*J Vet Intern Med* 2010;24:1427–1438

# Clinical Signs, Imaging Features, Neuropathology, and Outcome in Cats and Dogs with Central Nervous System Cryptococcosis from California

J.E. Sykes, B.K. Sturges, M.S. Cannon, B. Gericota, R.J. Higgins, S.R. Trivedi, P.J. Dickinson, K.M. Vernau, W. Meyer, and E.R. Wisner

**Background:** *Cryptococcus* spp. is a fungal pathogen with a predilection for the central nervous system (CNS).

**Objectives:** To compare the clinical, advanced imaging, and neuropathologic findings in dogs and cats with CNS cryptococcosis, and to evaluate outcome of treatment in these animals.

**Animals:** Twenty-six cats and 21 dogs with CNS cryptococcosis.

**Methods:** Medical records were reviewed for clinical findings and results of CNS imaging. Archived cerebrospinal fluid and CNS tissue specimens were reviewed for pathology. Findings in cats were compared with those in dogs and the effects of variables on survival were determined by survival curve analysis.

**Results:** When present, pain was localized to the cervical region in dogs and was generalized or localized to the thoracolumbar spine or pelvic limbs in cats. Magnetic resonance imaging (MRI) findings were variable but correlated with CNS histopathological findings of meningitis, meningitis with gelatinous pseudocyst formation, and granulomatous mass lesions. Peripherally enhancing brain lesions were seen only in cats. Histopathologically, the inflammatory response was milder in cats compared with dogs. Remissions of $\geq$1 year occurred in 32% of treated animals. Altered mentation was associated with negative outcome. Glucocorticoid use after diagnosis was associated with improved survival in the first 10 days.

**Conclusions and Clinical Importance:** Lesions seen on MRI reflected neuropathological findings and were similar to those reported in human patients. The immune response to infection may differ between cats and dogs, or relate to the infecting cryptococcal species. Long-term ($>$6 month median survival time) survival may be possible in animals surviving $\geq$4 days after diagnosis.

**Key words:** Brain; Cryptococcal antigen latex agglutination serology; *Cryptococcus*; Fungal; Magnetic resonance imaging; Mycoses.

Cryptococcosis primarily is caused by 2 encapsulated fungi, *Cryptococcus neoformans* and *Cryptococcus gattii*. In dogs and cats, the nasal cavity is thought to be the initial site of infection, although the lung and the gastrointestinal tract also have been suggested as portals of entry.[1–3] Other commonly reported sites of involvement include the skin, lymph nodes, central nervous system (CNS), and eyes.[1–4] Although the reported incidence of cryptococcosis is lower in dogs than in cats, CNS involvement may be more common in dogs[1] in addition to widespread dissemination to other parenchymal organs.[1,2,5–7] Pathologic findings suggesting extension of nasal disease through the cribriform plate with subsequent meningoencephalitis have been reported in several cases.[1–3] CNS involvement also may follow hematogenous dissemination.

In humans, CNS involvement is manifested as meningitis, meningoencephalitis, or tumor-like intraparenchymal masses containing yeast organisms and inflammatory cells (cryptococcomas).[8,9] Severe meningitis and systemic dissemination are common in AIDS patients, who usually are infected with *C. neoformans* and often fail to mount a clinically relevant inflammatory response.[8] Extension of infection from the meninges along perforating arteries into the Virchow-Robin (VR) spaces results in cystic collections of yeast organisms known as gelatinous pseudocysts, which can sometimes be seen on magnetic resonance imaging (MRI).[9–12] Large, intraparenchymal

**Abbreviations:**

| | |
|---|---|
| AIDS | acquired immunodeficiency syndrome |
| CALAS | cryptococcal antigen latex agglutination serology |
| CNS | central nervous system |
| CSF | cerebrospinal fluid |
| CT | computed tomography |
| FLAIR | fluid attenuation inversion recovery |
| MRI | magnetic resonance imaging |
| MST | median survival time |
| TNCC | total nucleated cell count |
| VMTH | Veterinary Medical Teaching Hospital |
| VR | Virchow-Robin |

*From the Veterinary Medical Teaching Hospital (Cannon, Gericota, Trivedi), the Department of Medicine and Epidemiology (Sykes), the Department of Surgical and Radiological Sciences, (Wisner, Dickinson, Vernau, Sturges), and the Department of Pathology, Microbiology and Immunology (Higgins), School of Veterinary Medicine, University of California, Davis, CA; Molecular Mycology Research Laboratory, CIDM, Westmead Millennium Institute, Sydney Medical School-Westmead, The University of Sydney at Westmead Hospital, Westmead, NSW, Australia (Meyer). Dr Trivedi is presently affiliated with Animal Surgical and Emergency Center, Los Angeles, CA. A portion of this work was presented as an abstract at the 2004 American College of Veterinary Internal Medicine Forum.*[a]

*Corresponding author: Jane E. Sykes, BVSc(Hons), PhD, DACVIM, Department of Medicine and Epidemiology, 2108 Tupper Hall, University of California, Davis, School of Veterinary Medicine, Davis, CA 95616; e-mail: jesykes@ucdavis.edu.*

*Submitted June 24, 2010; Revised August 16, 2010; Accepted September 14, 2010.*



*10.1111/j.1939-1676.2010.0633.x*

cryptococcomas are more commonly reported in immunocompetent patients. These often are contrast-enhancing on T1-weighted (T1W) spin-echo images, reflecting the immune response to the organism. Because *C. gattii* tends to infect immunocompetent humans, contrast-enhancing cryptococcomas are more common in patients infected with *C. gattii* compared with those infected with *C. neoformans*.[13,14] Properties of cryptococcal species and strain also may influence the inflammatory response.[15]

Much of our knowledge about clinical signs, diagnosis, advanced imaging, and neuropathology findings in dogs and cats with CNS cryptococcosis has been based on single case reports,[16–22] small case series,[5,23] or book chapters.[4,24,25] CNS pathology in dogs and cats with cryptococcosis and how it relates to the host inflammatory response, infecting cryptococcal species, and the results of CNS imaging have not been investigated. The objectives of this study were to describe and compare the clinical, neuroimaging, and neuropathologic findings in cats and dogs with CNS cryptococcosis, and to examine factors associated with outcome.

## Materials and Methods

### Criteria for Case Selection

Patients included in this study were a subset of patients described in an epidemiological study of cats and dogs with cryptococcosis presenting to the University of California, Davis, Veterinary Medical Teaching Hospital (VMTH) from August 1988 to February 2010.[1] Cryptococcosis was confirmed in these patients by isolation or identification of the organism by cytology or histopathology.[1] Animals were not included if organisms were isolated from a nonsterile site in the absence of positive cytology, antigen testing, or histopathology results. Animals with CNS involvement were identified from this group for further evaluation based on (1) involvement of the CNS based on an abnormal neurologic examination that was temporally associated with a diagnosis of cryptococcosis, (2) cryptococcal organisms within cerebrospinal fluid (CSF), or (3) intralesional organisms consistent with *Cryptococcus* spp. within the CNS at necropsy.

### Diagnosis of Cryptococcosis

Cryptococcal serology and identification of *Cryptococcus* spp. by cytology, histopathology, and microbiologic methods were performed as described previously.[1] CSF cryptococcal antigen latex agglutination serology (CALAS) was performed in some animals lacking visible organisms within the CSF, and some animals with negative serum CALAS titers. From 2006 onward, *C. neoformans* was differentiated from *C. gattii* with L-canavanine-glycine-bromthymol blue agar.[1] Molecular subtyping of *C. gattii* isolates was performed as described.[1]

### Procedures

Information obtained from the medical records included signalment; neurologic examination findings; duration of neurologic signs; the presence and duration of extraneural signs before development of neurologic signs; results of diagnostic tests including serology, CSF analysis, microbiology, and pathology; and treatments administered.

### Computed Tomography (CT) Imaging and MRI

Contiguous transverse, 1.5 or 3 mm collimated CT images of the brain were acquired with a low frequency reconstruction filter. A single slice CT scanner[b] was used before 2001, after which a helical scanner was used.[c] Contrast-enhanced CT images were acquired after administration of ionic[d] or nonionic[e] iodinated contrast medium (880 mg I/kg, IV).

MRI sequences were obtained with a 1.5[f] (after 2002) or 0.23[g] Tesla MRI system. Transverse images with a 3–5 mm image collimation and an interslice gap of 0.5–1 mm were generated with T1W and T2W sequences. Additional T1W images were acquired after administration of gadopentate dimeglumine[h] (0.1 mmol/kg, IV). Fluid attenuation inversion recovery (FLAIR) images were acquired on some animals.

All available CT and MRI images were reviewed (E.R.W., M.S.C., B.K.S.) without knowledge of pathologic findings, and a consensus interpretation was reached. Lesions were categorized by distribution (focal, multifocal, or diffuse), type (parenchymal or meningeal), location, presence of a mass or mass effect, compression of the ventricular system, or effacement of sulci. Images were compared before and after administration of contrast to detect lesion enhancement, which was defined semiquantitatively as nonenhancing or minimally, moderately, or intensely contrast-enhancing. The character of enhancement was defined as uniform, nonuniform, or peripherally enhancing.

MRI abnormalities were described as isointense, hypointense, hyperintense, or mixed relative to signal intensity of normal gray matter. Perilesional T2W hyperintensity suggesting the presence of perilesional edema was described as absent, mild, or marked, and was determined by assessing parenchymal hyperintensity on T2W images that extended beyond regions of contrast enhancement on gadolinium-enhanced T1W images. Perilesional T2W hyperintensity was considered absent if hyperintensity on T2W images did not extend beyond the primary lesion boundaries as defined by the contrast-enhanced T1W image, mild if T2W hyperintensity extended $<2$ slice thicknesses beyond the mass boundaries, and marked if T2W hyperintensity extended $\geq 2$ slice thicknesses from the primary lesion margins.

### Pathology

The results of gross and histopathologic examination of the CNS at necropsy, including archived paraffinized-tissue specimens, were reviewed (B.G., R.J.H.) without knowledge of findings on advanced imaging. Lesions were classified according to pattern (parenchymal, meningeal, with or without pseudocyst formation) and location (ventricles, choroid plexus, cerebrothalamic, midbrain, pons and medulla, cerebellum, spinal cord). Recuts were performed when necessary in order to obtain representative sections of each location. Using a previously described scoring system,[9] organism numbers were subjectively scored as 1+ (rare) to 3+ (abundant). The magnitude of the inflammatory response was subjectively scored as 0 (absent), 1+ (mild), 2+ (moderate), or 3+ (severe). Extraneural tissues were examined to document the presence or absence of organisms outside of the CNS and the presence or absence of nasal or pulmonary involvement. Correlations between histopathologic findings and those of CSF analysis and MRI were investigated.

### Outcome

The time to death, euthanasia, or loss to follow-up were recorded. Deaths were classified as related or unrelated to CNS cryptococcosis. Death was assumed to be related to cryptococcosis if clinical signs related to cryptococcosis that were present at the time of diagnosis failed to resolve or progressed at the time of euthanasia or death. Where possible, necropsy findings were used to

determine whether death or euthanasia was related to cryptococcosis. For animals discharged from the VMTH, information on outcome was obtained by telephone conversations with owners, referring veterinarians, or both.

### Statistical Analysis

Data are presented as mean ± SD when normally distributed. A Fisher exact test was used to detect differences in categorical variables between dogs and cats by use of frequency data. The Mann-Whitney test was used for comparison of continuous variables between groups. The D'Agostino and Pearson omnibus normality test was used to test data for normality. For survival analysis, Kaplan-Meier curves were constructed, with animals lost to follow-up or alive at the time of writing being censored in the analysis. The associations between outcome and the following variables were determined: species (dog or cat), age, magnitude of the serum CALAS titer, previous glucocorticoid treatment, mental status on presentation (normal or abnormal), history of seizures, history of CSF collection, and treatment with single or multiple antifungal drugs. Survival curves were compared by the log rank test; hazard ratios and 95% confidence intervals were determined. All analyses were performed with a statistical software package.[i] Significance was defined as $P < .05$.

## Results

A total of 26 cats and 21 dogs with CNS cryptococcosis were identified. Organisms were detected within the CNS after CSF analysis or necropsy in 15 (58%) cats and 17 (81%) dogs. The remaining 11 cats and 4 dogs were diagnosed with CNS involvement based on an abnormal neurologic examination that was temporally associated with detection of *Cryptococcus* organisms at extraneural sites, and in 8 cats and 2 dogs, retinal lesions suggestive of cryptococcosis also were present.

The infecting species was determined for 6 cats and 7 dogs. *C. neoformans* was isolated from 2 cats and 5 dogs. *C. gattii* was isolated from 4 cats and 2 dogs. Three cats were infected with *C. gattii* molecular type VGIII and 1 with VGIIa. One dog was infected with *C. gattii* molecular type VGIIa and the other with VGIIb.

### Signalment and Clinical Signs

***Cats.*** There were 2 Siamese, 1 Himalayan, and 1 Manx cat, and the remainder were mixed breed cats. Twelve (46%) were spayed females, 12 (46%) were neutered males, and 2 (8%) were intact males. Age ranged from 1 to 17 years (8 ± 4.3 years). FeLV antigen and FIV antibody test results were negative for all 21 and 19 cats evaluated, respectively. Neurologic signs were documented at presentation in 25 (96%) cats. The single cat lacking neurologic signs was diagnosed with CNS involvement at necropsy. The duration of neurologic signs before presentation ranged from 1 to 270 days (median, 8.5 days; n = 22). Signs reported by owners in the history of cats with CNS cryptococcosis were lethargy (12 [48%]); behavioral changes (10 [40%]); gait abnormalities (15 [60%]); vestibular signs, including head tilt, ocular signs consistent with nystagmus, and tight circling (8 [32%]); seizures (8 [32%]); mydriasis (4 [16%]); blindness (3 [12%]); and facial twitching (2 [8%]). Apparent pain was reported in 2 (8%) cats, and was localized to the thoracolumbar region or pelvic limbs.

Extraneural signs preceded the onset of neurologic signs in 18/25 (72%) cats for durations ranging from 7 days to 4 years (median, 52.5 days). In 5 of these cats, clinical signs were nonspecific (lethargy, inappetence, or weight loss) and may have reflected intracranial disease. In the remaining cats, upper respiratory (6), lower respiratory (3), or cutaneous (4) signs preceeded the onset of neurologic signs.

***Dogs.*** Of the 21 dogs, there were 6 American Cocker Spaniels, 4 Labrador Retrievers, 4 mixed breed dogs, and 1 each of other purebred dogs. Twelve (57%) were spayed females, 6 (29%) were neutered males, and 3 (14%) were intact male dogs. Age ranged from 1 to 7 years (3.9 ± 1.6 years). Neurologic signs were present in 20 dogs. The duration of neurologic signs ranged from 1 to 365 days (median, 8 days). There was no difference in the duration of neurologic signs between cats and dogs. Historical abnormalities suggestive of CNS disease in dogs with cryptococcosis included lethargy (11 [52%]), behavioral changes (4 [19%]), gait abnormalities (15 [71%]), seizures (9 [43%]), muscle tremors or twitching (5 [24%]), vestibular signs including tight circling and a head tilt (4 [19%]), mydriasis (2 [10%]), and blindness (1 [5%]). Apparent pain was reported in 7 (33%) dogs, which involved the cervical region (4), head (2), and was generalized in 1 dog.

Extraneural signs occurred before the onset of neurologic signs in 9/21 (43%) dogs, and ranged in duration from 2 days to 4 months (median, 7 days), shorter than was seen in cats ($P = .03$). Clinical signs were nonspecific in 5 dogs (lethargy, inappetence, vomiting, weight loss) and upper respiratory (1), upper respiratory and cutaneous (1), swelling of the eye (1), or associated with cryptococcal arthritis (1) in the remaining dogs.

### Neurological Examination

***Cats.*** Complete neurologic examination was done on 18 (69%) of the 26 cats. Altered mentation was present in 12 cats. Cranial nerve abnormalities (14/18) included absent or slow menace responses bilaterally (9), absent or slow pupillary light responses bilaterally (9), spontaneous nystagmus (7), mydriasis (5), head tilt (3), anisocoria (3), absent or weak palpebral (2) or corneal (2) reflexes, miosis (1), and impaired facial sensation (1). Gait abnormalities (15 cats) included ataxia in all limbs (including sensory, vestibular, or cerebellar ataxia) (8), ambulatory paraparesis (2), circling (2), and nonambulatory paraparesis (3). Two cats had generalized tremors. Postural reaction deficits were present in 10 cats. A decreased patellar reflex was present in 1 cat. Spinal palpation elicited apparent pain in 6 cats, which was generalized (3) or localized to the thoracolumbar or lumbar spine (3). Neuroanatomical location was determined for 16 cats as multifocal or diffuse CNS (7), central vestibular or cerebellar (5), forebrain (2), T3-L3 spinal cord (2), L4-caudal spinal cord (1), and brainstem (1).

***Dogs.*** A neurologic examination was done in 17 (81%) dogs. Altered mentation was present in 9 dogs,

including obtundation (7), and stupor or coma (2). Cranial nerve abnormalities (13 dogs) included an absent menace response (8), absent or slow pupillary light responses (6), spontaneous nystagmus (5), strabismus (5), absent or weak gag reflexes (4), bilateral mydriasis (3), anisocoria (3), impaired facial sensation (2), absent or slow physiologic nystagmus (2), absent corneal reflex, impaired tongue movement, and blindness (1 dog each). Gait abnormalities (15 dogs) consisted of ataxia in all limbs (8), circling (3), ambulatory paraparesis (2), stiffness (2), and nonambulatory paraparesis (1). Two dogs exhibited generalized tremors. Postural reaction deficits were present in 12 dogs. Lower motor neuron signs (4 dogs) included absent or slow withdrawal reflexes (3), and an absent cutaneous trunci reflex (2). Apparent cervical pain was present on palpation in 8 dogs, and was the only finding in 1 dog. Neuroanatomical localization was determined for all 16 dogs as forebrain (5), multifocal CNS (4), cervical spinal cord (C1-T2) (3), cerebellar or central vestibular (2), and cerebral (1).

### *Serum CALAS Testing*

Serum CALAS titers in cats ranged from 64 to 262,144 (n = 20) and in dogs, 0 to 65,536 (n = 11). There was no difference in titer magnitude between cats and dogs. Two dogs had negative titers. One of these 2 dogs had a CSF CALAS titer of 16 and organisms were visualized within the CSF. The other dog had a CSF CALAS titer of 128, and although organisms were not visualized in the CSF, *C. gattii* was isolated from the CSF and a retrobulbar mass.

### *CSF Analysis*

***Cats.*** Thirteen CSF samples from 11 cats were analyzed (Table 1). Two cats with myelopathic signs had cisternal and lumbar samples collected. The collection site in the remaining cats was cisternal (4) or unknown (5). One cisternal sample had a normal CSF total nucleated cell count (TNCC) and protein concentration. In this cat, a lumbar sample had neutrophilic pleocytosis (24 cells/μL) and CSF hyperproteinemia (56 mg/dL). The other cat for which cisternal and lumbar CSF was analyzed had neutrophilic pleocytosis and mild CSF hyperproteinemia (29 and 35 mg/dL) at both sites.

Using cytologic examination, cryptococcal organisms were detected within the CSF of 9 cats. Of the 2 remaining cats, 1 had CSF pleocytosis (6 cells/μL) and a positive CSF CALAS titer of 1 : 32. Fungal culture of the CSF was negative, and histopathology after necropsy on the day of CSF collection disclosed meningitis with 3+ organisms. The other cat had neutrophilic CSF pleocytosis (24 cells/μL) and CSF hyperproteinemia (56 mg/dL). Fungal culture, CSF CALAS serology, and histopathology were not performed.

***Dogs.*** Seventeen CSF samples were evaluated from 15 dogs (Table 1). Results of cisternal and lumbar CSF analysis were available for 2 dogs with signs of diffuse CNS disease. For the remaining 13 dogs, the site was

**Table 1.** Results of CSF analysis from 11 cats and 15 dogs with CNS cryptococcosis.

| Variable | No. Tested[a] | No. with High Values | Mean±SD | Median | Range | *P* Value | Reference Range[b] |
|---|---|---|---|---|---|---|---|
| RBC (cells/μL) | | | | | | .17 | < 1200 |
| Cats | 10 | 2 | 745 ± 1434 | 111 | 2–4650 | | |
| Dogs | 15 | 1 | 153 ± 361 | 15 | 0–1410 | | |
| TNCC (cells/μL) | | | | | | .27 | < 2 |
| Cats | 10 | 9 | 201 ± 444 | 21 | 0–1440 | | |
| Dogs | 15 | 15 | 297 ± 522 | 67 | 6–1665 | | |
| Total protein (mg/dL) | | | | | | .01 | < 25 |
| Cats | 10 | 8 | 45 ± 35 | 39 | 8–132 | | |
| Dogs | 12 | 11 | 494 ± 1031 | 161 | 11–3700 | | |
| Neutrophils (%) | | | | | | .003 | NA |
| Cats | 9 | 9 | 65 ± 21 | 68 | 20–92 | | |
| Dogs | 14 | 13 | 30 ± 23 | 25 | 0–68 | | |
| Small mononuclear cells (%) | | | | | | .20 | NA |
| Cats | 9 | 8 | 14 ± 14 | 10 | 0–42 | | |
| Dogs | 14 | 14 | 22 ± 17 | 19 | 1–56 | | |
| Large mononuclear cells (%) | | | | | | .09 | NA |
| Cats | 9 | 9 | 22 ± 13 | 26 | 5–38 | | |
| Dogs | 14 | 14 | 40 ± 24 | 45 | 7–78 | | |
| Eosinophils | | | | | | .10 | NA |
| Cats | 9 | 2 | 0.4 ± 1 | 0 | 0–3 | | |
| Dogs | 14 | 8 | 7 ± 15 | 1 | 0–51 | | |

CNS, central nervous system; CSF, cerebrospinal fluid; TNCC, total nucleated cell count.

Results stated are from the cerebellomedullary cistern if both lumbar and cisternal samples were collected (2 cats and 2 dogs). Differential cell counts are reported for samples with increased TNCC only.

[a]Total protein was not measured in some samples due to insufficient quantity of CSF. Large numbers of organisms or cell clumping precluded quantitation of TNCC or differential cell counts in some samples.

[b]CSF with <2 nucleated cells/μL and <1,200 RBCs/μL is considered within the reference range for this laboratory.

cisternal (6) or unknown (7). All dogs had increased TNCC. The only dog with a normal protein concentration had a mild, mixed pleocytosis. In 1 dog, cisternal and lumbar TNCCs were similar (46 and 33 cells/μL), although neutrophils predominated in the cisternal sample (>50%) and macrophages predominated in the lumbar sample. In the other dog, the TNCC was higher in the cisternal sample (1,665 versus 120 cells/μL) but the differential count was similar. Total protein concentration was only determined in the lumbar sample from the 1st dog (738 mg/dL).

Cryptococcal organisms were detected in CSF of 11 dogs. In 3 of 4 dogs lacking organisms in the CSF, positive CSF CALAS titers of 16, 32, and 128 were detected, and fungal culture of the CSF was positive in the latter sample and negative in the other 2 samples. The dog with the CSF titer of 16 was treated with antibacterials and anti-inflammatory doses of dexamethasone sodium phosphate for 4 days, after which a second CSF sample showed a higher TNCC and many cryptococcal organisms. CSF CALAS titers and fungal culture of the CSF were not performed on the remaining CSF sample that lacked visible cryptococcal organisms. Histopathology was performed after necropsy of this dog and the dog with a CSF titer of 128, and both had meningitis with 3+ organisms.

There was no difference in the magnitude of the CSF inflammatory response between dogs and cats, but the percentage of neutrophils was higher in cats and the protein concentration was higher in dogs (Table 1). Regardless of species, for CSF samples for which corresponding histopathology was available, samples with TNCC of <10 cells/μL had inflammation scores of 0 or 1+ on histopathology, and samples with TNCC ≥ 24 cells/μL had scores of 2+ or 3+.

### *Imaging*

***Cats.*** MRI of the brain and cervical spinal cord to the level of the second cervical vertebra was performed on 7 cats. MRIs from 6 cats were available for review. The remaining MRI examination was reported as unremarkable. Brain imaging was abnormal in 5/6 cats, and 1 cat had abnormal medial retropharyngeal lymph nodes. Multifocal (3) or solitary (2) brain parenchymal lesions were present in 5 cats. The most common sites affected were the cerebrum (4), cerebellum (2), and thalamus (2). Less common sites included the midbrain and optic chiasm (1 each). No cranial cervical spinal cord involvement was noted. There was no predilection for gray or white matter. Lesions were hyperintense on T2W images, hypointense on T1W images, and enhanced markedly (3) or mild to moderately (2) with contrast. In 3 cats, lesions appeared fluid-filled on T2W images but with more T1W intensity than expected for acellular fluid (hereafter referred to as high T2, low T1 lesions). Lesions were well-delineated (3) or poorly defined (2), and enhanced peripherally (4) or uniformly (1) (Figs 1 and 2). A mass effect was noted in 4 cats, and the lesions had surrounding T2 hyperintensity, consistent with edema.

FLAIR sequences were obtained in 2 cats. In 1 cat, there were multifocal, mild to moderate hyperintensities within the olfactory and frontal lobes, which were less intense than on the comparable T2 sequence. In another cat, FLAIR revealed isointensity of a high T2, low T1 lesion, with additional multifocal hyperintensities within the cerebrum, similar in location and intensity to the T2W images.

Mild to moderate meningeal enhancement was present in 4 cats, which was diffuse (1), regional (1), or focal (2), and involved the dura (2) or both the dura and pia (2). Unilateral optic nerve involvement was seen in 2 cats, manifested as asymmetrical nerve enlargement, T2 hyperintensity, and marked contrast enhancement of the nerve. Extension of disease across the calvarium was detected in 2 cats with adjacent frontal sinus fluid opacification. Cribriform plate compromise also was noted in these 2 cats, and 1 of the cats had retrobulbar disease extension. Cerebellar herniation was noted in 1 cat. Mild medial retropharyngeal lymph node enlargement without alteration in enhancement pattern was noted in 2 cats (1 unilateral, 1 bilateral) and unilateral enlargement of the mandibular lymph nodes was observed in 1 cat. One cat had moderate medial retropharyngeal lymph node enlargement with heterogenous contrast enhancement.

***Dogs.*** MRIs of the brain and cervical spinal cord to the level of the second cervical vertebra were available for review in 7 dogs, and all were abnormal. For 1 dog, sagittal postcontrast T1W images of the cervical spine to the level of the 5th cervical vertebra were available for review. Findings for 2 dogs have been reported

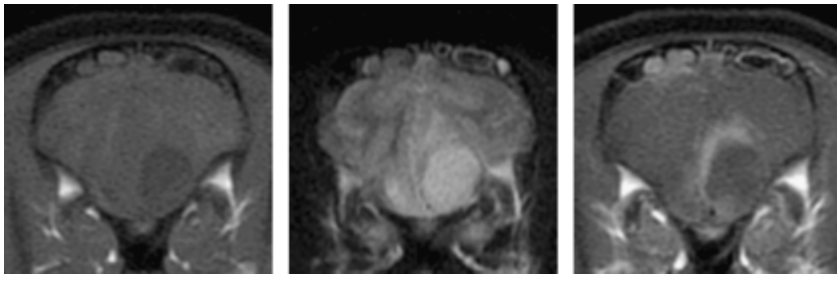

**Fig 1.** Transverse T1W precontrast (left), T2W (center), and T1W postcontrast (right) magnetic resonance imaging of the brain of a cat with cryptococcosis. There is a mass in the left forebrain causing rightward displacement of the falx cerebri. This mass is T2 hyperintense, T1 hypointense, and rim-enhancing. These signal characteristics are consistent with a pseudocyst lesion, confirmed by histopathology (see Fig 4).

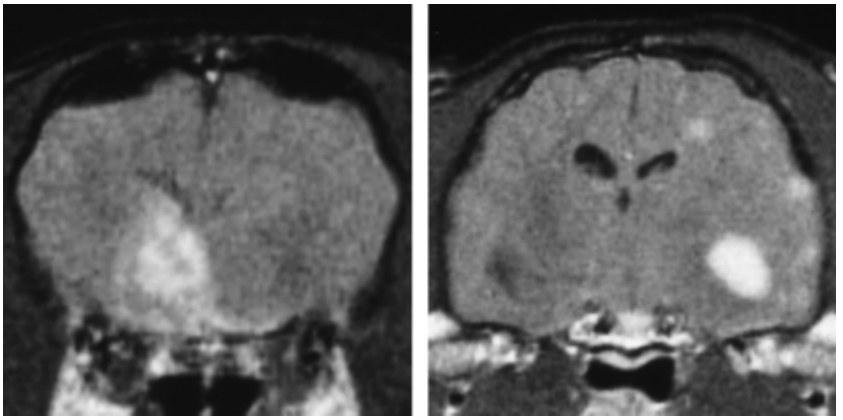

**Fig 2.** T1-weighted postcontrast transverse magnetic resonance images of a cat with cryptococcosis at the level of the frontal and temporal lobes. There are multifocal variably sized contrast-enhancing lesions throughout the brain parenchyma. Histopathology revealed granulomatous inflammatory lesions throughout the brain parenchyma, similar to the dog shown in Fig 4B.

previously.[22] Five dogs had multifocal parenchymal lesions, and 2 had isolated meningeal lesions (Fig 3). The most common sites for parenchymal lesions were the cerebrum (4), cerebellum (3), and cranial cervical spinal cord (2). Less common sites were the caudate nucleus (2); and thalamus, brainstem, hippocampus, optic chiasm, and periventricular region (1 each). A predilection for gray versus white matter was not noted. Lesions were hyperintense on T2W images. T1W signal intensity of lesions was iso- to hypo-intense (3), hyperintense (1), and both hypointense and hyperintense (1). Contrast enhancement was noted in 4 dogs with small multifocal parenchymal lesions, and was marked and uniform (2), or mild to moderate and heterogenous (2). Lesion

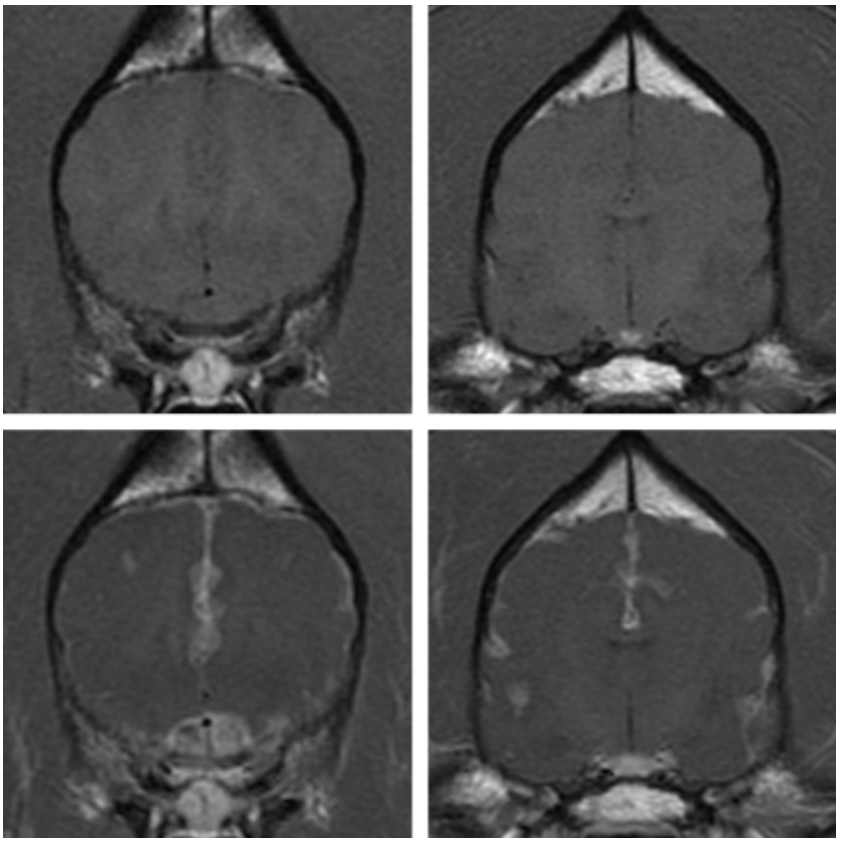

**Fig 3.** T1-weighted precontrast (top) and postcontrast (bottom) transverse MRI of the brain of a dog with cryptococcosis. There is severe diffuse meningeal enhancement surrounding the cerebrum and along the falx cerebri. The optic chiasm is enlarged and contrast-enhancing (bottom left).

borders were well-defined (2), or moderately defined (2). Ring-enhancing lesions or high T2, low T1 lesions were not detected. A mass effect was noted in 1 dog. Another dog had a dilated fourth ventricle. Surrounding T2 hyperintensity consistent with edema was seen in all dogs with parenchymal disease. A FLAIR sequence in 1 dog revealed hyperintense parenchymal lesions similar in character to those seen on the comparable T2W sequence.

Meningeal enhancement was present in 5 dogs, and was mild to moderate (3) or severe (2) (Fig 3). In 1 dog with severe enhancement, diffuse thickening and hyperintensity of the meninges were identified on precontrast T2W and FLAIR sequences. Distribution was diffuse or multifocal (4) or focal (1), and involved the dura (1) or both the dura and pia (2) (Fig 3). In 2 dogs it was not possible to determine the meningeal layer involved because of isolated spinal cord involvement. The cranial cervical spinal cord was involved in 3 dogs. Bilateral optic nerve involvement was present in 1 dog, manifested as asymmetrical nerve enlargement, T2 hyperintensity, and marked contrast enhancement of the nerve (Fig 3). Disease extension across the calvaria was suspected in 2 dogs, 1 with adjacent frontal sinus nodular lesions, and the other with extension across the cribriform plate. Moderately enlarged, nonuniformly enhancing, medial retropharyngeal, and mandibular lymph nodes were present in 1 dog.

A CT scan of the brain was available for 2 additional dogs. Ventriculomegaly and multifocal small contrast-enhancing lesions throughout the brain parenchyma were seen in 1 dog. In the 2nd dog, there was extension of a peripherally contrast-enhancing mass in the left caudal nasal cavity through the cribriform plate into the olfactory lobe and the retrobulbar space.

### *Gross Pathology*

Descriptions of gross CNS pathology at necropsy were available for review from 11 cats and 15 dogs. Gross pathological abnormalities were similar in dogs and cats, and included gray gelatinous mass lesions associated with the brain and spinal cord (4 cats, 2 dogs), meningeal edema and congestion (1 cat, 4 dogs), enlargement and softening of the olfactory bulbs (3 dogs), increased meningeal opacity (2 cats, 1 dog), multifocal parenchymal nodules (2 cats, 1 dog), intracranial mucopurulent material (2 dogs), multifocal meningeal nodules (2 dogs), and cerebral edema (1 cat, 1 dog). Cerebellar herniation through the foramen magnum was present in 3 cats and 1 dog.

### *Histopathology*

Archived histopathology specimens were available for review from 11 cats and 14 dogs. All animals had meningeal involvement. The infecting species was known for 1 cat (*C. gattii* molecular type VGIII) and 6 dogs (4 *C. neoformans* and 2 *C. gattii*). Three histopathologic patterns were identified, which could not be correlated with infecting species or history of treatment with antifungal or anti-inflammatory drugs (Table 2): (1) pseudocyst formation, with expansion of cryptococcal organisms along VR spaces with random, multifocal, variably sized, intraparenchymal pseudocysts; (2) diffuse meningitis alone, without pseudocyst formation or parenchymal involvement; and (3) meningoencephalitis without apparent pseudocyst formation.

**Table 2.** Histopathologic findings at necropsy and medication history in 11 cats and 14 dogs with CNS cryptococcosis.

| Variable | Cats (n = 11) | Dogs (n = 14) |
|---|---|---|
| CNS location | | |
| Cerebrothalamic | 11 | 13 |
| Cerebellum | 11 | 11 |
| Pons/medulla | 9 | 9 |
| Midbrain | 9 | 4 |
| Spinal cord | 2[a] | 6[b] |
| Ventricles | 3 | 3 |
| Choroid plexus | 2 | 5 |
| Lesion distribution | | |
| Pseudocyst | 9 | 7 |
| Meningitis only | 1 | 3 |
| Meningoencephalitis | 1 | 4 |
| Extraneural location | | |
| Nasal cavity or lungs | 7 | 11 |
| Any extraneural lesions | 7 | 14 |
| Organism numbers | | |
| 1+ | 2 | 3 |
| 2+ | 1 | 5 |
| 3+ | 8 | 6 |
| Inflammatory response | | |
| 0 | 4 | 0 |
| 1+ | 2 | 3 |
| 2+ | 4 | 2 |
| 3+ | 1 | 9 |
| History of antifungal drug therapy | 5 | 6 |
| History of glucocorticoid therapy | 4 | 5 |

[a]One cat also had spinal nerve root involvement.
[b]Two dogs had central canal involvement.

***Cats.*** Nine cats (including the cat with *C. gattii* infection) had diffuse, minimally inflammatory meningitis, with pseudocyst formation (Fig 4A and 4C). Lesion locations are shown in Table 2. One cat had diffuse meningitis alone, and extraneural lesions were not identified. The remaining cat had meningoencephalitis, with a diffuse, intensely inflammatory meningitis, and large, randomly dispersed, multifocal, granulomatous coalescing parenchymal lesions with sheets of necrosis. Lesions were absent in the lungs and nasal cavity, but infection was otherwise widely disseminated to a variety of organs.

MRIs had been performed in 3 of these cats, 2, 3, and 13 days before death. Two cats had the pseudocyst pattern and 1 had meningoencephalitis. The cats with pseudocysts had high T2, low T1 lesions, both with peripheral enhancement (Fig 1), 1 of which had some central enhancement. Meningitis was identified in 1 of these cats on MRI. The cat with meningoencephalitis had uniformly enhancing T2-hyperintense, T1-hypointense lesions (Fig 2).

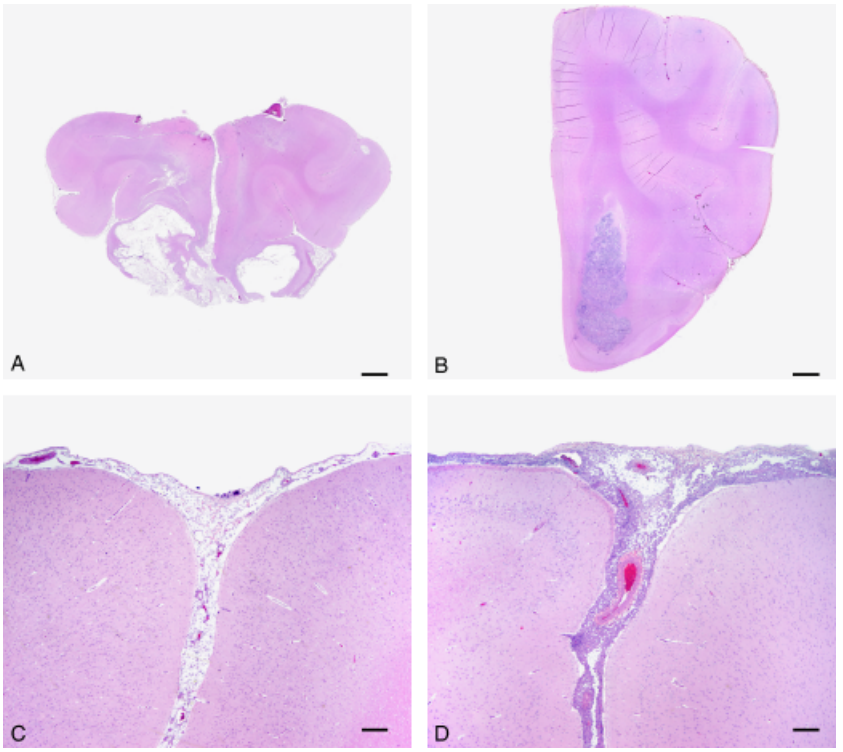


**Fig 4.** (**A**) Brain from the cat in Figure 1. The right and left frontal lobes have multiple large cryptococcal pseudocysts located ventrally, which are filled with gelatinous material. The meninges are expanded by similar gelatinous material. Hematoxylin and eosin (HE) stain, bar = 2 mm. (**B**) Brain from a dog with intensely inflammatory meningitis and granuloma formation. The right frontal lobe has a focal expansile intraparenchymal granuloma. HE stain, bar = 2 mm. (**C**) Brain from a cat with gelatinous pseudocyst formation. The meninges are thickened by few (1+) inflammatory cells and numerous (3+) organisms that extend to and distend the VR spaces. HE stain, bar = 260 μm. (**D**) Brain from a dog with gelatinous pseudocyst formation. The meninges and VR spaces are expanded by numerous (3+) inflammatory cells and organisms.

***Dogs.*** The pseudocyst pattern was identified in 7/14 dogs (including 3 with *C. neoformans* and 2 with *C. gattii* infection) (Fig 4D). Multifocal ependymitis (2) and mild choroid plexitis (3) also were seen in these dogs. In contrast to cats, 6 of the 7 dogs had a moderate to severe granulomatous meningeal inflammatory response admixed with organisms. Three of the 14 dogs (including a dog with *C. neoformans* infection) had mild meningitis alone, and few organisms were present. The 4 remaining dogs had meningoencephalitis characterized by multifocal, intensely inflammatory meningitis, with multiple, large, expansile coalescing granulomas dispersed randomly throughout the cerebrum (2) or restricted to the frontal lobe or occipital cortex (2) (Fig 4B). The inflammatory response was pyogranulomatous with central necrosis, abundant organisms, and an outer border of plasma cells and lymphocytes.

MRIs were performed in 4 of the dogs, 0, 1, 7 and 8 days before death. One dog with pseudocysts histologically had mild to moderate meningeal enhancement on MRI. Severe meningeal enhancement was noted in 1 dog with meningitis only (Fig 3). Two dogs had meningoencephalitis. One of these dogs had marked meningeal enhancement of the cervical spinal cord along with multiple contrast-enhancing mass lesions in the brain. The other had generalized mild meningeal enhancement and small punctate parenchymal lesions with heterogenous contrast enhancement. A CT scan 31 days before death and before the onset of neurologic signs, in 1 additional dog with the pseudocyst pattern, showed a peripherally enhancing nasal and retrobulbar mass with cribriform plate destruction but no evidence of CNS lesions.

### *Outcome*

***Cats.*** Six (23%) cats were alive at the completion of the study. Five of these cats were alive at ≥12 months, and 1 was alive 7 days after diagnosis. Four cats were lost to follow-up 3–40 days after diagnosis. Sixteen (62%) cats died (5) or were euthanized (11) from 0 to 19 days after diagnosis. Death or euthanasia was related to cryptococcosis in all 16 cats. Two cats developed respiratory or cardiac arrest after recovery from CSF collection with or without imaging. Nine (35%) cats were not treated, because they were euthanized before diagnosis (2); they were euthanized or died after diagnosis because of clinical deterioration, perceived poor prognosis, or financial limitations (5); or they were discharged before treatment was initiated and were lost to follow-up (2). Median survival time (MST) after diagnosis for all cats was 13 days (0–4,050 days), and was 19 days for cats treated with antifungal drugs. However, the MST was not reached for cats surviving ≥3 days after diagnosis.

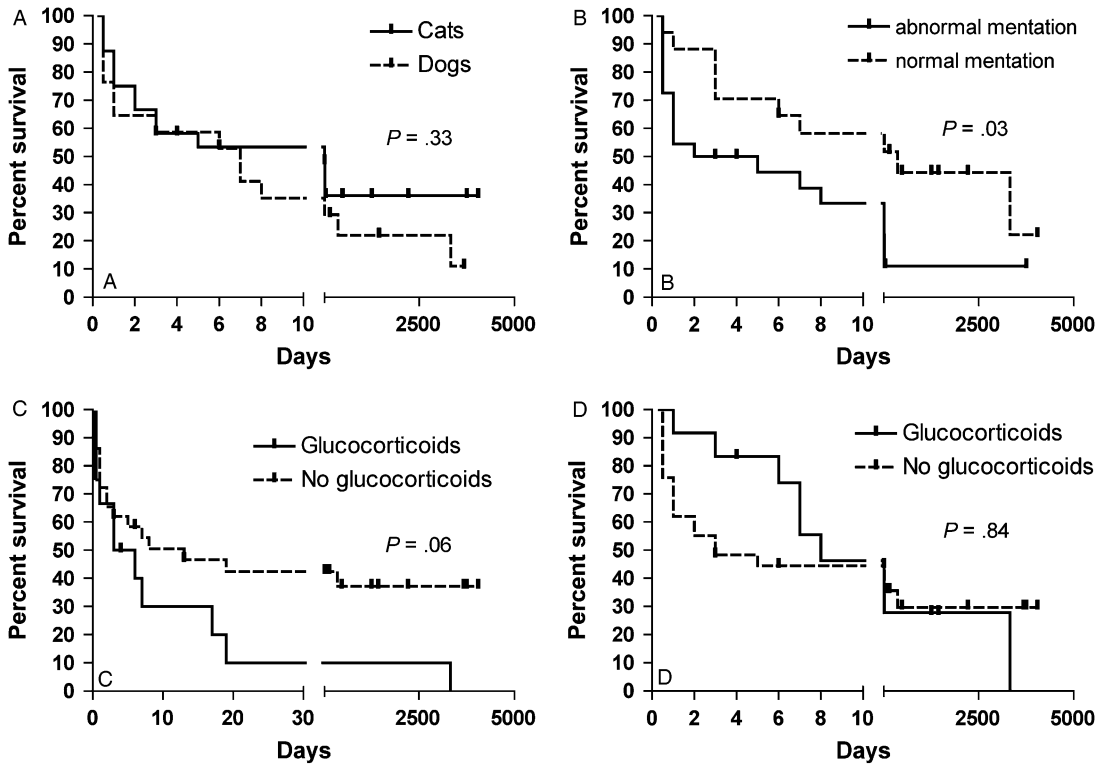


**Fig 5.** Kaplan-Meier survival curves for 26 cats and 21 dogs after diagnosis with CNS cryptococcosis. (**A**) Influence of host species on outcome. (**B**) Influence of mental status at presentation on outcome. (**C**) Influence of glucocorticoid therapy before diagnosis. (**D**) Influence of glucocorticoid therapy after diagnosis.

Seventeen (65%) cats were treated with antifungal drugs. Seven cats were treated with a single drug, either fluconazole (6) or ketoconazole (1). Ten cats were treated with multiple antifungal drugs, including liposomal amphotericin B (4), SC (4) or IV (1) deoxycholate amphotericin B, flucytosine (7), or fluconazole (8). Three were treated with flucytosine, fluconazole, and amphotericin B; 3 with fluconazole and amphotericin B; and 2 with fluconazole and flucytosine. One of these cats was treated with surgical debulking of a mediastinal mass, but experienced cardiac arrest postoperatively. Flucytosine was tolerated by all but 1 cat, which developed gastrointestinal signs in association with flucytosine therapy. There was no difference in survival between cats administered single versus multiple antifungal drugs, but 4 of 10 cats receiving multiple antifungal drugs had long-term ($>12$ months) survival times (MST not reached), whereas only 1 of 7 cats receiving single antifungal drugs had a survival time $>12$ months (MST 19 days). Of the 5 cats with long-term survival times, 2 experienced periodic exacerbations of disease and 1 had a persistently increased titer, but all were alive at writing.

***Dogs.*** All dogs except 3, which were lost to follow-up at 3, 36, and 120 months after diagnosis, were dead at completion of the study. Seventeen dogs died or were euthanized because of neurologic deterioration from cryptococcosis and 1 dog was euthanized for an unrelated illness 9 years after being diagnosed with cryptococcosis. Three dogs developed respiratory or cardiac arrest after recovery from CSF collection with or without imaging. Nine (45%) dogs were not treated, because they died or were euthanized just before diagnosis (4), or immediately after diagnosis because of clinical deterioration and a perceived poor prognosis, sometimes with client financial limitations (5). Five (25%) dogs survived $\geq$5 months from diagnosis, and 15 (75%) survived $\leq$8 days. MST from diagnosis, regardless of treatment, was 7 days (0–3,680 days), and after institution of antifungal treatment was 12 days. MST increased to 190 days for dogs surviving $\geq$4 days from diagnosis. Overall, no differences in survival from diagnosis were detected between dogs and cats (Fig 5A). However, within the first 3 months of illness, mortality was higher in dogs than in cats ($P = .02$).

Eleven (52%) dogs were treated with systemic antifungal drugs. Seven were treated with a single drug (fluconazole [5] or itraconazole [4]; treatment of 2 dogs was changed from 1 azole to another). Four dogs were treated with combinations of liposomal amphotericin B (3), deoxycholate amphotericin B (2), flucytosine (2), fluconazole (3), or itraconazole (1). One of the dogs treated with flucytosine developed a severe cutaneous drug eruption. There was no difference in survival between dogs treated with single and dogs treated with multiple antifungal drugs. Four of the 7 dogs receiving single antifungal drugs had survival times $\geq$5 months. Of the 5 dogs with long-term survival times, 2 were disease-free and off therapy, 1 had been euthanized after a year because of

**Table 3.** Influence of variables in 26 cats and 21 dogs with CNS cryptococcosis on outcome.

| Variable | Number of Cats | Number of Dogs | MST (days) | Hazard Ratio | 95% CI | *P* Value |
|---|---|---|---|---|---|---|
| Altered mental status on presentation | | | | | | |
| Yes | 18 | 9 | 3.5 | 2.2 | 1.1–5.5 | .03 |
| No | 7 | 11 | 365 | | | |
| History of seizures | | | | | | |
| Yes | 8 | 9 | 19 | 0.5 | 0.2–1.1 | .08 |
| No | 18 | 12 | 6 | | | |
| Antemortem CSF collection | | | | | | |
| Yes | 11 | 13 | 7 | 0.9 | 0.4–2.0 | .77 |
| No | 15 | 8 | 6 | | | |
| Glucocorticoid treatment before diagnosis | | | | | | |
| Yes | 7 | 7 | 4.5 | 2.0 | 1.0–5.8 | .06 |
| No | 19 | 14 | 13 | | | |
| Treatment with glucocorticoids after antifungal therapy | | | | | | |
| Yes | 4 | 6 | 8 | 0.9 | 0.4–2.1 | .84 |
| No | 22 | 15 | 3 | | | |

CNS, central nervous system; CSF, cerebrospinal fluid; MST, median survival time.

persistent neurological signs, 1 had intermittent seizures but was otherwise well, and 1 was lost to follow-up.

Because outcome did not differ between dogs and cats, groups were combined to evaluate factors influencing outcome (Table 3; Fig 5). The only variable associated with decreased survival was altered mental status on presentation ($P = .03$). Although glucocorticoid use after diagnosis did not influence long-term outcome, survival in the first 10 days was improved with glucocorticoid use ($P = .008$).

## Discussion

This study compares the clinical features of canine and feline cryptococcosis affecting the CNS, reports typical findings on advanced imaging, and correlates imaging findings with gross and histopathological findings, which has not been previously performed in cats and dogs. In addition, long-term outcome with treatment is reported, which has not been studied in a population of animals with CNS cryptococcosis in the United States.

Signs relating to CNS involvement were similar to those described previously,[4,5,16–21] often reflecting the neuroanatomical location of CNS lesions. Apparent spinal or head pain was present in many animals, generally involving the cervical region in dogs and the thoracolumbar or lumbosacral spine in cats. However, despite the high prevalence of meningeal involvement seen at necropsy in this study, hyperesthesia was rarely reported. Extraneural signs in cats were of longer duration compared with dogs, 1 cat having signs of chronic cryptococcal rhinosinusitis for 4 years before developing CNS signs. This may reflect differences in cryptococcal strains infecting cats compared with dogs, or differences in the immune response to the organism among host species. Chronic infections, sometimes associated with minimal signs of disease, have been reported previously in dogs, cats, and humans.[4,26–28]

In this study, CSF analysis was useful for diagnosis of cryptococcal meningitis and meningoencephalomyelitis. The higher magnitude of the increased CSF protein concentration seen in dogs may reflect the more profound inflammatory response to the organisms seen within the brain parenchyma, and possibly the difference in the nature of the cellular immune response in dogs compared with cats, which was primarily a mixed or granulomatous pleocytosis in dogs compared with a primarily neutrophilic response in cats. The fact that abundant organisms were identified within the meninges at histopathology in some animals that lacked visible organisms within the CSF emphasizes the need to perform fungal cultures and antigen testing on all animals in which cryptococcosis is suspected.

Although MRI findings in humans with CNS cryptococcosis have been well described,[10–12] there are only isolated case reports documenting findings in dogs and cats with cryptococcosis, with no direct correlation made to histopathologic findings.[18,20–22,24] In humans, noncontrast enhancing lesions that are hyperintense on T2W and have lower intensity on T1W images (high T2, low T1 lesions) within the thalamus, basal ganglia, periventricular white matter, and cerebellum represent gelatinous pseudocysts. These result from a proliferation of fungi and gelatinous capsular material in the VR spaces. Noncontrast enhancing lesions and an absence of meningeal enhancement are common findings in human immunodeficiency virus-infected patients with cryptococcal meningoencephalitis because of an impaired inflammatory response to the organism.[12] Ring enhancement and multiple enhancing parenchymal nodules are reported less commonly. Parenchymal cryptococcomas with uniform contrast enhancement tend to occur in immunocompetent individuals.[13,14] The presence of gelatinous pseudocysts in cats in this study was reflected by the presence of multifocal high T2, low T1 parenchymal mass lesions, which enhanced only peripherally with contrast, reflecting a relative lack of inflammation within the pseudocysts. FLAIR imaging from 1 cat in this study suggested the material within the lesion was cellular or proteinaceous, although this was

not confirmed by histopathology. Standard MRI sequences appear insensitive for documenting meningitis in cats, and a normal brain MRI did not rule out CNS cryptococcosis. Dogs, by comparison, had a marked inflammatory response to CNS *Cryptococcus* spp. infection histologically, and frequently showed ill-defined contrast-enhancement of parenchymal lesions on MRI as well as meningeal enhancement.

Cryptococcal species and strains also may vary in their ability to incite an inflammatory response.[15] *C. gattii* induces minimal inflammation in mouse models when compared with *C. neoformans*. The relative lack of inflammation in cats relative to dogs as determined by histopathology may reflect differences in organism strains infecting cats compared with dogs,[1] although additional studies including more isolates of known identity are required to verify this hypothesis. Alternatively, an underlying unrecognized immunodeficiency may exist that impairs the inflammatory response to the organism in cats. Interestingly, it is dogs, rather than cats, that develop widespread dissemination of infection to a variety of parenchymal organs, a feature of AIDS-related cryptococcosis in humans.[8]

In this study, MSTs were short owing to rapid deterioration of many patients after presentation, sometimes before achieving a diagnosis. Survival times did not differ between cats and dogs, but within the first 3 months of clinical signs, mortality was higher in dogs than in cats, and no dogs were alive at the end of the study, compared with 5 cats ($P = .05$). Prolonged survival times did occur in some patients. Survival $\geq$3 days after diagnosis in cats and $\geq$4 days after diagnosis in dogs was associated with dramatic prolongation in the MST after survival curve analysis. These data suggest that wherever possible, attempts should be made to treat cats and dogs with CNS cryptococcosis for $\geq$4 days, as long-term survival times may be possible.

In human patients with cryptococcomas, surgical debulking has been recommended for large ($\geq$3 cm) lesions with mass effect.[29] Whether surgical debulking might benefit animals with CNS cryptococcomas requires further study. Surgical debulking was offered to the owners of 1 cat with a large cryptococcoma, but the owners elected euthanasia. In the future, advanced imaging by MRI may prove useful for identification of small animal patients that may benefit from a surgical approach.

Prognostic variables identified for CNS cryptococcosis in humans have included abnormal mental status, history of seizures, high antigen titers within the serum and CSF, poor host inflammatory response (CSF cell count $<$20/$\mu$L), and high CSF opening pressure.[30,31] We chose not to evaluate CSF TNCC because of the low number of samples with cell counts $<$20 cells/$\mu$L. Seizures and high serum CALAS titers were not associated with a poor outcome in this study, but altered mental status was a negative prognostic factor. Altered mental state may reflect globally increased intracranial pressure with CNS infection or the burden of lesions within the CNS.

The beneficial effects of glucocorticoid therapy on survival within the first 10 days may have been related to modulation of the inflammatory response after fungal death. The use of glucocorticoids to treat CNS cryptococcosis in humans is controversial. Favorable clinical responses were documented in immunocompetent humans infected with *C. gattii* after glucocorticoid therapy.[32] Judicious use of dexamethasone in conjunction with antifungal drugs also may be beneficial in the short term for dogs and cats with CNS cryptococcosis. Many animals that underwent treatment for CNS cryptococcosis deteriorated precipitously in the first few days of antifungal treatment, such that euthanasia was recommended or requested by the owner. However, with meticulous supportive care and the use of glucocorticoids during this phase, some of these animals had unexpected recoveries.

Concern has been raised regarding increased likelihood of cerebellar herniation after CSF collection in dogs and cats with cryptococcosis.[4] Although some cats and dogs in our study failed to recover from anesthesia after CSF sampling, there were many animals that recovered without adverse outcome or clinical deterioration, and a history of CSF sampling did not significantly influence outcome. Nevertheless, in order to limit cost and mortality associated with invasive diagnostic procedures requiring anesthesia, when possible, a diagnosis of cryptococcosis should be made on the basis of serum antigen testing or aspiration cytology of other organs. Negative results using these methods do not rule out cryptococcosis,[1] so when progressive CNS disease is present and a diagnosis of cryptococcosis cannot be made by serum antigen testing or aspiration cytology of other organs, CSF collection should be considered for diagnosis.

This study establishes the clinical presentation, CSF findings, MRI appearance, pathology, and outcomes of therapy of CNS cryptococcosis in a subset of dogs and cats in California. Limitations of this study related to its retrospective nature and the small number of cases for which both MRI and pathology findings were available. The identity of the cryptococcal species and molecular type were unknown for many cases. Not all animals had organisms detected within the CNS by CSF cytology or histopathology, although CNS signs in the remaining animals, the majority of which had retinal lesions, occurred coincident with the diagnosis of extraneural cryptococcosis and other causes of the CNS signs were unlikely. Additional prospective studies with more animals that correlate infecting cryptococcal species with MRI and pathology findings are indicated in dogs and cats in the future. The results for outcome were limited by the fact that some animals were lost to follow-up, treatment protocols were not uniform, and antifungal drug susceptibility testing was not performed before treatment. Some animals were euthanized based on perceived poor prognosis or client financial limitations, and may have in fact responded to treatment. Nevertheless, many patients underwent rapid clinical deterioration within hours of presentation, and others had prolonged survival times after diagnosis after antifungal treatment.

## Footnotes

[a] Stevenson TL, Dickinson PJ, Sturges BK, et al. Magnetic resonance imaging of intracranial cryptococcosis in dogs and cats. J Vet Intern Med 2004;18:409 (abstract).
[b] 9800 Third Generation CT scanner, General Electric Co, Milkwaukee, WI
[c] fx/I Helical CT scanner, General Electric Co
[d] Conray 400, Mallinckrodt Inc, St Louis, MO
[e] Isovue 370, Bristol Myers Squibb Co, New York, NY
[f] Signa LX, General Electric Co
[g] Resonex 5000, Resonex Inc, Sunnyvale, CA
[h] Magnevist, Bayer HealthCare, Wayne, NJ
[i] GraphPad Prism, version 4.00, San Diego, CA

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