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

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

2 **Cases**

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24 **Abstract:**

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

28

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

33

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

38

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

#### 44 **Introduction**

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

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

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

62

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

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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	<i>M. microti</i>	Early re-instigation of antibiotics following slight clinical deterioration.
2	DSH	11	FN	Central Scotland	3.6	No abnormalities detected	Negative	<i>M. microti</i>	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	<i>M. microti</i>	Delayed antibiotic tapering due to persistent abnormalities. Early re-instigation of antibiotics following slight clinical deterioration.

4	British Shorthair	10	MN	Cheshire, England	3.8	Hyperglobulinaemia	Negative	<i>M. bovis</i>	Reduction of antibiotics 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	<i>M. microti</i>	Discontinuation of antibiotics with improvement to detectable abnormalities.
6	DSH	3	FN	West Midlands, England	4.1	No abnormalities detected	Negative	Tuberculosis complex	Reduction of antibiotics with early improvement to detectable abnormalities.
7	DSH	7	MN	South Scotland	5	No abnormalities detected	Negative	<i>M. microti</i>	Reduction of antibiotics with improvement to detectable abnormalities.
8	Burmilla	8	ME	South Scotland	4.6	No abnormalities detected	Negative	<i>M. microti</i>	Discontinuation of antibiotics with improvement to detectable abnormalities.
9	DSH	7	MN	Central Scotland	5.7	No abnormalities detected	Negative	<i>M. microti</i>	Continuation of antibiotics with partial improvement to detectable abnormalities.

77 Legend: DSH: domestic short hair, MN: male neutered, FN: female neutered, ME: male entire, FIV: feline immunodeficiency

78 virus, FeLV: feline leukaemia virus.





80 **Case Series Description**

81 **Case 1**

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

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

102 Bayer) [4mg/kg] 25mg PO q24h, which was given as an antimicrobial monotherapy for six months with  
103 calcitriol supplementation as previously described. Two further CT examinations were performed, at four and  
104 six months after disease recurrence, and were normal. Eleven months after recurrence, after two months off  
105 pradofloxacin, the cat was re-presented as the owner observed a mildly increased sleeping respiratory rate  
106 (21bpm; this cat's normal sleeping respiratory rate was <20bpm). Despite a normal clinical examination, a CT  
107 scan demonstrated a diffuse mild reticular lung pattern with areas of ground glass opacity (Figure 1c); the serum  
108 calcium concentration was increased and serum 25-hydroxyvitamin D concentration was low. Triple antibiotic  
109 therapy was restarted (rifampicin and azithromycin, dosed as above, plus pradofloxacin [Veraflox liquid, Bayer]  
110 [~5mg/kg] 30mg PO q24h), and calcitriol treatment was restarted at [2ng/kg] 12.5mcg PO q24h (body weight  
111 6.5kg). After two-months of treatment repeat CT examination was normal. Due to the history of several episodes  
112 of disease it was recommended that the triple antibiotic therapy be continued for a further four months, followed  
113 by three months of double antibiotic therapy (azithromycin and pradofloxacin, dosed as above). The cat  
114 remained clinically normal throughout this period and treatment was discontinued a total of 20 months after the  
115 initial recurrence. Two months later another IGRA returned a negative result and the serum calcium and 25-  
116 hydroxyvitamin D concentrations were within normal limits. A further episode of mycobacterial  
117 recurrence/reinfection occurred after eight months without treatment. The cat was again re-presented following  
118 observation of a mildly increased sleeping respiratory rate (23bpm; body weight 7.1kg). Whole body CT  
119 demonstrated mild diffuse thoracic and abdominal lymphadenomegaly, and a diffuse but patchy, mild to  
120 moderate reticulonodular lung pattern. A repeated IGRA was positive and consistent with *M. microti* infection.  
121 Triple antibiotic therapy was prescribed for three months (rifampicin, pradofloxacin and azithromycin, dosed  
122 as above, for a 7kg cat), followed by double antibiotic therapy for a further nine months (pradofloxacin and  
123 azithromycin, dosed as immediately above). During this period, the cat remained well, and a further four full-

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

## 128 **Case 2**

129 Case 2 was first presented for weight loss and generalised lymphadenomegaly. Radiographs revealed a diffuse  
130 interstitial lung pattern (CT was not available at the clinic at that time). Excisional biopsy of the popliteal lymph  
131 nodes was performed; histopathology revealed a granulomatous lymphadenitis and Zeihl Neelsen (ZN) staining  
132 identified intra-lesional acid-fast bacilli indicative of mycobacterial infection. A triple antibiotic protocol was  
133 instigated (rifampicin [11mg/kg] 40mg PO q24h; marbofloxacin [2.7mg/kg] 10mg PO q24h; clarithromycin  
134 [11mg/kg] 40mg PO q12h) for two months followed by rifampicin and marbofloxacin (same doses) for four  
135 months. Revisits revealed initially static peripheral lymphadenomegaly, which resolved over the four months  
136 of maintenance treatment. Repeat thoracic radiography at the end of the maintenance phase revealed no  
137 abnormalities and treatment was therefore discontinued. Four months following the end of treatment the cat  
138 presented to an emergency clinic with acute respiratory signs. Laryngeal swelling was identified and following  
139 stabilisation with corticosteroids, furosemide, chlorphenamine (all at standard doses), plus additional oxygen,  
140 the laryngeal swelling resolved. Radiography revealed a thoracic mass consistent with an enlarged cranial  
141 mediastinal lymph node. This was confirmed on full body CT examination using a VetMouseTrap device,  
142 which also revealed moderate mineralisation within the mass lesion (Figure 3a). Fine needle aspiration (FNA)  
143 of the mass yielded a non-diagnostic sample whilst an IGRA was consistent with *M. microti* infection. Given  
144 the previous history of mycobacterial lymphadenitis, with an owner who was reticent to restart triple therapy,

145 the cat was started on single antibiotic therapy (pradofloxacin liquid [7mg/kg] 25mg PO q24h) to see if this  
146 might reduce the size of the thoracic mass and so give weight to the diagnosis that it may be tuberculous. One  
147 month later the cat was clinically well and CT revealed a static appearance to the mass. Antibiotic therapy was  
148 discontinued as it did not appear to be effective. Three months later the CT appearance remained unchanged,  
149 and a repeat IGRA was inconclusive. The cat represented the next month with hypersalivation and difficulty  
150 eating. Physical examination revealed thickening of the caudal aspect of the right mandibular ramus, with  
151 loosening of the associated teeth. On CT this lesion was characterised by moderate bone lysis with concurrent  
152 proliferation, moderate regional lymphadenomegaly was noted. The thoracic mass remained static in  
153 appearance, but the surrounding lung had a mild patchy ground glass appearance (Figure 3b). The appearance  
154 of the mandibular lesion was not considered typical for tuberculous osteomyelitis. Biopsy of the mandibular  
155 mass and local lymph nodes resulted in a diagnosis of squamous cell carcinoma with reactive lymphoid  
156 hyperplasia. The owner opted for palliative therapy with meloxicam (Metacam, Boehringer Ingelheim  
157 0.05mg/kg PO q24h), and after three weeks the cat was euthanased. Post mortem examination was performed  
158 and histopathology of the enlarged cranial mediastinal lymph node revealed large numbers of acid-fast bacilli  
159 within the node and the peri-nodal connective tissue. As indicated by CT, granulomatous inflammatory changes  
160 extended into the adjacent pulmonary parenchyma. The lymph node was confirmed to be PCR positive for *M.*  
161 *microti* by the Mycobacterial Reference Laboratory, Leeds University Teaching Hospital. A timeline of this  
162 case is shown in Figure 4.

### 163 **Case 3**

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

166 marked circumferential jejunal thickening; FNA of the mandibular and jejunal lymph nodes and the abnormal  
167 jejunal wall revealed granulomatous inflammation with acid-fast bacilli indicative of mycobacterial infection.  
168 An IGRA was consistent with *M. microti* infection and the cat was started on triple antibiotic therapy (rifampicin  
169 [10mg/kg] 50mg PO q24h; azithromycin [8mg/kg] 40mg PO q24h; pradofloxacin tablets [5mg/kg] 25mg PO  
170 q24h), plus calcitriol supplementation ([2ng/kg] 10mcg PO q24h). Two months later the cat was clinically well,  
171 although the right mandibular lymph node remained slightly enlarged. A conscious full-body CT examination  
172 using a VetMouseTrap device was performed, revealing improved but persistent mesenteric  
173 lymphadenomegaly. Given the clinical and imaging findings, the triple antibiotic therapy described above was  
174 maintained for another four months, giving a total treatment duration of six months, after which the mandibular  
175 and mesenteric lymph nodes were palpably normal and antibiotics was discontinued (body weight 6.4kg at this  
176 time). Three months later the cat represented with weight loss, lethargy and inappetence (body weight 6.0kg).  
177 The peripheral lymph nodes were of normal size but harsh inspiratory lung sounds and multiple palpable  
178 abdominal masses were noted. Both abdominal ultrasound and full-body CT were performed, confirming the  
179 presence of marked thoracic and abdominal lymphadenomegaly, and focal marked jejunal thickening as had  
180 been previously described. A diffuse, mild reticulonodular lung pattern was also noted. A FNA of the mesenteric  
181 lymph nodes again revealed granulomatous inflammation with acid fast bacilli. Triple antibiotic therapy was  
182 resumed at the dose rates detailed previously, but despite an initially improved demeanour the cat continued to  
183 lose weight and after five months of treatment was euthanased. Post mortem examination was not performed.  
184 A timeline of this case is shown in Figure 4.

#### 185 **Case 4**

186 Case 4 initially presented with weight loss, dyspnoea and coughing. Physical examination revealed tachypnoea  
187 (respiratory rate 40bpm), with increased inspiratory and expiratory effort and noise. Thoracic CT examination  
188 revealed a moderate multifocal alveolar pattern with regions of pulmonary cavitation affecting multiple lung  
189 lobes, most marked within the right caudal lobe, and a moderate thoracic lymphadenomegaly (Figure 5a). A  
190 right caudal lung lobectomy was performed and histopathology revealed necrotising and pyogranulomatous  
191 bronchopneumonia; however, no acid fast bacteria were identified. Tissue was submitted for culture and blood  
192 for IGRA, and treatment with marbofloxacin ([2mg/kg] 8mg PO q24h) was started. A good clinical response  
193 was noted in the initial two-month post-operative period; however, tissue culture and IGRA both confirmed  
194 *Mycobacterium bovis* infection, and a standard triple antibiotic protocol was introduced (marbofloxacin  
195 [2mg/kg] 8mg PO q24h; azithromycin [10mg/kg] 40mg PO q24h; rifampicin [20mg/kg] 80mg PO q24h –  
196 although the dose of rifampicin was high). After two months of triple antibiotic treatment, CT was repeated  
197 revealing residual patchy ground glass opacity, with collapsed cavities within the remaining lung lobes, but  
198 subjectively normal thoracic lymph nodes. Due to the improved pulmonary appearance and the good clinical  
199 condition of the cat, triple antibiotic therapy was reduced to dual therapy (marbofloxacin and rifampicin, dosed  
200 as above). After a further four months, the appearance of the lungs on CT examination was unchanged (Figure  
201 5b) and a repeat IGRA remained positive. Antibiotic treatment was discontinued, and the cat remained well,  
202 with a negative IGRA result obtained six months later. A timeline of this case is shown in Figure 4.

### 203 **Case 5**

204 Case 5 initially presented with coughing, resting tachypnoea (respiratory rate 55bpm), and exercise intolerance.  
205 Body weight and condition score (1.5/5) were low. Thoracic and abdominal CT examination revealed a diffuse  
206 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 [ $\sim$ 5mg/kg] 15mg PO q24h; azithromycin  
211 [ $\sim$ 10mg/kg] 30mg PO q24h; rifampicin [ $\sim$ 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 [ $\sim$ 5mg/kg] 20mg PO q24h; azithromycin [ $\sim$ 10mg/kg] 40mg PO q24h; rifampicin

228 [~10mg/kg] 40mg PO q24h), followed by ongoing double therapy (pradofloxacin and rifampicin, dosed as  
229 above). Two months after the start of antibiotic therapy the cat was clinically well. The CT showed marked  
230 improvements, with residual diffuse mild pulmonary ground glass appearance, mild multifocal  
231 lymphadenomegaly and partial resolution of the renal mass lesions. Antibiotics were discontinued after a six-  
232 month course, and the cat remains clinically well 12 months later. A timeline of this case is shown in Figure 4.

### 233 **Case 7**

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

### 246 **Case 8**



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

#### 264 **Case 9**

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

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

## 281 **Discussion**

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

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

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

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

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

309 in small animals,<sup>17</sup> pyrazinamide is ineffective against *M. bovis* infections<sup>18</sup> which comprise approximately  
310 15% of feline mycobacterial infections,<sup>2</sup> and dihydrostreptomycin should be reserved for human use.<sup>19</sup>  
311 Therefore, small animal anti-tuberculosis therapy, when undertaken, should consist of a triple combination of  
312 rifampicin (for its potency and its ability to kill non-replicating [latent] tuberculous Mycobacteria<sup>20</sup>  
313 [recommended doses 10-15mg/kg PO q24h]), a fluoroquinolone (ideally pradofloxacin as it has better efficacy  
314 against Mycobacteria than older fluoroquinolones,<sup>21,22</sup> and a better safety profile in cats<sup>23</sup> [pradofloxacin  
315 recommended doses 3-7mg/kg PO q24h]) and a macrolide (such as clarithromycin [7-15mg/kg PO q12h] or  
316 azithromycin [5-15mg/kg PO q24h]) for a minimum of three months as standard.<sup>9,24</sup> It is recommended that  
317 treatment should be given for two to three months after apparent clinical resolution, which typically results in  
318 four to six months of treatment.<sup>9,24</sup> The efficacy of combination long-term treatment is supported by the cases  
319 in this series, as all were treated with either two or three antibiotics for at least six months; only one of the cats  
320 died from tuberculosis, and another was found to have latent tuberculosis after euthanasia for an unrelated  
321 disease. This gives a sustained complete remission rate of eight of nine cases (~90% remission), which is much  
322 higher than the 40% previously reported.<sup>6</sup> This is much more in line with our recent experiences, as following  
323 the introduction of sustained triple therapy the prognosis for feline tuberculosis appears to be closer to 70-80%  
324 success when treating cutaneous and/or pulmonary tuberculosis caused *M. bovis* or *M. microti* (DGM and COH,  
325 unpublished data 2016). Prolonged therapy is therefore recommended in all cases, and due care is required  
326 when advising clients on discontinuing treatment.

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

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

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

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

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

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

### 368 **Conclusions**

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

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

375

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378 included in the study.

379

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381 sectors.

382

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384

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455

456

457 **Figure captions:**

458

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

465

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

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

471

472 **Figure 3.** The CT images at the level of the third sternebra from case 2 on two different occasions. (a)  
473 Image acquired four months after cessation of antibiotic therapy for disseminated tuberculosis showing an  
474 enlarged cranial mediastinal lymph node (\*). (b) Image acquired five months later, showing a static  
475 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.

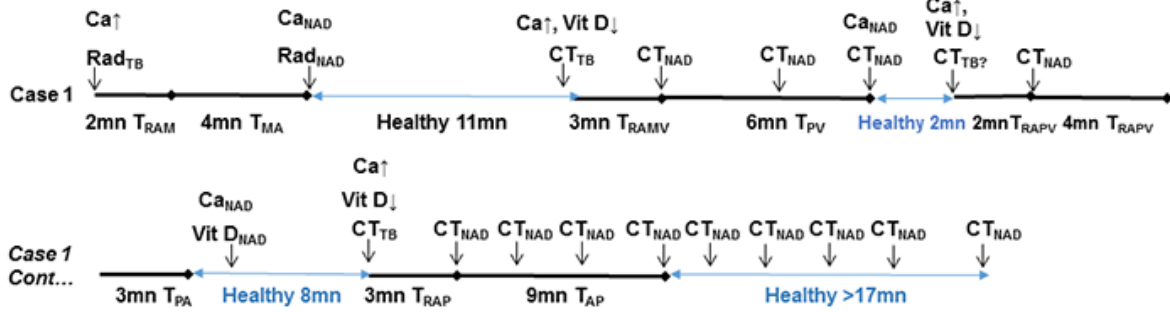
492

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

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

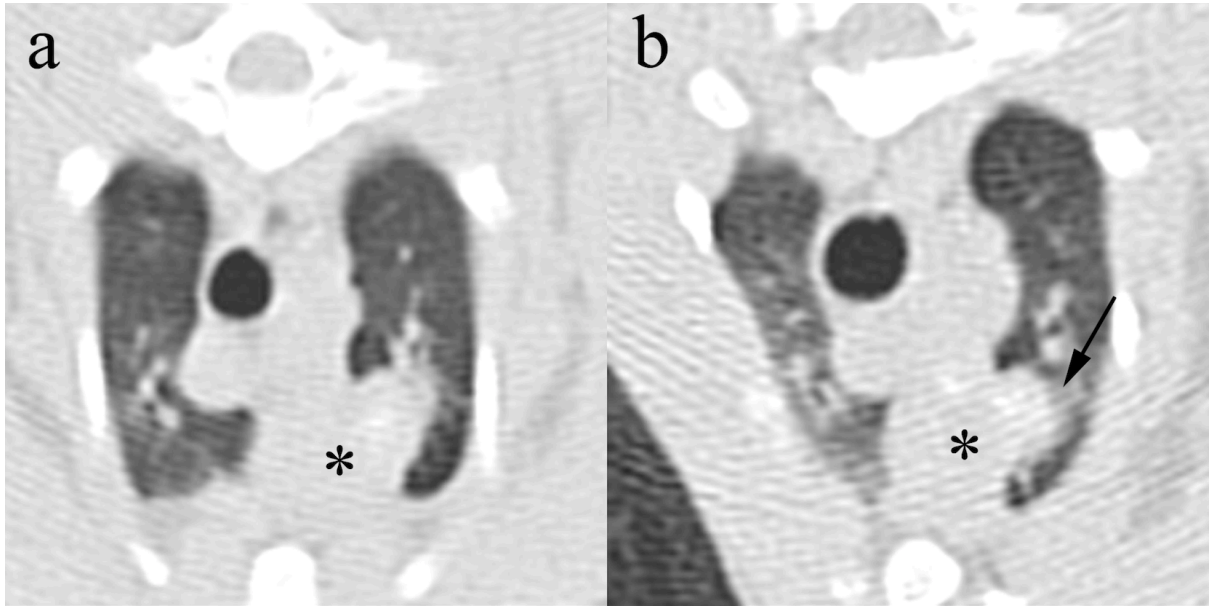


**Figure 1.** CT appearance of lung parenchyma in case 1 at the level of the accessory lung lobe on three different occasions. (a) Diffuse, moderate reticulonodular pattern identified on the first occasion of disease recurrence following eleven months of clinical remission. (b) Normal pulmonary appearance 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.

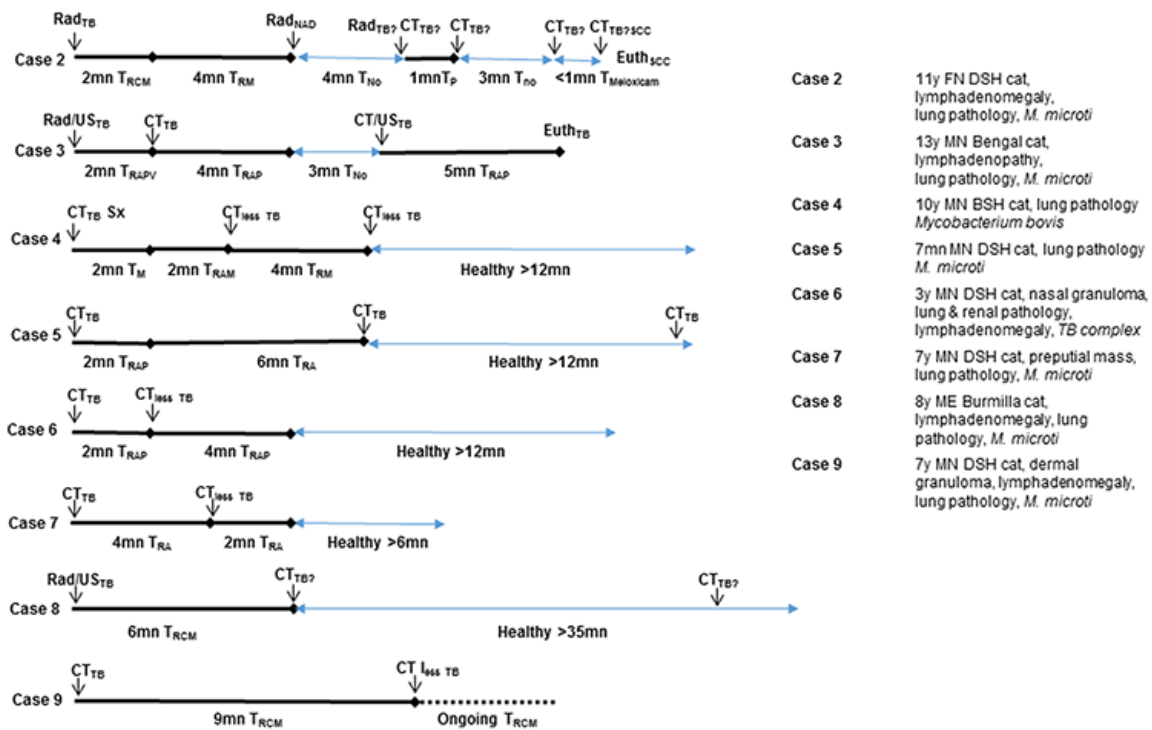


**Figure 2.** A timeline of diagnostic investigations and treatment for case 1; a seven year old male neutered Oriental cat with pulmonary TB caused by *Mycobacterium microti*.

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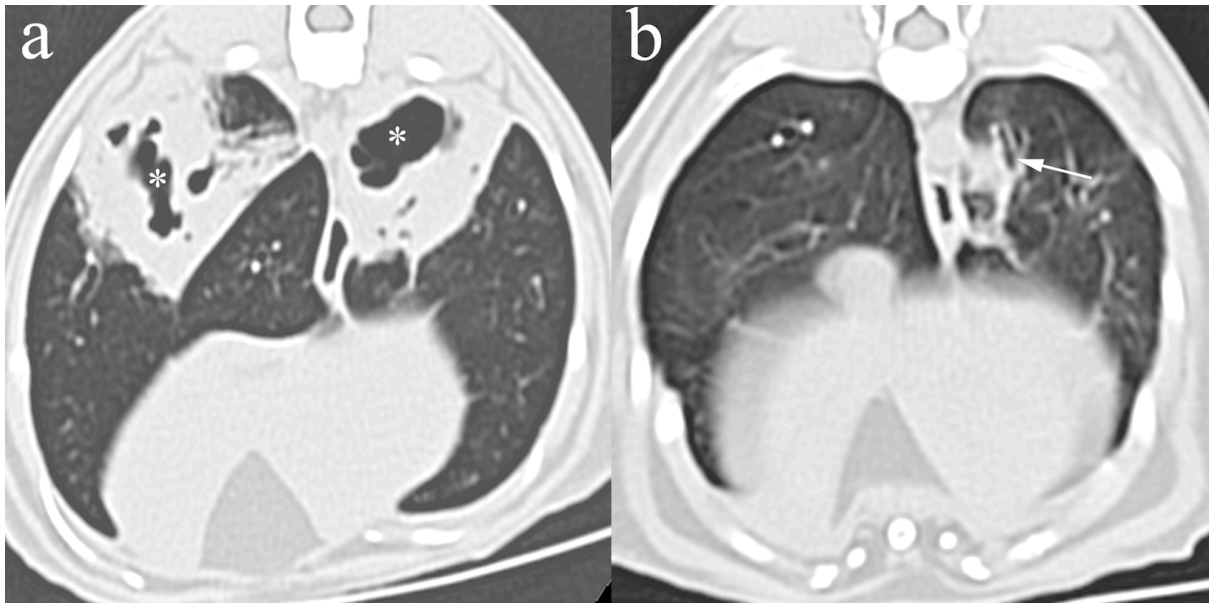


**Figure 3.** CT images at the level of the third sternebra from case 2 on two different occasions. (a) Image acquired four months after cessation of antibiotic therapy for disseminated tuberculosis showing an enlarged cranial mediastinal lymph node (\*). (b) Image acquired five months later, showing 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.

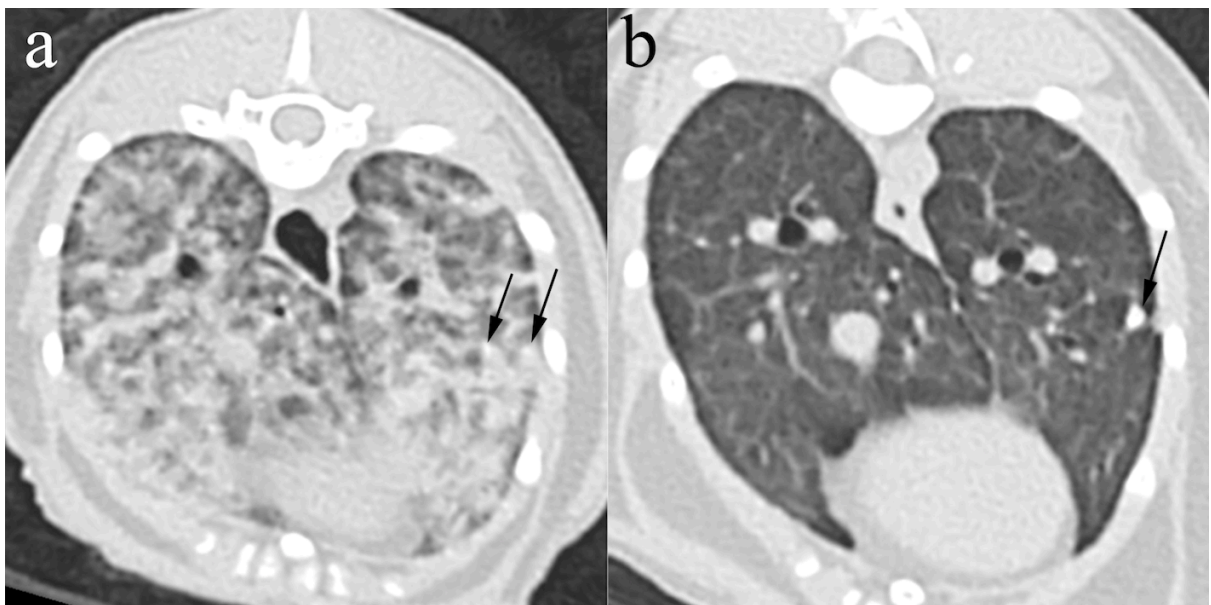


**Figure 4.** A timeline of diagnostic investigations and treatments for cases 2-9.

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.