Disseminated *Mycobacterium avium* complex infection following renal transplantation in a cat

Alison Griffin, BVSc; Alisa L. Newton, VMD; Lillian R. Aronson, VMD, DACVS; Dorothy Cimino Brown, DVM, DACVS; Rebecka S. Hess, DVM, DACVIM

Because of immunosuppression in cats that have undergone renal transplantation, rare infectious diseases should be considered in the differential diagnosis after more common infectious diseases have been excluded.

*Mycobacterium avium* complex is a rare cause of disseminated mycobacterioses in human and feline transplant recipients.

Organisms of the *M. avium* complex remain viable for at least 2 years and are found in water, soil, dairy products, and tissues of infected birds and mammals.

An 11-year-old 3.9-kg (8.6 lb) spayed female domestic shorthair cat with a history of chronic renal failure and renal transplantation 18 months previously was referred to the Veterinary Hospital of the University of Pennsylvania because of a 2-month history of progressive lethargy, weight loss (0.68 kg [1.5 lb]), decreased appetite, vomiting, diarrhea, and polyuria, polydipsia, coughing, or sneezing. The cat previously was referred to the Veterinary Hospital of the University of Pennsylvania because of a 2-month history of progressive lethargy, weight loss (0.68 kg [1.5 lb]), decreased appetite, vomiting, diarrhea, and polyuria, polydipsia, coughing, or sneezing. The cat was being treated with cyclosporine (3.5 to 8 mg/kg [1.6 to 3.6 mg/lb], PO, q 12 h). The mean blood cyclosporine concentration, determined by means of high-performance liquid chromatography, was 401 ng/mL (target range, 300 to 500 ng/mL) during the first 6 months after transplantation and 206 ng/mL (target range, 200 to 300 ng/mL) during the subsequent 12 months. The cat had received prednisolone at a gradually decreasing dosage (initially, 1.5 mg/kg [0.7 mg/lb], PO, q 12 h) for the first 6 months after transplantation. In the 10 days prior to examination at the University of Pennsylvania, the cat had received two 5-day courses of antimicrobials for treatment of a possible bacterial infection.

Physical examination revealed signs of mild depression and an unkempt coat. The body condition score was 4 on a scale from 1 to 9. Rectal temperature was slightly elevated (39.7°C [103.5°F]), and a grade II of V systolic cardiac murmur could be auscultated. The abdomen was not deeply palpated, as this could cause avulsion of the renal allograft from its attachment to the renal artery and vein.

Diagnostic procedures performed on admission included a CBC; serum biochemical panel; urinalysis; bacterial culture of a urine sample; measurement of serum total thyroxine (*T₄*) concentration; assays for heartworm antibody and antigen; assays for infection with FeLV (ELISA), FIV (ELISA), and feline coronavirus (immunofluorescent antibody assay); determination of *Toxoplasma* titer; thoracic and abdominal radiography; and abdominal ultrasonography.

Hematologic abnormalities included nonregenerative anemia with a PCV of 21% (reference range, 32 to 48%), mean corpuscular volume (MCV) of 42 fl (reference range, 36.7 to 53.7 fl), and mean corpuscular hemoglobin concentration (MCHC) of 33.8 g/dL (reference range, 30.1 to 35.6 g/dL). Mild neutropenia (15,000 cells/µL; reference range, 2,000 to 14,000 cells/µL) and lymphopenia (690 cells/µL; reference range, 800 to 6,100 cells/µL), both consistent with stress, were also identified. Two nucleated RBCs/100 nucleated cells were noted. In the absence of an RBC regenerative response, this was thought to most likely be secondary to splenic or bone marrow disease. Results of serum biochemical analyses were normal. Urine specific gravity was 1.040, with 3+ (300 µg/dL) protein on dipstick analysis. Results of tests for heartworm infection and infection with FeLV, FIV, coronavirus, and *Toxoplasma* spp were negative, and the serum *T₄* concentration was low-normal (1.3 µg/dL; reference range, 1.0 to 4.0 µg/dL). Results of thoracic radiography were unremarkable. On abdominal radiographs, the renal allograft could be seen in the caudal portion of the abdomen. The native kidneys appeared small, and there was evidence of mesenteric lymphadenopathy or peritoneal effusion. Abdominal ultrasonography confirmed that the native kidneys were small with loss of the normal parenchymal structure. The renal allograft appeared normal ultrasonographically. Two large heteroechoic masses, thought to be mesenteric lymph nodes, surrounded the portal vein. Because of the history of renal transplantation and immunosuppression, differential diagnoses included infectious disease, lymphosarcoma, and other neoplasia.

The next day, the cat underwent anesthesia and ultrasound-guided fine-needle aspiration and needle biopsy of the enlarged lymph nodes. Aspirates were submitted for cytologic examination and aerobic and anaerobic bacterial culture; biopsy specimens were submitted for histologic examination. Samples for cytologic examination were of low cellularidad, precluding a cytologic diagnosis. The cat recovered well from the procedure and was discharged.

Three days following the initial admission, the cat was reexamined because of anorexia and lethargy. Physical examination findings included mild dehydration (5%) and a decreased heart rate, compared with...
Coagulation abnormalities included a prolonged prothrombin time (65 sec; reference range, 33 to 32 mm Hg; base excess, –8.6 mmol/L [reference range, –4 to +4 mmol/L]), high lactate concentration (5.6 mmol/L; reference range, 0.6 to 2.5 mmol/L), and high BUN concentration (64 mg/dL; reference range, 15 to 32 mg/dL). The PCV was unchanged (21%) with a total solids concentration of 7.0 g/dL. Ionized calcium concentration was within reference limits (1.25 mmol/L; reference range, 1.13 to 1.33 mmol/L). Electrocardiography revealed a normal sinus rhythm, the systolic blood pressure was 140 mm Hg, and there was no evidence of peritoneal effusion during abdominal ultrasonography. Because there was no evidence of abdominal bleeding or peritonitis, the cat was treated overnight with a balanced electrolyte solution (5 mL/kg/h, IV), and oral administration of cyspocorine (30 mg, PO, q 12 h) was continued.

The next morning, physical examination revealed progression of signs to marked depression, hypothermia (36.3° C [97.4°F]), bradycardia (102 beats/min), and hypotension (systolic blood pressure, 70 mm Hg). Differential diagnoses included septic peritonitis, progression of an infectious or neoplastic disease causing lymphadenopathy, and cardiac disease.

Diagnostic tests included a CBC, serum biochemical profile, coagulation profile, electrocardiography, echocardiography, abdominal ultrasonography, and abdominocentesis. Hematologic abnormalities included mature neutrophilic leukocytosis (27,000 neutrophils/µL) with lymphopenia (280 cells/µL) and monocytosis (1,100 cells/µL; reference range, 0 to 700 cells/µL). The anemia had worsened (PCV, 18%) and was nonregenerative (MCV, 44 fL; MCHC, 32.8 g/dL). Biochemical abnormalities included high BUN (77 mg/dL; reference range, 15 to 72 mg/dL), phosphorus (8.3 mg/dL; reference range, 3.0 to 6.6 mg/dL), and potassium (4.9 mmol/L; reference range, 3.5 to 4.8 mmol/L) concentrations and high alanine aminotransferase (1,610 U/L; reference range, 4 to 175 U/L) and aspartate aminotransferase (542 U/L; reference range, 33 to 152 U/L) activities. Albumin (1.6 g/dL; reference range, 2.4 to 3.8 g/dL), total calcium (8.0 mg/dL; reference range, 9.1 to 11.2 mg/dL), bicarbonate (14 mmol/L; reference range, 16 to 23 mmol/L), and cholesterol (77 mg/dL; reference range, 96 to 248 mg/dL) concentrations were low. Serum creatinine concentration was within reference limits (1.9 mg/dL; reference range, 1.0 to 2.0 mg/dL). Blood ammonia concentration was measured after food was withheld because of the high hepatic enzyme activities and was slightly high (65 µmol/L; reference range, 11 to 35 µmol/L). Coagulation abnormalities included a prolonged prothrombin time (470% of control value) and partial thromboplastin time (175% of control value). Platelet numbers were adequate (358,000/µL; reference range, 175,000 to 500,000/µL), and concentration of fibrin degradation products was within reference limits (< 5 µg/mL; reference range, <5 µg/mL). Echocardiography revealed mild left atrial enlargement with normal systolic and diastolic function. Electrocardiography revealed bradycardia with a junctional escape rhythm, atrioventricular dissociation, and intermittent sinus capture. This was thought to be secondary to systemic disease. During an atropine response test, the heart rate did not increase, and there was no evidence of improved atrioventricular association. Limited abdominal ultrasonography revealed a moderate amount of peritoneal fluid. Cytologic evaluation of the fluid revealed a modified transudate with no evidence of infectious agents or degenerative neutrophils. Differential diagnoses included hypoalbuminemia, abdominal inflammation, and neoplasia.

Supportive treatment included administration of a balanced electrolyte solution (2.5 mL/kg/h [1.1 mL/lb/h], IV) to which glucose and potassium were added as required, a continuous rate infusion of isoproterenol hydrochloride (0.06 µg/kg/min [0.027 µg/lb/min], IV), administration of dexamethasone sodium phosphate (0.25 mg/kg [0.11 mg/lb], IV, q 12 h), and heat support. Administration of cyspocorine was discontinued.

With this treatment, the cat’s rectal temperature remained between 35.9 and 38.1°C (96.7 and 100.6°F). The pulse rate was 86 to 160 beats/min, and the respiratory rate was 30 to 44 breaths/min. The cat remained hypotensive with a systolic blood pressure of 60 to 90 mm Hg. Urine output was adequate.

On the next day (fifth day after initial admission), serum alanine aminotransferase (3,399 U/L) and aspartate aminotransferase (4,233 U/L) activities had increased. Results of a coagulation profile were unchanged. The blood ammonia concentration decreased to 38 µmol/L, and the metabolic acidosis had resolved. Because of concerns with hypotension, sepsis, and coagulation status, dopamine hydrochloride (5 to 12 µg/kg/min [2.2 to 5.4 µg/lb/min], IV), ampicillin (22 mg/kg [10 mg/lb], IV, q 8 h), enrofloxacin (5 mg/kg [2.3 mg/lb], IV, q 24 h), and vitamin K1 (0.3 mg/kg [0.22 mg/lb], SC, q 12 h) were added to the treatment regimen.

Despite treatment, the cat remained hypotensive. On the sixth day after initial admission, treatment with dobutamine hydrochloride was initiated (5 µg/kg/min [2.2 µg/lb/min], IV), and administration of isoproterenol was discontinued. Results of aerobic bacterial culture of a urine sample and of aerobic and anaerobic bacterial culture of lymph node specimens were negative.

Histologic examination of the presumptive lymph node specimens revealed granulomatous inflammation consisting of sheets of large histiocytic cells, rare multinucleate giant cells, and areas of necrosis. An infectious cause was suspected, and special staining of sections was performed. Examination of sections stained with Ziehl-Neelsen acid-fast stain revealed a myriad of acid-fast bacilli within histiocytic cells. The presumptive diagnosis was mycobacteriosis.
Because of the grave prognosis, the owner elected to have the cat euthanatized. At necropsy, the abdomen contained a moderate amount of straw-colored effusion with clots of fibrin. Both native kidneys were small and irregular with pitted cortical surfaces. The renal allograft appeared grossly normal. Within the mesentery in the region of the mesenteric lymph nodes was a large (6.5 × 3.5 × 1.5 cm), soft, bright yellow mass. Except for an obvious capsule, no nodal architecture was detected on cut section. Plaques of similar material surrounded the attachment site of the donor kidney to the body wall and a focal adhesion of the stomach to the body wall (previous gastrosomy tube site). The liver was enlarged, mottled yellow-red, and friable. The spleen contained pinpoint white-tan nodules throughout the parenchyma. The heart was mildly enlarged but otherwise grossly normal.

On histologic examination, granulomatous inflammation was present in the mesenteric mass (mesenteric lymph nodes), spleen, liver, small and large intestines, lungs, and bone marrow as well as along the capsule of the donor kidney at the abdominal wall attachment site and the gastric adhesion site. The normal architecture of the mesenteric lymph nodes was completely effaced and replaced by sheets of epithelioid macrophages with abundant finely granular amphophilic cytoplasm. Small clusters of neutrophils and lymphocytes were admixed among the macrophages. Large zones of liquefactive necrosis were present throughout the node.

In the other affected organs, the architectural disruption was less severe. The granulomatous hepatitis was predominantly focused on portal areas (Fig 1). Additionally, in some lobes, there was severe coagulation necrosis of centrilobular to midzonal hepatocytes with multifocal hemorrhage and congestion of the central veins. It was hypothesized that the necrosis may have been secondary to hypoxemia resulting from a combination of chronic anemia and granulomatous pneumonia. The bone marrow was extremely cellular, and the normal erythroid and myeloid precursors were replaced by similar epithelioid macrophages. Examination of sections of the liver and small intestine stained with Ziehl-Neelsen acid-fast stain revealed innumerable acid-fast filamentous bacteria within histiocytes (Fig 2). A sample of the mesenteric lymph node was submitted to the National Jewish Medical and Research Center, Mycobacteriology Reference Lab, for mycobacterial culture and species identification. Mycobacterium avium was identified.

In the native kidneys, there were severe chronic lymphoplasmacytic tubulointerstitial nephritis with severe interstitial fibrosis and glomerulosclerosis. Innumerable acute glomerular microthrombi were found in the renal allograft along with mild multifocal lymphoplasmacytic tubulointerstitial nephritis, suggesting that the cat had developed disseminated intravascular coagulation (DIC) prior to death. This was consistent with the clinical finding of prolonged prothrombin time and partial thromboplastin time. Although thrombocytopenia and high fibrin degradation product concentrations are thought to be sensitive indicators of DIC in human beings and dogs, in a report1 of 21 cats with DIC, only 57 and 24%, respectively, had these laboratory abnor-

Mycobacterium avium is an acid-fast, slow-growing, opportunistic, saprophytic organism that can cause tuberculous lesions that are clinically indistinguishable from those associated with classic tuberculosis. The classic tuberculous mycobacteria are highly pathogenic and include M tuberculosis and M bovis, whereas the nontuberculous mycobacteria include opportunistic species such as M avium, M kansasii, and M fortuitum.2 Of these opportunistic mycobacteria, M avium and a closely related pathogen, M intracellulare, are the most likely to cause bacteremia and disseminated disease.2 Considerable overlap occurs between the properties of M avium and M intracellulare, so they are usually grouped together and known as M avium-M intracellulare or M avium complex (MAC). Serotyping by means of agglutination reactions has been used to differentiate MAC isolates; serovars 1 through 6 and 8 through 11 are assigned to M avium, and serovars 17, 19, 20, and 25 are assigned to M intracellulare.3 Only serotypes 1 and 4 have been isolated from cats.4 Serotyping was not performed in this case.
SMALL ANIMALS/EXOTIC

Mycobacterium avium complex organisms are ubiquitous. They remain viable for at least 2 years and are found in water, soil, dairy products, and tissues of infected birds and mammals. Birds are primarily infected, and their feces contain large numbers of bacilli. Infection in dogs and cats is thought to occur as a result of ingestion of infected meat or contact with soils or fomites contaminated by poultry carcasses or feces. Infection in human beings, pigs, cattle, deer, sheep, goats, and other mammals has also been reported. An immunosuppressed human who had lived with the cat described in the present report had been found to have localized M avium infection 6 years prior to admission of the cat to the veterinary teaching hospital. However, there is no evidence for spread of MAC organisms between or within mammals and people, and the strains that infect humans and animals are different.

In cats, disseminated tuberculous disease is typically caused by M bovis, although there are rare reports of M tuberculosis and MAC infection. Seventeen cats with MAC infection have been described in the veterinary literature. Ten cats had disseminated disease, had cutaneous infections, and had intracranial lesions. Five of the cats with disseminated disease were Siamese, and 2 of these 5 cats were related. One cat tested positive for FeLV infection involving the bone marrow, as determined by means of immunofluorescent antibody testing. Predisposing causes for MAC infection were not described in other previous case reports. In the cat described in the present report, infection was thought to develop secondary to long-term immunosuppressive treatment.

The cat described in the present report had undergone renal transplantation and received cyclosporine for 18 months and prednisolone for 8 months. Cyclosporine inhibits activation and proliferation of T lymphocytes by interfering with interleukin-2 synthesis via inhibition of calcineurin. This causes depressed cell-mediated immunity, leading to an increased susceptibility to intracellular pathogens such as mycobacteria. Corticosteroids act via increased production of the inhibitory molecule interleukin-10. This molecule inhibits activation of the transcription factor NF-kB, which mediates many immune functions including cytokine synthesis. Corticosteroids decrease lymphocyte proliferation, inhibit T-cell-dependent immunity, and decrease cytokine gene transcription.

In a retrospective study of 66 cats that underwent renal transplantation, 6 died because of infection. Three cats had systemic infections (actinobacillosis, mycobacteriosis, and toxoplasmosis), 2 had pyelonephritis, and 1 had bacterial septicemia associated with a retroperitoneal abscess. The cat with mycobacteriosis was described only in passing, as it was not the focus of the report. Therefore, information regarding this previous case is incomplete. Infection apparently developed 11 months after transplantation and was disseminated, but the type of mycobacterial infection was not reported. Mean cyclosporine concentration in this cat was 875 ng/mL, which is substantially higher than the currently recommended target range of 300 to 500 ng/mL. Acute fatal toxoplasmosis following transplantation in 3 cats and a dog has also been reported.

Mycobacterial infections ranging from asymptomatic to fatal can develop in human transplant recipients, but nontuberculous infections are uncommon, and disseminated disease attributable to nontuberculous mycobacteria is rare. In a retrospective study of 1,219 human renal transplant recipients in the United States, 10 were reported to have developed mycobacterial infections. In 7 of these patients, infection was caused by M tuberculosis. Nontuberculous mycobacteria accounted for infections in the remaining 3 patients (MAC in 2 and M marinum in 1). Mycobacterium avium complex has also been reported rarely as a cause of localized infection in human beings with lung and bone marrow transplants and has been reported as a cause of disseminated disease in a human renal transplant recipient. In contrast, disseminated MAC infection is the most common systemic bacterial infection in human beings with acquired immunodeficiency syndrome (AIDS) in developed countries. Up to 25% of all human beings with AIDS will acquire a MAC infection during their lifetimes.

In summary, this report describes a confirmed, rare form of disseminated nontuberculous mycobacterial infection in a cat that had received a renal transplant and had acceptable serum cyclosporine concentrations. Because of immunosuppression in cats that have undergone renal transplantation, rare infectious diseases should be considered in the differential diagnosis after more common diseases have been excluded. It is likely that these rare infections will be identified more frequently as the number of cats undergoing renal transplantation increases.

References


Neoral, Novartis Pharmaceuticals Corp, East Hanover, NJ.


