Cerebral Blastomyces dermatitidis infection in a cat

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Case Description—An 8-year-old domestic shorthair cat was evaluated because of signs of depression, circling, and visual deficits.

Clinical Findings—The cat had no cutaneous lesions, and results of an ophthalmologic examination and thoracic radiography were within reference limits. Computed tomography of the brain revealed a mass lesion involving the right parietal, temporal, and occipital lobes; the mass was in broad-based contact with the skull and smoothly marginated and had strong homogenous enhancement after contrast agent administration. During craniectomy, samples of the mass were collected for cytologic and histopathologic evaluations and microbial culture. A diagnosis of Blastomyces dermatitidis-associated meningoencephalitis with secondary pyogranulomatous inflammation was made.

Treatment and Outcome—Amphotericin B (0.25 mg/kg [0.11 mg/ml], IV) was administered on alternate days (cumulative dose, 1.75 mg/kg [0.8 mg/ml]). To minimize the risk of nephrotoxicosis, assessments of serum biochemical variables (urea nitrogen and creatinine concentrations) and urin analyses were performed at intervals. The third dose of amphotericin B was postponed 48 hours because the cat became azotemic. The cat subsequently received fluconazole (10 mg/kg [4.5 mg/ml], PO, q 12 h) for 5.5 months. Six months after discontinuation of that treatment, the cat appeared healthy and had no signs of relapse.

Clinical Relevance—Brain infection with B dermatitidis is typically associated with widespread disseminated disease. The cat of this report had no evidence of systemic disease. Blastomy- cosis of the CNS should be considered as a differential diagnosis for brain lesions in cats from areas in which B dermatitidis is endemic. (J Am Vet Med Assoc 2007;231:1210–1214)

### Case Description

An 8-year-old male neutered domestic shorthair cat was referred to the College of Veterinary Medicine, University of Tennessee because of circling to either side, head pressing, and intermittent blindness of 3 days’ duration. The cat’s body weight had also decreased from 6.1 kg (13.5 lb) to 5.3 kg (11.6 lb) during the preceding 6 months despite an apparently normal appetite. A CBC, plasma biochemical analyses, thyroid hormone concentration assessment, urinalysis, systolic blood pressure measurement, thoracic and abdominal radiography, and abdominal ultrasonography performed by the referring veterinarian revealed no abnormalities except for a cysto- lith. Results of tests for FeLV antigen, FIV antibody, and Mycoplasma hominis DNA were negative; serum anti-Toxoplasma gondii IgM antibody was not detected, but the anti-IgG antibody titer was 1:512 and the anti-feline coronavirus antibody titer was 1:1,600. Prior to referral, the cat had received amoxicillin trihydrate-clavulanate potassiuma (11.8 mg/kg [5.4 mg/lb]), PO, q 12 h; enrofloxacinb (3.2 mg/kg [1.5 mg/lb]), PO,

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<th>PET</th>
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<td>Computed tomography</td>
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q 12 h); oral fatty acid and vitamin E supplementationc; and single doses of dexamethasonec (2 mg/kg [0.9 mg/lb], SC), phenobarbital (2 mg/kg, IV), and cobalamin (188 µg/kg [85.5 µg/lb], IM).

On initial physical examination, the cat had signs of depression and an apathetic attitude; it had a tendency to turn and circle to the right. There was anisocoria (the right pupil was larger than the left). Menace response was absent on the left and inconsistent on the right; pupillary light reflexes were normal in both eyes. The other cranial nerves, postural reactions (proprioceptive positioning, visual and tactile placing, hemiwalking, and hopping), and spinal cord reflexes were considered normal. No active lesions were detected via ophthalmologic examination, although there was an old retinal scar in the right eye. The depressed attitude, circling, and blindness indicated a lesion of the right cerebral hemisphere. The anisocoria was consistent with increased intracranial pressure causing attenuation of the midbrain or the parasympathetic portion of the right oculomotor nerve.

Thoracic radiography (3 views) revealed no abnormalities. Crystalline fluids were administered IV (2 mL/kg/h) prior to anesthesia. The cat was premedicated with butorphanol (0.4 mg/kg [0.18 mg/lb], IV) and glycopyr-
Helical CT of the brain was performed before and after administration of iohexol (350 mg of iodine/mL, 2.2 mL/kg [1 mL/lb], IV). Transverse CT images were obtained from the level of the cribriform plate to the level of the C1 vertebra (slice thickness, 3 mm). Image evaluation was performed in a soft tissue and bone window. On the images obtained before administration of contrast agent, a mass lesion associated with the right cerebrum, involving parietal, temporal, and occipital lobes was evident; the mass was slightly hyperattenuated, compared with adjacent normal brain parenchyma. After administration of contrast agent, the mass had pronounced and homogenous enhancement in the CT images. The primary differential diagnosis was a meningioma; additional differential diagnoses were other neoplasms and granulomatous lesions of infectious or noninfectious etiologies.

The cat underwent a right rostroventral cranietomy to remove the mass and obtain histologic diagnosis. No abnormalities were evident when the bone flap was removed. On opening the dura, an area of the parietal cortex was swollen, slightly discolored, and protruded beyond the edges of the craniectomy. Samples of the mass were obtained for cytologic and histopathologic evaluations and microbiologic culture. The abnormal-appearing tissue was surgically debulked with suction and blunt dissection. There was no clear demarcation between normal and abnormal tissue.

On completion of the procedure, the cat was allowed to recover from anesthesia. Postoperative analgesia consisted of buprenorphine (0.01 mg/kg, IV, q 6 h). The cat’s neurologic status temporarily worsened immediately after surgery, and a single bolus of mannitol was administered (0.5 g/kg [0.23 g/lb], IV, over a 20-minute period) to control presumed brain edema that developed secondary to surgical manipulation. Prednisone was also administered (1.0 mg/kg [0.45 mg/lb], PO, q 24 h) for 3 days to reduce post-surgical swelling of the cerebrum.

Impression smears prepared from the brain biopsy specimens were highly cellular and consisted of many nondegenerate neutrophils and macrophages; few multinucleated giant cells; and many extracellular (and occasionally intracellular), deeply basophilic, broad-based budding yeast with thick, refractile cell walls. These yeast forms measured 10 to 20 µm in diameter and were consistent with Blastomyces dermatitidis (Figure 2). This diagnosis was confirmed by findings of the histologic evaluation and results of fungal culture of specimens of the mass. Blastomyces dermatitidis antigens were detected in a urine sample obtained after surgery, whereas the result of an agar gel immunodiffusion test for anti-B der-

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**Figure 1**—Transverse CT images (obtained after IV administration of a contrast agent) of the brain of a cat evaluated because of signs of depression, circling, and visual deficits. A—Image at the level of the tympanic bullae and mesencephalon. Notice that there is a contrast-enhanced broad-based mass associated with the right cerebrum and involving the parietal, temporal, and occipital lobes (arrows). B—Image at the level of the pituitary fossa and diencephalon. Notice the marked leftward shift of the falx cerebri (arrow). Compared with normal brain parenchyma, the white matter tracts are hypoattenuated, which is consistent with edema. R = Right.
**matritidis** antibodies performed on a serum sample that had been obtained before surgery was negative. A jugular catheter was placed to facilitate parenteral antifungal treatment. Amphotericin B (0.25 mg/kg [0.11 mg/lb]) was diluted in 60 mL of 3% dextrose solution, protected from light, and administered as a continuous rate infusion over a 6-hour period; this was repeated on alternate days until 5 doses had been administered. Diuresis was performed via IV administration of a crystalloid solution at twice the maintenance rate until completion of the second dose of amphotericin B, after which fluid administration was tapered over 24 hours and eventually discontinued. To assess renal status, plasma biochemical variables were assessed prior to each amphotericin B treatment. High concentrations of BUN (51 mg/dL; reference interval, 17 to 35 mg/dL) and creatinine (2.3 mg/dL; reference interval, 0.7 to 2.1 mg/dL) were detected prior to the third dose of amphotericin B; this necessitated postponement of treatment for 48 hours and reinstatement of maintenance IV fluids until discharge of the cat from the hospital. The fluid rate was increased to twice the maintenance rate 4 hours before and 2 hours after subsequent amphotericin B treatments. Thereafter, the renal plasma biochemical variables remained within the reference intervals.

Ten days after craniectomy, PET of the brain was performed. One hour after injection of 1.39 mCi of fluorine 18 (18F)-fluoro-2-deoxyglucose, the cat was anesthetized as before and positioned in sternal recumbency. A 20-minute acquisition was performed with the cat's head centered in the gantry of a PET scanner designed for use with laboratory animals. There was a large photopenic void in the right parietal or temporal lobe corresponding to the area of the previous surgery; along the cranial margin of the right parietal lobe, photopeny corresponded to the area of the previous surgery; along the cranial margin of the surgical site, there was an area of mild increased radiopharmaceutical uptake that was more metabolically active than the adjacent cerebral cortex (Figure 3). However, the PET imaging confirmed that most of the lesion had been successfully excised.

The cat was discharged from the hospital 12 days after surgery and received another 2 doses of amphotericin B (administered on alternate days by the referring veterinarian), such that the cumulative dose received was 1.75 mg/kg (0.8 mg/lb). After the last dose of amphotericin B, the cat developed a persistently high rectal temperature (39.7°C to 40.2°C [103.5°F to 104.3°F]; upper reference limit, 39.2°C [102.5°F]) for 24 hours. Treatment was then switched to fluconazole (10 mg/kg [4.5 mg/lb], PO, q 12 h) for 170 days. Hepatic plasma biochemical variables were monitored intermittently during the period of fluconazole treatment, and no abnormalities were detected. At the time of discontinuation of the treatment, the cat had a serum anti-T. gondii IgG antibody titer of 1:4,096; clindamycin (15 mg/kg [6.8 mg/lb], PO, q 12 h) was administered for 28 days. The cat's neurologic status was apparently normal at the time that fluconazole administration was discontinued and remained unchanged 6 months later at a follow-up examination.

**Discussion**

Blastomycosis is a rare systemic mycotic infection in cats that is caused by the dimorphic fungus *B. dermatitidis*. In North America, the organism is endemic in the Mississippi, Missouri, and Ohio River Valleys, although sporadic outbreaks of infection have been reported in the mid-Atlantic states. The infectious mycelial phase grows in moist, acidic soil and develops microscopic conidia. Pulmonary disease associated with inhalation of those conidia can range from a self-limiting local infection to severe pyogranulomatous pneumonia. In 3 case series of blastomycosis in cats, the most frequently affected organs were the lungs, CNS, skin, regional lymph nodes, eyes, gastrointestinal tract, and urinary system. Disseminated blastomycosis has been associated with a guarded to poor prognosis; for most reported cases the diagnosis was made at necropsy.

Infection with *B. dermatitidis* that leads to neurologic involvement has been associated with widely disseminated disease. Therefore, the cat of this report was unusual in that it had cerebral blastomycosis but no other systemic lesions. There were no cutaneous abnormalities, and findings of an ophthalmologic examination and thoracic radiography were unremarkable. The neuroanatomic localization of the fungal infection was in the right cerebral hemisphere. In a retrospective study, 2 of the 3 most common signs of intracranial neoplasia in 160 cats were altered mental state (42 cats [26.2%]) and circling (36 [22.5%]); blindness (16 [10%]) and head pressing (15 [9.4%]) were also evident. More specifically, the combination of clinical signs in the cat of this report suggested a cerebral lesion. The direction of circling is typically ipsilateral to the lesion, although the direction can be contralateral to the lesion. In the cat of this report, anisocoria with mydriasis in the right eye could be explained by compression of the ipsilateral oculomotor nerve. The normal postural reactions indicated that the lesion spared the upper motor ascending sensory and descending upper motor neurons involved in postural reactions.

![Figure 3](image-url)
On the basis of histologic findings and fungal culture results, the mass removed from the cat of this report was identified as a *B dermatitidis*-associated granuloma of the brain. Meningioma is the most commonly diagnosed supratentorial lesion in cats.\(^7\)\(^-\)\(^11\) Computed tomographic imaging criteria for the diagnosis of meningiomas include spherical to ovoid shape of the mass with broad-based contact to the underlying skull; smooth to irregular margins; tissue displacement (but not infiltration) by the mass; isoattenuation or hyperattenuation of the mass, compared with normal brain parenchyma; and strong uniform contrast enhancement. Concurrent edema is common\(^12\) and, in most cases of cats with meningioma, is mild and peritumoral. However, moderate or severe edema can develop.\(^13\) All these imaging features were identified in the cat of this report, and meningioma was therefore the initial primary differential diagnosis. Additional differential diagnoses were other neoplasms and granulomatous lesions of infectious or noninfectious etiologies.\(^12\),\(^14\) The CT appearance of *B dermatitidis*-associated granulomas in humans is nonspecific; lesions can be isodense to slightly hyperdense. The imaging findings alone are insufficient to make a diagnosis, and biopsy is necessary to confirm the diagnosis. Biopsy may occasionally be surrounded by a small area of edema.\(^15\) In a report\(^16\) that detailed the CT findings of intracranial blastomycosis in a dog, marked periventricular enhancement and ventriculomegaly were described. For that dog, a diagnosis of pyogranulomatous meningoencephalitis and ependymitis was made on the basis of necropsy findings. The authors of that report\(^16\) proposed that bloom artifacts (the appearance of false thickness in a strongly hyperdense structure) caused by the skull may have obscured evidence of meningitis, whereas ependymitis is a rare manifestation of intracranial blastomycosis in dogs.

Blastomycosis may be diagnosed via cytologic examination of impression smears of cutaneous lesions or fluids (CSF, vitreous humor, bronchoalveolar lavage fluid, peritoneal lavage fluid, urine, and prostatic washes) and fine-needle aspirates of affected tissues (peripheral lymph nodes, lungs, and joints).\(^2\) The 10- to 20-μm-diameter, broad-based budding yeast has a characteristic appearance, which may be best observed by use of special stains (ie, periodic acid-Schiff, Grindley’s fungal, and Gomori’s methenamine silver stains).\(^1\) The organism often causes a pyogranulomatous or, less commonly, supplicative inflammation. Fungal culture of exudates, fine-needle aspirates, or biopsy material may identify *B dermatitidis*. Microbial culture should be done by experienced technicians because transmission of *B dermatitidis* from a culture specimen to humans has been reported.\(^17\)

At present, serologic testing for *B dermatitidis* in infected dogs involves an agar immunodiffusion test against a crude yeast autolysate. This assay may achieve 90% sensitivity in dogs with chronic disease.\(^18\) In 2 reports, 1 of 3 and 1 of 4 cats with blastomycosis yielded positive results by use of this assay. There is also a urine antigen assay that is quite sensitive for diagnosis of blastomycosis in dogs.\(^19\) In the cat of this report, a urine sample collected after surgery yielded positive results by use of this assay.\(^20\),\(^21\)

Early reports\(^2\),\(^3\) of case series of cats with blastomycosis identified poor results of treatment. This may reflect the low rate of antemortem diagnosis and lack of azole drugs. In a more recent report\(^3\) of 8 cats with *B dermatitidis* infection, 2 cats were euthanized, and of the remaining 6 cats that were treated, 3 survived. Two of the surviving cats received itraconazole, whereas the third cat that had ocular and CNS signs was given fluconazole (5 mg/kg [2.3 mg/lb], PO, q 12 h) and was alive 1 year after treatment.

Amphotericin B is recommended as an initial treatment of humans\(^21\) and dogs\(^22\) with mycotic infections of the CNS. However, toxic effects of the drug on the kidneys limit the cumulative dose that can be administered, and CNS penetration is poor. Patients to which amphotericin B is administered need to be evaluated for nephrotoxicosis before each dose. An initial single IV dose of 0.25 mg of amphotericin B/kg has been recommended in cats, followed by an increased dose of 0.5 mg of amphotericin B/kg administered 3 times each week (provided that the BUN concentration does not exceed 50 mg/dL).\(^23\) For a cumulative dose of 4 mg/kg (1.75 mg/lb), diuresis has been suggested to reduce the nephrotoxic effects of amphotericin B.\(^24\) In the cat of this report, discontinuation of IV fluid therapy after the second amphotericin B dose did result in mild azotemia, which resolved completely when fluid diuresis was reinstated. At present, it is recommended that amphotericin B is administered via constant rate infusion over a 15-minute period; in the experience of one of the authors, increasing the duration of the administration period may reduce the risk of nephrotoxicosis.

Triazole antifungal drugs inhibit the P450 enzymes that are necessary for the development of ergosterol. Fluconazole at a dose of 25 to 50 mg administered orally twice daily has been advocated for the treatment of CNS mycoses in cats because the drug can cross the blood brain barrier. It has low protein binding and is only slightly hydrophobic; in CSF, concentrations can reach 60% to 80% of that in serum.\(^6\)

It is difficult to determine optimal duration of treatment in animals with cerebral fungal infection. Via PET, small *B dermatitidis*-associated granulomas in dogs have been detected.\(^23\)-\(^27\) Use of the radiotracer \(^18\)F-fluoro-2-deoxyglucose permits PET imaging of macrophages with enhanced glycolysis. Positron emission tomography has typically been used to detect and stage malignancies; however, this technique also has applications in infectious and inflammatory conditions.\(^5\) In the cat of this report, a postoperative PET scan was performed to establish baseline metabolic activity within the resected area. Results indicated that there was 1 area along the cranial margin of the surgical site that was slightly more metabolically active than the surrounding cerebral cortex. It could not be determined whether this represented an inflammatory reaction associated with surgery or an area of residual infection. A repeat PET examination was planned to measure residual metabolic activity and help determine the duration of treatment; however, the owner declined that option, and the cat was treated empirically for 5.5 months instead. As
this case report illustrates, *B dermatitidis* infection can be limited to the cerebrum and may be successfully treated with a combination of amphotericin B and fluconazole. Blastomycosis of the CNS should be considered as a potential differential diagnosis for intracranial masses in cats in areas in which *B dermatitidis* is endemic.

a. Clavamox, GlaxoSmithKline, Research Triangle Park, NC.


c. DermaCps, DVM Pharmaceuticals, JVA Corp, Miami, Fla.

d. Azium, Schering Plough, Kenilworth, NJ.


f. Omnipegue 350, Amersham Health, Princeton, NJ.

g. MiraVista Diagnostics, Indianapolis, Ind.


i. MicroPET P4 scanner, Siemens Preclinical Molecular Imaging/Concorde, Knoxville, Tenn.

j. Dilucan, Pfizer, New York, NY.


l. Sporanox, Janssen Pharmaceutica, Titusville, NJ.

m. Diflucan, Pfizer, New York, NY.

n. Concorde, Knoxville, Tenn.


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v. Dilucan, Pfizer, New York, NY.


x. Sporanox, Janssen Pharmaceutica, Titusville, NJ.

References


