Pulmonary *Mycobacterium tuberculosis* infection with giant tubercle formation in a dog: a case report

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ABSTRACT: An eight-year-old, 4.9 kg, intact male mongrel dog presented with progressive weight loss, anorexia, vomiting, diarrhoea, and open-mouth breathing. A thoracic radiograph showed significant pleural effusion. Upon removal of the pleural effusion, an oval-shaped soft-tissue density mass was identified above the heart base. Two months later, the dog's condition worsened severely, and he was euthanised. A complete necropsy showed all intrathoracic structures were encapsulated by a fibrinous material. A large granuloma was attached between the right cranial lung lobe and the trachea. The cytological evaluation of the pleural effusion showed numerous negative-staining rod structures. Ziehl-Neelsen staining confirmed the presence of acid-fast bacilli. A polymerase chain reaction test confirmed *Mycobacterium tuberculosis* infection. This work is the first case report of canine pulmonary *M. tuberculosis* infection in South Korea. To the best of our knowledge, the formation of giant tubercles in canine pulmonary tuberculosis has not been reported recently.

Keywords: dog; *M. Tuberculosis*; pleural effusion; tubercles; tuberculosis

List of abbreviations

ALP = alkaline phosphatise, **ALT** = alanine aminotransferase, **AST** = aspartate transaminase, **IL-6** = interleukin-6, **PCR** = polymerase chain reaction, **TB** = tuberculosis, **TNCC** = total nucleated cell count

Tuberculosis (TB) is a contagious disease in humans and animals and has a wide range of hosts (Gay et al. 2000; Hackendahl et al. 2004; Turinelli et al. 2004; Sykes et al. 2007; Parsons et al. 2008; Posthaus et al. 2011; Martinho et al. 2013; Engelmann et al. 2014). TB is caused by members of the mycobacterium TB complex that includes *M. tuberculosis*, *M. bovis*, *M. microti*, *M. canettii*, *M. africanum*, and *M. pinnipedii*, all of which form tubercles. Non-tuberculosis mycobacteria include *M. avium* and *M. intracellulare* (Etienne et al. 2013). According to previous reports in the 1980s, *M. tuberculosis* was responsible for approximately 75% of reported canine mycobacterium infections caused by close contact with an infected human (Foster et al. 1986). However, only a few case reports of canine *M. tuberculosis* infection have been reported within the past 10 years (Sykes et al. 2007; Parsons et al. 2008; Martinho et al. 2013; Engelmann et al. 2014).

Mycobacteria species have lipid-rich walls that provide resistance to environmental stressors including heat, pH, disinfectants, and antibiotics. They are aerobic, intracellular, obligate, opportunistic, saprophytic, non-motile, nonspore-forming, and Gram-positive bacilli with wide variations in host affinity (Hackendahl et al. 2004; Sykes et al. 2007; Engelmann et al. 2014). Three general clinical disease forms are described in the literature (Foster et al. 1986; Hackendahl et al. 2004; Sykes et al. 2007): internal tubercular granuloma formations (tuberculosis type), localised cutaneous nodule formations (leprosy type), and the subcutaneous inflammation type (*M. avium* complex). Among them, thoracic involvement with tubercle formation is the type most frequently observed with TB infections in dogs because *M. tuberculosis* requires a high oxygen concentration for replication and survival (Gay et al. 2000; Engelmann et al.

2014). Pleurisy and pleural effusion may also develop concurrently and in association with pulmonary TB infection (Gay et al. 2000; Turinelli et al. 2004; Sykes et al. 2007; Parsons et al. 2008). However, the formation of giant tubercles in the thoracic cavity, and a comparison of different types of pleural effusion with pulmonary TB have not been described yet in veterinary medicine.

This case report describes the clinical diagnostic features, a gross lesion, and the cytological and histopathological characteristics of a pulmonary *M. tuberculosis* infection with the formation of a giant tubercle in a dog.

Case description

An eight-year-old, 4.9 kg, intact male mongrel dog presented with progressive weight loss, anorexia, vomiting, diarrhoea, and open-mouth breathing. On initial physical examination, severe emaciation, pyrexia (39.2 °C), and muffled heart sounds were detected. A 0.5 ml whole blood sample in an EDTA tube and a 1 ml whole blood sample in a lithium-heparin tube were collected. A complete blood cell count (VetAutoread™Haematology Analyser; IDEXX Laboratories, Inc., South Korea), serum blood chemistry analysis (VetTest® Chemistry Analyser; IDEXX Laboratories, Inc., South Korea) and electrolyte analysis (Roche 9180 Electrolyte Analyser, F. Hoffmann-La Roche Ltd., South Korea) were performed. Based on the results presented in Table 1, the dog also had neutrophilia, mild lymphopaenia, thrombocytosis, increased aspartate aminotransferase (AST) and alkaline phosphatase (ALP) activities, mild azotaemia, hyperlactataemia, hypoalbuminaemia, and hyperglobulinaemia. Additional urinalysis revealed concentrated urine (specific gravity, 1.035).

A thoracic radiograph showed significant pleural effusion. Upon removal of the fluid, the re-evaluated thoracic radiograph showed a left caudal lung lobe collapse, a hyper-inflated right lung, mild thickening of the right pleural membrane on the ventrodorsal view, an oval-shaped soft-tissue density mass above the heart base, and an enlarged perihilar lymph node on the right lateral view (Figure 1A–1D). Fluid from the left thoracic cavity was found to be an exudate. The classification as an exudate is based on the total protein content and a total nucleated cell count (TNCC) of 9.3×10^3/μl,

Table 1. Hematological findings in the dog with tuberculosis

Parameter	Recorded value	Reference values
Complete blood count results[1]		
Packed cell volume (%)	40.05	37–55
Red blood cells (M/μl)	7.14	5.69–9.08
White blood cells (K/μl)	11.72	5.84–20.26
Lymphocytes (K/μl)	1.10	2.04–4.66
Monocytes (K/μl)	0.40	0.24–2.04
Neutrophils (K/μl)	10.20	4.27–9.06
Eosinophils (%)	4.30	2–10
Platelets (K/μl)	712	173–486
Serum chemistry results[2]		
ALT (IU/l)	27	10–94
AST (μkat/l)	1.2	0.2–1.1
ALP (IU/l)	965	0–90
BUN (mmol/l)	14.99	2.50–11.42
Creatinine (μmol/l)	194.5	44.2–123.8
Lactate (mmol/l)	4.1	0.5–2.5
Amylase (μkat/l)	16.3	6.3–25.6
Lipase (μkat/l)	6.27	1.53–8.96
Triglyceride (mmol/l)	0.94	0.11–5.65
Total cholesterol (mmol/l)	4.53	2.99–8.20
GGT (μkat/l)	0.05	0.02–0.11
Creatine kinase (μkat/l)	1.84	0.87–8.99
Glucose (mmol/l)	6.33	2.94–6.49
LDH (IU/l)	123	40–130
Total bilirubin (μmol/l)	3.42	1.71–10.26
Inorganic phosphate (mmol/l)	2.20	0.61–2.55
Calcium (mmol/l)	2.45	2.25–2.98
Total protein (g/l)	72	53–76
Albumin (g/l)	20	32–47
Globulin (g/l)	51	15–35
Albumin : Globulin ratio	0.39	0.89–2.68
Sodium (mmol/l)	144	146–156
Potassium (mmol/l)	4.7	3.9–5.5
Chloride (mmol/l)	120	113–123

ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; GGT = gamma-glutamyl transferase; LDH = lactate dehydrogenase
[1]reference values were from Moritz et al. (2004)
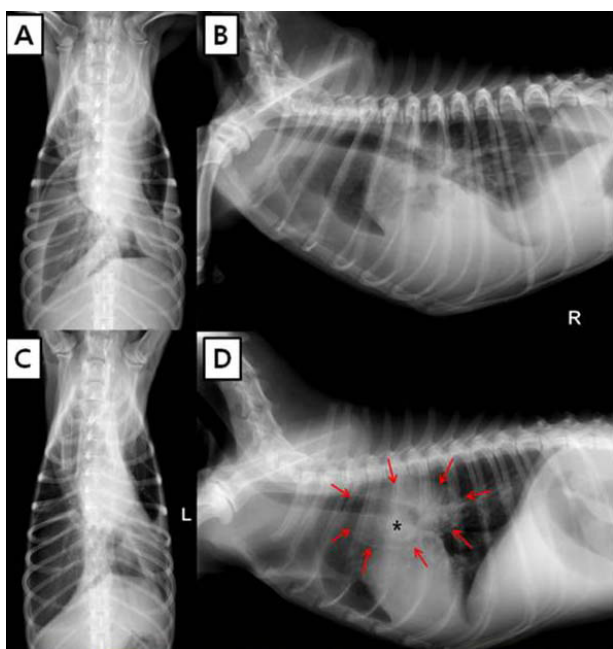[2]reference values were from Michigan State University's Veterinary Clinical Center Laboratory, 1999

Figure 1. Survey radiograph of the thorax. (**A**, **B**) Severe pleural effusion can be seen. (**C**) After removal of the pleural fluid, microcardia and hyperinflated right lung lobes are evident. (**D**) An oval-shaped soft-tissue density mass (arrows) and enlarged tracheobronchial lymph nodes (asterisk) were noticed

with 70% neutrophils and 30% vacuolated macrophages, with no apparent bacterial or fungal agents (Figure 4A and 4B; Table 2). The routine bacterial cultures were performed with Mueller-Hinton broth to which one 1ml of pleural fluid was added. After one day of incubation, the collected fluid was incubated for an additional two days on a Mueller-Hinton agar plate and a blood agar plate. Both cultures were negative. Additional anaerobic bacterial culture was not performed in this case.

A heart-based tumour was excluded via echocardiography. An additional computed tomography (Asteion Super 4 apparatus, Toshiba, Tokyo, Japan) scan was performed. The computed tomography scan showed pleural fluid, enlargement of intratho-

racic lymph nodes, and a 3 × 4 cm mass on the right side of the trachea, with mineralisation and multiple nodules. Iatrogenic pneumothorax resulting from thoracocentesis was detected. No evidence of metastasis was observed on the abdominal computed tomography scan (Figure 2).

Based on these results, the dog was tentatively diagnosed with a primary pulmonary tumour with secondary pleural effusion and inflammation. The dog's owner requested conservative therapy consisting of intermittent removal of the pleural effusion; however, two months later, the dog's condition severely worsened. The owner refused further treatment and elected euthanasia.

A complete necropsy was performed. Abundant effusion in the pleural cavity was noted bilaterally. Based on the protein and TNCC concentrations in Table 2, the fluid on the left side at necropsy was an exudate and quite similar to the fluid at presentation while the fluid on the right side was haemorrhagic. Removal of the fluid revealed that all intrathoracic structures were encapsulated by a fibrinous material. Enlargement of the intrathoracic lymph nodes and severe adhesions between the lobes of the lungs and the parietal pleural membranes were noted (Figure 3A). A large, yellowish granuloma, 7 × 5 × 3 cm, was attached between the right cranial lung lobe and the trachea (Figure 3B). Upon dissection of the granuloma, creamy, caseous material and purulent fluid were noted (Figure 3C). A cross-section of the lung parenchyma showed miliary granulomatous lesions. Caseous, foamy material was observed when pressure was applied on the lung parenchyma (Figure 3D).

On cytological evaluation of the haemorrhagic fluid from the right thoracic cavity (Figure 4C) and granuloma (Figure 4D), numerous intracellular negative-staining rod structures were observed within macrophages. Histological examination of the lung tissue showed chronic granulomatous pneumonia and pleurisy characterised by diffuse, moderate-to-marked accumulation of mononuclear phagocytes
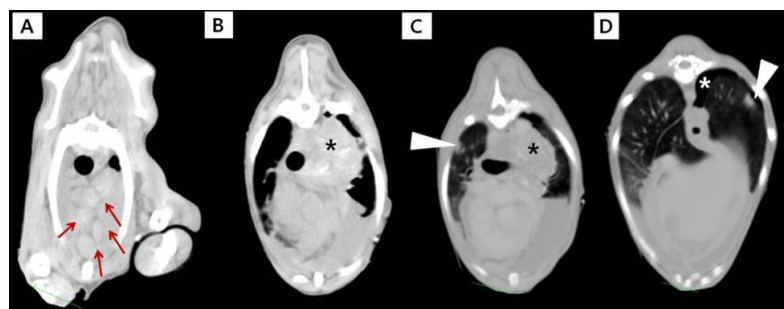

Figure 2. Computed tomography scans of the thorax. (**A**) Enlarged intrathoracic lymph nodes can be seen (arrows). (**B**) A 3 × 4 cm heterogeneous mass with mineralisation is visible on the right side of the trachea, above the heart base (black asterisk). (**C**, **D**) Multiple pulmonary nodules (arrowheads) and iatrogenic pneumothorax (after thoracocentesis) are visible (white asterisk)

Table 2. Pleural effusion analysis in the dog with tuberculosis, at the time of initial presentation and at necropsy examination

Analyte	Presentation	Post-mortem	
		left	light
Pleural cavity	left	left	light
Colour	translucent, yellowish	translucent, yellowish	red
Protein (g/dl)	4.5	4.4	3.8
TNCC (×10³/μl)	9.3	7.2	5.4
Cell types	neutrophils (70%) and macrophages (30%)	neutrophils (65%) and macrophages (35%)	RBCs with few macrophages
Presence of bacteria	no	no	yes
Classification	exudate	exudate	haemorrhagic

RBC = red blood cell, TNCC = total nucleated cell count

mixed with smaller numbers of neutrophils and lymphocytes (Figure 5A). The pleural tissue was markedly thickened and was characterised by increased amounts of reactive fibrosis, with diffuse, moderate-to-marked infiltration of mononuclear phagocytes and smaller numbers of lymphocytes and neutrophils consistent with chronic pleurisy (Figure 5B). The granuloma had caseation necrosis and multifocal areas of dystrophic calcification without viable cells; it was later identified as a giant caseous-type tubercle (Figure 5C). Ziehl-Neelsen staining of the lung tissue and pleural fluid confirmed the presence of acid-fast bacilli inside the macrophages (Figure 5D).

Based on the gross, cytological and histological examinations, mycobacterial infection with giant tubercle formation was diagnosed. Because TB is an official zoonotic disease in South Korea, pleural fluid samples and tissue samples fixed in 10% neutral buffered formalin were sent to the Animal and Plant Quarantine Agency of South Korea for PCR testing and species identification. The results of PCR testing confirmed that the organism was *Mycobacterium tuberculosis*.

DISCUSSION AND CONCLUSIONS

M. tuberculosis is the most host-specific strain of all mycobacteria and is primarily a human pathogen. Humans are the only reservoir hosts for *M. tuberculosis;* companion animals are predominantly
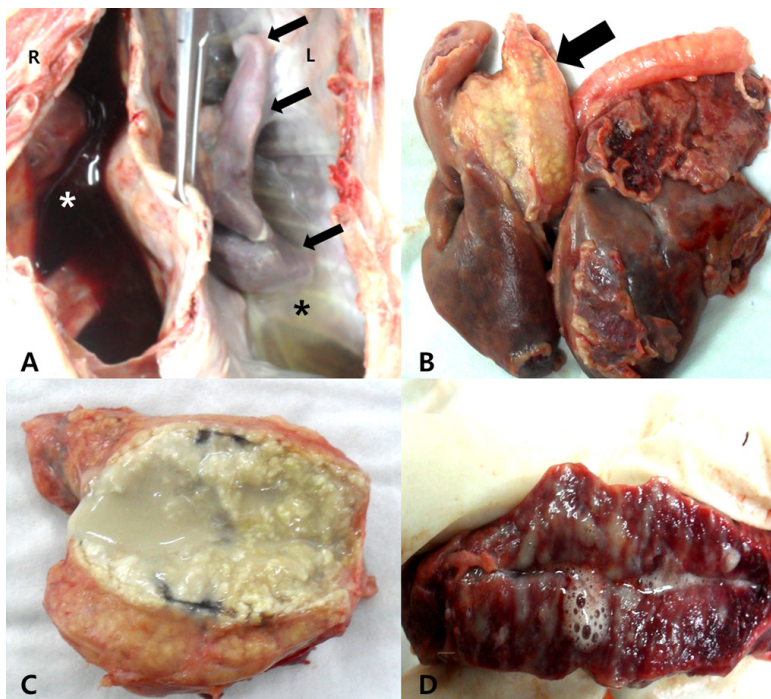

Figure 3. Necropsy findings in a dog with pulmonary TB. (**A**) Abundant pleural fluid was removed from the left (L) pleural cavity (black asterisk). A small amount of haemorrhagic fluid can be seen in the right (R) pleural cavity (white asterisk). The entire pleural space was covered with fibrinous material and severe adhesions can be seen between the lung lobes and the parietal pleura (arrows). (**B**) A large yellowish granuloma (giant tubercle) can be seen between the right side of the trachea and the right cranial lung lobe. (**C**) Dissection of the granuloma revealed caseous, creamy material and purulent fluid. (**D**) Dissection of the lung revealed multiple small yellowish tubercles. When pressure was applied on the lung parenchyma, caseous and foamy material was exuded
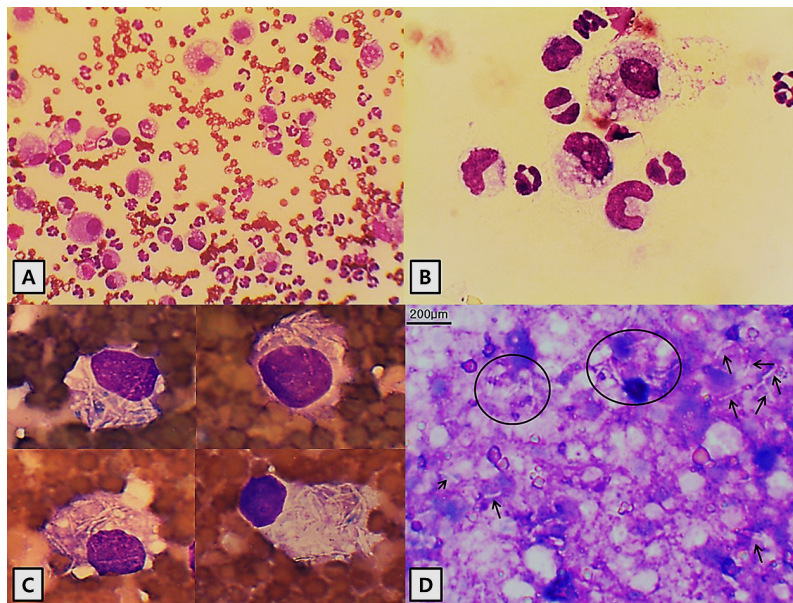
Figure 4. Cytological examination of the pleural fluid at presentation (A, B) and post-mortem (C, D). (**A, B**) A sediment smear of the left pleural effusion shows a predominance of neutrophils, with fewer macrophages. Bacteria were not observed. (Diff-Quik stain, A, × 400; B, × 1000). (**C**) A sediment smear of the right pleural fluid contains a large number of erythrocytes in the background. Macrophages contain numerous negative-staining rod structures consistent with Mycobacterium sp. (Diff-Quik stain, × 1000). (**D**) Impression of the large tubercle (granuloma) contains scattered negative-staining rod structures (arrows and circular area) (Diff-Quik staining, × 400)

infected through prolonged exposure to infected humans via inhalation of respiratory secretions or ingestion of contaminated food (Hackendahl et al. 2004; Turinelli et al. 2004; Sykes et al. 2007; Parsons et al. 2008; Martinho et al. 2013; Engelmann et al. 2014). Dog-to-human transmission has not been identified except in one case in which a person was infected with TB during a necropsy (Posthaus et al. 2011). TB-infected dogs can carry high mycobacterium loads in their respiratory secretions; thus, the risk of dissemination into the environment can be high. Such dissemination may then serve as a source of infection for other animals or humans. Euthanasia is recommended for animals with TB

because of the hazards they pose to human health (Gay et al. 2000; Hackendahl et al. 2004; Sykes et al. 2007; Parsons et al. 2008; Posthaus et al. 2011).

The dog in this case lived in an urban area, remained predominantly inside the house, and rarely went out for walks. There was no known family history of TB and no known exposure to a person infected with TB. All of the family members had negative results on *M. tuberculosis* screening tests, despite sharing the household with the infected dog. In this case, the source of infection was not established; the dog could have been spontaneously exposed or been in contact with aerosolised, bacteria-contaminated material.
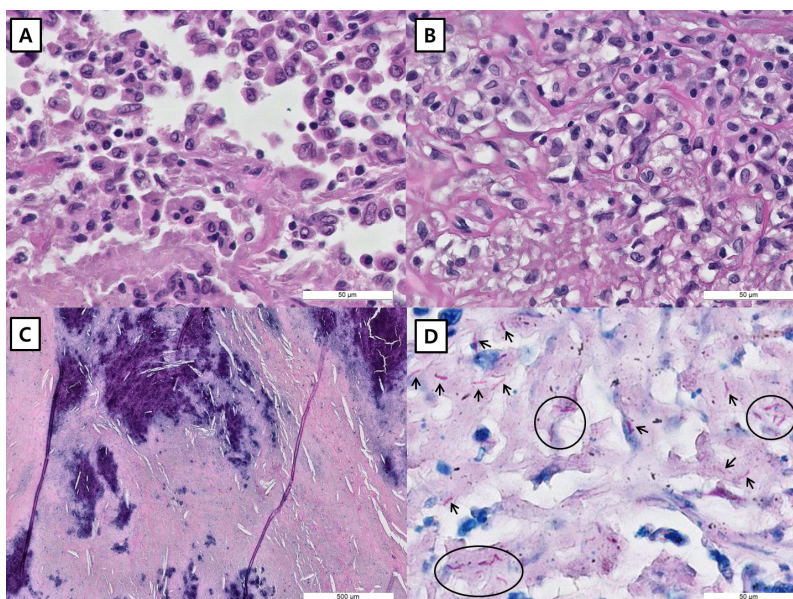

Figure 5. Histopathologic examination of the lung, pleura and granuloma. (**A**) The lung tissue contains many macrophages, indicative of chronic granulomatous pneumonia. (**B**) The pleura is expanded by granulomatous inflammation (pleurisy). Haematoxylin and eosin (H&E) staining (bar = 50 μm). (**C**) The granuloma has caseation necrosis and multifocal areas of calcification consistent with tubercles. H&E staining (bar = 500 μm). (**D**) Acid-fast staining of the lung tissue identified numerous acid-fast stained bacilli (arrows and circular area). Ziehl-Neelsen staining (bar = 50 μm)

Diagnosing TB is challenging because the clinical signs are non-specific and similar to chronic disease processes. Some of these clinical signs include non-productive coughing, weight loss, pyrexia, dyspnoea, diarrhoea, vomiting, and anorexia. Further, infected dogs can remain subclinical for long periods of time (Gay et al. 2000; Hackendahl et al. 2004; Turinelli et al. 2004; Parsons et al. 2008). As is characteristic of TB, it was difficult to determine the approximate time of exposure or onset of infection in this dog. Further, the dog had a pulmonary mass accompanied by the non-specific clinical signs mentioned above; the presenting clinical signs appeared to be more closely related to chronic progression of the tumour rather than to other diseases, including TB.

Cytological and histopathological examinations are useful for detecting rod-shaped, negative-staining bacilli on routine stains or acid-fast bacilli on Ziehl-Neelsen staining (Gay et al. 2000; Hackendahl et al. 2004; Parsons et al. 2008; Martinho et al. 2013). Definitive diagnosis of mycobacterial organisms and species can be made using bacterial culture, and molecular genetic techniques such as PCR or restriction fragment length polymorphism analysis (Hackendahl et al. 2004; Parsons et al. 2008; Martinho et al. 2013; Engelmann et al. 2014).

Laboratory findings are non-specific for canine TB and are reported to include leukocytosis, non-regenerative anaemia, increased ALP and alanine aminotransferase (ALT) activities, azotaemia, and hyperglobulinemia (Hackendahl et al. 2004; Martinho et al. 2013). Neutrophilia and lymphopenia in patients with bacterial infections are frequently associated with acute/chronic inflammatory processes and/or the illness-induced glucocorticoid-mediated stress response. The term acute inflammation refers to the type of inflammatory reaction, not to the duration of disease. When inflammation is prolonged and there is an active need for neutrophils in the inflamed tissue, the acute inflammatory pattern can be seen (Stockham and Scott 2008).

Thrombocytosis is commonly found with chronic inflammatory diseases, including pulmonary TB (Baynes et al. 1987; Unsal et al. 2005). According to findings in human medicine (Unsal et al. 2005), interleukin-6 (IL-6), produced by various immune-associated cell types including T cells, B cells, fibroblasts and monocytes, is responsible for reactive thrombocytosis in pulmonary TB. When the *M. tuberculosis* organism is phagocytosed by macrophages, production and secretion of IL-6 is increased and activates the inflammatory cascade. This process leads to systemic effects, including an acute phase reaction and reactive thrombocytosis (Unsal et al. 2005). Further, when chronic inflammation persists, production of acute-phase proteins, immunoglobulins, and complement proteins may increase. However, the concentration of albumin, a negative acute-phase protein, usually decreases due to a reduction in albumin synthesis. This process leads to hypoalbuminaemia and hyperglobulinaemia. Further, pleural effusions also contribute to hypoalbuminaemia via loss of protein into the pleural space (Stockham and Scott 2008). In sum, in the present canine case, thrombocytosis, together with the neutrophilia, lymphopaenia, hypoalbuminaemia, and hyperglobulinaemia, were all likely a result of the chronic active inflammation induced by pulmonary TB. Since the dog had normal urine concentration, prolonged anorexia, and gastrointestinal disturbance, pre-renal azotaemia due to dehydration was confirmed.

Elevated serum AST, ALT, and ALP levels are often related to diffuse liver involvement in human TB patients (Sharma et al. 2012). Further, hepatocyte damage can occur with hypoxia and inflammation (Stockham and Scott 2008). In this case, the concentrations of other liver enzymes, including serum ALT, bilirubin, and gamma-glutamyl transferase, were not increased. Further, serum potassium levels and lactate dehydrogenase concentrations were in the normal range; haemolysis was thus ruled out as a cause of AST elevation (Stockham and Scott 2008; Koseoglu et al. 2011). Given these findings, further hepatic investigation was not performed. However, in human medicine, liver biopsy and histopathological examinations are recommended to diagnosis TB when serum hepatobiliary enzyme levels are elevated (Sharma et al. 2012).

Hyperlactataemia is often concomitant with shock, severe sepsis, neoplasia, seizure, poisoning, acute hepatic failure, and low cardiac output states. Additionally, inadequate utilisation of oxygen, and presence of tissue hypoxia can be a contributing factor (Pang et al. 2007; Stockham and Scott 2008). In the present case, hypoxia associated with the severe pleural effusion and pleural adhesion together with bacterial sepsis were likely responsible for the hyperlactataemia. Lactate measurement in pleural effusion can also help in distinguishing septic ef-

fusion from other types (Pang et al. 2007) but was not done in this case.

Pleural effusion is a common finding in pulmonary TB. However, only few studies in veterinary medicine have reported the pathogenesis of tuberculous pleural effusion. In human medicine, the formation of pleural effusion in TB is associated with the rupture of a subpleural caceous focus in the lung into the pleural space and a delayed hypersensitivity reaction to tuberculous protein, which leads to increased protein permeability in the pleural capillaries. In addition, decreased pleural fluid clearance from the pleural space also contributes to the formation of pleural effusion; this occurs when the lymphatics in the parietal pleura are obstructed by lymphocytic pleurisy (Light 2010). Further, mesothelial cells are prevented from entering the pleural space by intense covering of the pleural surface with lymphocytic infiltration and fibrin material (Light 2010). Thus, as described herein, mesothelial cells are seldom observed with tuberculous pleural effusion. In this case study, severe pleurisy and a delayed hypersensitivity were thought to be the major causes of the observed pleural fluid formation.

Tubercles are normally categorised as nodular, grey, miliary, or caseous. Calcified and fibrous tubercles are observed less frequently than the other types in dogs (Hackendahl et al. 2004; Turinelli et al. 2004). Coagulation necrosis is not as common in canine lesions as in bovine or human lesions; however, when present, massive caseation develops, with a white-grey, soft, crumbly material, as described herein. Tubercles with caseation, calcification, and fibrin walls encapsulating the lymph nodes or organs, as reported in this case, are an unusual finding in dogs (Turinelli et al. 2004).

In summary, the remarkably large mass on the diagnostic images and concurrent inflammatory exudate without obvious bacteria mimicked a pulmonary tumour with secondary inflammation, such that canine tuberculosis was not suspected. However, at necropsy, the mass was discovered to be a giant tubercle, and acid-fast organisms were observed in macrophages in the pleural fluid, confirming the diagnosis of TB. The haemorrhagic pleural effusion was an additional unusual finding in this case. Granulomas should be considered in the differential diagnosis of intrathoracic masses, and bilateral serial evaluation of pleural fluid is recommended to aid in the diagnosis. In addition, cytological evaluation of the intrathoracic lymph nodes and mass via fine-needle aspiration, and liver biopsy when serum AST, and ALP are elevated, which were not performed in this case, may be helpful in making an accurate diagnosis.

This is the first case of canine pulmonary *M. tuberculosis* in South Korea. However, tuberculosis is an important disease in both human and animals, and its zoonotic potential should be fully explored. Recognition of the variable clinical characteristics of pulmonary TB in dogs might be helpful in making a diagnosis, especially in countries where *M. tuberculosis* is still prevalent.

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