Diagnosis and treatment of blastomycosis affecting the nose and nasopharynx of a dog

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Case Description—A 2-year-old 38.9-kg (85.58-lb) sexually intact male German Shepherd Dog was examined because of a 4-month history of severe nasal swelling and nasal mucosa congestion. The signs were slowly progressive.

Clinical Findings—Physical examination revealed that the dorsal aspect of the dog's nose was swollen and hard. Mucous membranes in both nostrils were hyperemic and edematous. Diagnostic investigation revealed severe nasal osteolysis and pyogranulomatous rhinitis and nasopharyngitis attributable to blastomycosis.

Treatment and Outcome—Oral administration of itraconazole was initiated (5 mg/kg [2.27 mg/lb], q 12 h for 5 days and then q 24 h). After a treatment period of 3 months, the nose had regained its normal appearance. After 5 months of treatment, the *Blastomyces* infection was eliminated as confirmed by results of rhinoscopy and biopsy specimen examination. No relapse was evident within 1 year after discontinuation of treatment.

Clinical Relevance—In dogs, nasal and nasopharyngeal blastomycosis can result in severe osteolysis of the nasal bone. Resolution of disease can be achieved with oral administration of itraconazole for a period of at least 5 months. (*J Am Vet Med Assoc* 2008;233:1112–1116)

A 2-year-old 38.9-kg (85.58-lb) sexually intact male German Shepherd Dog was referred to the Veterinary Teaching Hospital at the University of Georgia because of a 4-month history of slowly progressive nasal swelling and nasal mucosa congestion. Beginning 1 month prior to the initial evaluation, the dog was incapable of breathing through its nostrils and frequently panted and sneezed. Despite treatment with antimicrobials (clindamycin and enrofloxacin) for 4 weeks prior to this initial evaluation, no improvement was observed. The owners had also noticed decreased appetite, but there was no obvious weight loss. The dog lived primarily outdoors and had never traveled outside the state of Georgia; its vaccination status was current, and it was regularly dewormed. No other previous health problems were known.

On physical examination, the dog was bright, alert, and responsive and excessive panting was evident. Rectal temperature was within reference limits. The dog's heart rhythm was regular (rate, 140 beats/min), although dyspnea, characterized by a loud stertorous breathing, prevented ideal auscultation of the lungs and heart. No nasal discharge was present at this time. The right and left mandibular lymph nodes were approximately 1.5 cm and 1 cm in diameter, respectively. The dorsal aspect of the nose was severely swollen, hard, and firm on palpation. The right side was more affected than the left. The mucous membranes in both nostrils were hyperemic, and severe tissue swelling was evident.

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Abbreviation

CT	Computed tomography

The other findings of the physical examination were unremarkable.

The dog was hospitalized (day 1) for further examinations. Initial diagnostic tests included a CBC, serum biochemical analyses, urinalysis, and thoracic radiography. Results of the CBC included marked leukocytosis (26.8×10^3 WBCs/μL; reference range, 5.1×10^3 WBCs/μL to 13×10^3 WBCs/μL) with neutrophilia but no bands (18.22×10^3 neutrophils/μL; reference range, 2.9×10^3 neutrophils/μL to 12×10^3 neutrophils/μL), lymphocytosis (3.21×10^3 lymphocytes/μL; reference range, 0.4×10^3 lymphocytes/μL to 2.9×10^3 lymphocytes/μL), monocytosis (2.14×10^3 monocytes/μL; reference range, 0.1×10^3 monocytes/μL to 1.3×10^3 monocytes/μL), and eosinophilia (3.21×10^3 eosinophils/μL; reference range, 0 to 1.3×10^3 eosinophils/μL); Hct was 44.3% (reference range, 35% to 57%). Mild thrombocytopenia (196×10^3 platelets/μL; reference range, 211×10^3 platelets/μL to 621×10^3 platelets/μL) was detected, but the platelet estimate on the blood smear was considered normal. No serum biochemical abnormalities were identified. Urinalysis revealed a urine specific gravity of 1.050, 1+ protein, and 2+ bilirubin.

No abnormalities were detected via thoracic radiography. A fine-needle aspirate specimen was collected from the right mandibular lymph node. Cytologic examination of the specimen revealed that the nucleated cells were mostly a mixture of small-, medium-, and large-sized lymphocytes with small lymphocytes predominating. Plasma cells were common. Low numbers of nondegenerated neutrophils, macrophages, and eosinophils and rare mast cells were observed. Microorganisms were not detected. Findings were compatible with lymphadenitis.

On day 2 of hospitalization, the dog was anesthetized and a nasal CT examination and rhinoscopy were performed. Results of a coagulation profile (assessments of prothrombin time, activated partial thromboplastin time, and thrombin time) and evaluation of buccal mucosal bleeding time performed prior to anticipated biopsy procedures were within reference limits.

Helical CT[a] images of the skull from the most rostral aspect of the nose to the most caudal aspect of the frontal sinuses were obtained with reconstructed 2.5-mm slices acquired before and after IV administration of 60 mL of contrast medium (iothalamate sodium[b]). Poorly enhanced, hyperattenuated material was present bilaterally within the nasal cavity, from the alar fold to approximately the level of the second premolar teeth. There was also evidence of osteolysis of the horizontal part of the palatine bone and of the nasal and incisive bones. The remainder of the caudal aspect of the nasal cavity was unremarkable until the level of the cribriform plate of the ethmoid bone, where uniformly enhancing hyperattenuating material was observed in the right side, extending dorsally to the medial compartment of the frontal sinus and caudally to the right olfactory bulb of the brain with lysis of the internal surface of the right frontal bone (**Figure 1**). A small soft tissue density growth was present within the nasopharynx. There was no evidence of a foreign body. The findings were suggestive of a chronic inflammatory condition (eg, fungal infection or plasmacytic-lymphocytic inflammation) or, less likely, neoplasia. Rhinoscopy was performed by use of a 2.9-mm rigid cystoscope[c] and revealed bilaterally edematous, inflamed, and friable nasal mucosa (**Figure 2**). No fungal colonies were visible. Endoscopy of the nasopharynx was performed by use of a 6.0-mm flexible bronchoscope.[d] A soft tissue mass (approx 2 × 3 cm) with a hyperemic and slightly irregular surface was identified in the ventral region of the nasopharynx. These findings were consistent with severe rhinitis and nasopharyngitis. Multiple biopsy samples were obtained from both nasal passages and from the mass in the nasopharynx; specimens were submitted for histologic examination and fungal culture.

Because CT revealed contrast medium enhancement of the olfactory bulb, a CSF sample was obtained to investigate the possibility of CNS dissemination of the underlying disease. Clear and colorless CSF was obtained via cisternal puncture. Results of a Pandy test performed on the fluid sample were negative; further analysis revealed protein concentration of 17.4 mg/dL (reference range, 13 to 35 mg/dL), 4 WBCs/μL (reference range, 0 to 5 WBCs/μL), and 2,073 RBCs/μL (reference range, 0 to 30 RBCs/μL). Cytologic evaluation of the CSF revealed a moderate degree of blood contamination. No erythrophagocytosis or organisms (free or phagocytized) were observed. The WBCs were predominately neutrophils with a few monocytes and lymphocytes. This was interpreted as normal CSF with blood contamination. Unfortunately, no fungal culture or PCR analysis of the collected CSF was performed. A neurologic examination of the dog was undertaken on day 3 of hospitalization; results were considered normal.

Histopathologic findings for the tissues collected from the right nasal cavity and nasopharynx were similar. The lamina propria and submucosa were expanded by multifocal to coalescing granulomas of epithelioid macrophages that often had a central collection of neutrophils. Granulomas were surrounded by lymphocytes, plasma cells, and neutrophils. In the center of some granulomas and surrounded by neutrophils were

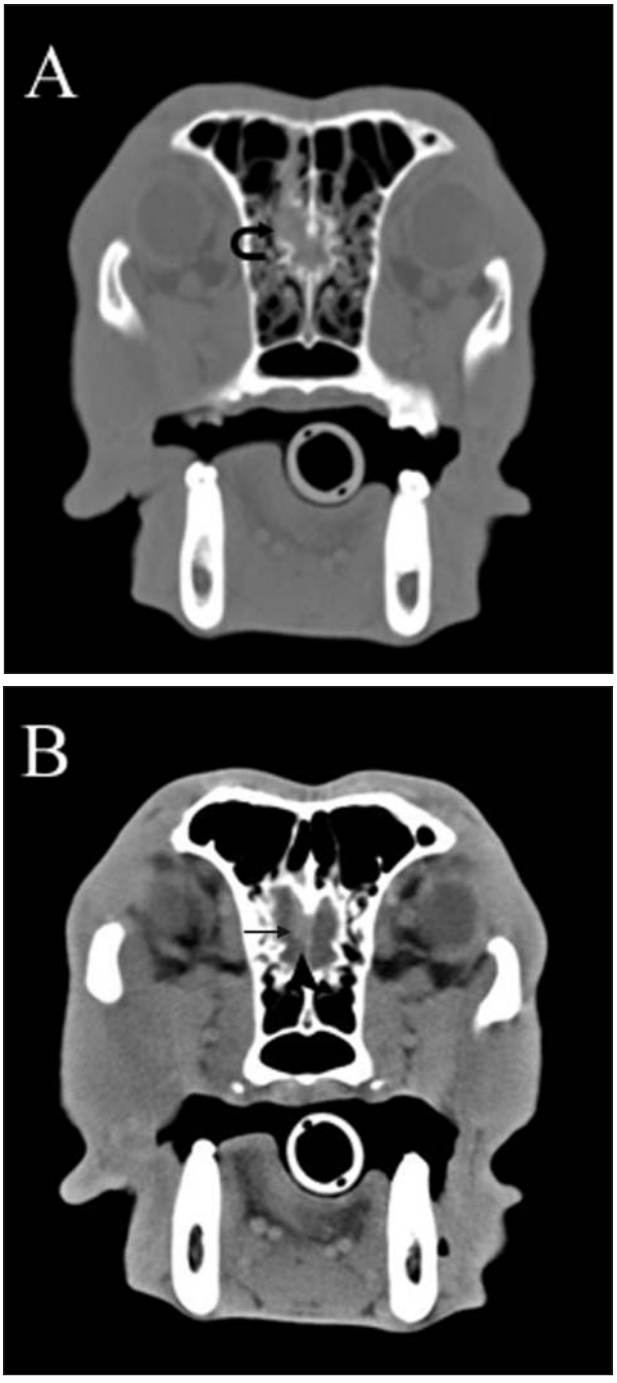

Figure 1—Computed tomographic images (obtained after administration of contrast medium) of the head of a dog with blastomycosis affecting the nose and nasopharynx. A—Image obtained by use of a CT bone window. Notice the lysis of the internal surface of the frontal bone (curved arrow). B—Image obtained by use of a CT soft tissue window. Notice the contrast medium enhancement of the right olfactory bulb (straight arrow). In both panels, the right side of the dog's head is to the left of the image.

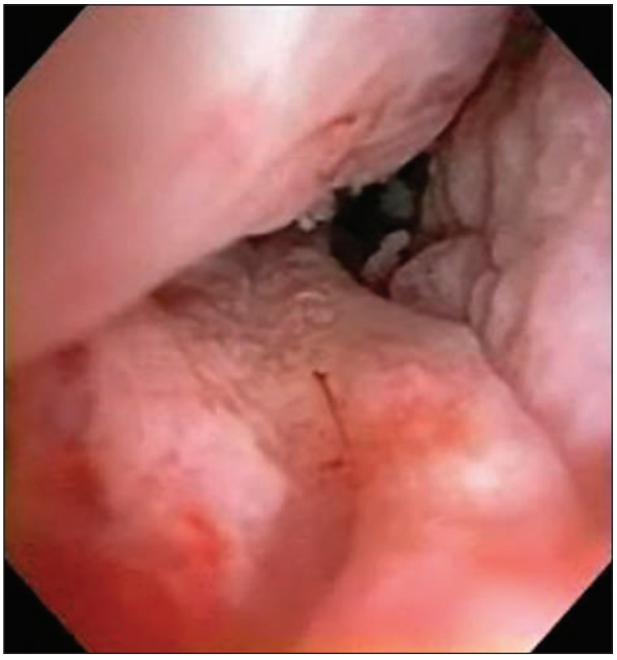

Figure 2—Endoscopic view obtained during rhinoscopy of the nasal cavity of the dog. Notice that the nasal mucosa is swollen, inflamed, and friable. No obvious fungal colonies are evident. The dorsal aspect of the nasal cavity is toward the top of the image.

1 to several spherical yeast forms with lightly basophilic cytoplasm and a thick, double-contoured wall. The organisms stained with periodic acid–Schiff and Gomori methenamine silver stains and were compatible with *Blastomyces dermatitidis*. The histopathologic diagnosis was granulomatous to pyogranulomatous rhinitis and nasopharyngitis with intralesional *Blastomyces*-like yeast. There was a light growth (2 colonies) of *B dermatitidis* from tissue submitted for fungal culture.[e] A test for *Blastomyces* antigen (ELISA) in serum and urine or further PCR analysis of the biopsy specimens was not performed because results of histologic examination and fungal culture were indicative of blastomycosis. A diagnosis of nasal and nasopharyngeal blastomycosis was established, and oral administration of itraconazole[f] (5 mg/kg [2.27 mg/lb], q 12 h for 5 days and then q 24 h) was initiated.

Follow-up examinations were performed every month to reassess the swelling of the nose and to check for adverse effects of the antifungal treatment (eg, anorexia or hepatotoxicosis). The dog responded well to itraconazole administration. After 2 months, the nasal congestion was less severe and the external nasal swelling had substantially decreased to a small lump. A CBC revealed mild leukocytosis (17.4×10^3 WBCs/µL) with neutrophilia (13×10^3 neutrophils/µL) and monocytosis (1.6×10^3 monocytes/µL). The neutrophilia and monocytosis were attributed to ongoing inflammation. No abnormalities were detected via serum biochemical analyses. At this time, an ELISA was performed to detect *Blastomyces* antigen[g] in serum and urine and results were negative.

After 3 months of treatment, the nasal swelling had completely resolved, no abnormal airway sounds could be auscultated, and the dog was clinically normal. The dog was anesthetized, and rhinoscopy[c,d] was again performed to evaluate the nose and nasopharynx and to obtain biopsy samples to confirm resolution of the disease. The nasal cavity and nasopharynx appeared normal rhinoscopically. Histologic examination of tissue samples collected from the right nasal passage and pharynx revealed minimally hyperplastic mucosa. The lamina propria and submucosa were multifocally expanded by an infiltrate of a small number of macrophages, lymphocytes, and plasma cells. Sections stained with periodic acid–Schiff and Gomori methenamine silver stains were unremarkable. These findings were interpreted as chronic, mild lymphoplasmacytic rhinitis. Oral administration of itraconazole was continued for 2 months and then discontinued. Overall, itraconazole was administered for a total duration of 5 months. One year after discontinuation of the treatment, the dog was doing well and was without any clinical signs; its nose had no abnormalities on physical examination.

Discussion

Blastomycosis is one of the most common systemic fungal diseases in dogs in North America. This mycotic infection is caused by the thermally dimorphic fungus *B dermatitidis*, which exists in mycelial and yeast forms. Localized disease is considered extremely rare. The typical route of infection is inhalation of aerosolized conidia. From the respiratory tract, the developing yeast form may disseminate hematogenously or by way of lymphatic system throughout the body and affect multiple organ systems, most commonly the CNS, lymphatic and skeletal systems, eyes, and skin. Multifocal involvement of different organ systems is common.[1–3] Anorexia, signs of depression, lethargy, weight loss, cachexia, and fever are common features of disease. Most dogs have lung lesions characterized by a severe, diffuse miliary to nodular interstitial or bronchointerstitial pulmonary pattern. Some dogs may develop tracheobronchial lymphadenomegaly. Ocular lesions develop in as many as 52% of dogs. Bone involvement occurs in as many as 30% of affected dogs. Lesions usually affect the appendicular skeleton and are typically osteolytic with periosteal proliferation and soft tissue swelling. The nares and nasal passages are an uncommon site for infection in dogs.[4–6] Rarely, the cardiovascular system (eg, the myocardium or endocardium) is affected.[7]

Diagnosis of blastomycosis is typically made by cytologic or histopathologic detection of *B dermatitidis* yeast in affected tissues. Purulent to pyogranulomatous lesions develop in *B dermatitidis*–infected tissues. The broad-based budding yeasts are best detected with special stains, such as periodic acid–Schiff and Gomori methenamine silver stains. Polymerase chain reaction testing of fixed, paraffin-embedded tissue or unfixed clinical specimens is gaining clinical importance in the diagnosis of blastomycosis.[4,6,8,9]

The dog of this report was unusual because blastomycosis of the nose and nasopharynx in dogs has not been described in detail, to our knowledge. A similar case of a 2-year-old sexually intact female German Shorthair Pointer with facial swelling associated with blastomycosis osteomyelitis of the skull has been docu-

mented as a personal observation.[2] There is 1 report[10] that describes pharyngeal-laryngeal blastomycosis in a dog with laryngeal paralysis. However, specific treatment recommendations for nasal and nasopharyngeal blastomycosis are lacking. In dogs, osteolytic lesions, periosteal proliferation, and soft tissue swelling caused by blastomycosis have only been detected on radiographic views of long bones.[1,2] Involvement of mucosal surfaces, including the nose and larynx, is more common in humans.[11–13] In humans, osteolytic lesions of the face are also reported.[14]

The signalment and housing conditions of the dog of this report are typical for dogs affected by blastomycosis. Young, large-breed, and purebred dogs are predominately affected. This dog lived outdoors in proximity to a body of water in the state of Georgia. These circumstances are also identified risk factors. According to the dog's medical record, the first clinical signs were detected in October, a month in which typically more diagnoses of blastomycosis in dogs are made.[4–6] Although 88% of dogs with blastomycosis have respiratory tract involvement and even 8% have nasal discharge at initial evaluation,[4] no detailed description has been published in which the organism has been identified as causing severe nasal disease. This is interesting because the presence of nasal discharge in dogs with blastomycosis suggests that there may be mild nasal, pharyngeal, or laryngeal involvement in some affected dogs. Possibly, involvement of the upper portion of the respiratory tract has remained undiagnosed in those dogs because of the presence of other more clinically important findings. It is also possible that nasal discharge is caused exclusively by lung disease. In the dog of this report, no nasal discharge was detected at the time of admission but the dog had been sneezing. In the human medical literature, a few cases of blastomycosis with primary nasal involvement have been described.[12,13] In a review[11] of 102 cases, the laryngeal region was affected in many as 21.7% of patients and the nose was affected in as many as 8.7% of patients. Most humans have signs of lung involvement by the time blastomycosis is diagnosed. In humans, the lungs are typically the primary target organ because the *Blastomyces* spores are inhaled and then transform in the lungs at body temperature to the yeast phase, which triggers a strong inflammatory response capable of inducing a granulomatous reaction. During this acute inflammatory phase, infection may spread from the lungs to other body regions such as the nose.[11,13] In a report[12] of a human with blastomycosis, no radiographic pulmonary lesions were identified at the time the patient was examined because of nasal swelling; however, lung involvement in that patient cannot be excluded because primary lung lesions can be self-limiting. It is likely that this was also true for the dog of this report because no lung abnormalities were detected radiographically at the time of the initial evaluation. Nevertheless, the question of whether the dog had a primary pulmonary infection is of little relevance clinically. It is also possible that a traumatic inoculation of the spores in the nasal cavities occurred without lung involvement. It has to be mentioned that no additional assessments, such as cytologic examination, fungal culture, or PCR assay of fluid collected during bronchoalveolar lavage, were undertaken in this patient. Overall, the respiratory tract is the primary target of *Blastomyces* organisms in dogs, and thoracic radiographic findings are apparently normal in only 6% of affected dogs.[4]

The dog of this report had leukocytosis at the time of the initial evaluation, which is a common finding among dogs with blastomycosis. There were no other clinicopathologic abnormalities such as a mild left shift, hypoalbuminemia, hyperglobulinemia, or hypercalcemia.[4] This might be explained by the fact that the disease was confined to the nose at that time. The CT findings for this dog were characterized as poorly contrast medium–enhanced soft tissues and osteolysis in the nasal region. Computed tomomographic findings in humans with blastomycosis that affects the nose and nasopharynx include contrast medium–enhanced soft-tissue densities, masses, and destruction of the bone.[14,15]

In dogs with blastomycosis, the CNS is involved in as many as 6% of cases.[4] In a case report[15] of a dog with intracranial blastomycosis, a marked contrast enhancement of the lining of the ventricles was evident via CT examination; this was most consistent with ependymitis, which was confirmed subsequently via necropsy and histologic examination. Because of the CT findings, involvement of the forebrain in the dog of this report was possible, but no abnormalities were identified via CSF analysis or neurologic examinations. However, CNS involvement cannot be excluded on the basis of these findings alone because no fungal culture or PCR analysis of CSF was performed. Moreover, dogs with CNS involvement might respond to itraconazole treatment because of possible disruption of the blood-brain barrier or the lipophilic nature of the drug. It is hypothesized that blastomycosis-affected humans with involvement of the nasopharynx could be predisposed to CNS disease as a result of continuous spread of the organism from the nasal cavity, in addition to the risk of hematogenous spread.[11]

Serologic and PCR analyses may help to establish a diagnosis of blastomycosis. Neither test was performed initially for the dog of this report because the diagnosis could be obtained rapidly via histologic examination and fungal culture of biopsy samples that were obtained from both nasal passages and from the mass in the nasopharynx.[2] However, antigen ELISAs were performed on serum and urine samples 2 months after treatment initiation in an attempt to gain some information regarding treatment success. Follow-up of antigen-positive dogs could be beneficial in monitoring the progress of antifungal treatments.[8] Because the antigen ELISAs were not performed before initiating treatment in the dog of this report, interpretation of the negative results 2 months after commencement of treatment remains difficult, but it may reflect a defect in the sensitivity or specificity of the assay or treatment-induced elimination of the organism.

In retrospective studies[4,16] of dogs with blastomycosis, treatment with itraconazole was as effective as treatment with amphotericin B and ketoconazole. Administration of itraconazole requires less monitoring, and the drug can be given orally. Initially, itraconazole is given orally at a dosage of 5 mg/kg every 12 hours

for 5 days and then every 24 hours for a minimum of 60 days or at least 1 month beyond clinical or radiographic resolution of the disease.[1,3,16] At this dosage, the drug is usually tolerated well and adverse effects such as anorexia and hepatotoxicosis develop infrequently.[16] Prognosis is good in blastomycosis-affected dogs without CNS involvement or severe pulmonary involvement.[1,2,4,16] As many as 24% of dogs with blastomycosis relapse during the first 6 months after completion of treatment. The likelihood of relapse is related to the severity of the initial disease. Reinfection after successful treatment does not appear to occur. In the dog of this report, no relapse occurred over a period of 1 year after discontinuation of treatment. Therefore, it can be assumed that a 5-month period of treatment with itraconazole successfully eliminated blastomycosis from the dog's nose and nasopharynx without causing any adverse effects. Nevertheless, relapses have occurred as long as 3 years after diagnosis.[4] One year after discontinuation of treatment in the dog of this report, the osteolytic lesions were probably completely resolved because no nasal abnormalities were grossly evident and the dog was clinically normal. Ideally, another CT examination should have been performed to verify the resolution of the bone lesions. This report highlights that blastomycosis of the nasal and nasopharyngeal regions develops in dogs and can be successfully managed with at least a 5-month period of oral treatment with itraconazole.

a. SOMATOM AR Star, Siemens AG, Munich, Germany.
b. Conray 400LM, Mallinkrodt Inc, St Louis, Mo.
c. Karl Storz GmbH & Co KG, Tuttlingen, Germany.
d. Olympus America Inc, Center Valley, Pa.
e. Infectious Diseases Laboratory, College of Veterinary Medicine, University of Georgia, Athens, Ga.
f. Sporanox, Ortho-McNeil Inc, Raritan, NJ.
g. MiraVista Diagnostics, Indianapolis, Ind.

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