. These are classified into those with identifiable causes and those without. The latter are termed idiopathic interstitial pneumonias (IIP) and include idiopathic pulmonary fibrosis (IPF).^{1,2} A similar, modified classification for ILD has been proposed for dogs and cats.³

Pulmonary fibrosis (PF) in cats shares some features with the human condition IPF, yet is not well characterised.^{4–7} In published cases of feline PF (also referred to as 'IPF-like disease'), abnormalities reported on thoracic radiographs are highly variable and non-specific.^{4,5} Interstitial, bronchial and alveolar lung patterns were all described equally and often in combination, with a diffuse or multifocal distribution being most common.^{4,5} Furthermore, pulmonary masses, pulmonary bullae, pleural effusion and

cardiomegaly were also reported in several cases.⁵ Pulmonary neoplasia, in particular carcinoma, has been described in cats with IPF-like disease, although a causal relationship between the two conditions has not been determined.^{4,7} CT is a core part of the diagnostic pathway of IIP in human medicine.^{8,9} There are three reported cases of feline IPF-like disease with CT descriptions; one with a generalised reticular pattern

¹Institute of Veterinary Science, University of Liverpool, Neston, UK

²Diagnostic Imaging Department, Willows Veterinary Centre & Referral Service, Solihull, UK

Corresponding author:

Eleanor C Duffy BVSc, Small Animal Teaching Hospital, Institute of Veterinary Science, University of Liverpool, Leahurst, Chester High Road, Neston, Cheshire CH64 7TE, UK
Email: eleanorduffy@hotmail.com



with traction bronchiectasis and honeycombing, and the remaining two with a focal area of soft tissue consolidation/mass within a lung lobe, with or without additional small areas of increased soft tissue attenuation.^{5,6} In the current case series, the authors present the clinical, CT and histopathological findings of two cats with a confirmed diagnosis of PF.

Case series description

Case 1

A 5-year-old neutered male domestic shorthair cat was presented to its primary practice for investigation of a 7-month history of tachypnoea. The owners reported a respiratory rate (RR) varying from 30 to 60 breaths per min (brpm). Empirical therapy was initiated and a number of drugs, including antibiotics, diuretics and corticosteroids were tried, initially in combination for approximately 6 weeks, and followed by systemic corticosteroid monotherapy for approximately 3 months. Although the owners reported an initial reduction in RR with systemic corticosteroid administration, this improvement was short-lived, lasting only a couple of weeks. A presumptive diagnosis of feline asthma was made and a treatment regime with fluticasone propionate (Flixotide Evohaler; GSK), salbutamol (Ventolin HFA Aerosol with Adapter; GSK) and etamiphylline (Millophylline-V; Dechra) was initiated, with minimal response.

The cat was referred to the University of Liverpool Small Animal Teaching Hospital (SATH), by which time it had developed lethargy and hyporexia, with resultant weight loss. On clinical examination, the cat was tachypnoeic with a RR of 68brpm and increased inspiratory

and expiratory effort. Thoracic auscultation revealed bilaterally harsh bronchovesicular sounds. The heart rate was 160 beats per min (bpm) and cardiac auscultation was normal. Rectal temperature was not attempted. Haematology was within normal limits, while biochemistry revealed a moderate increase in alkaline phosphatase (ALP; 128 U/l [reference interval (RI) 0–40 U/l]), a severe increase in alanine transaminase 420 U/l (RI 7–50 U/l) and a mild increase in urea 7.9 mmol/l (RI 2.5–7.5 mmol/l).

Thoracic CT was performed using an 80-slice CT scanner (Toshiba Aquilion Prime; Canon Medical System) with the cat under general anaesthesia. The cat received butorphanol 0.3 mg/kg (Torbugesic; Zoetis) and medetomidine 0.002 mg/kg (Domitor; Vetoquinol) intramuscularly, followed by alfaxalone 2 mg/kg (Alfaxan; Jurox) intravenously. Following intubation, isoflurane (IsoFlo; Zoetis) was used to maintain anaesthesia. For the duration of general anaesthesia, the cat remained in sternal recumbency, had an oxygen saturation above 96% and was breathing spontaneously without the need for positive pressure ventilation. On CT there was a mild, generalised increase in volume of the lungs, consistent with hyperinflation (no positive pressure ventilation was performed), in addition to mild generalised thickening of the bronchial walls. Throughout the pulmonary parenchyma there was a generalised, marked reticular pattern and patchy ground-glass attenuation, associated with multifocal parenchymal bands, pleural thickening and irregular pleural margins (Figure 1). Small, multifocal areas of pulmonary consolidation were present throughout the lungs and moderate-to-marked cylindrical bronchiectasis

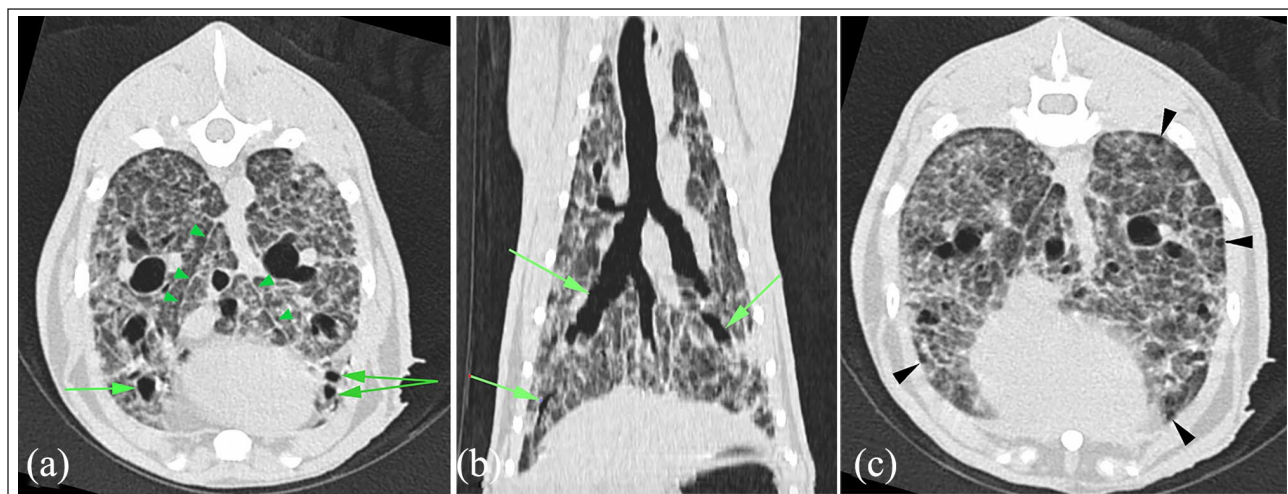


Figure 1 (a,c) Transverse and (b) dorsal CT images with lung reconstruction and lung window (window width 1500; window length 500) of case 1. Mild bronchial wall thickening and a generalised reticular pattern with patchy ground-glass attenuation are present. In some regions of the lung, ground-glass attenuation appeared more severe in the peribronchial tissues (not shown). (a,b) Multiple dilated bronchi (arrows) are visible throughout the lungs, consistent with traction bronchiectasis. Pleural thickening (arrowheads) is also noted. (c) Multiple peripheral gas-filled structures are also present, consistent with bronchiolectasis, bullae, blebs or pneumatocele formation (arrowheads)

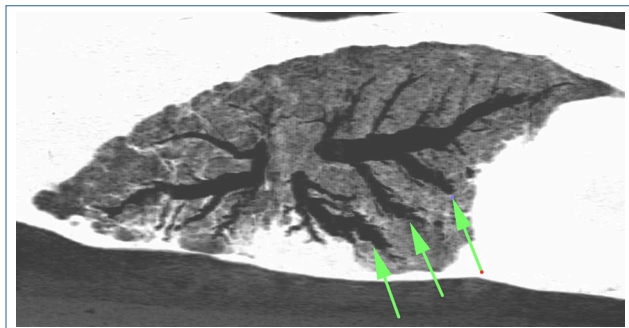


Figure 2 Parasagittal, minimum intensity projection CT image with lung reconstruction and lung window (window width 1500; window length 500) of case 1, showing the generalised cylindrical traction bronchiectasis (arrows)

(suspected traction bronchiectasis) affecting the lobar bronchi, in addition to the first and second segmental bronchi, was noted (Figure 2). Occasional, small subpleural gas-filled cavities were present, consistent with terminal bronchiolectasis, bullae, blebs or pneumatoceles (Figure 1). The right ventricle of the heart was subjectively dilated and there was mild dilation of the main pulmonary artery and lobar pulmonary arteries. The tracheobronchial and sternal lymph nodes were mildly enlarged (up to 8 mm in the short-axis dimension).¹⁰ Within the cranial abdomen, there was generalised hepatomegaly, although the hepatic parenchyma and margination were normal. Collectively, these findings were suggestive of severe, fibrotic interstitial lung disease, with suspected secondary pulmonary hypertension and cor pulmonale.

Given the severity of the pulmonary lesions, the owner elected for euthanasia. Gross pathological findings at post mortem were restricted to the lungs and intrathoracic lymph nodes. The lungs were diffusely firm and dark red to brown with multinodular pleural surfaces and a multinodular appearance to the cut surface. The mediastinal and tracheobronchial lymph nodes had a mottled red and cream cut surface, without appreciable enlargement. On histopathology, approximately two-thirds to three-quarters of the lung architecture was distorted by multifocal to coalescing areas of partial to complete consolidation. In these areas, there was severe and extensive smooth muscle hyperplasia, interstitial fibrosis, metaplasia of type I pneumocytes, and enlarged and often atypical type II pneumocytes. Where alveolar lumens were still visible, this was consistent with honeycomb lung. There was a multifocal mild-to-moderate inflammatory component, predominantly composed of lymphocytes and plasma cells with small foci of neutrophils. Collectively, these histopathological features were consistent with a diagnosis of pulmonary fibrosis. The remaining alveoli were often enlarged and alveolar capillaries were markedly congested. No gross or histological cardiac abnormalities were reported.

Case 2

A 2-year-old neutered female domestic shorthair cat was presented to the primary practice with a 2-month history of acute onset coughing, hyporexia and lethargy. Clinical examination was considered normal, except for bilaterally harsh bronchovesicular sounds. Conscious thoracic radiographs were described by the referring veterinary surgeon as having an increased opacity over the right craniodorsal lung field, in addition to a discernible diffuse bronchial pattern. Unfortunately, the radiographs were not available for review. The cat received empirical therapy consisting of a combination of corticosteroids, antibiotics and diuretics, but despite temporary improvement, lasting approximately 1 week, the cough persisted.

On referral to the SATH, the cat was bright with a RR of 44 brpm. Thoracic auscultation revealed loud crackles, rales and rhonchi throughout the lung fields. Cardiac auscultation was normal with a heart rate of 204 bpm. The rectal temperature was 37.5°C.

Haematology revealed leukocytosis ($29.5 \times 10^9/l$; RI 13.8–19.8 $\times 10^9/l$) with mature neutrophilia ($26.8 \times 10^9/l$; RI 7.9–11.5 $\times 10^9/l$), lymphopenia ($1.46 \times 10^9/l$; RI 4.5–6.3 $\times 10^9/l$) and thrombocytosis ($820 \times 10^9/l$; RI 105–365 $\times 10^9/l$). Biochemistry revealed hypokalemia (3.3 mmol/l; RI 3.8–5.3 mmol/l), hypophosphatemia (0.67 mmol/l; RI 1.1–2.3 mmol/l), increased urea (12 mmol/l; RI 2.5–7.5 mmol/l) and a mild increase in ALP (84 U/l; RI 0–40 U/l).

Thoracic CT was performed using an 80-slice CT scanner, under general anaesthesia. The cat received medetomidine 0.02 mg/kg (Domitor; Vetoquinol) and 4 mg/kg ketamine (Anesketin; Dechra Veterinary Products) intramuscularly, followed by propofol 1 mg/kg (PropoFlo Plus; Zoetis) intravenously, and, following intubation, isoflurane was used to maintain anaesthesia. The cat was in sternal recumbency, breathing spontaneously without the need for positive pressure ventilation, and oxygen saturation remained above 98% for the duration of the procedure. The study revealed marked consolidation of the ventral half of the right caudal lung lobe, associated with multiple branching air bronchograms (Figure 3). Within the caudodorsal aspect of that lobe and towards the midline, there was a small, relatively well-circumscribed, focal area of ground-glass attenuation within the subpleural region (Figure 4). The ventral margin at the tip of the left caudal lung lobe was irregular with subpleural thickening (Figure 5). There was mild bronchial wall thickening and mild cylindrical bronchiectasis affecting the right cranial, middle, caudal and accessory lung lobes, with the bronchiectasis becoming more severe within the region of pulmonary consolidation. The lobar bronchus supplying the right middle lung lobe was also moderately to markedly dilated and there was a small area of consolidation within the ventral aspect of the lobe. Additional findings included mild dilation of the right cardiac ventricle

despite a normal diameter of the main pulmonary artery and pulmonary vessels, and subjective enlargement (up to 6 mm in height) of the right and middle tracheobronchial lymph nodes. Bronchoscopy was attempted but subsequently abandoned owing to marked airway constriction and marked reduction in oxygen saturation (80%). Bronchoalveolar lavage (BAL) was performed blind with poor yield.

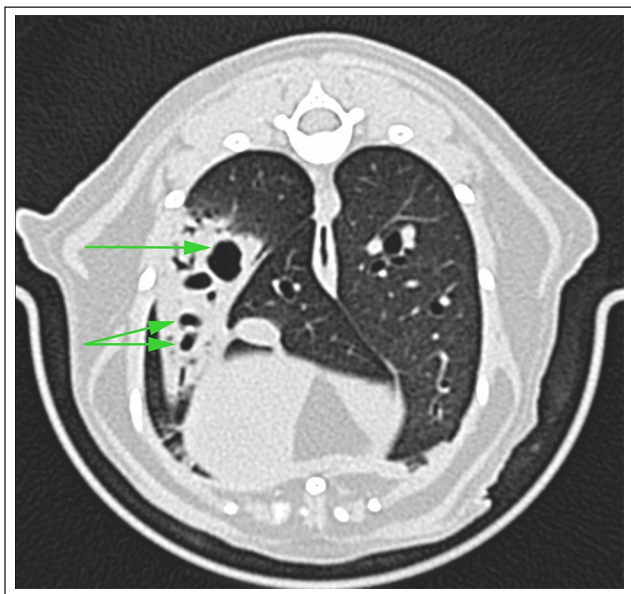


Figure 3 Transverse CT image with lung reconstruction and lung window (window width 1500; window length -498) of case 2. A focal area of marked consolidation is visible within the ventral aspect of the right caudal lung lobe in association with moderate bronchiectasis of the corresponding bronchi (arrows)

Treatment was initiated with salbutamol (200 µg inhaled q12h) and fluticasone propionate (125 µg inhaled q12h). *Mycoplasma felis* and *Pasteurella* species, possible oral or upper airway contaminants, were cultured from the BAL sample. The cat was treated with antibiotics at the clinical discretion of the attending veterinarian, with alteration in treatment based on clinical response. Following the receipt of antibiotic sensitivity testing, antibiotic therapy was adjusted as indicated and treatment with marbofloxacin (Marbocyl [Vetoquinol] 2.1 mg/kg PO q24h) was initiated. Marked clinical improvement followed and at the time of reassessment 9 weeks later, there had only been one episode of coughing observed during the preceding month. Despite this, the RR was around 50brpm and, on thoracic auscultation, harsh bronchovesicular sounds and infrequent crackles were noted.

Repeat CT identified lung changes similar to those on the initial scan. A third CT 3 weeks later, performed in case the CT findings lagged behind clinical improvement, revealed unchanged pathology. Oxygen saturation remained above 98% for the duration of each repeat CT. Following discussion with the owner, right caudal lung lobectomy and partial right middle lung lobectomy were performed.

Histopathology of the excised tissue confirmed the presence of marked changes in the right caudal lung lobe, which were characterised by prominent atelectasis and proliferation of smooth muscle throughout the tissue. In some areas, the alveoli were lined by tall columnar epithelial cells. The alveolar walls were thickened by fibrosis and further smooth muscle proliferation. There were several areas of complete parenchymal collapse and replacement fibrosis. These changes were consistent with pulmonary fibrosis. There were also mild changes in the right middle lung lobe with increased numbers of

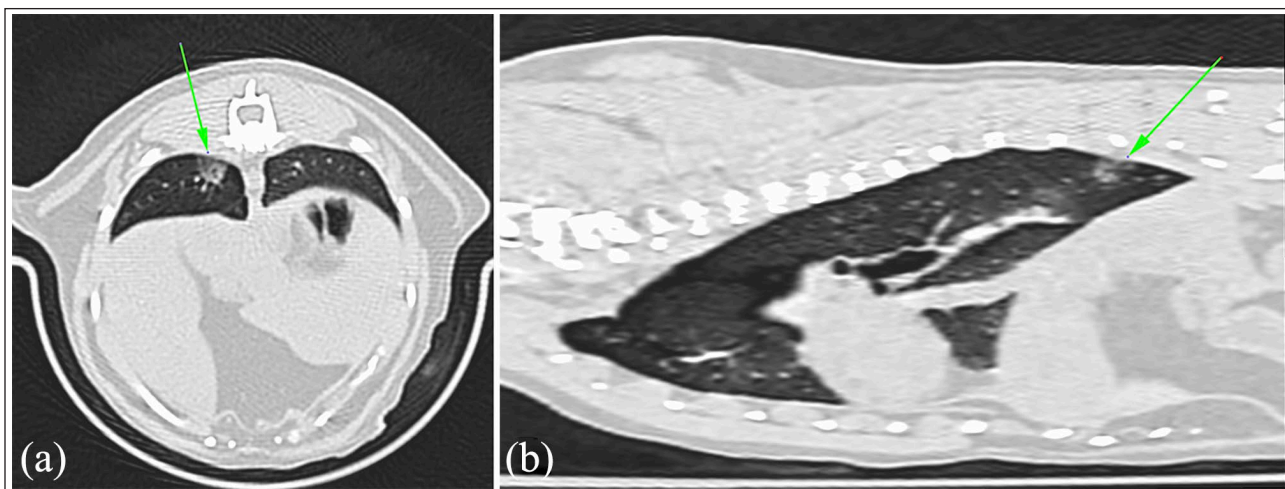


Figure 4 (a) Transverse and (b) parasagittal CT images with lung reconstruction and lung window (window width 1500; window length -498) of case 2, showing a focal area of subpleural ground-glass attenuation in the dorsal part of the right caudal lung lobe (arrows)



Figure 5 Transverse CT image with lung reconstruction and lung window (window width 1500; window length -498) of patient 2, showing subpleural thickening of the ventral margin of the left caudal lung lobe (arrow)

alveolar macrophages. Bronchi and bronchioles were filled with mucin along with further macrophages and some neutrophils and there was mild peribronchiolar lymphoid cuffing. These mild changes were consistent with mild bronchitis and bronchiolitis.

The cat continued to receive inhaled fluticasone and was monitored by the primary practice until death occurred acutely while at home, 4 years after first presentation. A post mortem was declined.

Discussion

The diagnosis of IPF in humans requires extensive exclusion of known causes of ILD, including environmental exposures, connective tissue diseases, drug toxicities and possible chronic hypersensitivities that may mimic IPF.¹¹ This is done via a thorough medical evaluation with history taking and physical examination focusing on comorbidities, medication use, environment and family history. This is then supported by physiological testing and laboratory findings,^{8,11} including screening for autoantibodies, immunoglobulins against organic antigens and serum angiotensin-converting enzyme and pulmonary function tests.¹ Where an identifiable cause for ILD cannot be found, specific combinations of patterns on CT and surgical lung biopsy, where indicated, can then lead to the diagnosis of IPF.^{8,11} The extent to which we can conclusively exclude other triggers or diseases that can lead to end stage PF in cats, due to practical constraints such as exposure to unknown environments or unknown previous history, limits the confidence in diagnosing true IPF in cats. Instead, these cases could be considered PF of unknown aetiology.

Following exclusion of known causes of ILD, human IPF can be diagnosed through specific combinations of histopathological and/or radiological diagnosis of usual interstitial pneumonia (UIP).⁸ In UIP, zones of normal tissue are seen in close association with areas of advanced tissue remodelling causing fibrosis and honeycomb change,^{8,12} often described in a pattern of temporal heterogeneity. Characteristics of UIP include minimal inflammation, areas of honeycombing where clusters of irregular, fibrotic, cystic airspaces are filled with mucus and inflammatory cells (known as fibroblast foci), fibrotic zones with proliferating fibroblasts and myofibroblasts occurring at the interface of normal and fibrotic lung, hyperplasia of type II pneumocytes and smooth muscle metaplasia within the interstitium.^{11,13} Cats have been identified as a potential model for human IPF owing to their similarities in the clinical and histopathological findings of UIP.⁷ Comparable histological features were found in both cats reported here.

UIP has a characteristic appearance on CT in humans. Consistent features include honeycombing and reticular changes, often associated with traction bronchiectasis, a subpleural or basal predominance, and an absence of inconsistent features of UIP, such as profuse micronodules, discrete cysts and consolidation.¹¹ Ground-glass opacities are common but must be less extensive than the reticular opacities. Where clinically appropriate, the UIP pattern on CT is considered sufficient for a diagnosis of IPF in human medicine.^{9,11} In other reported cases of feline IPF-like disease, the CT findings were diffuse, focal or multifocal, with areas of pulmonary consolidation, and no basal predominance was reported.^{5,6} This could mean that basal and subpleural predominance is not a feature of feline PF. Similarly, a honeycomb pattern has only been described in one of the three cases with CT description,⁶ and was not present in either of our cases. Traction bronchiectasis has been inconsistently described in previous studies of feline PF,^{4,5} although it could be missed on radiographs, and was present in both our cases. Therefore, despite having compatible histopathological features, most reported cases of feline PF, including ours, do not meet the specific criteria outlined for UIP in humans on CT.

The focal nature of the lesions in case 2, affecting predominantly the ventral half of the right caudal lung lobe and, to a lesser extent, the right middle lung lobe, is interesting. Localised pulmonary fibrosis secondary to previous pulmonary disease, such as bronchopneumonia, could not be conclusively excluded. In a previous study of nine cats with IPF-like disease,⁵ two cats had focal soft tissue pulmonary masses that were confirmed to be PF on histopathology following lung lobectomy. PF in cats appears, therefore, to have a variable distribution and should be considered as a differential in clinically appropriate cases where a focal lesion is present. This variable distribution could also reflect the historical

involvement of a causative agent, even if that agent is no longer present at the time of diagnosis.

In cats with PF, invasive pulmonary diagnostics under general anaesthesia are poorly tolerated and appear to cause a rapid deterioration. Five of 12 cats subjected to tracheal wash and/or bronchoscopy and BAL in one study either died or were euthanased within 24 h of the procedure.⁴ Two of three cats in another study died during surgical lung biopsy.¹⁴ Our second case had marked respiratory compromise during bronchoscopy leading to abandonment of the procedure. This risk should be duly considered in any diagnostic work-up in a cat where PF is suspected. Considering the focal distribution of the alveolar lesion in case 2 and the suspicion of chronic bronchitis and bronchopneumonia, bronchoscopy and BAL were considered justified.

Right cardiac enlargement was noted in both cases on CT; this may have reflected pulmonary hypertension, although this was not confirmed via echocardiography in either case, or reported at post mortem in case 1. The dynamic changes of the heart during the cardiac cycle may also affect appearance, so could reflect overinterpretation of normal variation.¹⁵

Case 2 lived for 4 years following lung lobectomy and the disease was stable over this time. The average survival time of cats with IPF-like disease previously reported was 5.5 months.⁷ In the largest study of IPF-like disease in cats,⁴ only 4/23 lived for one or more years after initial presentation, and only one of these cats survived for an extended period of time equivalent to our second case. It is noteworthy that in these two case series, 6/23 and 3/16 cats, respectively, had concurrent pulmonary neoplasia that could have impacted the survival time.^{4,7} The prolonged survival time in our second case was likely due to the localised nature of the disease, rendering it amenable to surgical excision.

Conclusions

The two cats presented here provide further evidence that PF of unknown aetiology in cats incorporates a wide spectrum of fibrotic lung diseases. Although some histological features are comparable to human IPF, the variable distribution, lack of a CT UIP pattern and frequent inability to exclude causative agents prompt us to avoid the use of the terms IPF or IPF-like disease in cats. The focal disease and 4-year survival time of case 2 presents evidence that the prognosis may be better than previously thought, especially in select cases where the disease is amenable to surgical intervention. This should prompt interest in identifying these cases early, and attempts should be made to identify any known inciting agent. A larger-scale study is required to document the full range of CT changes that may be observed with this condition and would enable further classification of fibrotic pulmonary diseases in cats.

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article

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Ethical approval This work involved the use of non-experimental animals only (including owned or unowned animals and data from prospective or retrospective studies). Established internationally recognised high standards ('best practice') of individual veterinary clinical patient care were followed. Ethical approval from a committee was therefore not necessarily required.

Informed consent Informed consent (either verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (either experimental or non-experimental animals) for the procedure(s) undertaken and use of data (either prospective or retrospective studies). No animals or humans are identifiable within this publication, and therefore additional informed consent for publication was not required.

ORCID iD Erin M O'Connell  <https://orcid.org/0000-0003-0400-9291>

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