

Coccidioidomycosis in Animals-2010

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Introduction

Coccidioidomycosis (Cocci), otherwise known as Valley Fever, San Joaquin Valley Fever, or desert fever is caused by the dimorphic fungi, *Coccidioides immitis* and *Coccidioides posadasii*. Cocci occurs in most mammal species, but the greatest numbers of reported cases are in humans and dogs [1]. It is prevalent in the southwestern United States and Mexico, and is the most commonly recognized cause of systemic mycosis from this geographic area. In a study conducted to evaluate the incidence of cocci in dogs from the Arizona counties, Pima and Maricopa, 28% were infected by the age of two [1]. Clinical features include acute and chronic pneumonia and disseminated disease with a variety of extra-pulmonary lesions including meningitis. Diagnosis may be difficult in some cases, and is usually made based upon positive serologic tests for antibodies or visualization of spherules in the tissues. Antigen detection has been recently introduced but its role in diagnosis in animals remains to be established. Amphotericin B is the treatment of choice for most severe cases and fluconazole or itraconazole in mild cases or following clinical improvement in response to amphotericin B.

Epidemiology

Figure 1. Endemic area in North America



Cocci is endemic in the hot, semi-arid southwestern United States, northern Mexico, and Central America. The etiological agents include *Coccidioides immitis*, most often seen in California or *Coccidioides posadasii*, in Arizona. Cocci grows in the soil as mycelia with lateral growing “barrel” shaped arthroconidia. Cocci lies dormant in the mycelial phase during times of drought, but heavy rain causes germination of the arthroconidia and production of more mycelia. Infection occurs most often during dry weather when conidia are easily dispersed following periods of heavy rain [2,3]. Wind or disturbances to the soil also promote exposure. Though most cases occur within the endemic areas, cocci has been detected in

humans or animals that had traveled to endemic areas. Cases also have been reported in subjects with no exposure to the endemic areas, presumably caused by exposure to dust on cars that had been driven through in endemic areas [4].

Pathogenesis

In nearly all cases infection occurs by inhalation of the arthroconidia. Fewer than ten conidia can initiate infection [5]. Once inhaled, arthroconidia are distributed through the alveoli, where they are phagocytosed and develop into spherules, which then enlarge and undergo endospore formation. Once rupture of spherules occurs, endospores are released into surrounding tissues, and spread locally or disseminate hematogenously to extra pulmonary sites. These endospores then develop into spherules and continue the cycle, until host control is achieved [2,6,7]. The time between inhalation of arthroconidia to formation of spherules is approximately

48-72 hours; however, clinical signs of respiratory illness usually do not manifest for 2 or more weeks [2,6]. Infection also may occur by accidental inoculation into the skin following sharp injuries with contaminated instruments [8]. Coccidioidomycosis is not communicable [7] except in rare cases in humans in which transmission has occurred by transplantation of an infected organ [9] or accidental inoculation into the skin. Reactivation of latent disease is thought to occur in immunosuppressed patients as well [9].

Cell mediated immunity is the key mechanism of defense in coccidioidomycosis [6]. T lymphocytes recognizing *Coccidioides* antigens are produced during the first four to six weeks of infection and activate macrophages to halt progression. In humans, those with impaired cell mediated immunity experience severe forms of progressive coccidioidomycosis. Those conditions that predispose humans to advanced cocci are AIDS, solid organ transplantation, immunosuppression, malignant conditions, pregnancy, diabetes, old age, and African Americans or Filipinos race or ethnicity. Though antibodies are produced in cocci, they are not believed to play a significant role in recovery from the infection [6,10].

Risk Factors

In dogs, factors that place an animal at higher risk of cocci are youth (<6 years old), large breed, and working and sporting breeds. Dogs that are outdoors during the day are five times more likely to become infected [11]. Increased roaming space and walking in the desert increase risk of infection. Though infection is common in dogs from endemic counties, most are not symptomatic [1]. In cats there appears to be no breed predilection; however, middle aged cats experience cocci more commonly. Feline leukemia and feline immunodeficiency virus are not thought to increase cat's susceptibility to cocci [12].

Clinical Presentation

Dogs with cocci present with a variety of signs and symptoms, most common of which are fever, cough, anorexia, and lethargy. Between 60% and 80% of dogs exhibit pulmonary involvement alone [5,13], while cats are more likely to exhibit findings of disseminated cocci [12].

Primary pulmonary.

In dogs a chronic dry or moist cough, often described as retching, fever of 102.5 F (39.4 C), anorexia, weight loss, listlessness, and depression are prominent findings. Cough can be caused by lung involvement or constriction of the trachea due to enlarged mediastinal and/or hilar lymph nodes. Radiographic abnormalities are present in about three quarters of cases, of which about half lack respiratory signs [13]. Radiographs usually show hilar or mediastinal lymphadenopathy (50 to 75%) with or without pulmonary infiltrates [12-14]. Hilar or mediastinal lymphadenopathy, although not specific for coccidioidomycosis, may be the basis for empirical treatment in suspected cases [14]. Lung involvement may be characterized by consolidation, diffuse interstitial or miliary infiltrates, or pulmonary nodules [13,14]. Only 25% of cats with cocci present with respiratory

Figure 2. Chest radiograph



signs [12], even though lung involvement was noted at autopsy in nearly all fatal cases [5]. Radiographic findings in cats include hilar lymphadenopathy, pneumonia, pleural effusions and pleural thickenings [12]. These findings indicate that radiography may be useful in the absence of respiratory signs or symptoms in dogs and cats in which cocci is suspected.

Disseminated. Disseminated disease in dogs commonly presents as lameness due to osteomyelitis [4,13,15,16]. Appendicular bone involvement is most common. Additional signs of disseminated disease include draining tracts in skin, bone tenderness and swelling, and regional lymphadenopathy. Signs of dissemination to the CNS include seizures, ataxia, behavioral changes and coma. Cardiac involvement manifests as heart failure, arrhythmia, syncope, and sudden death.

In cats, draining skin lesions, abscesses, subcutaneous masses, and regional lymphadenopathy are the most prevalent signs, found in over half of cases [12]. Other sites of dissemination include musculoskeletal lesions, presenting as lameness in most cases [12]. Neurological and ocular abnormalities occur in about 20% of cases, and present as blindness, uveitis, iritis, paresis, seizures, and impairment of coordination.

Diagnosis:

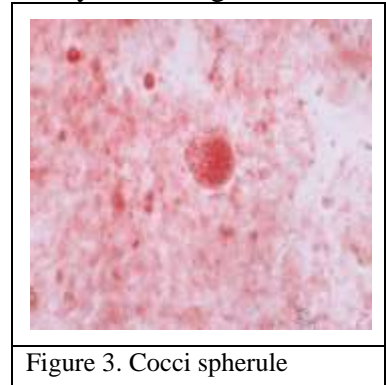
To diagnose cocci, one must first suspect it: in one report the diagnosis had been considered in only 13% of cases prior to referral [13]. The clinical signs resemble those in a variety of other infectious, malignant, and inflammatory or immunologic conditions, further complicating the diagnosis.

Serology. Demonstration of antibodies to *Coccidioides* is the basis for diagnosis of most cases [12,13]. For example, 71% of cases in dogs in the UC- Davis series were diagnosed based on serology [13]. The agar gel immunodiffusion (AGID) method detects IgM antibodies against the tube precipitin antigen (AGID-TP) and IgG antibodies to the complement fixation antigen (AGID-CF). In the UC-Davis experience, AGID was positive in all 20 canine cases that were tested [13], showing IgG antibodies alone or combined with IgM in 19 and IgM antibodies alone in one case. AGID-CF titers were $\geq 1:16$ in 40% of the cases, and did not correlate with severity of infection. Of cats with coccidioidomycosis, the diagnosis was based on cytology, histology or culture in 71% and serology in 29% of cases in one report, but of those in which AGID was performed, IgG antibodies were detected in all and IgM antibodies in 83% [12].

Detection of antibodies may not distinguish active from past infection, however. In a prospective study, 60 of 485 dogs had positive AGID results, of which 70% had clinical cocci [1]. Overlap occurred in the AGID titers in clinically infected and sub-clinically infected cases. Also, those investigators indicated they have observed dogs in which positive AGID and clinical signs were present, yet necropsy revealed a different diagnosis and cocci did not contribute to the death of the animal [17]. Furthermore, a negative AGID test does not rule out cocci. If the initial test is negative, repeat testing and performance of other diagnostic tests may be needed to make the diagnosis.

Despite the limitations of antibody testing, in the appropriate clinical setting, including cases in which thoracic adenopathy is present radiographically, titers of 1:16 or higher are highly suggestive of cocci [10]. However, one third of dogs with clinical cocci had titers of a least 1:16 compared to 9.5% of sub-clinically infected dogs, demonstrating overlapping titers [1]. As with all tests, clinical judgment is required in interpretation of serology for diagnosis of coccidioidomycosis.

Direct microscopy and culture. A definitive diagnosis can be obtained by observing cocci spherules or growing the organism from the tissues or body fluids. Pathology is characterized by pyogranulomatous inflammation. Spherules are large, round, thick walled structures that vary in size from 20 to 100um and contain endospores of 3 to 5um diameter size [17]. Immature spherules without endospores can be mistaken for other fungi or debris. The sensitivity of these methods, however, is unclear. In one study, seven of 24 (29%) dogs were diagnosis based upon visualization of spherules or isolation of the organism [13]. Samples taken from draining skin lesions and pleural fluid are more likely to contain spherules than are respiratory samples.



In some instances, culture may yield the only laboratory basis for diagnosis [13]. Laboratory personnel are at risk for exposure when attempting to culture the organism [18], and for that reason culturing should be done in laboratories skilled in and equipped for the safe handling of *Coccidioides*. Up to 3 weeks may be required for isolation of the organism [17].

Antigen Detection. *Coccidioides* antigen detection is useful for diagnosis of cocci in humans, positive in about 70% of cases [19,20]. Antigen was detected in the urine or serum in only 19% of cases in dogs, however (Wheat, unpublished). In that study the diagnosis was based upon AGID in 96% and microscopy in only 4% of cases. Reasons for the lower sensitivity in dogs than humans may include lesser severity of infection, as most of the humans were immunocompromised and had culture proven disease. A study is in progress to determine the role of antigen detection in proven cases based on demonstration of spherules in body fluids or tissues.

Treatment:

Antifungal therapy includes amphotericin B and azoles. Amphotericin B is effective, but must be given intravenously and causes many side effects, including renal impairment. It is reserved for cases with rapidly progressing disease or who are unable to take or have failed azoles in humans [3]. Treatment guidelines for use of amphotericin B in animals are available in the Veterinary Drug Handbook [21] and are reviewed elsewhere [5].

Fluconazole is the treatment of choice in most cases and can be given intravenously or orally. Fluconazole crosses the blood brain barrier and penetrates ocular fluids making it the medication of choice in patients with CNS or eye involvement [17]. Itraconazole is only available for oral administration. It concentrates in the skin and may be preferred in patients with cutaneous [22] or bone lesions [3]. Itraconazole is not as well tolerated as fluconazole and is more expensive. Both may cause hepatotoxicity.

The role of the newer azoles (posaconazole, voriconazole) is uncertain, but they are active against *Coccidioides* and have been used successfully in a small number of cases in humans. Nikkomycin, a chitin synthase inhibitor, is active *in vitro* and was effective in experimental infection but is not commercially available. The echinocandins, which work by inhibiting glucan synthase, show *in vitro* activity and efficacy in experimental models but have not been used enough in patients to assess their effectiveness.

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