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BLASTOMYCOSIS IN NONDOMESTIC FELIDS


Abstract: Blastomycosis was diagnosed in six nondomestic felids from eastern Tennessee, including two Asian lions (Panthera leo persicus), one African lion (Panthera leo), one Siberian tiger (Panthera tigris), one cheetah (Acinonyx jubatus), and one snow leopard (Panthera uncia). Clinical signs included lethargy, anorexia, weight loss, dyspnea, sneezing, ataxia, and paresis. Variable nonspecific changes included leukocytosis, mononcytosis, moderate left shift of neutrophils, moderate hypercalcemia, hyperproteinemia, and hyperglobulinemia. Thoracic radiographs revealed interstitial and alveolar changes, consolidation or collapse of a lung lobe, bullae formation, and a pulmonary mass. Agar gel immunodiffusion (AGID) serology for Blastomyces dermatitidis was performed in five felids and was positive in three. The tiger had cerebral blastomycosis and was positive for AGID serologic tests of both cerebrospinal fluid and serum. One percutaneous lung aspirate in the snow leopard and one bronchial aspirate in an Asian lion demonstrated B. dermatitidis organisms, whereas tracheal wash samples and a nasal discharge were nondiagnostic in others. Treatment with itraconazole was attempted in four cats. The tiger improved before euthanasia, whereas the others did not survive beyond initial treatments. In four felids, B. dermatitidis was found in the lungs and tracheobronchial lymph nodes, associated with a florid pyogranulomatous reaction; the tiger had a pyogranulomatous encephalomylitis, and the cheetah had a single pulmonary granuloma. Thoracic radiography, cytologic examination of lung lesion aspirates, and B. dermatitidis AGID serology should be performed on clinically ill zoo felids in endemic areas to rule out blastomycosis.

Key words: Blastomycosis, Blastomyces dermatitidis, Panthera sp., Acinonyx jubatus, nondomestic felid.

INTRODUCTION

Blastomyces dermatitidis is a spore-forming saprophytic fungus that thrives in moist, acidic soils rich in decaying vegetation.1,6 Precipitation or fog, and proximity to waterways or excavation sites may increase the prevalence of infective spores.2,8,9 “Ecological niches” or “point sources” where organisms grow well seem to exist.11 In the United States, blastomycosis is endemic in the Mississippi, Missouri, St. Lawrence, and Ohio river valleys, the Great Lakes and mid-Atlantic state regions, and it is common in eastern Tennessee.

Most commonly, the infective spores are inhaled and establish a primary pulmonary infection.7,11 At body temperature, the organisms transform into yeasts that can disseminate to the skin, eye, bone, lymph nodes, and brain, causing fatal pyogranulomatous disease.4,7,11,15

Blastomycosis in endemic areas has been reported commonly in humans and dogs, occasionally in domestic cats, and rarely in sea lions (Zalophus californianus and Eumetopias jubata),1,12 dolphins (Tursiops truncatus),3,19 wolves (Canis lupus),20 an Indian fruit bat (Pteropus giganteus),17 a ferret (Mustela putorius furo),14 and an African lion (Panthera leo).18

We describe, retrospectively, the clinical and pathologic findings in six infected nondomestic felids from Knoxville, Tennessee. The diagnosis and treatment of a polar bear (Ursus maritimus) with blastomycosis at the Knoxville Zoological Gardens (KZG, 3500 Knoxville Zoo Drive, P.O. Box 6040, Knoxville, Tennessee 37914, USA) has been previously reported.16

Because of the relatively frequent occurrence of the disease, serologic screening by agar gel immunodiffusion (AGID) is now part of the routine health monitoring protocol for carnivores at the KZG.

MATERIALS AND METHODS

Medical records and necropsy reports of all nondomestic felids held at the KZG from 1980 to 2001 were reviewed; animals living at the facility for <1 yr were excluded. In this article, the terms “felid” and “cat” will refer only to nondomestic species unless otherwise specified. Those with a histologically confirmed B. dermatitidis infection were included in the study population. Additionally, a snow leopard (Panthera uncia) housed in a private collection in Knoxville with blastomycosis con-
Table 1. Signalement of six large felids with blastomycosis in Knoxville, Tennessee, USA, from 1980 to 2001, and the times from both onset of clinical signs and diagnosis to death.

<table>
<thead>
<tr>
<th>Felid No.</th>
<th>Species</th>
<th>Sex</th>
<th>Age at death (yr)</th>
<th>Time at zoo (yr)</th>
<th>Time from onset of signs to death (days)</th>
<th>Time from diagnosis to death (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>African lion (<em>Panthera leo</em>)</td>
<td>M</td>
<td>17</td>
<td>16</td>
<td>120</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Asian lion (<em>Panthera leo persicus</em>)</td>
<td>M</td>
<td>14</td>
<td>1</td>
<td>4</td>
<td>ND†</td>
</tr>
<tr>
<td>3</td>
<td>Asian lion</td>
<td>M</td>
<td>6</td>
<td>6</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>Siberian tiger (<em>Panthera tigris</em>)</td>
<td>M</td>
<td>8</td>
<td>8</td>
<td>37</td>
<td>34</td>
</tr>
<tr>
<td>5</td>
<td>Cheetah (<em>Acinonyx jubatus</em>)</td>
<td>M</td>
<td>13</td>
<td>3</td>
<td>100</td>
<td>ND†</td>
</tr>
<tr>
<td>6</td>
<td>Snow leopard (<em>Panthera uncia</em>)</td>
<td>M</td>
<td>13</td>
<td>NA†</td>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>

† Not diagnosed (diagnosed postmortem).
† Not applicable (did not reside at zoo).

firmed at the University of Tennessee Veterinary Medical Teaching Hospital (UTVMTH) was included in the study. Serum from a cheetah (*Acinonyx jubatus*) was tested by *B. dermatitidis* AGID postmortem. Eighteen of 19 felids, including four tigers (*Panthera tigris*), one Asian lion (*Panthera leo persicus*), four African lions, three cheetahs, two snow leopards, and two bobcats (*Lynx rufus*), presently housed at the KZG were opportunistically tested from 1995 to 2002 by AGID serology at the UTVMTH Microbiology Laboratory. The immunodiffusion antigen (Gibson Laboratories, Inc., 1040 Manchester Street, Lexington, Kentucky 40508, USA) used was a concentrated culture filtrate, produced from the yeast form of *B. dermatitidis* and containing specific A precipitinogen, that forms a precipitin band when reacted with homologous antiserum (Gibson Laboratories) containing A antibody.

The UTVMTH database for 1983–2001 was searched for domestic cats (11,892 total admissions) with a diagnosis of blastomycosis. Seventeen medical records (0.002% prevalence) with a clinician’s diagnosis of blastomycosis were reviewed in detail.

RESULTS

Of the 138 large nondomestic felids housed at the KZG from 1980 to 2001, five (3.6%) had blastomycosis (Table 1), including one African lion (felid 1), two Asian lions (felids 2 and 3), one Siberian tiger (felid 4), and one cheetah (felid 5). A sixth felid with blastomycosis, a snow leopard (felid 6), was housed on dirt substrate at a site 24.2 km from the KZG.

The five infected cats at the KZG had lived there for a median of 6 yr before diagnosis. The three lions were housed in the same enclosure, with a substrate of dirt and grass and a small stream. The tiger and cheetah lived in different enclosures approximately 10 m from the lions’ enclosure and were housed on similar substrate but with no free moving water.

All affected felids were lethargic, depressed, anorexic, and had apparent weight loss, prompting the initial workup. Dyspnea and sneezing were noted in five felids (felids 1, 2, 3, 4, and 6), and three of these (felids 1, 2, and 6) had coughing and nasal discharge. Three felids (felids 1, 4, and 5) had ataxia and hind-end paresis.

Complete blood counts and chemistry panels were performed in all the felids with blastomycosis. Felid 3 had leukocytosis, with a white blood cell (WBC) count of 27,400 cells/μl. The WBC counts for the other cats were 6,800–16,800 cells/μl. Felid 6 had a marked increase in band cells (3,600 cells/μl), three felids (felids 1, 2, and 3) had low numbers of band cells (148–1,370 cells/μl), and two (felids 2 and 3) had a mild monocytosis (1,096–1,337 cells/μl). Abnormal serum chemistries included a slight hypercalcemia (3.15–3.2 mmol/L) in two felids (felids 2 and 3) and moderate hyperproteinemia (94 g/L) and hyperglobulinemia (70 g/L) in felid 6. Three felids (felids 1, 5, and 6) had azotemia (blood urea nitrogen [BUN] levels of 17, 21, and 79 mmol/L; creatinine levels of 345, 265, and 1,732 μmol/L, respectively). All cats tested negative for feline leukemia virus by enzyme-linked immunosorbent assay, and all five cats serologically tested (felid 3 was not) for feline coronavirus had antibody titers of <1:40. The African lion had a negative *B. dermatitidis* AGID serologic test 5 yr previously. Heartworm tests were negative for all three felids tested (felids 4, 5, and 6).

Blastomycosis was diagnosed antemortem in four of the six felids (felids 1, 3, 4, and 6) on the basis of cytology or a combination of serology and radiographs (Table 2). Three of these were positive by AGID test of serum, whereas felid 6 was negative. The cerebrospinal fluid from the tiger (felid
Table 2. Summary of antemortem serologic, cytologic, and radiographic findings in six large felids with blastomycosis in Knoxville, Tennessee, USA, from 1980 to 2002.

<table>
<thead>
<tr>
<th>Felid No.</th>
<th>Species</th>
<th>Antemortem diagnosis and treatment</th>
<th>AGIDa serology</th>
<th>Radiographic pulmonary lesion</th>
<th>Organisms identified on cytology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>African lion</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>NPc</td>
</tr>
<tr>
<td>2</td>
<td>Asian lion</td>
<td>-</td>
<td>NPc</td>
<td>+</td>
<td>+b</td>
</tr>
<tr>
<td>3</td>
<td>Asian lion</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+d</td>
</tr>
<tr>
<td>4</td>
<td>Siberian tiger</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+e</td>
</tr>
<tr>
<td>5</td>
<td>Cheetah</td>
<td>-</td>
<td>+</td>
<td>NPf</td>
<td>NPf</td>
</tr>
<tr>
<td>6</td>
<td>Snow leopard</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+f</td>
</tr>
</tbody>
</table>

a Agar-gel immunodiffusion.  
b Tracheal wash fluid.  
c Not performed.  
d Bronchial aspirate.  
e Nasal discharge.  
f Tested retrospectively.  
g Percutaneous lung aspirate.

4) with encephalomyelitis was also positive by AGID test. The cheetah’s (felid 5) serum, collected 1 yr before death but tested retrospectively, was also negative. Of the 19 felids presently housed at the KZG, 18 tested negative by AGID serology.

Thoracic radiography of five felids (felids 1, 2, 3, 4, and 6) showed interstitial and alveolar changes, consolidation or collapse of a lung lobe, or bullae formation (Fig. 1a). Felid 4 had an ovoid mass within the lung on initial radiographs that was not present after 1 mo of antifungal therapy. Cytologic examination of two tracheal washes and one nasal discharge specimen in three felids (felids 1, 2, and 4) were nondiagnostic. A bronchial aspirate in felid 3 and a percutaneous lung aspirate in felid 6, however, revealed large, thick-walled, broad-based budding yeasts, consistent with *B. dermatitidis*, and pyogranulomatous inflammation, represented by numerous neutrophils, macrophages, and occasional multinucleated giant cells. The *B. dermatitidis* organisms were often seen in clusters of numerous yeasts (Fig. 2).

Felids 2 and 6 died, whereas the others were euthanatized because of rapidly declining conditions. Treatment was attempted in four felids (felids 1, 2, 3, 4, and 6) using itraconazole (*Sporanox*®, 10 mg/ml suspension, Janssen Pharmaceutica N.V., Beerse, Belgium, distributed by OrthoBiotech Inc., Raritan, New Jersey 08869, USA; 5 mg/kg, p.o., s.i.d.) Some cats received generic itraconazole provided by the manufacturer as an investigational drug. Poor appetite prevented drug administration in felids 1 and 3, which were euthanatized shortly after diagnosis. The snow leopard was given an initial dose of itraconazole while still immobilized after diagnosis but it died during anesthetic recovery. The tiger was immobilized, given a single amphotericin B injection (50 mg vial, Gensia Sicor Pharmaceuticals, Inc., Irvine, California 92618, USA; 0.25 mg/kg, i.v.) and gavaged with itraconazole; it began feeding the following day and received itraconazole p.o. for 30 days. A transient improvement was noted in this tiger, but medication was discontinued when hepatotoxicity was suspected, based on clinical pathology. At the time of its euthanasia, after 30 days of therapy, the cerebrospinal fluid (CSF) itraconazole concentration was 10.1 µg/ml. Table 1 lists the times from onset of clinical signs to death for all cats and from diagnosis to death for the four treated cats.

At postmortem, five felids (felids 1, 2, 3, 5, and 6) had pulmonary lesions that, except for felid 5, were widespread through all lung lobes (Fig. 1b). Lung lesions consisted of 1- to 5-mm-diameter tan, firm nodules that coalesced to form diffuse consolidation in some areas. On sectioning, lungs exuded purulent material, and some foci of necrosis and calcification were evident. The cheetah had a single incidental encapsulated mineralized granuloma. All three lions also had marked enlargement of the tracheobronchial lymph nodes. The tiger’s lesions were restricted to the brain and spinal cord.

Histologically, the pulmonary and lymph node lesions consisted of multifocal to coalescing pyogranulomas, interspersed with diffuse infiltrates of macrophages and neutrophils that obliterated alveolar spaces. The pyogranulomas had loosely arranged epithelioid macrophages and, rarely, multinucleated giant cells surrounding small clusters of macrophages. Encapsulation was not present except in the cheetah with the single granuloma. Within some pyogranulomas spherical fungi, 10–20 µm in
Figure 1. Left lateral radiographic projection (a) of the cranial thorax of a snow leopard with blastomycosis, showing consolidation of cranial and middle lobes and extensive air-bronchogram pattern; left lateral gross necropsy photograph (b) of the left lung, showing irregular contour to surface of lung lobes caused by nodules and diffuse consolidation. Cr = cranial lobe; M = middle lobe; Cd = caudal lobe.
diameter with a double wall, granular contents, and rare broad-based budding (compatible with *B. dermatitidis*), were present. Organisms were notably scarce relative to the severity of the pyogranulomatous inflammation. The tiger with encephalomyelitis had diffuse and nodular pyogranulomatous inflammation containing intact and fragmented spherical fungi. These lesions were most severe in the ependyma of the ventricles and central canal and extended into the adjacent brain and spinal cord parenchyma. The distribution and histologic character of the blastomycosis lesions are summarized in Table 3.

**DISCUSSION**

The 3.62% prevalence of blastomycosis among felids at the KZG was dramatically higher than the 0.002% prevalence in client-owned domestic cats seen at the UTVMTH and than the 0.005% prevalence in domestic cats in the Veterinary Medical Database of Purdue University. The infections in the Purdue domestic cats were primarily from Oklahoma, Tennessee, and Wisconsin. The confinement of zoo animals within a small area limits the usefulness of comparing their infection rates with rates in geographically dispersed domestic cats, but such a comparison may illustrate the point source hypothesis. Culture swabs were not obtained from the zoo enclosures because *B. dermatitidis* is notoriously difficult to recover from environmental sources. All three infected lions lived in the same enclosure with access to a waterway, and all six infected cats’ enclosures had dirt and grass substrates. The only infected animal from a concrete enclosure at the KZG was the previously reported polar bear.

All non-domestic felids with blastomycosis were male. The male-to-female ratio of large cats at the KZG from 1980 to 2001 was 43:57. Males and females of each species were housed together. Similarly, 69% of 41 infected domestic cats in the Purdue study were male, as were 70% of 23 domestic cat cases reviewed in a retrospective study. Male domestic cats may have increased exposure to sources of *B. dermatitidis* due to behavior and lifestyle differences, although this is unlikely in the felids at the KZG, or males may be more susceptible to blastomycosis for unknown reasons.

Clinical signs in these infected felids were, as in domestic dogs and cats, nonspecific. Depression, lethargy, weight loss, and anorexia were noted in all felids. Ataxia and hind-limb paresis occurred in
Table 3. Distribution and histologic character of lesions in six large felids with blastomycosis in Knoxville, Tennessee, USA, from 1980 to 2002.

<table>
<thead>
<tr>
<th>Felid No.</th>
<th>Species</th>
<th>Organs affected</th>
<th>Extent of gross lesions</th>
<th>Histologic lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>African lion</td>
<td>lungs, pleura, and tracheobronchial lymph nodes</td>
<td>widely disseminated 1–5 mm diameter nodules in the lungs and pleura, tracheobronchial lymph nodes markedly enlarged</td>
<td>multifocal coalescing immature and mature pyogranulomas with fungi</td>
</tr>
<tr>
<td>2</td>
<td>Asian lion</td>
<td>lungs and tracheobronchial lymph nodes</td>
<td>diffuse consolidation of the lungs</td>
<td>coalescing pyogranulomas</td>
</tr>
<tr>
<td>3</td>
<td>Asian lion</td>
<td>lungs and tracheobronchial lymph nodes</td>
<td>disseminated 1–10 mm pulmonary nodules, large areas of cavitation, and hemorrhage</td>
<td>coalescing pyogranulomas with rare fungi</td>
</tr>
<tr>
<td>4</td>
<td>Siberian tiger</td>
<td>brain, spinal cord</td>
<td>periventricular in the brain extending throughout the central canal in the spinal cord</td>
<td>pyogranulomatous encephalomyelitis with fungi</td>
</tr>
<tr>
<td>5</td>
<td>Cheetah</td>
<td>lung</td>
<td>single pulmonary nodule</td>
<td>chronic mineralized granuloma with fungi</td>
</tr>
<tr>
<td>6</td>
<td>Snow leopard</td>
<td>lungs and tracheobronchial lymph nodes</td>
<td>widely disseminated 1–6 cm diameter nodular consolidation in the lungs with pleural adhesions</td>
<td>multifocal coalescing pyogranulomatous pneumonia and lymphadenitis with fungi</td>
</tr>
</tbody>
</table>

three felids, whereas dyspnea, sneezing, and coughing were seen in four. Neurologic signs are more common in domestic cats than in domestic dogs.\(^4,11,15\) It is possible that ataxia and paresis in our felids were caused by degenerative spinal disease, which has been noted in other felids at the KZG,\(^10\) although the spinal columns were not examined in any of the felids in this study.

Lesions in our blastomycosis-infected felids were similar to those that occur in domestic dogs and cats. Active areas with fungi present had aggregates of neutrophils and multinucleated giant cells, whereas epithelioid macrophages predominated in the surrounding regions where the infection was resolving. The lesions tended to coalesce rather than encapsulate, resulting in widespread damage to pulmonary parenchyma. The predominance of macrophages within the inflammatory cell population with only rare fungi present would account for the low sensitivity of cytologic diagnosis.

Clinical pathology abnormalities were few and inconsistent. In domestic cats, total protein concentration is consistently increased,\(^15\) but only one of our felids was hyperproteinemic, with hyperglobulinemia. Two were hypercalcemic, which can occur in domestic cats secondary to chronic granulomatous reactions. Hypercalcemia also occurs in dogs with granulomatous disease; the proposed mechanism in both species involves increased production of calcitriol by mononuclear cells.\(^5\)

The gold standard for blastomycosis diagnosis is the presence of refractile, broad-based budding \textit{B. dermatitidis} organisms on cytology or histopathology. \textit{Blastomyces dermatitidis} organisms were demonstrated twice in our felids, from bronchial and lung aspirates, whereas tracheal wash and nasal discharge specimens were nondiagnostic. In dogs, lung aspirates are more reliable in producing diagnostic material than are tracheal washes because infections are primarily interstitial.\(^11\) Percutaneous aspirates of pulmonary lesions noted on radiographs are a promising source of diagnostic material for felids; this likely would be a superior approach to tracheal washing because five of our six felids had pulmonary lesions.

Serology, in combination with history, clinical signs, and a radiographic pulmonary lesion, can support a diagnosis of blastomycosis, although its validity in nondomestic felids is unknown. Three of the four antemortem diagnoses in our study were based on positive serology with radiographic lesions and clinical signs. The AGID test has a \(>90\%\) specificity and sensitivity in the dog but may be negative in 30\% of early infections.\(^12\) It has been used less frequently in domestic cats; in two retrospective studies, only two of seven infected cats that had serologic testing were positive (29\% sensitivity).\(^4,15\) Seven domestic cats diagnosed with blastomycosis at the UTVMTH from 1983 to 2001 had AGID serologic testing performed, and two
were positive (28% sensitivity); there were no false positives. Three of the four felids that were tested antemortem in our study were positive. The cheetah (whose serum was collected 1 yr before death) was negative. Thus, AGID serology had a 60% sensitivity in our tested felids. No false positive serologic results have been found in KZG felids screened since 1980.

Treatment of blastomycosis is always challenging but is particularly difficult in zoo animals. Amphotericin B has been the drug of choice for the treatment in dogs but it is nephrotoxic and must be administered intravenously. Itraconazole is now more commonly used. In animals refusing oral medications, a single dose of amphotericin B (0.25 mg/kg i.v.) can improve appetite, as it did for the tiger in our study, allowing subsequent oral itraconazole treatment. Amphotericin B administration should be discontinued if BUN and creatinine concentrations increase abnormally.

Dogs with blastomycosis respond with equal success to itraconazole and amphotericin B. Remission rates have been similar in dogs treated with either drug, although a dosage of 5 mg/kg/day of itraconazole had fewer adverse effects than a dosage of 10 mg/kg/day. An initial itraconazole dosage of 5 mg/kg b.i.d. for 5 days should be given to dogs, followed by s.i.d. dosing for 60 days, or for 30 days after resolution of clinical signs. The most common adverse effect of itraconazole treatment, anorexia associated with hepatotoxicity, occurs in 8% of dogs. Itraconazole treatments in the tiger were discontinued after liver enzyme levels increased and the tiger’s condition declined. Serum itraconazole concentrations ≥2 µg/ml appear to be therapeutic in the dog. In a polar bear with blastomycosis, serum itraconazole concentrations ≤1.65 µg/ml were achieved with a dosage of 4.3 mg/kg/day, which was sufficient to cure the bear after 90 days of therapy. No serum concentrations were measured in the tiger, but unusually high CSF concentrations (10.1 µg/ml) were achieved and were adequate to kill most B. dermatitidis organisms in the cerebrum and resolve the pulmonary mass originally noted on radiographs. A lower dose may have provided a therapeutic drug concentration with less risk of hepatotoxicity.

Early diagnosis of blastomycosis in large felids is difficult to achieve but is necessary for effective treatment. Thoracic radiography, followed by cytologic examination of lung lesion aspirates and B. dermatitidis AGID serology should be performed for clinically ill zoo felids in endemic areas. Obtaining baseline AGID serology as part of annual physical examinations will increase the diagnostic value of the AGID test for zoo felids.

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LITERATURE CITED


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