Putative transmission of *Mycobacterium tuberculosis* infection from a human to a dog

Nicole C. Hackendahl, DVM; Dianne I. Mawby, DVM, MVSc, DACVIM; David A. Bemis, PhD; Shelley L. Beazley, DVM

- *Mycobacterium tuberculosis* is the most common species of the tuberculosis complex to be isolated from dogs and is typically transmitted from humans (reverse zoonosis).
- Clinical signs of *M tuberculosis* infection in dogs are often chronic and associated with the respiratory tract, but can vary depending on dissemination of the organism.
- Antemortem diagnosis of *M tuberculosis* infection can be challenging but can often be made via histopathologic and bacteriologic examinations.
- Treatment of an animal with a confirmed *M tuberculosis* infection is generally not recommended because of the potential for zoonosis, although natural transmission of tuberculosis from dogs to humans has not been reported.

A 3.5-year-old castrated male Yorkshire Terrier was evaluated at the **University of Tennessee College of Veterinary Medicine (UTCVM)** with the complaint of anorexia and vomiting. The dog's status for vaccinations, heartworm testing, and heartworm prevention was current. Other historical information included not thriving in comparison to littermates and nonprogressive, productive coughing for several months to a year. The exact date that the cough started could not be determined. In addition, the dog was living with a human with tuberculosis (caused by *Mycobacterium tuberculosis*) who had been receiving treatment for 6 months.

Diagnostic tests performed by the referring veterinarian included a CBC, serum biochemical panel, fecal flotation, thoracic radiographs, and contrast radiography of the digestive tract with barium. Abnormalities included nonregenerative anemia (PCV, 26.7% [reference range, 37% to 55%]; reticulocytes, 0.6%), hypoalbuminemia (1.96 g/dL [reference range, 2.7 to 3.8 g/dL]), hyperglobulinemia (4.99 g/dL [reference range, 2.5 to 4.5 g/dL]), hypoglycemia (72.4 mg/dL [reference range, 77 to 125 mg/dL]), and high activity of serum alkaline phosphatase (> 2,000 U/L [reference range, 23 to 212 U/L]). Fecal flotation yielded negative results for intestinal parasites. Thoracic radiographs revealed a mass at the bifurcation of the bronchi and dorsal elevation of the trachea. Contrast radiography with barium revealed dorsal elevation of the esophagus at the level of the heart, without evidence of constriction.

At the UTCVM, physical examination findings included emaciation, with a body condition score of 2/9. Rectal temperature, heart rate, and respiratory rate were 39°C (102.4°F), 60 beats/min, and 48 breaths/min, respectively. A raised, smooth, pink 7-mm nodule was detected in the center of the hard palate. Tracheal palpation did not elicit a cough, and hepatomegaly was detected via abdominal palpation.

Initial diagnostic tests performed at the UTCVM included CBC, serum electrolyte panel, coagulation panel, urinalysis, thoracic radiographs, and abdominal ultrasound. The CBC revealed microcytic, normochromic anemia (PCV, 33% [reference range, 37% to 55%]), mature neutrophilia (20.47 × 10^3 cells/mL [reference range, 3 to 11.5 × 10^3 cells/mL]), monocytosis (2.14 × 10^3 cells/mL [reference range, 0.15 to 1.35 × 10^3 cells/mL]), and thrombocytosis (521 × 10^3 platelets/mL [reference range, 200 to 500 × 10^3 platelets/mL]). The electrolyte panel revealed hypernatremia (158 mEq/L [reference range, 142 to 151 mEq/L]) and hyperchloridemia (119 mEq/L [reference range, 107 to 117 mEq/L]). The coagulation panel (prothrombin time, partial thromboplastin time) yielded results within reference ranges. Urinalysis revealed specific gravity of 1.020, 2+ protein, 3+ blood, 5 to 10 WBCs/hpf, and RBCs that were too numerous to count.

Thoracic and abdominal radiographs revealed enlarged tracheobronchial and cranial mediastinal lymph nodes and hepatomegaly (**Figures 1 and 2**). Abdominal ultrasonography revealed multifocal hypoechoic masses within both kidneys and the liver, mineralization of the liver and kidney parenchyma, and urinary cystic calculi in the urinary bladder.

A mucus sample was collected from the dog's oral cavity by the owner, when the dog was reported to be actively coughing, and maintained at room temperature (22°C [71.6°F]). The sample was evaluated cytologically within several hours of collection, which revealed many WBCs. Acid-fast bacteria were not observed. It was not certain whether this sample was respiratory or gastrointestinal in origin. During hospitalization, the dog did not cough or vomit, so an additional sample was not obtained. Cytology findings from fine-needle aspirates of the kidney and liver were nondiagnostic. The dog received supportive care consisting of SC administration of fluids with potassium supplementation. Because of concern of the potential zoonotic nature of an active tuberculosis infection, the dog was sent home with fluids for SC administration

From the Departments of Small Animal Clinical Sciences (Hackendahl, Mawby), Comparative Medicine (Bemis), and Pathobiology (Beazley), College of Veterinary Medicine, University of Tennessee, Knoxville, TN 37996-4544. Dr. Hackendahl's present address is the Department of Small Animal Clinical Sciences, College of Veterinary Medicine, University of Florida, Gainesville, FL 32610-0126.
Address correspondence to Dr. Hackendahl.

and a prescription for isoniazid, pending test results. Diagnostic specimens submitted at that time included a kidney biopsy specimen for histopathology, fungal and *Mycobacterium* culture, and an *M tuberculosis* DNA probe on the sample from the oral cavity. Financial and time constraints of the owner prevented additional diagnostic tests, including transtracheal lavage.

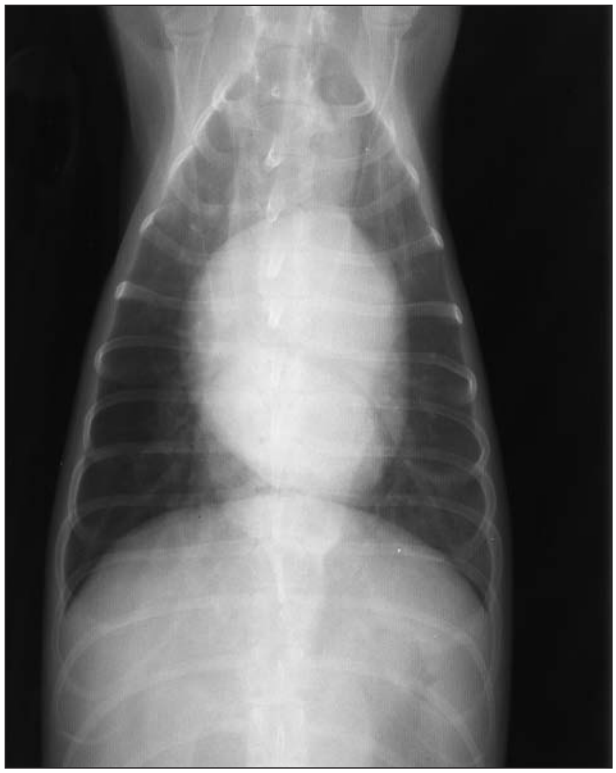

Figure 1—Ventrodorsal radiographic view of the thorax of a dog with *Mycobacterium tuberculosis* infection. Notice tracheobronchial and cranial mediastinal lymphadenopathy and hepatomegaly.

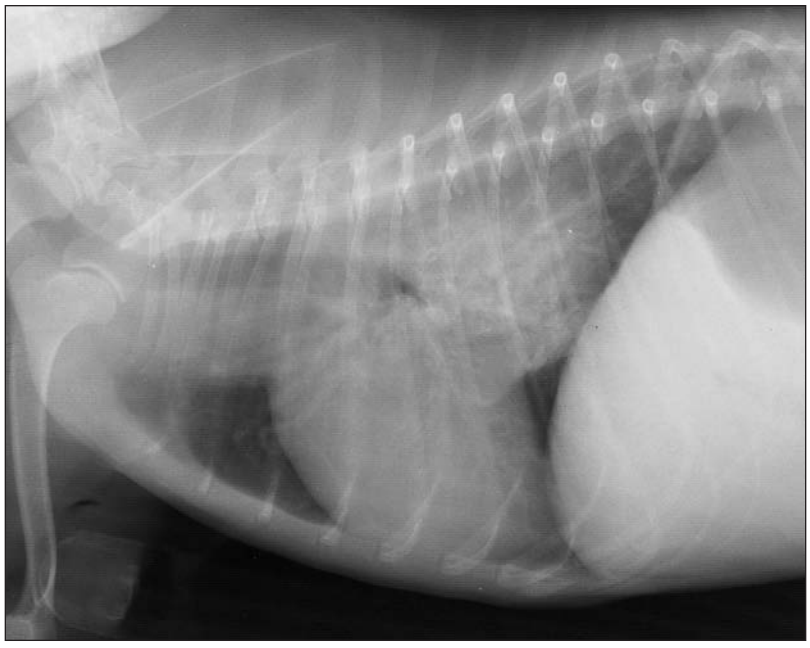

Figure 2—Lateral radiographic view of the same dog as in Figure 1.

After returning home, the dog continued to vomit but seemed to have a brighter demeanor. Ten days after evaluation at the UTCVM, the dog was evaluated by the referring veterinarian for urethral obstruction with calculi and was euthanatized because of financial constraints. The prescribed isoniazid was never administered.

Results from the pending diagnostic tests were received 1 to 5 weeks after the dog was discharged. Marked chronic interstitial nephritis and glomerulonephritis were seen microscopically, although no organisms were seen. Preliminary results of fungal and mycobacterial cultures of the kidney biopsy specimen and oral specimen were negative, and results of the *M tuberculosis* DNA probe on the oral specimen were negative.[a]

The dog was returned to the UTCVM for postmortem examination. The dog was emaciated and weighed 1.4 kg (3.1 lb). Multifocal to coalescing, raised, firm nodules were on the surface and extending into the parenchyma of the liver, kidneys, and omentum and within the lung, ranging from 1 mm to 2.5 cm in diameter. The nodules contained abundant, gritty, yellowish-tan, caseous material (**Figure 3**). Generalized lymph node enlargement was evident throughout the body. The middle tracheobronchial lymph node was markedly enlarged, with internal effacement by gritty, yellow, caseous material. Findings consistent with urolithiasis and urinary obstruction included innumerable dark brown calculi with granular, spiked surfaces ranging from < 1 to 2 mm in diameter within the lumen of the urethra and urinary bladder. Two similar calculi were found in the pelvis of the left kidney. Mild hydronephrosis of the left and right kidney and mild hydroureter of the left kidney were observed. Additional lesions included focal calcification of the ascending aorta and pulmonary artery, ulcerative glossitis and stomatitis, hypercellular bone marrow, and urinary cystitis. The vessel calcification and ulcerative glossitis and stomatitis were attributed to postrenal azotemia and uremia from urinary obstruction. A focal region of clotted blood was detected within the retroperitoneal cavity attached to the left kidney, presumptively from the kidney biopsy. Specimens were collected in neutral-buffered 10% formalin, processed routinely, and stained with H&E and acid-fast stains.

Histologically, granulomatous hepatitis, nephritis, omentitis, pneumonia, and tracheobronchial lymphadenitis were detected. Granulomas were characterized by a central region of necrosis with variable mineralization surrounded by large numbers of epithelioid macrophages, lymphocytes, and plasma cells; few multinucleated giant cells; and rare neutrophils (**Figure 4**). Extremely rare acid-fast bacilli were observed with acid-fast stains (2 organisms in the liver and 1 organism in the tracheobronchial lymph node). These lesions were consistent with tubercular granulomas. In addition to the renal tubercles, diffuse, global, membranoprolif-

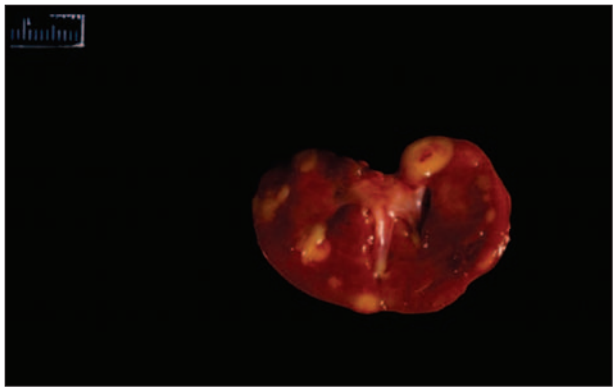

Figure 3—Photograph of a kidney from the same dog as in Figure 1. Notice the multifocal tubercles of various sizes within the cortex and medulla. Scale = 1 cm.

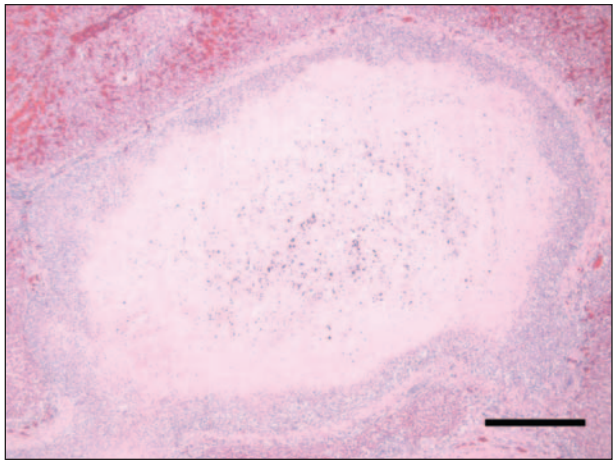

Figure 4—Photomicrograph of a typical hepatic tubercle in the same dog as in Figure 1. Notice the central region of necrosis and mineralization surrounded by a rim of epithelioid macrophages. H&E stain; bar = 500 mm.

erative glomerulopathy; chronic lymphoplasmacytic interstitial nephritis; suppurative pyelonephritis; ureteritis; urethritis; and cystitis were evident. Other findings included generalized metastatic mineralization of vessels and alveolar septae, marked myeloid hyperplasia, and ulcerative stomatitis. These additional findings were likely secondary to renal disease, urolithiasis, and urinary obstruction. Urolith analysis was not performed. In addition, the oral nodule was consistent with a chronic inflammatory condition, distinct from the granulomas found elsewhere. The importance of the oral nodule was not clear.

Fungal and routine bacterial cultures of tissue from the postmortem examination yielded negative results. Acid-fast bacteria were detected in liver and lymph node tissues, and **insertion sequence (IS)**-6110-based **polymerase chain reaction (PCR)** analysis performed at the **National Veterinary Services Laboratory (NVSL)** yielded positive results for *M tuberculosis* complex, and similar 16S rRNA and IS900-based PCR assays yielded negative results for *Mycobacterium avium* and *M avium* subsp *paratuberculosis*, respectively, on crude and purified DNA extracted from formalin-fixed liver and lymph node specimens. Isolates of *M tuberculosis* were ultimately obtained by culture in 3 laboratories from a kidney specimen (UTCVM, 1 colony); liver (NVSL); and lung, kidney, and lymph node (Tennessee Department of Public Health). **Restriction fragment length polymorphism (RFLP)** fingerprinting of the IS6110 gene performed at the CDC on a *Mycobacterium* isolate from the kidney of the affected dog matched that of an isolate obtained from a sputum sample from the dog's owner, confirming that they were infected with the same organism. Although possible, natural transmission of *M tuberculosis*, either dog to dog or dog to human, has not been reported to our knowledge, although transmission from a dog to a human via exposure at necropsy has been reported.[1,2] Therefore, it is most likely that this case represents human to dog transmission. This case was unique in that a diagnosis of *M tuberculosis* infection was obtained with PCR techniques and the isolates from the owner and dog were matched through RFLP fingerprinting. It is unclear why the dog was vomiting, although it is possible that the owner had mistaken vomiting for regurgitation caused by compression of the esophagus by enlarged lymph nodes. In retrospect, the diagnosis may have been obtained antemortem if samples for bacteriologic culture were collected from a laryngeal swab specimen or transtracheal lavage.

Mycobacterial species are aerobic bacilli that range from obligate pathogens to saprophytic, opportunistic pathogens, with wide variations in host affinity and pathogenic potential within the genus.[3] Mycobacteria are relatively resistant to environmental influences because of lipid-rich walls that retain acid-fast stains and are partially responsible for initiating the granulomatous inflammatory reaction within the host.[3-5] The 3 general clinical forms of disease caused by the genus are internal tubercular granulomas (tubercular complex), localized cutaneous nodules (leprosy), and spreading, subcutaneous inflammation (opportunistic mycobacterial infections, including the *M avium* complex).[4] The tubercular complex is caused by *M tuberculosis*, *Mycobacterium bovis,* and *Mycobacterium microti*[6]; *M tuberculosis* is primarily a human pathogen and is the most host-specific of the organisms of the tuberculosis complex. It can induce progressive disease in humans, nonhuman primates, dogs, and swine.[5,7]

Transmission of *M tuberculosis* is typically via inhalation of aerosolized droplets, which allows the bacilli to enter the lung tissue and cause local infection. Bacilli are then ingested by macrophages and transported to hilar lymph nodes, from which point progression of the disease depends on the status of the cell-mediated immunity of the host.

Mycobacterium tuberculosis infections can occur in dogs and cats but are much more common in dogs.[4,8-11] Humans are the only reservoir hosts for *M tuberculosis*; dogs and cats infected with *M tuberculosis* are far more likely to have been infected by humans than from other animals. The term reverse zoonosis has been used to refer to such an infection.[3-5] *Mycobacterium tuberculosis* organisms are not considered as infectious as other bacterial organisms because large inocula or frequent, prolonged exposures are usually required for transmission. In addition, infection requires close proximity and direct exposure to aerosolized droplets.[3,4]

Clinical disease in dogs is far less common than exposure and subsequent retrieval of the organism. In

1 study,[12] tubercle bacilli were cultured from pharyngeal swab specimens and the rectum of 7 of 48 clinically normal dogs and cats that were in regular contact with infected humans. However, in another study[13] with a similar protocol, *M tuberculosis* was not successfully cultured from 29 dogs with similar exposure criteria. From 1962 to 1979, *M tuberculosis* was diagnosed in 0.05% of the dogs necropsied at the Animal Medical Center in New York. All dogs had a history of contact with humans with clinical tuberculosis.[11]

In 5 case reports[8,10,14-16] of *M tuberculosis* infection in dogs between 1965 and 1992, findings ranged from localized disease to widespread systemic disease. All cases were diagnosed via bacteriologic culture, cytology, or histopathology.

Clinical signs in animals with *M tuberculosis* infections depend on the route of exposure and degree of localization or dissemination.[5] The disease is frequently subclinical, but common findings include cachexia, weakness, anorexia, dyspnea, and a low-grade fluctuating fever.[4,5,7]

Clinical signs associated with the primary sites of infection may include tonsilar enlargement and ulcerated, draining oropharyngeal lesions that can result in dysphagia, retching, and pytalism. Respiratory involvement often results in bronchopneumonia, pulmonary nodule formation, and hilar lymphadenopathy, with associated fever, weight loss, anorexia, and a harsh, nonproductive cough. Clinical findings associated with disseminated disease often are attributable to generalized lymphadenopathy or represent the site of granuloma formation. Less common clinical signs include granulomatous uveitis, CNS signs, lameness and spontaneous fractures, hemoptysis, hematuria, and icterus.[4]

Antemortem diagnosis of *M tuberculosis* infection in a cat or dog can be difficult. Results of routine diagnostic tests are nonspecific; CBC may reveal leukocytosis and nonregenerative anemia,[4] and mycobacteria within neutrophils have been detected on blood smears.[17] High serum globulin concentration and low serum albumin concentration may be found.[4] Thoracic radiography may reveal tracheobronchial lymphadenopathy, interstitial lung infiltration, lung consolidation, granuloma formation, calcified pulmonary lesions, and miliary infiltration. Abdominal radiography may reveal organomegaly, abdominal masses, or calcified mesenteric lymph nodes.[4]

Most *M tuberculosis* infections can be diagnosed antemortem with histopathologic and bacterial examinations of lesions, lymph nodes, or other affected tissues, revealing granulomas with or without acid-fast bacilli. If bacilli are present, they are usually in low numbers.[4] If acid-fast bacilli are detected, initiation of treatment is indicated while bacterial culture results are pending, especially if there is history of exposure. The organisms are not stained with routine stains such as Romanovsky stains and instead appear as rod-shaped negative images,[1] although this is a nonspecific finding, making culture and identification necessary for confirmation of the diagnosis.[1] Tissues for culture can be frozen (preferably at ultra-low temperatures) for culture at a later date.[3] In 1 case,[15] tuberculosis was diagnosed in a dog by bacteriologic culture of a laryngeal swab specimen. It was recommended to collect as much mucus on the swab as possible, and fluid from a transtracheal or bronchoalveolar lavage can also be used.[15] Mycobacteria are slow growing; 4 to 6 weeks may be necessary for culture, and biochemical testing may require an additional 2 weeks or longer.

Other antemortem diagnostic tests are available, such as radiometric testing, but such tests are not commonly available in veterinary laboratories.[7,18,19] A PCR assay can be performed on fixed tissue that contains organisms or on cultured organisms, but does not distinguish between members of the tubercular complex.[4,7] Nucleic acid probes applied directly to a clinical specimen or a culture have similar limitations.[4,7] Intradermal skin testing and provocative fever tests have been described in the literature; however, these tests can be inconsistent and unreliable and are recommended only if other tests do not substantiate a diagnosis.[4,5,10,16] The state veterinarian and state veterinary diagnostic laboratory should be contacted for specific information regarding test availability.

Gross postmortem findings often include generalized emaciation. Multifocal granulomas may be detected in many organs and are usually nodular; circumscribed; and gray, white, or yellow. In dogs, the primary site of infection is usually the bronchial lymph nodes, although generalized lesions can affect the pleura, pericardium, liver, kidney, heart, intestine, and CNS.[4] Granulomatous lesions, which consist of focal necrosis surrounded by plasma cells, macrophages, and connective tissue, sometimes with calcification, are seen. The organisms are usually intracellular in the periphery of the necrotic areas but can also survive and grow extracellularly in cavitary lesions.[4] Among 8 dogs with *M tuberculosis* infection in another report,[11] all had granulomatous lesions with few acid-fast bacilli in the periphery of necrotic areas.

Euthanasia is recommended for animals with confirmed *M tuberculosis* infection because of the possible human health hazard.[1,16] However, treatment can be attempted and should be initiated on the basis of a cytologic or histologic diagnosis because of the time lag to a definitive diagnosis via culture.

Treatment for dogs consists of multidrug therapy for a minimum of 6 to 9 months. Single drug treatments will often result in antimicrobial resistance.[4] Current treatment recommendations include combined administration of isoniazid, ethambutol, and rifampin. Pyrazinamide is sometimes substituted for ethambutol.[4] New treatments being studied in human cases of tuberculosis include the systemic use of corticosteroids and fluoroquinolones.[20,21]

Adverse effects of multidrug therapy in animals may include hepatoxicosis, optic neuritis, ototoxicosis, discoloration of tears and urine, gastrointestinal tract signs, and arthralgia.[4] Animals that are at high risk of infection because of exposure can be treated prophylactically with isoniazid for 6 to 12 months.[4]

If *M tuberculosis* infection in an animal is diagnosed or highly suspected, local health officials should be contacted.[10] Human exposure can be detected by use of an intradermal test within 3 to 8 weeks of exposure.[5] Humans with potential exposure should be tested with an intradermal test immediately to establish a negative reading and then 8 weeks later to detect seroconversion. The question of what to do with an exposed and possibly sensitized pet that is clinically normal remains.[13]

These pets are of little risk to humans unless they develop the active disease, but they require close monitoring. Whether the risk justifies the long, expensive, and potentially dangerous treatment is a question that must be addressed on an individual case basis.

[a]GenProbe MTD, Gen-Probe Inc, San Diego, Calif.

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