Systemic candidiasis in a dog

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- *Candida albicans* is a normal fungal inhabitant of the gastrointestinal, upper respiratory, and genital mucosae of dogs.
- Opportunistic infections in dogs may develop as a result of breaks in the normal mucosal barrier, immunosuppression, and treatment with broad-spectrum antimicrobials.

An 11-year-old 17.5-kg (38.5-lb) spayed female Scottish Terrier was evaluated at the **Virginia-Maryland Regional College of Veterinary Medicine (VMRCVM)** because of vomiting with hematemesis, diarrhea including melena, and anorexia of 5 days' duration. Diabetes mellitus had been previously diagnosed, and the dog was receiving human-recombinant NPH insulin (1.3 U/kg [0.59 U/lb], SC, q 12 h) but apparently remained poorly regulated. The dog had iatrogenic hypoadrenocorticism secondary to mitotane treatment of hyperadrenocorticism and was receiving fludrocortisone and dietary salt supplementation prior to the onset of vomiting. Also, a diagnosis of subclinical chronic renal failure had been made in this dog. Results of urinalysis performed prior to referral were consistent with a bacterial urinary tract infection. Treatments administered during the 24 hours prior to referral included IV fluids, regular insulin (0.2 U/kg [0.09 U/lb], IM, q 8 h), cefazolin, enrofloxacin, ampicillin, and metoclopramide.

On physical examination at the VMRCVM, the dog was recumbent, febrile (40.5°C [104.9°F]), and tachypneic (40 breaths/min) with increased respiratory effort. Tachycardia (180 beats/min), an irregular heart rhythm, and weak femoral pulses were detected. The mucous membranes were injected, and the capillary refill time was estimated to be 1 second. Signs of pain were elicited on palpation of the cranial portion of the abdomen. A grade 2 of 6 holosystolic murmur (which had been noted for several years) was ausculted over the left fourth intercostal space.

Diagnostic evaluation at the VMRCVM included a CBC, serum biochemical analyses, urinalysis, bacteriologic culture of urine, thoracic radiography, abdominal ultrasonography, and electrocardiography. Diabetic ketoacidosis was diagnosed on the basis of findings which included hyperglycemia, glucosuria, ketonuria, and metabolic acidosis. Also, results of the CBC were indicative of inflammation, and serum biochemical analyses revealed high amylase and lipase activities; these findings, in combination with signs of pain elicited on palpation of the cranial portion of the abdomen and ultrasonographic detection of an enlarged hypoechoic pancreas, were diagnostic of acute pancreatitis. Consolidation of the right middle lung lobe was identified via thoracic radiography, which was consistent with aspiration pneumonia. The iatrogenic hypoadrenocorticism was poorly controlled; glucocorticoid and mineralocorticoid supplementation had not been given in the preceding 5 days, which resulted in hyperkalemia (serum potassium concentration, 7.9 mEq/L; reference range, 3.4 to 4.6 mEq/L) and contributed to metabolic acidosis (CO_2 concentration, 5 mEq/L [reference range, 16 to 33 mEq/L] and anion gap, 39.9 mg/dL [reference range, 7.0 to 20.0 mg/dL]). Atrial fibrillation was diagnosed electrocardiographically but resolved after correction of electrolyte and acid-base abnormalities. The dog was azotemic and hyperphosphatemic (BUN, 62 mg/dL [reference range, 8 to 27 mg/dL]; serum creatinine concentration, 4.2 mg/dL [reference range, 0.6 to 1.4 mg/dL]; and serum phosphorus concentration, 7.6 mg/dL [reference range, 2.6 to 6.0 mg/dL]), and historical serum biochemical results and isosthenuria were consistent with chronic renal failure. Pyuria, bacteriuria, and bilateral renal pelvis dilation were observed ultrasonographically and supported a diagnosis of pyelonephritis.

To correct the electrolyte abnormalities and acidosis, the dog was administered physiologic saline (0.9% NaCl) solution (with bicarbonate initially) IV. A central venous catheter was placed in the left jugular vein, and another catheter was maintained in peripheral veins throughout hospitalization. A urinary catheter was placed to allow quantification of urine production, as it had been suspected to be inadequate prior to referral. A constant rate infusion of regular insulin was administered to treat diabetic ketoacidosis; dextrose was administered concurrently when blood glucose concentration was < 250 mg/dL (as indicated via blood glucose monitoring performed every 1 to 2 hours). Hydrocortisone was given via constant rate infusion (0.4 mg/kg/h [0.18 mg/lb/h]) for management of the hypoadrenocorticism.[1,2] Oxygen was administered via a nasal catheter. Ampicillin sodium-sulbactam sodium[a] (a broad-spectrum antimicrobial) was given IV (22 mg/kg [10 mg/lb], q 8 h) for management of aspiration pneumonia and probable pyelonephritis. The dog was treated with nebulized saline solution. On the day of initial evaluation (day 1), 136 mL of fresh frozen plasma was administered IV because of acute pancreatitis. Another transfusion of heparinized fresh frozen plasma (128 mL of plasma with 75 U/kg [34.1 U/lb] of heparin) was administered on day 2. After that, the dog received a low-dosage heparin treatment (75 U/kg, SC, q 8 h) for 5 days to minimize the potential for development of disseminated intravascular coagulation.

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Prothrombin time and activated partial thromboplastin time (evaluated prior to the administration of heparin) were within reference ranges.

During the following 36 hours, gradual clinical improvement was noted. Pyrexia resolved on day 3, and because urine production had been adequate, the urinary catheter was removed. Abnormalities in serum electrolyte concentrations and acid base status had resolved, and values were maintained within reference limits; ketonuria had also resolved, and moderate glycemic control was achieved. On day 3, nutrition was provided parenterally (partial parenteral nutrition; 20% lipid and 8.5% amino acid solutions with Vitamin B complex) through the central venous catheter. By day 5, results of a CBC indicated resolution of the left shift, and evaluation of thoracic radiographs confirmed that the aspiration pneumonia was resolving. Nasal administration of oxygen was discontinued, but other treatments were continued. Thrombocytopenia, prolongation of the activated partial thromboplastin time, and positive results of a D-dimer test were noted on day 5, which were consistent with disseminated intravascular coagulation. Because vomiting resolved on day 5, water and subsequently small amounts of food were offered to the dog starting on day 7. Partial parenteral nutrition was continued to meet the dog's resting energy requirement.

On day 9, the dog developed a persistently high rectal temperature (39.4°C [103°F]). Results of a CBC indicated neutrophilia (22,600 segmented neutrophils/µL; reference range, 460 to 17,800 neutrophils/µL) with a left shift (band neutrophils, 532/µL; reference limit, 0 band/mL). Abdominal ultrasonography was performed and revealed partial resolution of the pancreatitis and persistent bilateral renal pelvis dilation. Partial parenteral nutrition was discontinued; the central and peripheral venous catheters were removed, and the tips were collected for culture. Cystocentesis was performed, and a sample of urine was submitted for urinalysis and culture. The urinalysis revealed pyuria and yeast organisms with hyphae. Treatment with fluconazole[b] (5 mg/kg [2.3 mg/lb], PO, q 24 h) was initiated, and pyrexia resolved within 36 hours. A single blood sample for bacteriologic culture was obtained 24 hours after initiation of the fluconazole.

Candida albicans was obtained after culture of urine and the central and peripheral venous catheters. Because of the association of candidiasis with cardiac infections in humans,[3] an echocardiogram was performed. Echocardiographic findings suggested mitral and tricuspid valve regurgitation associated with endocardiosis, which could have been the explanation for the long history of a murmur. In addition, a large mass (most consistent with a thrombus) was identified in the right atrium (**Fig 1**). Treatment with low-molecular weight heparin[c] (2,500 units, SC, q 24 h) was begun to prevent further thrombus formation. Low-molecular weight heparin was selected, because it can be given SC once daily by the owners at home, and its use may be associated with a lower incidence of adverse effects than that associated with administration of unfractionated heparin.[4]

After 72 hours of fluconazole therapy, the dog was doing well clinically. At discharge, the dog was fed a low-fat diet and was receiving amoxicillin-clavulanic acid, fluconazole, prednisone, fludrocortisone acetate, and salt supplement PO and NPH insulin and low-molecular weight heparin SC. Thirty-six hours after discharge from the VMRCVM, the patient died at home. The owners described the sudden onset of dyspnea while the dog was lying in bed, which was followed shortly by death.

A postmortem examination was performed approximately 18 hours later. Findings included pulmonary artery thrombosis, steroid hepatopathy, absence of islets of Langerhans in the pancreas, adrenal cortical hypoplasia, glomerulonephritis and lymphoplasmacytic interstitial nephritis, and mild endocardiosis. Tissue samples for bacteriologic and fungal culture were not obtained, but histologic examination of tissues stained with periodic acid-Schiff stain revealed *Candida* organisms in the pulmonary artery thrombus, pancreas, liver, spleen, and heart and attached to the renal capsule (**Fig 2**).

Of the *Candida* spp, *C albicans* is most commonly identified in humans.[5,6] The yeast form of the organism is small, spherical, and reproduces by budding. Pseudohyphae are also produced, which are chains of elongate yeast separated by constrictions. Both the budding yeast form and pseudohyphae may be identified in tissue samples.[7] *Candida albicans* is a normal

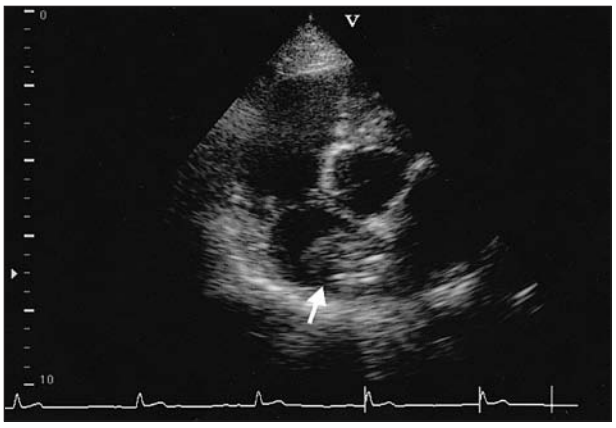

Figure 1—Left cranial, parasternal echocardiographic image of right ventricular inflow in a dog with systemic candidiasis. Notice the thrombus in the right atrium (arrow).

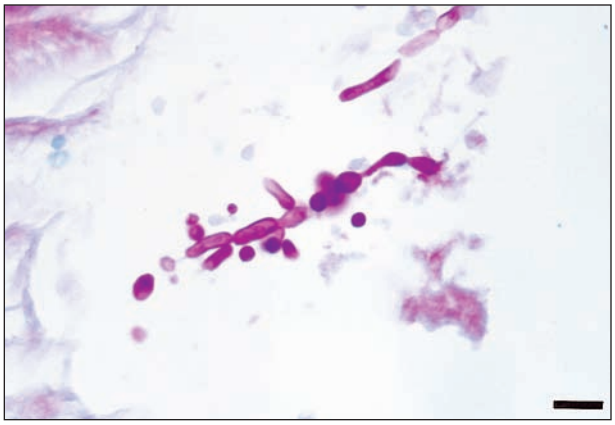

Figure 2—Photomicrograph of a portion of the renal capsule of a dog with systemic candidiasis. Pseudohyphae of *Candida albicans* are evident. Periodic acid-Schiff stain; bar = 25 µm.

fungal inhabitant of the gastrointestinal, upper respiratory, and genital mucosae of dogs and has been cultured from the ears, nose, oral cavity, and anus of clinically normal dogs.[7] Breaks in the mucosal barrier may result in opportunistic infections.[7]

In humans, *Candida* spp are the fourth most common cause of nosocomial infections.[6] Several of the risk factors for candidiasis that have been identified in studies in humans were present in the dog of this report, including diabetes mellitus, the placement of IV and urinary catheters, administration of broad-spectrum antimicrobials and corticosteroids, and provision of nutrition parenterally.[6-9] Venous catheters (particularly central venous catheters) are associated with increased risk for infection by *Candida* spp.[6,10-12] Precautions were taken to prevent a catheter-related infection, such as placement of catheters via a sterile technique, replacement of bandages and administration sets every 48 hours, and administration of nutrition parenterally through a designated port.

Urinary catheters may also serve as a portal for infection.[6,13] In the dog of this report, a urinary catheter was placed to allow quantification of urine output in the initial 48 hours after admission. Glucosuria resulting from diabetes mellitus may increase the risk of urinary tract infections, including those caused by *Candida* spp. Furthermore, diabetes mellitus diminishes host resistance as a consequence of impaired phagocytic activity of WBCs.[13]

Several of the medical treatments used in the dog of this report have been associated with an increased risk of candidiasis. Administration of broad spectrum antimicrobials may alter normal bacterial flora, particularly in the gastrointestinal and lower urogenital tracts, allowing colonization by *Candida* organisms.[7,9,13] Treatment with broad-spectrum antimicrobials prior to referral and during hospitalization (for the management of aspiration pneumonia and pyelonephritis) may have predisposed the dog of this report to a fungal infection. Corticosteroid administration may compromise gastrointestinal tract integrity and promote development of secondary infections via translocation of microorganisms across the gastrointestinal mucosa.[9] Additionally, corticosteroids can be immunosuppressive, but the dose of hydrocortisone administered via constant rate infusion to manage hypoadrenocorticism in the dog of this report was not likely to have been immunosuppressive. Parenteral administration of nutrition is also an important risk factor for the development of candidemia.[9,11] In addition to microbial invasion at the catheter site, infections may result from infusion of contaminated fluid or contamination of the extension set.[14]

In veterinary medicine literature, information regarding disseminated candidiasis is limited.[7,15-17] Clinical signs of generalized infections have been reported[7] and include pyrexia and erythematous skin lesions; myositis, osteomyelitis, and ocular infections have also been described. One report[15] of naturally occurring disseminated candidiasis involved a Rottweiler puppy with parvoviral enteritis; on postmortem examination, the puppy had pyogranulomatous lesions containing *Candida* organisms throughout multiple organs. Another report[16] described a dog with systemic candidiasis in which peripheral lymph node involvement with a fistulous tract connected to an area of osteomyelitis in the humerus was observed.[16] In another dog, *Candida* spp and *Aspergillus fumigatus* were identified post mortem via fungal culture of tissue from the lung and kidneys, although fungal organisms were not identified histologically.[17] Care must be used in the interpretation of results of fungal cultures that are performed with tissues obtained at necropsy because of the potential for contamination.[7] Localized candidal infections are reported to occur in chronically immunosuppressed dogs and include infections of the skin and nailbeds,[18-21] urinary tract,[22] ears,[23-26] and gastrointestinal tract.[27-31]

In humans, the clinical signs of systemic candidiasis are often nonspecific. Pyrexia is common,[5,9,12] and leukocytosis is detected in ≤ 50% of cases[9]; patients may present in septic shock.[5,12] Other clinical signs vary depending on the organ systems involved.[5,12] Alternatively, some individuals do not show signs of serious illness.[9] The dog of this report had acute onset of pyrexia with leukocytosis characterized by neutrophilia with a left shift; because of these clinical signs, cultures of urine and venous catheters were performed, and *C albicans* was identified.

Candidal infections may be diagnosed histologically or from the results of fungal culture. *Candida* spp grow well on blood agar and, therefore, are often isolated from samples submitted for bacteriologic culture.[7] Candidemia is diagnosed in humans on the basis of positive culture results of blood and samples obtained from multiple IV catheters or identification of histopathologic lesions.[5,12] In the dog of this report, bacteriologic culture of urine and 2 venous catheters resulted in growth of *Candida albicans*, and the organism was identified histologically from postmortem tissue samples; from such findings, it is not possible to know whether candidemia or candiduria is the primary problem.[13]

Fluconazole is often selected as the first-line treatment because it is effective,[10] has a low incidence of adverse effects,[10,11] and is cost-effective.[11] Although controversy exists regarding the need for IV administration of fluconazole in the initial treatment of candidemia, oral administration is generally thought to be effective. It is recommended that all IV catheters are removed or replaced in humans with candidemia, because catheters favor persistence of candidemia[32]; however, the benefit of this remains to be proven.[33] Nevertheless, this recommendation was followed for the dog of this report; after removal of the catheters, fluconazole was administered orally, and the dog had clinical improvement. However, 3 days after initiating fluconazole treatment, the dog died (presumably as a result of pulmonary thromboembolism).

Multiple predisposing factors for pulmonary thromboembolism were identified in the dog of this report. The placement of a central venous catheter or partial parenteral nutrition administration devices are both factors that have been shown to predispose dogs to the formation of thrombi[14,34]; central venous catheters have been identified as a risk factor for *Candida*-infected intracardiac thrombosis in infants.[3] Administration of supraphysiologic doses of corticos-

teroids is a risk factor for thromboembolism,[34] but the hydrocortisone dose administered to the dog of this report was appropriate for dogs with hypoadrenocorticism.[1,2] Sepsis and disseminated intravascular coagulation that developed in the dog of this report may have resulted in a hypercoagulable state and thrombosis formation.[34,35] Additionally, glomerulonephritis (diagnosed at necropsy) may have predisposed this dog to thromboembolism.[34]

Systemic candidiasis is an uncommon condition in dogs. However, the development of pyrexia and leukocytosis in dogs with risk factors that predispose them to *Candida* spp infections warrants evaluation via microbial culture of urine and vascular catheters used in those dogs.

[a]Unasyn, Roerig Division of Pfizer Inc, New York, NY.
[b]Diflucan, Roerig Division of Pfizer Inc, New York, NY.
[c]Fragmin, Pharmacia & UpJohn Co, Kalamazoo, Miss.

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