CANINE COCCIDIOIDOMYCOSIS

Case Report
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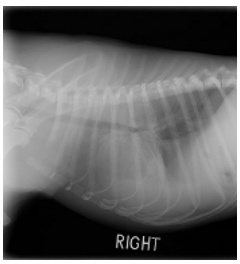
Signalment:
"Zeke"
4 year old male intact Rat Terrier
BW 7.0 kg

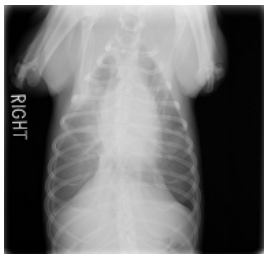
Discussion:

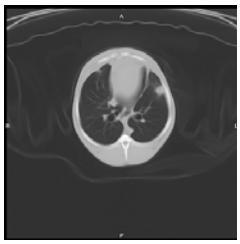
Zeke was referred to the VMSG for coughing, fever, lethargy and inappetence, which were partially responsive to antibiotic therapy (ampicillin and Baytril). Referral in-house blood panel showed leukocytosis with mature neutrophilia and monocytosis. Referral two-view thoracic radiographs (two sets, taken 8 days apart) showed nodular consolidation in the left ventral lung field and mild but progressive pleural effusion. In-house cytology of the pleural fluid reportedly showed large numbers of PMN's and mesothelial cells. Coccidioides IgM titer was negative, and IgG titer was weakly positive at <1:4.

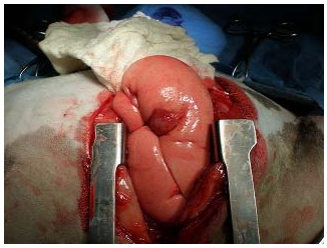
On presentation to the VMSG, Zeke was QAR with normal vital parameters. Lung sounds were decreased over the left ventral thorax. Complete cataract was noted OD. Right popliteal lymph node was enlarged and firm. On CBC/chemistry/UA, leukocytosis (41,000/μL) with mature neutrophilia (33,620/μL) and monocytosis (4,100/μL), mildly elevated ALP (211 U/L), hypoalbuminemia (1.9 g/dL) and hyperglobulinemia (4.9 g/dL) were evident. Thoracic ultrasound revealed a small volume of pleural effusion bilaterally, with a pocket of more hyperechoic fluid in the left mid thorax, and a focal nodular lesion in the peripheral left lung lobe at the level of the 6-7th intercostal space. In-house cytology of the consolidated ventral thoracic tissue and pleural effusion revealed many degenerate neutrophils and mesothelial cells, with no intracellular organism identified. Cardiac ultrasound was WNL.

Based on the above findings, foxtail migration was the highest differential, and Zeke was placed under general anesthesia for thoracic CT scan, tracheobronchoscopy and thoracotomy. On CT scan, a solitary 12 mm diameter pulmonary nodule was found in peripheral portion of the left mid ventral lung field (the left caudal lung lobe or caudal segment of the left cranial lung lobe). A small amount of pleural effusion was present. On tracheobronchoscopy, the left mainstem bronchus and the proximal left cranial and caudal bronchi were edematous and erythematous; but no luminal foreign body or purulent discharge were seen. Zeke then underwent an exploratory thoracotomy via left intercostal approach. A moderate amount of serosanguinous pleural effusion was noted during surgery. A 1 cm nodule was found on the caudal portion of the left cranial lung lobe, adhering to the left caudal lung lobe. The mediastinum ventral to the nodule was thickened, irregular and fibrotic from the lung to the pericardium to the diaphragm in the area of the pericardial ligament. The caudal portion of the left cranial lung lobe, the cranial portion of the left caudal lung lobe and a part of the mediastinum were resected and submitted for histopathology and aerobic, anaerobic and fungal cultures. A thoracostomy tube was placed for the management of post-operative pleural effusion and pneumothorax.









Peri-operative pain management was achieved with MLK (morphine/lidocaine/ketamine) IV infusion, fentanyl patch and bupivacaine intra-thoracic infusions via thoracostomy tube. Antibiotic therapy (ampicillin and Baytril) was continued. The thoracostomy tube was aspirated periodically to remove the pleural effusion, and the tube was removed on the 4th day post operatively. Histopathology results showed severe pyogranulomatous pneumonia, pleuritis and mediastinitis. Coccidioides organisms were identified in the biopsy specimens, and fungal culture confirmed *Coccidioides immitus* infection.

Etiology:

Coccidioides is a soil-borne fungus found primarily in the lower Sonoran life zone, which includes southwestern U.S., Mexico, and Central and South America. This zone is characterized by sandy, alkaline soils and high environmental temperatures, with low annual rainfalls and low elevation. *Coccidioides immitis* is limited to San Juaquin valley, while *C. posadasii* is found in all other areas. These species can only be separated by DNA analsys, and are indistinguishable on fungal culture or titer. During seasonal rainfalls, *Coccidioides spp.* germinate and produce mycelia. As the soil dries, multinucleate arthroconidia (arthrospores) develop, which subsequently become airborne under dry and windy conditions. When inhaled, arthroconidia convert into an immature spherule within 2-3 days. The spherule undergoes repeated internal divisions (endosporulation) to form a mature spherule filled with numerous endospores. The spherule gradually enlarges and eventually ruptures, releasing hundreds of endospores. Each endospore is capable of becoming a mature spherule or converts back to the mycelial form.

Coccidioidomycosis, also known as Valley Fever, is considered highly infectious, but not typically contagious. The major route of infection is inhalation, and only <10 arthroconidia are needed to produce clinical disease. Infection via cutaneous inoculation is uncommon. The incubation period is usually 1-3 weeks. After inhalation, the arthroconidia first enter the bronchioles and alveoli, and then extend into peribronchiolar tissue, eventually causing subpleural lesions. If disease progresses beyond the hilar lymph nodes, it is considered to have disseminated. Organs commonly affected by the disseminated disease include bones, eyes, heart, pericardium, testicles, brain, spinal cord, and visceral organs such as spleen, liver and kidneys. Disseminated disease usually manifests 4 months after development of the respiratory signs.

Clinical Signs:

The most common form of Coccidioidomycosis is subclinical lower respiratory tract infections. Clinically apparent respiratory disease often involves dry harsh cough, which results from hilar lymphadenopathy and/or diffuse pulmonary interstitial disease. Productive coughing may also be present as a result of alveolar infiltrates. Systemic signs of illness such as fever, inappetence, and weight loss are common.

Clinical signs associated with disseminated disease depend on the organs affected, and may include fever, anorexia, weight loss, depression, weakness, lameness, peripheral lymphadenopathy, draining skin lesions, seizures, bone or paraspinal hyperesthesia, keratitis, uveitis, and acute blindness. Congestive heart failure may be seen secondary to granulomatous pericarditis.

Diagnosis:

Common changes on the blood panel include mild nonregenerative anemia, moderate neutrophilic leukocytosis with left shift and monocytosis, hyperglobulinemia and hypoalbuminemia. Thoracic radiographs often show hilar lymphadenopathy and diffuse interstitial mixed with localized alveolar pattern. Miliary to nodular interstitial pulmonary pattern may also be seen. Pulmonary abscess formation, fibrosis, and bronchiectesis may be seen in severe pulmonary infection. Pericardial and pleural effusion may result due to right sided myocardial failure or, more commonly, due to pericarditis. Bone lesions are typically both lytic and productive.

Definitive diagnosis of Coccidioidomycosis can be made by demonstration of the organisms by cytology, biopsy or culture. On a cytology sample, the organism can be seen in unstained specimens as a large (10 to 80 μm), round, double-walled structure containing endospores. Special stains may be used for optimal visualization. Although cytology, biopsy or culture is required to make a definitive diagnosis, such procedures are often too invasive and cost-prohibitive. In many cases, a reasonably reliable presumptive diagnosis can be made based on the history, clinical findings, and serologic test results. IDEXX laboratory utilizes agar gel immunodiffusion (AGID) which detects the early IgM titer and the later and sustained IgG titer. Four scenarios are possible: 1) IgM negative/IgG negative or <1:4, consistent with no infection or early infection; 2) IgM positive/IgG negative or <1:4, consistent with early or mild infection; 3) IgM positive/IgG ≥ 1:4, consistent with early or active infection, 4) IgM negative/IgG ≥1:4, consistent with previous or current infection. Higher IgG titer indicates a more severer disease or a higher likelihood of dissemination. Negative serology in an infected individual reflects fulminating disease or anergy.

Coccidioides spp. grow readily on common fungal culture media and blood agar, but culturing is not recommended as mycelial growth is highly infectious to humans and animals, and microbiology staff should be warned of potential for this organism if suspected.

Management:

Treatment for canine Coccidioidomycosis typically involves long-term antifungal therapy. Ketoconazole (5-10 mg/kg PO BID) has traditionally been the initial drug of choice. The newer azoles, itraconazole (5 mg/kg PO BID) and fluconazole (5 mg/kg PO BID), are now available at reasonable costs at compounding pharmacies, and thought to have fewer side effects and to be more efficacious for treatment of Coccidioidomycosis in people, although no controlled studies have been done in dogs. Fluconazole is considered to have the best tissue penetration and is recommended in cases with CNS involvement. Potential side effects of the azoles include hepatotoxicity, GI intolerance and skin reactions. Treatment for 3 to 6 months beyond resolution of clinical signs and normalization of titers is recommended for pulmonary infection, while lifelong treatment is recommended for dogs with disseminated disease.

Amphotericin B may be used at a dose of 0.4-0.5 mg/kg IV q48-72h if a patient does not tolerate azoles. However, due to its narrow therapeutic index, nephrotoxicity and need for IV administration, it is not commonly used. The drug may also be administered SQ, but its efficacy has not been evaluated in treatment of canine Coccidioidomycosis. The new lipid-encapsulated formulation is available and is reportedly less nephrotoxic; however, it is often cost-prohibitive for general use.

Chitin synthesis inhibitors are newer antifungal agents that also interfere with fungal cell wall synthesis. Lufenuron (Program), the drug licensed for control of fleas in dogs and cats, has been used at 5 mg/kg PO SID; however, its efficacy in treatment of Coccidioidomycosis is controversial.

Prognosis:

The prognosis for localized respiratory Coccidioidomycosis is good even without treatment. Dogs with disseminated disease; however, will usually die or have to be euthanized shortly after the diagnosis, if not treated. More than 90% of dogs with disseminated disease respond positively to the azole therapy; however, relapse is common, and a long term maintenance therapy is required in many cases. Complete recovery rates vary with the severity of the disease and degree of dissemination, ranging from 90% with only pulmonary involvement to 0 % with multiple bone involvement. An overall recovery rate has been estimated to be 60%. CNS involvement carries poorer prognosis because of difficulty of drug penetration.

Follow-up:

Zeke's clinical presentation is considered unusual for canine Coccidioidomycosis as he did not have significant positive titers (IgM negative/ IgG<1:4) nor classic radiographic signs (lack of hilar lymphadenopathy but presence of pleural effusion). He was started on itraconazole 50 mg PO SID and lufenuron 50 mg PO SID for treatment of Coccidioidomycosis; Baytril 45.4 mg PO BID and amoxicillin 250 mg PO TID were continued for treatment of possible secondary bacterial infection. Tramadol 12.5 mg PO TID was prescribed for post-operative pain control. He was discharged after 7 days of hospitalization (6th day post-op). He developed a dry cough the night before discharge. Two-view thoracic radiographs showed minimal amount of pleural fluid/thickening at the surgical site and no evidence of pneumonia. Recheck appointment with the primary veterinarian was recommended in several days to assess recurrence of pleural effusion, at which time, his cough was still persisting. Typically even if the medical therapy works for this disease, it takes 2-4 weeks for the owner to note any clinical improvement. Chemistry panel was recommended in 2 weeks, then monthly for the first 4-6 months, to monitor for potential itraconazole-induced hepatotoxicity.

References:

1) Davidson AP: Coccidioidomycosis and Aspergillosis. In: Textbook of Veterinary Internal Medicine. 6th ed. St. Louis: Elsevier Inc. 2005: 690-699.
2) Greene RT: Coccidioidomycosis and Paracccidioidomycosis. In: Infectious Diseases of the Dog and Cat. 3rd ed. St. Louis: Elsevier Inc. 2006: 598-608.