Use of computed tomography imaging during long-term follow-up of nine feline tuberculosis cases

The Use of Computed Tomography Imaging During Long Term Follow-up of Nine Feline Tuberculosis Cases

Alison Major,[1a] Conor O'Halloran,[2ab] Andrea Holmes,[1] Stephanie Lalor,[3] Rebecca Littler,[4] Susanna Spence,[5] Tobias Schwarz,[2c] Danièlle Gunn-Moore[2c]

[1]University of Bristol/Langford Veterinary Services, School of Clinical Veterinary Science, Langford House, Langford, Bristol, BS40 5DU, UK

[2]Royal (Dick) School of Veterinary Studies and The Roslin Institute, Division of Veterinary Clinical Sciences, The University of Edinburgh, Hospital for Small Animals, Easter Bush Veterinary Centre, Roslin, Midlothian, EH25 9RG, UK

[3]Willows Veterinary Centre & Referral Service, Highlands Road, Solihull West Midlands, B90 4NH, UK

[4]Northwest Surgeons, Delamere House, Ashville Point, Sutton Weaver, Cheshire, WA7 3FW, UK

[5]Small Animal Hospital, University of Glasgow, Bearsden Road, Glasgow, G61 1QH, UK

[a]Joint first authors

[b]Corresponding author – Conor O'Halloran BVSc, MSc, Royal (Dick) School of Veterinary Studies and The Roslin Institute, Division of Veterinary Clinical Sciences, The University of Edinburgh, Hospital for Small Animals, Easter Bush Veterinary Centre, Roslin, Midlothian, EH25 9RG, UK

Email: Conor.O'Halloran@roslin.ed.ac.uk

[c]Joint last authors

Abstract:

Case Series Summary: Feline tuberculosis is an increasingly recognised potential zoonosis of cats. Treatment is challenging and prognosis can vary greatly between cases. Pulmonary infection requires extended courses of antibiotics, but methodologies for sensitively monitoring response to treatment are currently lacking.

In this case series we retrospectively examined the serial computed tomography (CT) findings in nine cats that had been diagnosed with tuberculosis. Changes in pathology (where applicable to tuberculosis) were correlated with the clinical presentation of each of the cats, the treatment protocol, plus previous and contemporary diagnostic investigations.

This study found that changes in CT findings during the medium to long term management of feline tuberculosis were highly variable between cats. The majority of cats had reduced pathology at re-examination during anti-tuberculous therapy, but pathology only resolved in a minority of cases. In some cases reoccurrence of pathology detected by CT imaging preceded clinical relapse, allowing for rapid therapeutic intervention.

Relevance and Novel Information: When considered in combination with clinical findings, CT studies can aid in decision making regarding tapering of antibiotic protocols, or reintroduction of therapy in cases of recurrence or reinfection. These cases also highlight that in some cases, persistent abnormalities can be detected by CT so complete resolution of CT pathology should not always be a goal in the management of feline tuberculosis.

Introduction

Feline tuberculosis is a highly variable and increasingly recognised disease in domestic pet cats in the British Isles.[1-3] Infection is assumed to be acquired from bites by prey species sustained during hunting, leading to the most typical clinical presentation of cutaneous lesion/s at "fight and bite sites" with or without regional lymph node involvement.[1-3] Disseminated disease can occur, resulting in non-specific signs related to the respiratory and/or alimentary tracts giving rise to variable findings on diagnostic imaging investigations.[4-7] Thoracic and/or abdominal pathology can more rarely result from acquisition of disease through inhalation or ingestion.[1,5] The radiological and computed tomography (CT) abnormalities associated with disseminated mycobacterial infection have previously been described.[2,4,7]

Advocated treatment protocols for feline tuberculosis typically consisted of an initial and a continuation phase.[8] The initial phase combines three antibiotic drugs lasting for two months, while the continuation phase comprises of two drugs for a further four months.[8] However, it is possible that treating with all three drugs until two months after apparent clinical resolution, which typically results in four to six months of treatment, may result in a better clinical outcome (DGM and COH, unpublished data, 2016).

Prognosis varies depending on the species of mycobacterium involved, the extent and severity of disease, and the compliance and tolerance of the patient to medication.[1,6] While many cases respond favorably to therapy, resulting in apparent cure or long term remission, other patients either fail to respond or go on to develop recurrence of signs following apparently successful treatment.[1,6]

In order to assist clinical decision making by veterinary surgeons and owners, a reliable method is needed to monitor the disease at all stages of management. The use of CT has already been shown to be a valuable tool in the initial diagnosis.[7] In this report, we describe the use of CT during the medium and long term follow-up of tuberculous disease in nine cats between June 2010 and May 2016. Table 1 shows signalment and summary data for all nine cases detailed below.

76 Table 1: Summary details of the nine case of feline tuberculosis where serial CT images were used as part of clinical follow-up

Case Number	Breed	Age (years)	Gender	Location in UK	Weight (kg) at initial presentation	Haematology & serum biochemistry (reference interval)	FIV / FeLV status	Diagnosis	Impact of CT evaluations
1	Oriental	7	MN	South Scotland	5	Total calcium 3.13mmol/L (1.95-2.83mmol/L) Ionised calcium 1.75mmol/L (1.05-1.45mmol/L)	Negative	*M. microti*	Early re-instigation of antibiosis following slight clinical deterioration.
2	DSH	11	FN	Central Scotland	3.6	No abnormalities detected	Negative	*M. microti*	Pulmonary dissemination of tuberculosis diagnosed. Mid-term static appearance of lesion irrespective of antibiotic therapy.
3	Bengal	13	MN	South Scotland	5	No abnormalities detected	Negative	*M. microti*	Delayed antibiotic tapering due to persistent abnormalities. Early re-instigation of antibiosis following slight clinical deterioration.

4	British Shorthair	10	MN	Cheshire, England	3.8	Hyperglobulinaemia	Negative	*M. bovis*	Reduction of antibiosis with improvement to detectable abnormalities.
5	DSH	7 months	MN	Bristol, England	2.8	Total calcium 3.95mmol/L (2.30-2.50mmol/L)	Negative	*M. microti*	Discontinuation of antibiosis with improvement to detectable abnormalities.
6	DSH	3	FN	West Midlands, England	4.1	No abnormalities detected	Negative	Tuberculosis complex	Reduction of antibiosis with early improvement to detectable abnormalities.
7	DSH	7	MN	South Scotland	5	No abnormalities detected	Negative	*M. microti*	Reduction of antibiosis with improvement to detectable abnormalities.
8	Burmilla	8	ME	South Scotland	4.6	No abnormalities detected	Negative	*M. microti*	Discontinuation of antibiosis with improvement to detectable abnormalities.
9	DSH	7	MN	Central Scotland	5.7	No abnormalities detected	Negative	*M. microti*	Continuation of antibiosis with partial improvement to detectable abnormalities.

Legend: DSH: domestic short hair, MN: male neutered, FN: female neutered, ME: male entire, FIV: feline immunodeficiency virus, FeLV: feline leukaemia virus.

79

Case Series Description

Case 1

Case 1 initially presented with anorexia and weight loss. Mild mandibular lymphadenomegaly and harsh lung sounds were noted on physical examination. Thoracic radiographs revealed a diffuse structured interstitial lung pattern; CT was not performed as the clinic did not have on-site access to CT at this time. The feline interferon gamma (IFN-γ) release assay (IGRA) was performed by Biobest Laboratories, Edinburgh, and indicated infection with *Mycobacterium microti*.[8] The cat was treated with a triple antibiotic protocol of rifampicin [generic, Mylan, Herts] (10mg/kg) 50mg PO q24h, marbofloxacin [Marfloquin, Virbac] (3mg/kg) 15mg PO q24h, and azithromycin [Zithromax, Pfizer] (6mg/kg) 30mg PO q24h for two months as the induction treatment phase; marbofloxacin was then discontinued and the remaining antibiotics continued for the maintenance phase. After six months, clinical remission from disease was achieved; serum calcium concentration was within the reference interval and repeat radiographs revealed no abnormalities, so antibiosis was stopped.

Eleven months after antibiotic treatment had been discontinued, the cat represented with a recurrence of lethargy and anorexia, with normal lung sounds but reduced thoracic compression. Body weight had increased to 6.2kg. A recurrence of hypercalcaemia was noted (ionised calcium 1.75 mmol/l) and serum 25-hydroxyvitamin D concentration was low (46 pg/ml, RI 14.9-61.0ng/ml). Full-body CT was performed using a VetMouseTrap device, revealing mild tracheobronchial, mediastinal and mesenteric lymphadenomegaly and a diffuse, moderate reticulonodular lung pattern (Figure 1a). Recurrence or reinfection of tuberculosis was assumed and triple antibiotic therapy was reinstated (drugs and doses as above, dosed for a 6kg cat). In addition, calcitriol supplementation was given at a dose of 2ng/kg PO q24h. Three months later the cat was reassessed, and clinical examination and whole-body CT were normal (Figure 1b). On the basis of completing three months of triple antibiotic therapy and resolution of clinical signs, treatment was changed to pradofloxacin (Veraflox tablets

Bayer) [4mg/kg] 25mg PO q24h, which was given as an antimicrobial monotherapy for six months with calcitriol supplementation as previously described. Two further CT examinations were performed, at four and six months after disease recurrence, and were normal. Eleven months after recurrence, after two months off pradofloxacin, the cat was represented as the owner observed a mildly increased sleeping respiratory rate (21bpm; this cats normal sleeping respiratory rate was <20bpm). Despite a normal clinical examination, a CT scan demonstrated a diffuse mild reticular lung pattern with areas of ground glass opacity (Figure 1c); the serum calcium concentration was increased and serum 25-hydroxyvitamin D concentration was low. Triple antibiotic therapy was restarted (rifampicin and azithromycin, dosed as above, plus pradofloxacin [Veraflox liquid, Bayer] [~5mg/kg] 30mg PO q24h), and calcitriol treatment was restarted at [2ng/kg] 12.5mcg PO q24h (body weight 6.5kg). After two-months of treatment repeat CT examination was normal. Due to the history of several episodes of disease it was recommended that the triple antibiotic therapy be continued for a further four months, followed by three months of double antibiotic therapy (azithromycin and pradofloxacin, dosed as above). The cat remained clinically normal throughout this period and treatment was discontinued a total of 20 months after the initial recurrence. Two months later another IGRA returned a negative result and the serum calcium and 25-hydroxyvitamin D concentrations were within normal limits. A further episode of mycobacterial recurrence/reinfection occurred after eight months without treatment. The cat was again re-presented following observation of a mildly increased sleeping respiratory rate (23bpm; body weight 7.1kg). Whole body CT demonstrated mild diffuse thoracic and abdominal lymphadenomegaly, and a diffuse but patchy, mild to moderate reticulonodular lung pattern. A repeated IGRA was positive and consistent with *M. microti* infection. Triple antibiotic therapy was prescribed for three months (rifampicin, pradofloxacin and azithromycin, dosed as above, for a 7kg cat), followed by double antibiotic therapy for a further nine months (pradofloxacin and azithromycin, dosed as immediately above). During this period, the cat remained well, and a further four full-

body CT examinations revealed a normal pulmonary parenchymal appearance. Given the normal imaging and clinical findings throughout this period, antibiotics were discontinued as planned, and the cat remains well without recurrence of clinical signs over 17 months later, during this time five CT scans revealed no detectable abnormalities. A timeline of this case is shown in Figure 2.

Case 2

Case 2 was first presented for weight loss and generalised lymphadenomegaly. Radiographs revealed a diffuse interstitial lung pattern (CT was not available at the clinic at that time). Excisional biopsy of the popliteal lymph nodes was performed; histopathology revealed a granulomatous lymphadenitis and Zeihl Neelsen (ZN) staining identified intra-lesional acid-fast bacilli indicative of mycobacterial infection. A triple antibiotic protocol was instigated (rifampicin [11mg/kg] 40mg PO q24h; marbofloxacin [2.7mg/kg] 10mg PO q24h; clarithromycin [11mg/kg] 40mg PO q12h) for two months followed by rifampicin and marbofloxacin (same doses) for four months. Revisits revealed initially static peripheral lymphadenomegaly, which resolved over the four months of maintenance treatment. Repeat thoracic radiography at the end of the maintenance phase revealed no abnormalities and treatment was therefore discontinued. Four months following the end of treatment the cat presented to an emergency clinic with acute respiratory signs. Laryngeal swelling was identified and following stabilisation with corticosteroids, furosemide, chlorphenamine (all at standard doses), plus additional oxygen, the laryngeal swelling resolved. Radiography revealed a thoracic mass consistent with an enlarged cranial mediastinal lymph node. This was confirmed on full body CT examination using a VetMouseTrap device, which also revealed moderate mineralisation within the mass lesion (Figure 3a). Fine needle aspiration (FNA) of the mass yielded a non-diagnostic sample whilst an IGRA was consistent with *M. microti* infection. Given the previous history of mycobacterial lymphadenitis, with an owner who was reticent to restart triple therapy,

the cat was started on single antibiotic therapy (pradofloxacin liquid [7mg/kg] 25mg PO q24h) to see if this might reduce the size of the thoracic mass and so give weight to the diagnosis that it may be tuberculous. One month later the cat was clinically well and CT revealed a static appearance to the mass. Antibiotic therapy was discontinued as it did not appear to be effective. Three months later the CT appearance remained unchanged, and a repeat IGRA was inconclusive. The cat represented the next month with hypersalivation and difficulty eating. Physical examination revealed thickening of the caudal aspect of the right mandibular ramus, with loosening of the associated teeth. On CT this lesion was characterised by moderate bone lysis with concurrent proliferation, moderate regional lymphadenomegaly was noted. The thoracic mass remained static in appearance, but the surrounding lung had a mild patchy ground glass appearance (Figure 3b). The appearance of the mandibular lesion was not considered typical for tuberculous osteomyelitis. Biopsy of the mandibular mass and local lymph nodes resulted in a diagnosis of squamous cell carcinoma with reactive lymphoid hyperplasia. The owner opted for palliative therapy with meloxicam (Metacam, Boehringer Ingelheim 0.05mg/kg PO q24h), and after three weeks the cat was euthanased. Post mortem examination was performed and histopathology of the enlarged cranial mediastinal lymph node revealed large numbers of acid-fast bacilli within the node and the peri-nodal connective tissue. As indicated by CT, granulomatous inflammatory changes extended into the adjacent pulmonary parenchyma. The lymph node was confirmed to be PCR positive for *M. microti* by the Mycobacterial Reference Laboratory, Leeds University Teaching Hospital. A timeline of this case is shown in Figure 4.

Case 3

Case 3 initially presented with mandibular lymphadenomegaly. Sternal lymphadenomegaly was noted on thoracic radiography and abdominal ultrasound revealed marked mesenteric lymphadenomegaly and focal

marked circumferential jejunal thickening; FNA of the mandibular and jejunal lymph nodes and the abnormal jejunal wall revealed granulomatous inflammation with acid-fast bacilli indicative of mycobacterial infection. An IGRA was consistent with *M. microti* infection and the cat was started on triple antibiotic therapy (rifampicin [10mg/kg] 50mg PO q24h; azithromycin [8mg/kg] 40mg PO q24h; pradofloxacin tablets [5mg/kg] 25mg PO q24h), plus calcitriol supplementation ([2ng/kg] 10mcg PO q24h). Two months later the cat was clinically well, although the right mandibular lymph node remained slightly enlarged. A conscious full-body CT examination using a VetMouseTrap device was performed, revealing improved but persistent mesenteric lymphadenomegaly. Given the clinical and imaging findings, the triple antibiotic therapy described above was maintained for another four months, giving a total treatment duration of six months, after which the mandibular and mesenteric lymph nodes were palpably normal and antibiosis was discontinued (body weight 6.4kg at this time). Three months later the cat represented with weight loss, lethargy and inappetence (body weight 6.0kg). The peripheral lymph nodes were of normal size but harsh inspiratory lung sounds and multiple palpable abdominal masses were noted. Both abdominal ultrasound and full-body CT were performed, confirming the presence of marked thoracic and abdominal lymphadenomegaly, and focal marked jejunal thickening as had been previously described. A diffuse, mild reticulonodular lung pattern was also noted. A FNA of the mesenteric lymph nodes again revealed granulomatous inflammation with acid fast bacilli. Triple antibiotic therapy was resumed at the dose rates detailed previously, but despite an initially improved demeanour the cat continued to lose weight and after five months of treatment was euthanased. Post mortem examination was not performed. A timeline of this case is shown in Figure 4.

Case 4

Case 4 initially presented with weight loss, dyspnoea and coughing. Physical examination revealed tachypnoea (respiratory rate 40bpm), with increased inspiratory and expiratory effort and noise. Thoracic CT examination revealed a moderate multifocal alveolar pattern with regions of pulmonary cavitation affecting multiple lung lobes, most marked within the right caudal lobe, and a moderate thoracic lymphadenomegaly (Figure 5a). A right caudal lung lobectomy was performed and histopathology revealed necrotising and pyogranulomatous bronchopneumonia; however, no acid fast bacteria were identified. Tissue was submitted for culture and blood for IGRA, and treatment with marbofloxacin ([2mg/kg] 8mg PO q24h) was started. A good clinical response was noted in the initial two-month post-operative period; however, tissue culture and IGRA both confirmed *Mycobacterium bovis* infection, and a standard triple antibiotic protocol was introduced (marbofloxacin [2mg/kg] 8mg PO q24h; azithromycin [10mg/kg] 40mg PO q24h; rifampicin [20mg/kg] 80mg PO q24h – although the dose of rifampicin was high). After two months of triple antibiotic treatment, CT was repeated revealing residual patchy ground glass opacity, with collapsed cavities within the remaining lung lobes, but subjectively normal thoracic lymph nodes. Due to the improved pulmonary appearance and the good clinical condition of the cat, triple antibiotic therapy was reduced to dual therapy (marbofloxacin and rifampicin, dosed as above). After a further four months, the appearance of the lungs on CT examination was unchanged (Figure 5b) and a repeat IGRA remained positive. Antibiotic treatment was discontinued, and the cat remained well, with a negative IGRA result obtained six months later. A timeline of this case is shown in Figure 4.

Case 5

Case 5 initially presented with coughing, resting tachypnoea (respiratory rate 55bpm), and exercise intolerance. Body weight and condition score (1.5/5) were low. Thoracic and abdominal CT examination revealed a diffuse marked nodular lung pattern with occasional scattered foci of pulmonary mineralisation (Figure 6a), marked

207 tracheobronchial lymphadenomegaly and mild peripheral and abdominal lymphadenomegaly. A FNA of lung
208 tissue revealed marked pyogranulomatous inflammation with acid-fast bacilli and was PCR positive for
209 *Mycobacterium tuberculosis* complex organisms. The IGRA suggested infection with *M. microti*. A standard
210 antibiotic protocol of two months' triple therapy (pradofloxacin [~5mg/kg] 15mg PO q24h; azithromycin
211 [~10mg/kg] 30mg PO q24h; rifampicin [~10mg/kg] 30mg PO q24h) was followed by ongoing double therapy
212 (azithromycin and rifampicin, dosed as above). At a recheck after eight months of treatment the cat was
213 clinically normal and had an improved body weight and body condition score (4.4kg and 2.5/5). Thorax CT
214 revealed only a mild diffuse reticulonodular lung pattern, but scattered pulmonary mineralisation was more
215 extensive than previously noted (Figure 6b). Antibiotic therapy was discontinued. The cat remained well and
216 the CT abnormalities were seen to be static at a revisit 12 months later. A timeline of this case is shown in
217 Figure 4.

218 **Case 6**

219 Case 6 presented with lethargy, intermittent dyspnoea, weight loss, stridor and nasal discharge. Clinical
220 examination revealed a moderate inspiratory dyspnoea with wheezing on auscultation, bilateral serous nasal
221 discharge, bilateral renomegaly and bilateral popliteal lymphadenomegaly. A CT examination of the head,
222 thorax and abdomen revealed an alveolar lung pattern within the right middle and ventral right caudal lung
223 lobes, with a diffuse moderate reticulonodular pattern, moderate multifocal lymphadenomegaly, mild bone lysis
224 over the nasal bridge and multiple mass lesions in both kidneys. Nasal biopsies confirmed mycobacterial
225 infection by histopathology, and was PCR positive for *Mycobacterium tuberculosis* complex organisms, but the
226 laboratory was unable to further define the species. A standard antibiotic protocol of two months' triple therapy
227 was prescribed (pradofloxacin [~5mg/kg] 20mg PO q24h; azithromycin [~10mg/kg] 40mg PO q24h; rifampicin

[~10mg/kg] 40mg PO q24h), followed by ongoing double therapy (pradofloxacin and rifampicin, dosed as above). Two months after the start of antibiotic therapy the cat was clinically well. The CT showed marked improvements, with residual diffuse mild pulmonary ground glass appearance, mild multifocal lymphadenomegaly and partial resolution of the renal mass lesions. Antibiotics were discontinued after a six-month course, and the cat remains clinically well 12 months later. A timeline of this case is shown in Figure 4.

Case 7

Case 7 presented with dysuria due to a well demarcated alopecic skin nodule of 2cm diameter over its prepuce. Physical examination revealed a mildly elevated resting respiratory rate (48 bpm). An incisional biopsy of the preputial lesion revealed granulomatous inflammation and rare acid-fast bacilli indicative of mycobacterial infection. An IGRA was strongly suggestive of an *M. microti* infection. A CT scan, performed using a VetMouseTrap device, revealed a focal region of alveolar pattern in the left cranial lung lobe with a diffuse mild reticulonodular pattern suggestive of pulmonary tuberculosis. The cat was placed on standard triple antibiotic therapy (pradofloxacin tablets [3mg/kg] 15mg PO q24h; azithromycin [6mg/kg] 30mg PO q24h; rifampicin [10mg/kg] 50mg PO q24h) for four months. By re-evaluation, the preputial lesion and dysuria had completely resolved and thoracic CT revealed an improvement in both the focal and diffuse pulmonary changes. The cat was changed to dual antibiotic therapy (rifampicin and azithromycin, dosed as above), and this was discontinued after an additional two months; the cat remains clinically well six months later. A timeline of this case is shown in Figure 4.

Case 8

Case 8 was presented for investigation of dyspnoea (respiratory rate 60bpm), bilateral mandibular lymphadenomegaly and palpable abdominal masses. Abdominal ultrasound showed a diffusely heterogeneous appearance to the spleen and mild generalised abdominal lymphadenomegaly. An exploratory laparotomy was performed to biopsy the abnormal structures. Histopathological analysis of the spleen and medial iliac lymph node revealed granulomatous splenitis and reactive lymphoid hyperplasia consistent with mycobacteriosis although no acid-fast bacteria were seen. Thoracic radiography revealed a severe diffuse mixed bronchial and nodular pattern with multiple foci of mineralisation in the caudodorsal lung fields. No thoracic lymphadenomegaly was evident. An IGRA indicated *M. microti* infection, so triple antibiotic therapy was instigated for six months (marbofloxacin [2mg/kg] 10mg PO q24h; rifampicin [16mg/kg] 75mg PO q24h; clarithromycin [8mg/kg] 35mg PO q12h). Re-evaluation after six months revealed that the initial clinical signs had resolved and a full body CT scan using the VetMouseTrap identified complete resolution of the previously noted lung pattern and abdominal lymphadenomegaly. Several small mineral foci remained visible within the lungs which were predominantly, but not exclusively, airway associated. Antibiotic therapy was discontinued at this point. The cat remained clinically well and at a routine revisit over 33 months later a full body CT was repeated using the VetMouseTrap. This study revealed normal pulmonary parenchyma and there was no evidence of lymphadenomegaly. More extensive and more widely distributed predominantly airway-associated mineralisation was present. A timeline of this case is shown in Figure 4.

Case 9

Case 9 was presented for investigations into stertorous breathing and a rapidly growing inter-ocular skin lesion. The CT examination of the head and thorax revealed a soft tissue mass lesion overlying the frontal and nasal bones with several associated small foci of bone lysis, plus a diffuse but asymmetrical, mixed lung pattern.

Moderate bronchial and reticulonodular patterns affected the right lung lobes, partial collapse and an alveolar pattern was noted within the accessory lung lobe, and multiple larger well-defined nodules (some showing internal mineralisation) were present within the left lung lobes, with more normal appearing parenchyma surrounding them. There was moderate sternal and cranial mediastinal and marked tracheobronchial lymphadenomegaly. Histopathology on an incisional biopsy of the soft tissue mass revealed a large mixed inflammatory cell infiltrate including epitheloid macrophages, suggestive of mycobacteriosis; ZN staining revealed large numbers of acid fast bacilli which were identified by PCR as *M. microti.* Triple antibiotic therapy was instigated for nine months (clarithromycin [11mg/kg] 65mg PO q12h; rifampicin [9mg/kg] 50mg PO q24h; marbofloxacin [1.8mg/kg] 10mg q24h). Within two months the stertor had resolved and the skin lesion had reduced in size; by the end of the nine month course of antibiosis all clinical signs had fully resolved. A CT scan showed improvement but not resolution of the mediastinal and sternal lymphadenopathy and diffuse lung changes. The left lung nodules had mildly more extensive mineralisation than previously. It was decided to continue treatment due to the continued presence of pathology and a timeline of this case is shown in Figure 4.

Discussion

The cases presented here are a cohort of cats with conclusive or strong evidence supporting a diagnosis of feline tuberculosis (culture, PCR and/or IGRA results). In contrast to previously published data on feline tuberculosis, the cases in this series are predominately *M. microti* infections, whereas national culture data shows that while *M. microti* can be cultured from 19% of cases with histopathological changes indicative of mycobacteriosis, *M. bovis* can usually be cultured from 15%.[2] The reason for the lack of *M. bovis* cases is unclear; it may result of our small sample size, the majority of which lived in regions of the UK where *M. microti* is more prevalent[2], or

it could indicate an underlying bias towards owners being more likely to treat cats with *M. microti*-infection rather than *M. bovis*, probably due to the higher zoonotic risk associated with the latter organism[9].

In line with previous studies, the majority of cats with tuberculosis in this study are males;[2] none were found to be co-infected with the FIV and FeLV, and the median age of cats infected with *M. microti* was seven years (range seven months - 13 years), compared to a previously documented median of eight years.[2]

The cases in this series demonstrated a range of clinical responses following diagnosis and treatment of disseminated feline tuberculosis, and in each case, repeated CT imaging contributed to decision making in ongoing clinical management within the context of contemporaneous investigations. It is recognised that the cases in this study show significant variability both in the use of CT and its timing in relation to treatment. This largely relates to the multi-centre nature of this study, as decision making varied depending on the preferences of the primary clinician.

A previous study found a sustained complete remission in only 40% of feline mycobacterial infections;[6] however, that study included many cases that were treated with sub-optimal drug regimens (e.g. short courses of fluoroquinolone monotherapy),[6,10] as well as including *M. avium* infections which are known to be refractive to treatment due to complex inherent drug resistance patterns.[11] Previously advocated treatment protocols for feline tuberculosis typically consisted of an initial and a continuation phase.[9] However, recent studies regarding multi-drug resistant *M. tuberculosis* (MDR-TB) in humans have suggested that using at least three and ideally four antibiotics given in combination throughout treatment significantly reduces the development of antimicrobial drug resistance.[12-15] Recommended first line anti-tuberculosis medications for humans consist of rifampicin, isoniazid, dihydrostreptomycin, ethambutol and pyrazinamide.[16] However, the use of these drugs does not readily translate into veterinary medicine; isoniazid has been associated with neurological side effects

in small animals,[17] pyrazinamide is ineffective against *M. bovis* infections[18] which comprise approximately 15% of feline mycobacterial infections,[2] and dihydrostreptomycin should be reserved for human use.[19] Therefore, small animal anti-tuberculosis therapy, when undertaken, should consist of a triple combination of rifampicin (for its potency and its ability to kill non-replicating [latent] tuberculous Mycobacteria[20] [recommended doses 10-15mg/kg PO q24h]), a fluoroquinolone (ideally pradofloxacin as it has better efficacy against Mycobacteria than older fluoroquinolones, [21,22] and a better safely profile in cats [23] [pradofloxacin recommended doses 3-7mg/kg PO q24h]) and a macrolide (such as clarithromycin [7-15mg/kg PO q12h] or azithromycin [5-15mg/kg PO q24h]) for a minimum of three months as standard.[9,24] It is recommended that treatment should be given for two to three months after apparent clinical resolution, which typically results in four to six months of treatment.[9,24] The efficacy of combination long-term treatment is supported by the cases in this series, as all were treated with either two or three antibiotics for at least six months; only one of the cats died from tuberculosis, and another was found to have latent tuberculosis after euthanasia for an unrelated disease. This gives a sustained complete remission rate of eight of nine cases (~90% remission), which is much higher than the 40% previously reported.[6] This is much more in line with our recent experiences, as following the introduction of sustained triple therapy the prognosis for feline tuberculosis appears to be closer to 70-80% success when treating cutaneous and/or pulmonary tuberculosis caused *M. bovis* or *M. microti* (DGM and COH, unpublished data 2016). Prolonged therapy is therefore recommended in all cases, and due care is required when advising clients on discontinuing treatment.

The majority of the cases in this series (cases 1, 4, 5, 7 and 8) demonstrated that where improvement in previously detected abnormalities can be identified on the basis of follow-up CT, tapering or cessation of treatment could be undertaken with greater confidence in the context of other clinical findings. However, for

some of the cases (6 and 9) significant changes remained at follow-up CT, despite the cats being clinically well, and as a result triple antibiotic therapy was continued.

A previous study into the diagnostic and monitoring capacity of standard radiography in feline tuberculosis cases showed that with prolonged antibiosis, detectable pathology is eliminated in the vast majority of cases.[4] By comparison, in this case series some of the abnormalities detectable by CT imaging remained present in the majority of cases, though not all cats underwent repeat imaging following complete cessation of treatment. It is likely that this discrepancy partly results from the greater sensitivity of CT in comparison with radiography for detection of milder changes, highlighting its value. However this must be considered when repeat CT imaging is used to decide whether antibiotic treatment can be discontinued; complete resolution of pulmonary pathology cannot be reliably anticipated, even with extended antibiosis. This highlights the value of ongoing follow up imaging to document the lack of progression of changes, which can then be considered clinically incidental.

In some cats undergoing treatment for feline tuberculosis, periods of clinical and/or radiological remission can be followed by recurrence of clinical signs, sometimes on multiple occasions (as seen in cases 1 and 3). It is difficult to determine if this represent recrudescence of disease following subclinical infection (latency) in the intervening periods, or reinfection. For example, cats who are habitual hunters have repeated exposure to a population of infected prey (as is the case for the cat in case 1). The return of clinical disease may be associated with extremely subtle clinical signs (as in case 1). The associated CT abnormalities may be similarly subtle (as in Figure 1c), but when a radiologically normal appearance has been documented during the remission period, these subtle changes can be considered significant, allowing for prompt reintroduction of treatment. This case also demonstrates the importance of careful and dedicated patient observation on the part of the owners;

monitoring sleeping respiratory rate is recommended in all cases of feline tuberculosis when undergoing treatment, even when there was initially no respiratory involvement.

When repeating diagnostic procedures, it is important to evaluate the potential benefit to the patient, in relation to the costs involved. In the cases in this series we feel that the major benefit is clear; namely that the decision to either reduce/discontinue or restart treatment could be made with greater confidence. With reference to CT examination, a number of costs should be considered. The risk of repeated radiation exposure during scanning is one. We feel that in a population largely consisting of middle-aged cats the risk is minimal, though it should not be entirely discounted, particularly in cases where large numbers of repeated scans are performed. The effect of sedation or general anaesthesia should also be considered. Within a referral hospital the risks of these are low, [30] but they may warrant consideration particularly in clinically unstable patients with significant multisystem disease. Finally, the financial cost to the owner should also be considered. In several of the cases in this series, some of the associated costs and risks were reduced by use of a VetMouseTrap device, which allows for full body scanning in a non-sedated patient. Despite a slight reduction in sensitivity arising from a reduction in image resolution, this technique provides a very useful relatively low cost and non-invasive option. Notwithstanding the use of a VetMouseTrap device, in many referral centres the cost to the owner of a CT examination, either thorax in isolation or multiple body regions, does not significantly exceed that of full radiological examination. In addition, as CT becomes more widespread in non-specialist practice, its advantage as far as increased sensitivity over radiology warrants further consideration.

Conclusions

The cases described in this case series demonstrate the value of repeat CT imaging in the management of mycobacterial disease. When considered in combination with clinical findings, CT studies can aid in decision

making regarding tapering of antibiotic protocols, or reintroduction of therapy in cases of recurrence or reinfection. These cases also highlight that in some cases, persistent abnormalities can be detected by CT, which may not necessarily indicate an active disease process, and care should be taken in the interpretation of these findings.

Acknowledgments

The authors would like to acknowledge all staff involved in the care, diagnosis and management of the cats included in the study.

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

The authors do not have any potential conflict of interest to declare.

References

1. Gunn-Moore DA, Dean R and Shaw, S. Mycobacterial infections in cats. *In Practice* 2014; 32: 444-452.
2. Gunn-Moore DA, McFarland S, Brewer J, et al. Mycobacterial disease in cats in Great Britain I: Bacterial species, geographical distribution and clinical presentation of 399 cases. *Journal of Feline Medicine and Surgery* 2011; 13**:** 934-944.

3. Gunn-Moore DA, Gaunt C and Shaw DJ. Incidence of Mycobacterial Infections in Cats In Great Britain: Estimate from Feline Tissue Samples Submitted to Diagnostic Laboratories *Transboundary Emerging Disease* 2013; 60 (4): 338-344.

4. Bennett A, Lalor S, Schwarz T, et al. Radiographic findings in cats with mycobacterial infections. *Journal of Feline Medicine and Surgery*. 2011; 13 (10): 718-724.

5. Jennings AR. The distribution of tuberculous lesions in the dog and cat, with reference to pathogenesis *Veterinary Record* 1949; 27: 380-384.

6. Gunn-Moore DA, McFarland SE, Schock A, et al. Mycobacterial disease in a population of 339 cats in Great Britain: II. Histopathology of 225 cases, and treatment and outcome of 184 cases. *Journal of Feline Medicine and Surgery.* 2011; 13 (12): 945-952.

7. Major A, Holmes A, Warren-Smith C, et al. Computed tomographic findings in cats with mycobacterial infections. *Journal of Feline Medicine and Surgery.* 2015; 18 (6): 510-517.

8. Rhodes SG, Gunn-Moore DA, Boschiroli L, et al. Comparative study of IFNγ and antibody tests for feline tuberculosis. *Veterinary Immunology and Immunopathology* 144: 129-134.

9. Greene CE and Gunn-Moore DA Mycobacterial Infections *Infectious Diseases of the Dog and Cat* Ed. Greene CE. 4th Edition. Saunders 2012 p. 495-510.

10. Devasia RA, Blackman A, Gebretsadik T, et al. Fluoroquinolone resistance in Mycobacterium tuberculosis: The effect of duration and timing of fluoroquinolone exposure. American Journal of Respiratory and Critical Care Medicine. 2009; 180(4): 365-70.

11. Jordan HL, Cohn LA, Armstrong PJ. Disseminated Mycobacterium avium complex infection in three Siamese cats. *Journal of the American Veterinary Medicine Association.* 1994; 204(1):90-3.

12. Yin J, Yuan J, Hu Y, Wei X. Association between directly observed therapy and treatment outcomes in multidrug-resistant tuberculosis: A systematic review and meta-analysis *PLoS ONE* 2016; 11 (3): art. no. e0150511
13. Pantel A, Petrella S, Veziris N, et al. Extending the definition of the GyrB quinolone resistance-determining region in Mycobacterium tuberculosis DNA gyrase for assessing fluoroquinolone resistance in M. tuberculosis. *Antimicrobial Agents and Chemotherapy*. 2012; 56 (4): 1990-1996.
14. Liu CH, Yang N, Wang Q, et al. Risk factors associated with fluoroquinolone-resistant tuberculosis in a Beijing tuberculosis referral hospital. *Respirology*. 2011; 16 (6): 918-925.
15. Jeon D, Kim D, Kang H, et al. Acquired drug resistance during standardized treatment with first-line drugs in patients with multidrug-resistant tuberculosis. *Tuberculosis and Respiratory Diseases*. 2009; 66 (3) pp198-204.
16. Schaberg T, Bauer T, Castell S, et al. Recommendations for therapy, chemoprevention and chemoprophylaxis of tuberculosis in adults and children. German Central Committee against Tuberculosis (DZK), German Respiratory Society (DGP) *Pneumologie* 2012; 66: 133-171.
17. Haburjak J and Spangler W. Isoniazid-induced seizures with secondary rhabdomyolysis and associated acute renal failure in a dog. *Journal of Small Animal Practice*. 2002; 43 (4): 182-186.
18. De Jong BC, Onipede A, Pym AS, et al. Does resistance to pyrazinamide accurately indicate the presence of Mycobacterium bovis? *Journal of Clinical Microbiology* 2005; 43: 3530-3532.
19. World Health Organisation. Global Tuberculosis Report 2015. 20th Ed. WHO, Geneva.
20. Ahmad S. New approaches in the diagnosis and treatment of latent tuberculosis infection. *Respiratory Research* 2010;11:169.

433 21. Govendir M, Norris JM, Hansen T, et al. Susceptibility of rapidly growing mycobacteria and Nocardia
434 isolates from cats and dogs to pradofloxacin. *Veterinary Microbiology.* 2011; 153 (3-4): 240-245.
435 22. Govendir M, Hansen T, Kimble B, et al. Susceptibility of rapidly growing mycobacteria isolated from
436 cats and dogs, to ciprofloxacin, enrofloxacin and moxifloxacin. *Veterinary Microbiology*. 2011; 147(1-
437 2):113-118.
438 23. Messias A, Gekeler F, Wegener A et al. Retinal safety of a new fluoroquinolone, pradofloxacin, in
439 cats: Assessment with electroretinography. *Documenta Ophthalmologica*. 2008; 116 (3): 177-191.
440 24. Gunn-Moore DA. Feline mycobacterial infections. *Veterinary Journal*. 2014; 201(2): 230-238.
441 25. Lalor S, Mellanby R, Friend E, et al. Domesticated Cats with Active Mycobacteria Infections have
442 Low Serum Vitamin D (25(OH)D) Concentrations *Transboundary and Emerging Diseases*. 2011; 59
443 (3): 279-281.
444 26. Yuvaraj B, Sridhar M, Kumar S, et al. Association of serum Vitamin D levels with bacterial load in
445 pulmonary tuberculosis patients. *Tuberculosis and Respiratory Diseases.* 2016; 79 (3):153-157.
446 27. Grobler L, Nagpal S, Sudarsanam T, et al. Nutritional supplements for people being treated for active
447 tuberculosis. *Cochrane Database of Systematic Reviews*. 2016; (6): art. no. CD006086.
448 28. Zittermann A, Pilz S, Hoffmann H, et al. Vitamin D and airway infections: A European perspective.
449 *European Journal of Medical Research*. 2016; 21 (1): art. no. 14.
450 29. Martineau A, Timms P, Bothamley GH, et al. High-dose vitamin D_3 during intensive-phase
451 antimicrobial treatment of pulmonary tuberculosis: A double-blind randomised controlled trial. *The*
452 *Lancet*. 2011; 377 (9761): 242-250.
453 30. Bille C, Auvigne V, Libermann S, et al. Risk of anaesthetic mortality in dogs and cats: An
454 observational cohort study of 3546 cases *Veterinary Anaesthesia and Analgesia.* 2012; 39 (1): 59-68.

Figure captions:

Figure 1. The CT appearance of lung parenchyma in case 1 at the level of the accessory lung lobe on three different occasions. (a) Diffuse, moderate reticulonodular pattern identified on the first occasion of disease recurrence following eleven months of clinical remission. (b) Normal pulmonary appearance three months later following triple antibiotic therapy and calcitriol supplementation. (c) Diffuse, mild reticular pattern noted concurrent with an increased sleeping respiratory rate but normal clinical examination, indicative of probable tuberculosis recurrence/relapse eleven months after image a.

Figure 2. A timeline of diagnostic investigations and treatment for case 1; a seven year old male neutered Oriental cat with pulmonary TB caused by *Mycobacterium microti*.

Rad – radiograph; TB – tuberculous changes; NAD – no abnormalities detected; mn – months; T – treatment; R – rifampicin; A – azithromycin; M – marbofloxacin; V – vitamin D; P – pradofloxacin; TB? – potentially tuberculous changes.

Figure 3. The CT images at the level of the third sternebra from case 2 on two different occasions. (a) Image acquired four months after cessation of antibiotic therapy for disseminated tuberculosis showing an enlarged cranial mediastinal lymph node (*). (b) Image acquired five months later, showing a static appearance of the lymph node but a mild ground glass appearance of the adjacent lung parenchyma (arrow)

476 indicative of regional extension of disease. The cat was concurrently diagnosed with a mandibular
477 squamous cell carcinoma.

478

479 **Figure 4.** A timeline of diagnostic investigations and treatments for cases 2-9.

480 Rad – radiograph; US – ultrasound; TB – tuberculous changes; NAD – no abnormalities detected; mn –
481 months; T – treatment; R – rifampicin; A – azithromycin; M – marbofloxacin; C - clarithromycin V –
482 vitamin D; P – pradofloxacin; TB? – potentially tuberculous changes; Euth – euthanasia; SCC – squamous
483 cell carcinoma; No – no treatment given; Sx – surgery; MN – male neutered; FN – female neutered; DSH
484 – domestic short haired; BSH – British short haired.

485

486 **Figure 5.** The CT appearance of the lung parenchyma in case 4 at the level of the accessory lung lobe on
487 two different occasions. (a) Multifocal regions of alveolar pattern with associated pulmonary cavitation (*)
488 identified at initial presentation. (b) Follow up imaging after right caudal lung lobectomy and eight months
489 of antibiotic treatment shows residual patchy ground glass appearance and collapsed pulmonary cavities
490 (arrow). An additional CT study performed four months' post surgery (not shown) showed very similar
491 residual changes.

492

493 **Figure 6.** The CT appearance of the lung parenchyma in case 5 at the level of the accessory lung lobe on
494 two different occasions. (a) Marked, diffuse nodular lung pattern with occasional foci of mineralisation
495 (arrows) identified at initial presentation. (b) Follow up imaging after eight months of treatment shows a

persistent mild reticulonodular pattern with mildly more extensive parenchymal mineralisation (arrow). Treatment was discontinued and a static appearance was recorded 12 months later, indicating these persistent changes do not reflect active disease.

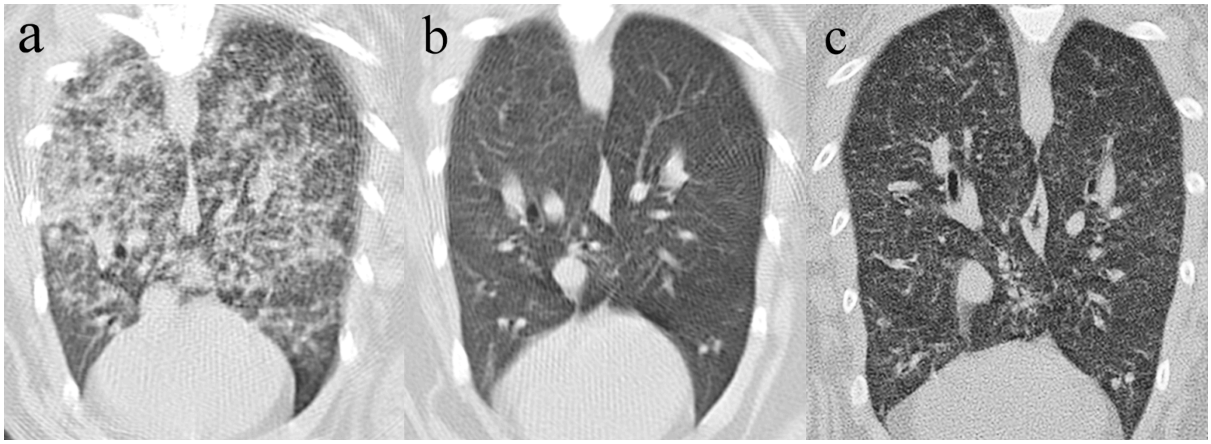

Figure 1. CT appearance of lung parenchyma in case 1 at the level of the accessory lung lobe on three different occasions. (a) Diffuse, moderate reticulonodular pattern identified on the first occasion of disease recurrence following eleven months of clinical remission. (b) Normal pulmonary appearance three months later following triple antibiotic therapy and calcitriol supplementation. (c) Diffuse, mild reticular pattern noted concurrent with an increased sleeping respiratory rate but normal clinical examination, indicative of probable tuberculosis recurrence/relapse eleven months after image a.

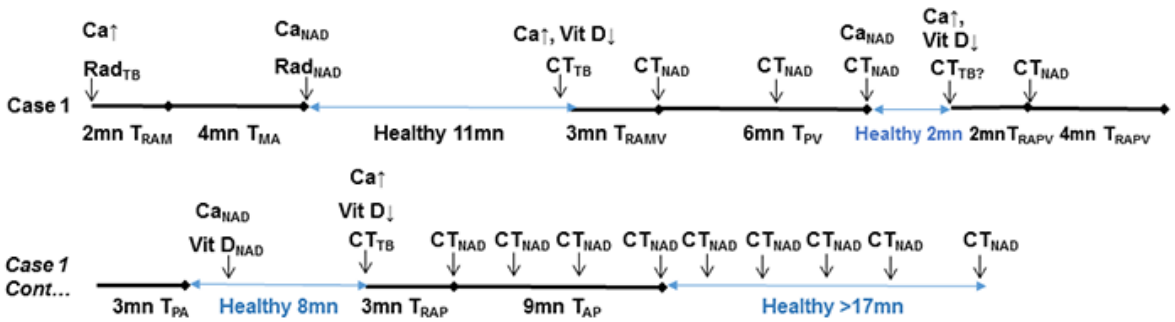

Figure 2. A timeline of diagnostic investigations and treatment for case 1; a seven year old male neutered Oriental cat with pulmonary TB caused by *Mycobacterium microti*.

Rad – radiograph; TB – tuberculous changes; NAD – no abnormalities detected; mn – months; T – treatment; R – rifampicin; A – azithromycin; M – marbofloxacin; V – vitamin D;
P – pradofloxacin; TB? – potentially tuberculous changes.

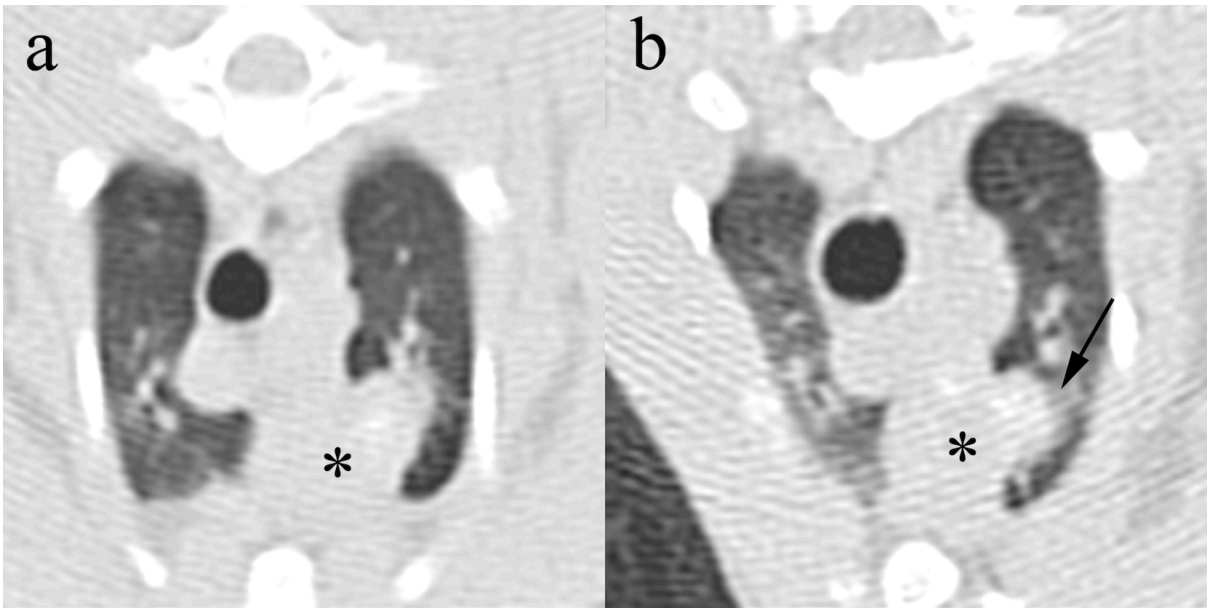

Figure 3. CT images at the level of the third sternebra from case 2 on two different occasions. (a) Image acquired four months after cessation of antibiotic therapy for disseminated tuberculosis showing an enlarged cranial mediastinal lymph node (*). (b) Image acquired five months later, showing a static appearance of the lymph node but a mild ground glass appearance of the adjacent lung parenchyma (arrow) indicative of regional extension of disease. The cat was concurrently diagnosed with a mandibular squamous cell carcinoma.

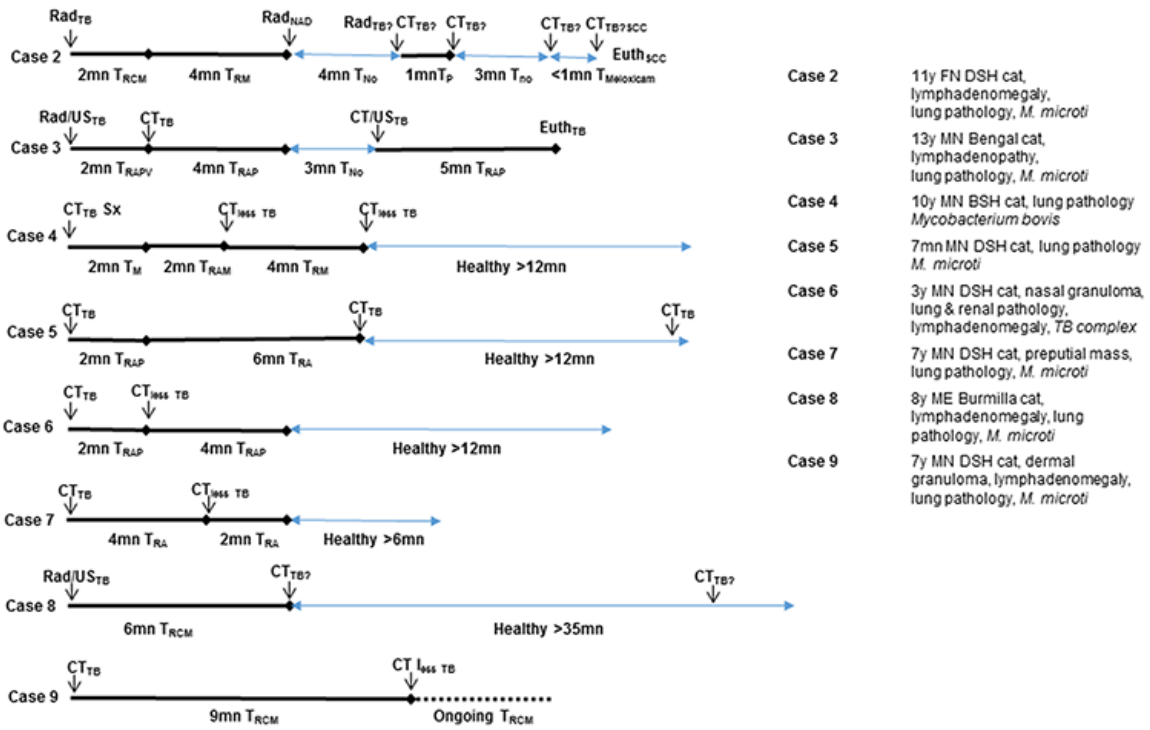

Figure 4. A timeline of diagnostic investigations and treatments for cases 2-9.

Rad – radiograph; US – ultrasound; TB – tuberculous changes; NAD – no abnormalities detected; mn – months; T – treatment; R – rifampicin; A – azithromycin; M – marbofloxacin; C - clarithromycin V – vitamin D; P – pradofloxacin; TB? – potentially tuberculous changes; Euth – euthanasia; SCC – squamous cell carcinoma; No – no treatment given; Sx – surgery; MN – male neutered; FN – female neutered; DSH – domestic short haired; BSH – British short haired.

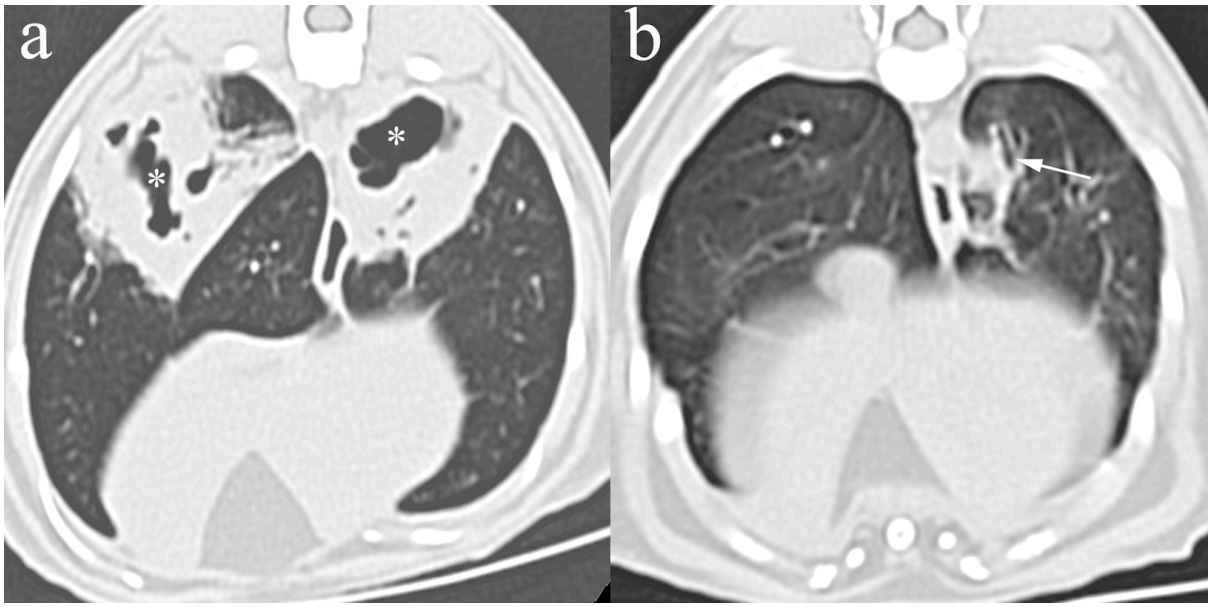

Figure 5. CT appearance of the lung parenchyma in case 4 at the level of the accessory lung lobe on two different occasions. (a) Multifocal regions of alveolar pattern with associated pulmonary cavitation (*) identified at initial presentation. (b) Follow up imaging after right caudal lung lobectomy and eight months of antibiotic treatment shows residual patchy ground glass appearance and collapsed pulmonary cavities (arrow). An additional CT study performed four months' post surgery (not shown) showed very similar residual changes.

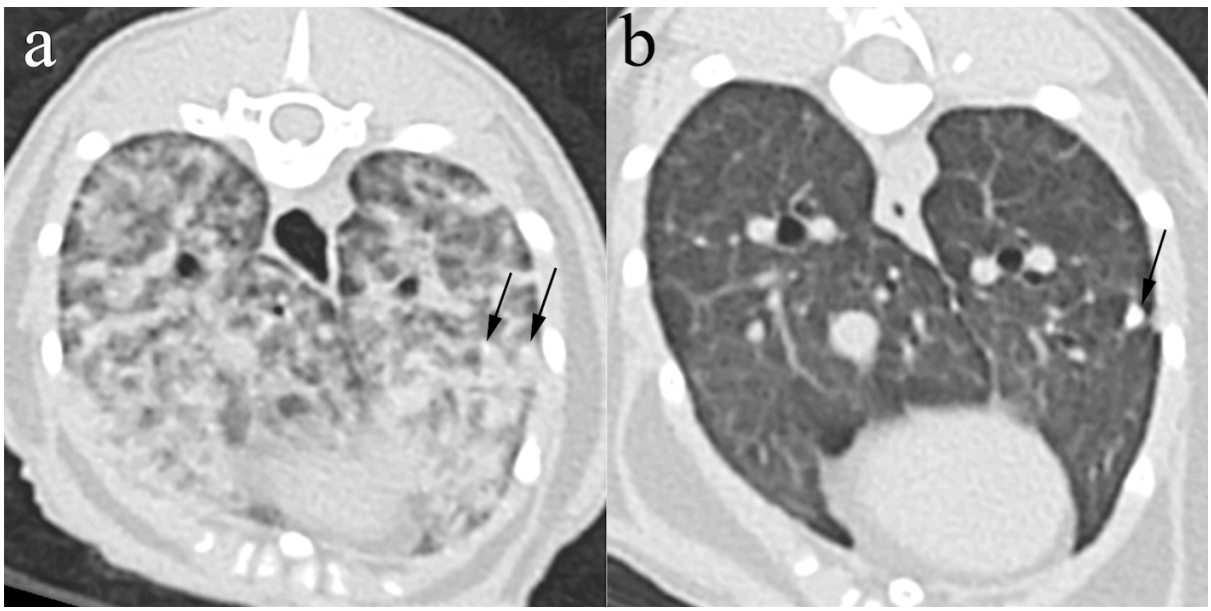

Figure 6. CT appearance of the lung parenchyma in case 5 at the level of the accessory lung lobe on two different occasions. (a) Marked, diffuse nodular lung pattern with occasional foci of mineralisation (arrows) identified at initial presentation. (b) Follow up imaging after eight months of treatment shows a persistent mild reticulonodular pattern with mildly more extensive parenchymal mineralisation (arrow). Treatment was discontinued and a static appearance was recorded 12 months later, indicating these persistent changes do not reflect active disease.