Clinical Features of Cats Diagnosed with Coccidioidomycosis in Arizona, 2004-2018

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Abstract

Objectives: The goal of this study was to describe the clinical presentation, diagnosis and treatment of coccidioidomycosis in cats residing in a region endemic for *Coccidioides* species.

Methods: A retrospective review of records was performed at both primary and tertiary care veterinary practices in Tucson and Phoenix, AZ. Data collected included signalment, clinical signs, physical exam findings, diagnostic test results, treatment and outcome.

Results: Fifty-one feline cases were identified from six different veterinary hospitals. Cats presented with clinical signs and laboratory abnormalities similar to what has been seen in dogs, including respiratory illness (20/51), neutrophilia (24/31), monocytosis (17/31), and hyperglobulinemia (16/30). However, cats at diagnosis were typically significantly ill, with 31/51 having disseminated infection, most commonly to the skin (n=22). Additionally, 43/44 cats that had serum antibody tests performed were positive, and median titer at diagnosis was 1:32 (range 1:4 – ≥1:256). Serum antibody titers reduced significantly ($P \leq 0.001$) in cats that responded to treatment compared with cats that did not clinically improve. 40/46 cats that were treated with oral flucaonzole

responded and did not require additional therapy. Fourteen cats developed recurrent disease and all but 1 had antifungal therapy successfully reinstituted.

Conclusions and relevance: Coccidioidomycosis is a disease of concern for cats residing in the region endemic for *Coccidoides* spp. Disease is most often disseminated at the time of diagnosis, possibly due to delays in presentation for care and recognition of the infection. Suspicion of disease, serum chemistries, blood cell counts, presence of antibody, and imaging aid in diagnosis of coccidioidomycosis in cats. Serum antibody reduction during treatment frequently correlated with an adequate response to medication. Consideration of coccidioidomycosis as a cause of illness will lead to earlier diagnosis and potentially better treatment outcomes in cats.

Introduction

Coccidioidomycosis, also known as Valley Fever, is a fungal disease prevalent in semiarid regions of the western hemisphere. In the United States, endemic regions are found in Arizona, California and parts of New Mexico, Texas, Nevada and Utah.[1,2] Recently, several locally acquired human cases were identified in eastern Washington state.[3,4] The causative agents are the dimorphic fungi *Coccidioides immitis* and *C. posadasii*, with no noteworthy variances in the disease course between the two species.[5]

Infection is acquired by inhalation of the 3 – 5 μm arthroconidia (spores) which grow from mycelia in the soil and are very easily aerosolized by natural or human-caused disturbance, such as digging, wind or construction.[1] In the lungs, the tiny spores easily reach the distal airways and rapidly transform into the parasitic spherule phase. Rapid expansion of the fungus by endosporulating spherules results in a respiratory infection ranging from subclinical to severe. In hosts that are unable to control the infection early, *Coccidioides* species may disseminate via the bloodstream to virtually any extrapulmonary tissue.[1,6]

Published literature on dogs with coccidioidomycosis cites a wide variety of clinical presentations, dependent on involved organ systems, but coughing, lethargy and anorexia are the most common features, followed by lameness from osteomyelitis.[6-8]

Typical clinicopathological findings in dogs include hyperglobulinemia, monocytosis and hypoalbuminemia.[9,10] Less information is available about the disease in cats. At one time, cats were believed to be resistant to infection by *Coccidioides* species;[11] however, published case reports have proven this to be incorrect.[5,11-13] As the historic incidence of coccidioidomycosis is not known in cats, it cannot be ascertained whether infections are increasing or whether veterinarians are more aware of the disease in this species.

The purpose of this retrospective study was to learn more about how coccidioidomycosis presents, progresses, and is treated in the feline species.

Materials and Methods

Study Design and Case Selection: A retrospective record review of feline coccidioidomycosis cases was performed at six veterinary practices in Arizona - three feline only practices, two specialty referral hospitals and one general small companion animal practice (four in Tucson, two in Phoenix). Records between 2004 and 2018 (where available) were searched for potential cases. All database searches were performed by staff at each clinic, except for one specialty hospital in Tucson. At that location, investigators performed the database search for the available years (2011 to 2018) using the search terms “coccidioidomycosis,” “cocci,” and “Valley Fever.” Cases were included in this study if they were definitively diagnosed via cytology, histology

or culture or if they had at least two of the following: clinical signs that can be related to coccidioidomycosis in other species, positive anticoccidioidal antibody serology, clinicopathological changes similar to canines and radiographs supportive of the diagnosis. Cases were excluded if inadequate information was available and if the diagnosis was inconclusive.

Data Collection: Medical records were reviewed by one of the authors. The data collected included signalment, lifestyle, clinical signs, complete blood cell count (CBC), serum chemistries, radiographs or other imaging, coccidioidal serology, treatment and outcome. As multiple diagnostic laboratories were used, clinicopathological data was collected as the laboratory interpretation rather than the raw data. Coccidioidal serology was performed by commercial laboratories, which used agar gel immunodiffusion (AGID) to identify antibodies (IgG and IgM) and quantitate IgG. Semi-quantitation of IgG is obtained by serial dilution of positive serum and an endpoint titer is reported.

Statistical Analysis: Descriptive analysis of collected data was performed in Microsoft Excel (2016). Data were migrated to GraphPad Prism version 7.00 for Windows (GraphPad Software) for statistical analysis. The non-parametric Mann-Whitney U test was performed to compare titers. Significance was set at $P \leq 0.05$.

106 **Results**

107 *Case inclusion:* Fifty-one feline cases of coccidioidomycosis were included in the
108 analysis. While demographic data of the hospital populations was largely unavailable,
109 we were able to obtain estimates of patient visits for 2 hospitals (1 feline only, 1
110 specialty). For these 2 clinics, the feline coccidioidomycosis cases represented 0.23%
111 and 0.15%, respectively, of the feline patient visits.
112 *Signalment:* Most of the cats were domestic crossbreeds (n = 46, 90%). There was one
113 of each of the following breeds: Abyssinian, Himalayan, Maine Coon, Persian, and
114 Siamese. Age at diagnosis ranged from 1 year to 15.5 years (mean = 6.8 years, SD = 4).
115 There were 30 neutered males (59%) and 21 females (41%), of which all but one was
116 spayed. Most cats were reported as indoor only (n = 30), with 15 indoor/outdoor and
117 one outdoor only. Lifestyle information was unavailable for five cats. Body weights at
118 time of diagnosis ranged from 1.86 kg to 7.82 kg (mean = 4.58 kg, SD = 1.27).
119 Eighteen cats had lost weight from a previous visit while 12 cats had no weight loss.
120 Information about previous weight was unavailable for 21/51 of the cats. Five cats had
121 comorbidities that could have affected immune function. These were feline
122 immunodeficiency virus (n = 3), feline leukemia virus (n = 1) and diabetes mellitus (n =
123 1).

Clinical signs: Clinical signs at presentation are summarized in Table 1. Dermal lesions were the most commonly reported complaint (n=22, 43%), with most of those lesions described as nodular (13/22). Additional descriptions of dermal lesions included non-healing wounds (7/22) and crust or plaque-like lesions (2/22). Respiratory signs were present in 20 (39%) cats. These cats were described as having some form of respiratory distress (14/20), including tachypnea, wheezing, or labored breathing. Six of the 20 cats presented with a cough only, while 12/20 cats had both a cough and respiratory distress described. Signs associated with systemic illness, such as decreased appetite or anorexia (n=14) or fever (≥103°F or 39.4°C, n=4) were less frequently reported. Lameness, paresis or paraparesis was seen in 11 (22%) cases.

Radiography and imaging: Radiographs were acquired in 22 cats at the time of diagnosis (19 thoracic, two thoracic and skeletal and one skeletal only). One cat had a thoracic ultrasound performed and four cats had both thoracic ultrasound and radiographs performed. Results are summarized in Table 1. Half of the cats had multiple radiographic abnormalities noted. Overall, a bronchial, interstitial and/or alveolar pattern or consolidation of one or more lung lobes were noted most frequently (n = 9 [41%] each). Hilar lymphadenopathy was observed in six (27%) of the cases. Four cats (18%) had solitary lung masses/nodules and five (24%) had pleural effusion.

(Figure 1) All three cats with skeletal radiographs performed were found to have an osteomyelitis characteristic of fungal infection in a forelimb. Thoracic ultrasound showed pericardial effusion in two cats. One cat had a computed tomography scan of the thorax. (Figure X)

Hematology and Serum Chemistries: Thirty cats had serum chemistries and a CBC performed at the time of diagnosis and one additional cat had only a CBC performed. Three cats (6%) had no abnormalities noted on either the serum chemistries or the CBC. Neutrophilia was present in 24 (47%) cats, monocytosis was present in 17 (33%) cats, and hyperglobulinemia was present in 14 (27%) cats. (Table 3)

Serology: Forty-four cats had coccidioidal serology performed at the time of diagnosis and 43 were seropositive. Titers ranged from 1:4 to ≥1:256 (median 1:32). The seven cases in which serology was not performed were definitively diagnosed through cytology, histopathology or culture, as was the seronegative cat. Post-diagnosis serology results were available for 40 cats. The latest available serology result for each of these 40 cats was compared to the serology results at diagnosis, with the available follow up time ranging from 2 months to 12 years (mean = 2.76 years, SD = 2.67). The post-diagnosis serology results ranged from negative to ≥1:256 (median ≤1:4).

The 40 cats with follow up serology were divided into two groups based upon whether there was clinical improvement after treatment was initiated. Thirty-three cats were clinically improved compared with the time of diagnosis, with the follow up examination and serology occurring as early as 3 months post-diagnosis. Seven cats were clinically worse. Interestingly, all of these cats were about 1 year post-diagnosis at the time this assessment was made. On average, the cats with clinical improvement had the titer decrease by three dilutions, while cats that were not clinically better had an average increase of the titer by one dilution. There was a statistically significant difference in the change in quantitative dilutions between these groups ($P \leq 0.001$).

Clinical pathology: Cytology, histology and/or culture were performed and confirmed the diagnosis of coccidioidomycosis in 18 (35%) of the cats in the population; all but one of these cats had disseminated disease. The most common confirmed site of dissemination was to the cutaneous or subcutaneous tissue (n = 6), followed by ocular tissue (n = 4). One cat each had dissemination to the pleural space, a cranial thoracic mass, the liver and an extradural mass. Four cats had positive culture and/or cytology from multiple sites.

Disseminated disease: In addition to the 17 cats that received a confirmation of extrapulmonary dissemination through histology, cytology or culture, 14 cats (27%) had

a combination of evidence supporting a diagnosis of disseminated disease by the treating veterinarian, although etiologic testing was not pursued. Of these, nine cats had dermal lesions consistent with coccidioidomycosis. Two cats had skeletal radiographic changes characteristic for fungal osteomyelitis. Two cats had both dermal and ocular disease and one cat was believed to have dissemination to the skin, eye, and tongue based on records. Sites of dissemination are summarized in Table 4.

Treatment: Treatment was instituted in 50/51 cats, while the remaining cat was euthanized at diagnosis due to the severity of the disseminated disease. The most commonly prescribed antifungal was fluconazole as sole agent and the typical dosage of fluconazole was 50 mg/cat PO q12h. Itraconazole was the only other antifungal drug given as the first line agent.

Forty-six (92%) cats were treated with fluconazole initially and 40 of those never received another antifungal drug. Six cats received additional antifungal drugs, either concurrently or sequentially, due to failure to respond to fluconazole alone. Additional antifungal drugs included itraconazole, amphotericin B, posaconazole and terbinafine. Twenty-five cats were still receiving oral antifungal medication at the time of the review (22 on fluconazole, 2 on itraconazole, and 1 on posaconazole). For this group of cats, the time on antifungal medication ranged from 6 months to 7.5 years.

Itraconazole was instituted as the initial treatment in the other four (8%) cats. One of these cats was maintained on itraconazole only. One cat, which had severe skeletal disease requiring amputation of the affected limb, was changed to fluconazole post-amputation. The remaining two cats received multiple therapies. Treatment is summarized in Table 5.

A recurrence of coccidioidomycosis was described in 14 cats. All of these cats received additional antifungal therapy, which was successful in 13/14. Fourteen cats were deceased at the time of the review. As previously described, 1 cat was euthanized at diagnosis due to the severity of disease and 1 was euthanized after failing to respond to antifungal therapy after a recurrence of disease. Five cats were euthanized for unrelated medical conditions, and the circumstances of the death or euthanasia could not be determined for the remaining 7 cats.

Discussion

Reports of cats with coccidioidomycosis have appeared in the literature only within the past five decades and constitute a few case reports and retrospective reviews.[5,11,12,14,15] These cases represent a small fraction of the cats residing within the endemic region for *Coccidioides* species. While coccidioidomycosis is reportable in humans in Arizona, it is not currently reportable in veterinary species, allowing only for

213 estimates of the impact of disease in our animal populations. Previous work has shown
214 that the rates of infection and disease in dogs are similar to or higher than those seen in
215 people;[16] however, the frequency of disease and subclinical infection in cats is
216 unknown.

217 In this study population, the average age at diagnosis was 6.8 years, which is
218 similar to cats in a previous retrospective study.[11] Two-thirds of the cats diagnosed with
219 coccidioidomycosis lived exclusively indoors at the time of diagnosis, suggesting that
220 being outdoors exposed to soil is not requisite for acquiring infection. This has also
221 been noted in cats with blastomycosis,[17,18] cryptococcus,[19] and histoplasmosis.[20] Spores
222 may be introduced to indoor cats through air conditioners, open doors and windows or
223 on fomites that enter the residence (people, other animals).

224 Though primary pulmonary disease with a cough is the most common
225 presentation of coccidioidomycosis in dogs and humans,[2,8] respiratory disease has been
226 previously reported to be present in only 25% of cats.[11] In contrast to previous findings,
227 40% of the cats in this population exhibited significant respiratory signs. Interestingly,
228 hilar lymphadenopathy was not frequently identified on the thoracic radiographs of this
229 cohort, despite being a common finding in dogs with coccidioidomycosis.[10,21,22] What is
230 most notable about cats is that >60% of this population had disseminated disease at the

231 time of diagnosis, and nearly half of all the cats in this study had dermal lesions as the
232 primary feature leading to diagnosis of coccidioidomycosis. For all cats residing in the
233 endemic region, even those exclusively indoors, coccidioidomycosis should be
234 considered as a differential diagnosis for antibiotic-unresponsive dermal lesions,
235 respiratory distress or cough, pleural effusion, ocular disease, chronic skeletal
236 pain/lameness or paresis/paralysis. Coccidioidomycosis should be strongly considered
237 in cats that present with chronic dermal lesions that do not respond to empirical
238 treatment.

239 Clinicopathologic abnormalities were more common in this feline population
240 compared to previous reports.[11] The most common abnormalities were
241 hyperglobulinemia, neutrophilia, and monocytosis, which are supportive of a diagnosis
242 of coccidioidomycosis based on canine disease.[9,10] While the CBC and serum
243 chemistries can aid in the diagnosis of coccidioidomycosis, the lack of inflammatory
244 parameters cannot rule out coccidioidomycosis in cats.

245 Agar gel immunodiffusion uses doubling serial dilutions of serum to quantitate
246 anticoccidioidal antibody levels. The assay has been demonstrated to have high
247 specificity for anticoccidioidal antibodies, although there are no published validity
248 studies of its use in felines.[23] In dogs, overlap in titers has been shown with clinical and

subclinical disease and the magnitude of the titer does not consistently correlate with the presence or severity of illness.[16] Additionally, negative serology does not rule out coccidioidomycosis in humans or dogs.[9,21,24] The overwhelming majority of the cats in this study that were tested did have anticoccidioidal antibodies, which is similar to the only other review of feline coccidioidomycosis, in which all affected cats were seropositive.[11] At this time, the rates of healthy seropositive cats as well as seronegative cats with clinical coccidioidomycosis is unknown. A serosurvey of both healthy and sick cats, as has been done in dogs,[16] would be needed to determine this information. Interestingly, the single seronegative cat in this case series did have histological confirmation of infection.

Confirmation of the presence of the fungus through histopathology, cytology, and/or fungal culture is considered the gold standard for diagnosis; however, dogs are typically diagnosed through a combination of clinicopathology, diagnostic imaging and relevant clinical signs.[6] The large number of cats in this study with confirmed coccidioidomycosis is likely due to two factors: 1) the frequency of and 2) the location of dissemination. Extrapulmonary dissemination is rare in humans.[2,25] It appears to be more common in canines, with previous studies showing dissemination rates from 20% to 42% of cases.[10,26] The most common site of dissemination in canines is to the skeletal

system and biopsy is infrequently pursued due to cost and invasiveness of the testing as well as a strong radiographic indication of disease. However, the dermatologic dissemination seen in cats[5,11,12,15] allows for easily obtained aspirates and biopsies. Also, the specimens for definitive diagnosis are usually obtained after lesions have failed to respond to antimicrobial or other empiric treatments. Two cats in this study had confirmed dissemination to the skeletal system, but one cat was confirmed on necropsy and the other was confirmed upon amputation of the limb. The two cats with suspected skeletal dissemination based upon radiographs did not have confirmatory biopsy performed.

Most cats in this study were treated with the oral antifungal fluconazole, as is typical for dogs in Arizona.[6] Fluconazole, while fungistatic, has the advantage of a high bioavailability and excellent tissue penetration.[27,28] The tissue penetration makes fluconazole a particularly good choice due to the level of disseminated disease in multiple tissues, including ocular, seen in these cats. It is likely that fluconazole was chosen due to convenience, availability and familiarity, but it appears that most cats were treated successfully with it. Most of the cats in this study that were successfully treated required medication for over a year, and often several years. Recurrence of disease was evident in over a quarter of the cats in this cohort, although all but one of

the cats were treated to clinical remission. While coccidioidomycosis in cats may require lengthy treatment with antifungal therapy and monitoring for recurrence, overall most cats will respond to treatment.

A limitation of this study is the retrospective nature of data collection. In order to identify the greatest number of cases, we purposefully approached feline only and specialty hospitals. This may have created a bias towards cats that were more ill at the time of diagnosis. However, the cases from the general small animal practice in Tucson did not have notable differences in the severity of illness. We were reliant upon most of the veterinary clinics to perform their own database searches and we suspect that the true number of feline coccidioidomycosis cases is underrepresented in this review. We were also unable to control for radiographic interpretation, diagnostic laboratory, and recommendations made to owners. There is currently no information regarding the number, sex, lifestyle, and breed of cats living in Tucson and Phoenix, making it impossible for us to identify risk factors for disease. A longitudinal study of coccidioidomycosis in cats would provide stronger evidence about the presentation of disease and outcome for cats residing in the endemic region.

The cases in this study indicate that cats experience significant clinical disease as a result of infection with *Coccidioides* species. Extrapulmonary dissemination was

303 evident in over half of the cats, often with spread to multiple organ systems. It is
304 possible that the independent nature of cats and their ability to hide subtle indications of
305 illness leads them to be diagnosed later in the course of disease. However, most of the
306 cats in this study were reported to live exclusively indoors, suggesting that this
307 population of cats did have owners who could monitor their cats daily for behavioral
308 changes indicating illness. The extent of disease associated with coccidioidomycosis
309 reported here and in previous work[11] may indicate a difference in host control of disease
310 compared with dogs or humans.

311 **Conclusions**

312 Coccidioidomycosis presents a diagnostic challenge in any species due to the
313 overlap of clinical signs, clinicopathologic changes and radiographic abnormalities
314 between coccidioidomycosis and other diseases. The results of our study indicate that
315 clinical suspicion of coccidioidomycosis should be high in cats with dermatologic
316 lesions or severe respiratory illness. Positive serology appears to be well correlated with
317 clinical illness, although biopsy and culture samples can provide a definitive diagnosis.
318 Orally administered fluconazole was the treatment of choice in this population of cats
319 and proved to be effective in most animals treated.

320

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Conflicts of Interest

One author (MK) is the owner of a veterinary hospital in Tucson that participated in this retrospective review. There are no other conflicts of interest to report.

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409

410 Figure

411 Figure 3. Coronal section of thorax (A) and sagittal section of thoracic spine (B) of a SF
412 domestic shorthair with acute onset of hind limb paralysis. (A) The thoracic section
413 shows an enlarged mediastinal lymph node (LN) as well as a fungal granuloma (G) and
414 pulmonary infiltration in the right cranial lung lobe. (B) There is a contrast-enhancing
415 space occupying lesion of the spinal cord. Coccidioides was identified ….. by ….. and
416 the cat responded completely to oral fluconazole.

417 Table 1: Presenting clinical signs

	n (%)
Respiratory signs	20 (39%)
Respiratory distress	8 (40%)
Cough	7 (35%)*
Both	5 (25%)*
Fever	4 (9%)
Anorexia/decreased appetite	14 (27%)
Weight loss	18 (35%)
Lameness/paraparesis/paresis	11 (22%)
Dermatologic lesions	22 (43%)**
Nodules	13 (59%)*
Non-healing wounds	8 (36%)*

418 * These reflect the percentage of animals that presented with that category of clinical signs; ** One cat
419 with dematologic lesions did not have a description of the lesions provided in the record

420

421 Table 2: Radiographic abnormalities noted

	Radiographic Changes	n
Single Radiographic Abnormality Noted	Hilar Lymphadenopathy	1
	Bronchial/Interstitial/Alveolar Pattern	4
	Lobe Consolidation	1
	Mass/Nodule	2
	Pleural Effusion	2
	Osteomyelitis	1
Multiple Radiographic Abnormalities Noted	Hilar Lymphadenopathy & Lobe Consolidation	2
	Hilar Lymphadenopathy & Bronchial/Alveolar/Interstitial Pattern	2
	Hilar Lymphadenopathy, Lobe Consolidation, & Bronchial/Alveolar/Interstitial Pattern	1
	Bronchial/Interstitial/Alveolar Pattern & Lobe Consolidation	1
	Bronchial/Interstitial/Alveolar Pattern & Pleural Effusion	1
	Pleural Effusion & Lobe Consolidation	2
	Lobe Consolidation, Mass/Nodule, & Osteomyelitis	1
	Bronchial/Interstitial/Alveolar Pattern & Osteomyelitis	1

422 * 22 cats had radiographs (19 thoracic only, 1 skeletal only, and 2 thoracic and skeletal)

423 Table 3: Serum chemistry and CBC abnormalities

	n (%)
Neutrophilia	16 (53%)
Monocytosis	12 (40%)
Hyperglobulinemia	13 (43%)
Hypoalbuminemia	7 (23%)

424 Table 4: Sites of Dissemination

Location	**Confirmed (n=17)**[*]	**Suspected (n=14)**[†]
Cutaneous/subcutaneous	7	12
Ocular	5	3
Pleural Effusion	1	0
Hepatic	2	0
Skeletal	2	2
Tongue	2	1
Extradural mass	1	0
Pericardium	1	0
Joint	1	0

Spleen	1	0
Lymph Node	1	0

425 *4 cats within this group had confirmed dissemination to multiple sites; †3 cats within

426 this group had suspected dissemination to multiple sites

427

Table 5: Antifungal Treatments

Initial Treatment	Additional Therapies
Fluconazole (n=46)	none (n=40)*
	itraconazole (n=4)
	itraconazole, terbinafine, amphotericin B, posaconazole (n=1)
	posaconazole, itraconazole (n=1)
Itraconazole (n=4)	none (n=1)
	fluconazole (n=1)
	fluconazole, amphotericin B, terbinafine (n=1)
	fluconazole, amphotericin B (n=1)†

*One cat in this group had amphotericin B discontinued after one dose due to rising renal values; the cat was then maintained on fluconazole alone

†This cat was euthanized approximately one year after diagnosis due to worsening disseminated disease