Case Report Rapport de cas

Central nervous system blastomycosis in a dog

M. Casey Gaunt, Susan M. Taylor, Moira E. Kerr

Abstract — An adult golden retriever was presented for progressive neurologic dysfunction. Clinical examination suggested brainstem disease. Blastomycosis was diagnosed based on fine-needle aspiration cytology of a normal sized lymph node and a positive blastomycosis urine antigen test. Systemic blastomycosis with neurologic involvement was confirmed at necropsy.

Résumé — Blastomycose du système nerveux central chez un chien. Un Labrador retriever adulte a été présenté pour un dysfonctionnement neurologique progressif. Un examen clinique a suggéré une maladie du tronc cérébral. La blastomycose a été diagnostiquée à l'aide d'une cytologie par aspiration à l'aiguille d'un ganglion lymphatique de taille normale et une analyse urinaire positive pour la présence de l' antigène de la blastomycose. La blastomycose systémique avec affection neurologique a été confirmée à la nécropsie.

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Case description

A 6-year-old spayed female, golden retriever from Kenora, Ontario was referred to the Veterinary Teaching Hospital at the Western College of Veterinary Medicine (WCVM) for evaluation of a 3- to 4-week history of depression and lethargy and a 1-week history of circling and ataxia. On initial presentation to the referring veterinarian, the dog was febrile (40°C), and had a small, firm mass between her 2nd and 3rd left lower incisors and a diffuse, painful swelling over the left mandibular area. Fine-needle aspiration cytology of the swollen mandibular region performed by the referring veterinarian revealed neutrophils and free erythrocytes. An infectious agent was not identified. The oral mass and mandibular swelling resolved after the administration of an anti-inflammatory medication (Ketoprofen; Novopharm, Toronto, Ontario), 1.0 mg/kg PO, q24h, and a systemic antibiotic (Amoxicillin; Nu Pharm, Richmond Hill, Ontario), 14 mg/kg PO, q8h for 1 wk. The dog became progressively more depressed and inappetent and lost weight in spite of treatment. Serum cortisol response to the administration of synthetic ACTH (Synacten; Novartis, Mississauga, Ontario), 0.25 mL IV, was evaluated, and did not support a diagnosis of hypoadrenocorticism as a cause for this dog's signs (basal cortisol concentration: 148.0 nmol/L; reference range: 0.0 to 165.5 nmol/L; 1 h post ACTH cortisol concentration: 364 nmol/L; reference range: 165 to 469 nmol/L).

Subcutaneous fluids and Dexamethasone (Vetoquinol, Lavaltrie, Quebec) 5 mg subcutaneously once; and then prednisone (Apotex; Toronto, Ontario), 25 mg PO, once 3 d later were administered, but the dog's condition did not improve. In the week prior to referral to the WCVM, the dog exhibited weakness and was noted to walk in circles in both directions. A single episode of vomiting, unaccompanied by diarrhea, occurred on the day prior to referral. Because of the perception that there was a high prevalence of blastomycosis in the city of origin, a urine sample was submitted for a blastomycosis urine antigen test (Mira Vista Diagnostics Blastomyces *dermatitidis* antigen immunoassay; Indianapolis, Indiana, USA); the result of this analysis was pending at the time of referral.

Questioning at the WCVM revealed that the dog had been considered normal prior to this illness. The dog was active and reportedly spent a great deal of time outside swimming in a river. The owners reported that within the past several years 2 humans and a dog in their immediate neighborhood had been diagnosed with blastomycosis.

On physical examination at the WCVM, the dog was thin, depressed, and reluctant to stand or walk. The dog panted intermittently, but respiratory effort and thoracic auscultation were normal. A cough could not be elicited on tracheal palpation. There was mild bilateral enophthalmous and the skin tent was prolonged, suggesting dehydration. The dog had a horizontal nystagmus with the fast phase towards the right.

A complete blood (cell) count (CBC), serum biochemistry profile, venous blood gas, and urinalysis were evaluated. Hematologic abnormalities included a mild, normocytic,

Department of Small Animal Clinical Sciences (Gaunt, Taylor); Department of Veterinary Pathology (Kerr), Western College of Veterinary Medicine, University of Saskatchewan, 52 Campus Drive, Saskatoon, Saskatchewan S7N 5B4.

Address all correspondence to Dr. M. Casey Gaunt; e-mail: casey.gaunt@usask.ca

normochromic, nonregenerative anemia (Hct 0.34 L/L; reference range: 0.38 to 0.55 L/L) and moderate lymphopenia (0.56×10^9/L; reference range: 1.2 to 5.0×10^9/L). Abnormalities in the serum biochemical profile included a mild decrease in urea (3.1 mmol/L; reference range: 3.5 to 11.4 mmol/L) and mild increases in cholesterol (6.51 mmol/L; reference range: 2.70 to 5.94 mmol/L) and alkaline phosphatase (152 U/L; reference range: 9 to 90 U/L). A complete urinalysis, performed on urine collected by cystocentesis, was normal.

An intravenous catheter was placed and replacement fluids (Normosol R; Hospira, Montreal, Quebec) were administered intravenously (IV) at a rate of 3 mL/kg body weight (BW)/h. The dog's neurologic signs worsened steadily over the next 10 h. Mentation was severely depressed. When the dog was stimulated to rise and walk, a wide base stance and moderate ataxia of all 4 limbs were apparent. A slight head tilt to the right was noted and the dog circled to the right. Conscious proprioception, as assessed by knuckling and hopping, was diminished in all 4 limbs and all limb reflexes were normal.

Thoracic radiography and abdominal ultrasonography were unremarkable. Echocardiography demonstrated insignificant tricuspid valve regurgitation. Fine-needle aspiration cytology of the left submandibular lymph node was consistent with a reactive lymph node and revealed moderate numbers of spherical, thick-walled, large yeast organisms that exhibited broad–based budding. The cytomorphology of the yeast was consistent with *Blastomyces* sp.

Therapy with itraconazole (Sporonox; Janssen-Ortho, Toronto, Ontario), 5 mg/kg PO, was initiated. The dog's neurologic status continued to deteriorate and the owner elected to euthanize the dog 12 h after the first dose of itraconazole was administered. The dog was submitted for post-mortem examination. On gross examination, a suppurative exudate was present in and around the pituitary gland and an approximately 1.0 cm in diameter focus of caseous necrosis was noted in the dorsolateral aspect of the left caudal lung lobe. *Blastomyces dermatitidis* was isolated from material cultured from the pituitary gland.

On histopathological examination, lesions were noted in the brain, lung, pituitary gland, and retropharyngeal lymph node. Histopathologic examination of sections from the cerebrum revealed a marked, multifocal periventricular infiltrate that consisted primarily of macrophages and neutrophils with fewer plasma cells and small lymphocytes. Occasionally multinucleated giant cells were seen. Multiple large (approximately 10 to 14 μm in diameter), spherical, thick-walled yeast organisms with rare broad-based budding were noted in the inflammatory infiltrate. Perivascular lymphoid cuffing was present in the periventricular regions of the cerebrum in close proximity to the inflammatory infiltrate.

Histological examination of the left caudal lung lobe revealed multiple, variably sized (0.1 to 0.5 mm), coalescing nodules comprised of an inflammatory infiltrate and intralesional yeast organisms, as described in the cerebrum. Inflammation and identical yeast organisms were identified on histopathological examination of the pituitary gland and retropharyngeal lymph node. The histopathological diagnosis was systemic blastomycosis.

The previously submitted urine blastomyces antigen enzyme-linked immunosorbent assay (ELISA) test result was available 1 wk later, with a strong positive result.

Discussion

Blastomycosis is a systemic fungal infection caused by the dimorphic fungus, *Blastomyces dermatitidis* and is most commonly identified in dogs and humans (1). The infective sporulated form of the organism is most likely to be found in sandy, acidic soils near bodies of fresh water (1–5). *Blastomyces* has a relatively wide distribution including the Mississippi, Missouri, and Ohio River Valleys, the mid-Atlantic States and southern Saskatchewan, Manitoba, Quebec, and Ontario (1,4,6).

Dogs at greatest risk for clinically apparent blastomycosis are sexually intact male dogs of sporting or hound breeds, 2- to 4-years-old, living in endemic regions. Living near a river or lake and access to excavated areas has also been demonstrated to increase the risk of infection. Most dogs with blastomycosis are diagnosed in late summer or early fall (2,5). Infection most commonly occurs following inhalation of spores from mycelial growth in contaminated soil (1–3). Although infection almost always begins in the lungs before being disseminated through hematogenous or lymphatic routes to other body tissues, lung lesions may resolve by the time infection in other sites becomes apparent (1–3). The most common sites of clinically apparent infection in the dog include lung, lymph nodes, eyes, skin, and bone (1,2,4,7).

Clinical signs in dogs with blastomycosis reflect the systemic inflammatory response and the site(s) of infection. Fever is present in 40% to 60% of affected dogs (1). Lung lesions occur in 65% to 85% of cases and may be clinically silent, or associated with cough, tachypnea, exercise intolerance, cyanosis, or respiratory distress (1–4,7). Lymphadenopathy is reported in 30% to 50% of cases, reflecting either reactive hyperplasia or actual infection of the lymph node by *Blastomyces* organisms with resultant pyogranulomatous inflammation (1,2). Ocular abnormalities are identified in 20% to 50% of cases and may include anterior uveitis, vitritis, chorioretinitis, optic neuritis, serous or granulomatous retinal separation, panophthalmitis, and secondary glaucoma (1–4,8). Granulomatous or ulcerative skin lesions occur in 30% to 50% of cases, particularly involving the nasal planum, the face, and nailbeds (1,2). Focal bone infections causing lameness and osteolysis are reported in up to 30% of infected dogs (1–3).

Neurologic symptoms are uncommon in dogs with blastomycosis; reported in only 3% to 6% of cases (2,3,9,10). Neurologic signs may reflect focal or multifocal disease, and are not distinguishable from signs caused by more common central nervous system conditions such as granulomatous meningoencephalitis, metastatic or primary neoplasia, aseptic meningitis, or other infectious causes of meningoencephalitis (9). Reported neurologic signs include depressed mentation, lethargy, neck pain, circling, cranial nerve deficits, head pressing, seizures, hypermetria, ataxia, and tetraparesis (4,9,11,12). Dogs with central nervous system blastomycosis almost always have clinically apparent significant involvement of extraneural sites, making their diagnosis relatively straightforward (3,6,9,11,12).

Diagnosis of blastomycosis is most reliably accomplished by demonstrating the organism in cytologic or histologic samples from infected tissues. In samples collected from infected sites there will be evidence of pyogranulomatous or purulent inflammation which should prompt a careful search for yeast cells (13).

Cytologic evaluation of samples obtained by transtracheal aspiration, bronchoalveolar lavage, and trans-thoracic lung aspiration have been evaluated in the diagnosis of pulmonary blastomycosis (7,14,15). Although earlier reports suggested that organisms were not likely to be identified in fluid obtained by transtracheal wash, 2 recent retrospective studies have demonstrated 69% and 76% diagnostic utility of this technique in dogs with radiographically evident pulmonary blastomycosis (7,14,15). Transthoracic fine-needle aspiration of solitary or diffuse pulmonary lesions has been reported to be diagnostic in approximately 80% of dogs with pulmonary blastomycosis, but occasionally requires evaluation of multiple samples (15,16). Cytologic evaluation of fine-needle aspirates from enlarged, infected, lymph nodes can be very reliable for diagnosis, but in some patients, lymphadenopathy merely reflects reactive hyperplasia, and no organisms are identified. Aspiration of enlarged lymph nodes has been reported to yield the diagnosis in 67% to 82% of cases (3,13).

Definitive diagnosis based on cerebrospinal fluid (CSF) analysis is rarely possible in dogs or humans with neurologic blastomycosis (9,11,12,17). Cerebrospinal fluid typically reveals a lymphocytic pleocytosis in both species, with a neutrophil concentration ranging from 5% to 40% of CSF leukocytes (9,11,17). A marked neutrophilic pleocytosis is occasionally seen, as is normal CSF cytology (11,17). *Blastomyces* organisms are almost never identified in CSF samples (9,11,17). Fortunately, in humans and in dogs, blastomycosis of the central nervous system rarely occurs in isolation, and cytologic identification of organisms in other infected tissues allows the diagnosis to be made (2,3,9,11,17). Cerebrospinal fluid was not evaluated in the dog reported herein, because the diagnosis was established based on lymph node aspirate cytology.

When cytologic samples from infected tissues are not diagnostic, and there is a high degree of suspicion for blastomycosis; serologic testing may be performed as an aid to diagnosis. Dogs with blastomycosis produce antibodies against the Wisconsin-1 (WI-01) and A-antigens of *B. dermatitidis* (4). Agar gel immunodiffusion (AGID) against the A-antigen is the most commonly used serologic test with a sensitivity of 40% to 90%, and specificity of 90% to 100% (1,2,4,14). The AGID is often negative early in the course of infection (2,4,14) making it unlikely that this test will substantially aid in the diagnosis of dogs without overt systemic blastomycosis. A radio-immunoassay (RIA) to detect serum antibodies against the WI-01 antigen has been reported to detect 92% of infected dogs while maintaining 100% specificity, but this test is not commercially available (1,4). Recently, an immunoassay to detect *B. dermatitides* antigen in urine has been described (18,19). This test is highly sensitive, detecting antigen in urine from 93% of humans and 100% of dogs with systemic or pulmonary blastomycosis, but cross-reactivity with other fungal agents (especially *Histoplasma*) and nonspecific false-positives have been reported (18,19).

The dog in this report was presented for vague clinical signs of illness and progressive neurologic deficits. There were no historical or physical findings to suggest multisystemic disease. Careful examination of the skin, lymph nodes, and eyes and auscultation of the lung were performed, specifically searching for abnormalities that might suggest a diagnosis of blastomycosis. Thoracic radiographs did not reveal any pulmonary parenchymal lesions, even when reviewed after the post-mortem examination had demonstrated many small inflammatory nodular lesions (< 0.5 mm diameter) and an approximately 1-cm diameter focus of caseous necrosis within the lung parenchyma. Dense pulmonary metastases will not be reliably detected on thoracic radiographs until they exceed 7 to 9 mm in diameter, while CT will often identify nodules 1 mm in diameter (20). Diagnosis was achieved when organisms were identified during cytologic evaluation of aspirates obtained from a normal-sized lymph node, and this was supported by establishing a positive urinary antigen test.

Blastomycosis should be considered as a potential differential diagnosis in all dogs with signs of intracranial disease living in an endemic area, even if no other sites of infection are identified during the clinical examination. This is especially important in dogs that have evidence of systemic inflammatory disease as manifested by a fever or a neutrophilic leukocytosis. Every effort should be made to identify disease in other sites, particularly in the lungs, lymph nodes, skin, or eyes. Even if no additional sites can be identified clinically, noninvasive cytologic sampling such as multiple lymph node aspirates and perhaps transtracheal wash may be warranted. Serologic testing and urinary antigen testing may support the diagnosis but should not replace cytologic identification of organisms for a definitive diagnosis. CVJ

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Book Review
Compte rendu de livre

Veterinary Clinical Pathology: An Introduction

Jackson M. Blackwell Publishing, Ames, Iowa, USA, 2007. 363 pp. ISBN 9780-8138-2140-5. $91.99.

Veterinary Clinical Pathology: An Introduction is a clinical pathology textbook primarily aimed towards veterinary students. The author, Marion Jackson, is a clinical pathologist at the Western College of Veterinary Medicine (WCVM) in Saskatchewan, Canada. The textbook follows the format of WCVM's third-year clinical pathology course that is primarily case-based with mini lectures to support class assignments. Consistent with that pattern, this textbook has a thorough introduction and information section at the beginning of each chapter followed by numerous applicable cases that include both small and large animal examples. The chapters cover all the main topics of clinical pathology including hematology, with separate chapters on leukocytes and erythrocytes; biochemistry with separate chapters on the renal, hepatobiliary, muscular, and digestive systems as well as additional chapters devoted to lipids and proteins; fluids, electrolytes and acid-base balance; cytology; endocrinology and coagulation.

I found this book an enjoyable read. The information is well-organized and flows nicely. It is not an exhaustive review so the reader is not distracted by minutia. At the end of each chapter's information section is a list of "Nuggets," which is a concise overview of important points for that topic. The examples are actual cases and therefore show the small changes and variety that accompany real-life scenarios. The glossary of terms is straightforward and nicely simplified.

Some of the organizational features are less than optimal. There is duplication of photos with black and white photos accompanying the information within chapters and the identical color photos in a separate color section. Data tables for the cases are often overwhelming due to numerous columns as results and reference ranges are reported in both SI and conventional units. This feature is quite unique and does allow readers of both the USA and countries using international units such as Canada to use the cases, but it makes the data confusing.

I highly recommend this textbook for clinical pathology students and professors. It is also appropriate for practicing veterinarians who wish to review clinical pathology but is less practical as a "quick go to reference" while working up a case. The index is clear and sends one to appropriate sections; however, because the book doesn't go into every imaginable rule out, a practitioner who wants to be sure he/she has considered every single possibility may be disappointed. In addition, the chapters themselves do not include rule out lists, but this is compensated for by an appendix that contains short lists of rule outs for all indices. This feature may be handy for some individuals as the lists are all together and can be quickly reviewed; however, the lists are separate from background information.

Reviewed by ***Sandra McConkey, DVM, PhD, Diplomate ACVP,*** *Associate Professor of Clinical Pharmacology, Atlantic Veterinary College, Department of Biomedical Sciences, University of Prince Edward Island, 550 University Avenue, Charlottetown, Prince Edward Island C1A 4P3.*