Ocular Blastomycosis

in the Canine Patient

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Class of 2018

Clinicopathologic Conference

Presented on September 22, 2017

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Introduction

Blastomycosis is one of the most common systemic fungal infections in North America, and dogs appear to be more susceptible than any other species.[1,2] Clinical signs can vary depending on the affected organs.[3] Respiratory signs are common because inoculation occurs by inhalation of the organism. Ocular blastomycosis develops from a disseminated infection. Complete ophthalmic exam, identification of the organism, thoracic radiographs, and urine antigen testing are useful in diagnosing the disease. Treatment involves topical and systemic administration of anti-inflammatory and antifungal medications.[1,3] Enucleation may be necessary in patients with endophthalmitis or secondary glaucoma that is refractory to medical management.[1] Early diagnosis is pertinent for preventing vision loss and can be life-saving for the patient.[4]

History and Presentation

Blastomycosis most commonly affects young (1 to 5 years old), large breed dogs. Retrievers and Doberman Pinschers are over-represented, and hunting and working dogs are at greater risk of developing an infection due to increased exposure to the organism.[1-9] Historically, intact males were thought to be more predisposed to infection, but sex predisposition is not consistent in the current literature.[2,4,9]

Clinical signs may develop days to months following exposure to the organism. Infected patients commonly develop nonspecific clinical signs, such as anorexia, weakness, lethargy, and depression, but patients can also develop specific clinical signs depending on the affected organ systems. Because infection first occurs in the lungs, respiratory signs (coughing, tachypnea, exercise intolerance) frequently occur with blastomycosis.[1,2,4] Physical examination reveals

tachypnea or dyspnea, harsh lung sounds, fever, cachexia, peripheral lymphadenopathy, and draining lesions of the subcutaneous tissue or skin.[1,2,4] Clinical signs associated with ocular, cutaneous or skeletal disease may also be evident. The central nervous system (CNS) and urogenital tract are less commonly affected.[4]

Ocular involvement occurs in approximately 40-48% of dogs with systemic infection.[1,3,8] The presence of conjunctivitis, keratitis, panuveitis, chorioretinitis, endophthalmitis or blindness is consistent with ocular dissemination, with endophthalmitits being the most common.[1,2,10] Commonly, the first indications of blastomycosis that owners notice are due to ocular involvement.[4] Rarely, ocular lesions may be the only sign of infection.[3]

Ocular manifestation of blastomycosis can present differently depending on the severity of disease and the segment of the eye that is affected.[6] Additionally, ocular disease can be unilateral or bilateral, and clinical signs and disease severity may differ between the eyes.[4] Early signs can include blepharospasm, ocular discharge, conjunctival hyperemia, corneal edema, aqueous flare, and miosis.[3,11] Cataracts can form if the lens capsule ruptures, which can lead to persistent inflammation.[1] Retinal hemorrhage, hyphema, buphthalmos, and blindness are signs of advanced disease resulting from retinal detachment, endophthalmitis, and secondary glaucoma.[1,2,3,6,10] Optic neuritis can be a manifestation of ocular or CNS involvement.[3,4] Exophthalmos due to a retrobulbar granuloma has been reported as an atypical presentation of ocular blastomycosis.[1]

Pathophysiology

Blastomycosis is caused by infective spores of the etiologic agent *Blastomyces dermatitidis* (*B. dermatitidis*), which is a thermally dimorphic, pathogenic fungus.[1] *B.*

dermatitidis is endemic in central and southeastern parts of the United States, including the Ohio, Missouri, and Mississippi River Valleys. It can also be found in the mid-Atlantic states, the Great Lakes region, and parts of Canada.[1,3,4,7,12] The mycelial form of the organism typically grows in moist, sandy, acidic soil containing decaying organic matter, whereas the yeast form resides inside the canine host.[2,4]

The mycelial form produces microscopic conidia that can be disseminated in the environment by any type of moisture, including bodies of water, dew, fog, mist, and rainfall.[4] Aerosolization of conidia can also be promoted by a disturbance of the soil, such as construction or excavation.[1,9] Infection is predominantly caused by inhalation of the fungal spores by the host, and direct inoculation of a wound is rare.[1] Once inside the host, the infective spores are phagocytized by macrophages and transported into the pulmonary interstitium.[1,9] The normal body temperature of the host promotes the transformation of spores into yeast forms. These organisms can then spread via the vasculature or lymphatics and cause pyogranulomatous inflammation in other organs, most commonly the lymph nodes, skin, and eyes.[1,2,8]

Once *B. dermatitidis* reaches the eye, the organisms invade the choroid, which initiates a significant inflammatory response. Posterior segment inflammation occurs initially and leads to anterior segment changes. Retinal detachment, endophthalmitis and secondary glaucoma eventually develop due to progressive inflammation.[2,3,11,13]

Differential Diagnoses

Ocular blastomycosis is a common cause of panuveitis in dogs and should be considered as a differential in patients with signs of uveal inflammation. Other top differentials for inflammation in the eye include immune-mediated disease; bacterial infection, such as

leptospirosis and prototheca; and other systemic fungal infections, including aspergillosis, coccidiomycosis, cryptococcosis, and histoplasmosis.[12,14] Considering the breeds that are predisposed to blastomycosis are also prone to eye injury while working or hunting, ocular trauma is an important differential.[12] Ocular neoplasia, such as lymphoma, can also be a cause of inflammation in the eye.

Diagnostic Approach/Considerations

In addition to a thorough physical examination, a complete ophthalmic examination should be performed on every patient with confirmed or suspected systemic blastomycosis. Evaluation of the fundus can be useful in diagnosing ocular involvement, assessing disease severity, and determining prognosis. Mydriasis is needed to assess the periphery of the fundus as early lesions can form in the periphery and may be small.[4] A white-to-gray granuloma beneath the retina, commonly in the nontapetal fundus, is indicative of pyogranulomatous inflammation, which is suggestive of fungal infection. Individual subretinal granulomas that increase in size over time may be present.[4,6,11] Complete detachment of the retina occurs with advanced ocular blastomycosis. Fundic examination may be difficult if corneal edema, severe anterior uveitis, vitreal hemorrhage, or cataracts are present.[11]

Ultrasonography of the eye can be performed to evaluate the posterior segment, especially when fundic examination is unrewarding. Common findings include intravitreal infiltration and hemorrhage due to retinal detachment.[12]

Blastomycosis can be definitively diagnosed via cytology or histopathology by identifying characteristic organisms in affected tissue.[2,4,12] Cytology samples can be obtained via impression smears of cutaneous lesions or fine-needle aspirates of abnormal tissue, such as

enlarged lymph nodes or pulmonary nodules. Cytological examination of fluid obtained via vitreocentesis can also be useful; however, this invasive procedure should be reserved for irreversibly damaged, nonvisual eyes.[1,2,4] *B. dermatitidis* yeast forms are large (5-20 micrometers), have a double cell wall, and exhibit broad-based budding.[1,2,4,5,9] Organisms are typically surrounded by suppurative or pyogranulomatous inflammation.[1,4] Histopathology of enucleated globes commonly reveals choroiditis and detachment of the retina. Fungal yeast forms can be found in the choroid, subretinal space, or within macrophages.[6] Inflammatory lesions can also be seen in the anterior segment. Because *B. dermatitidis* does not invade the anterior segment, this is thought to be a response to inflammation in the posterior segment rather than a response to fungal organisms. Cataracts, secondary glaucoma, anterior and posterior synechiae, and closure of the iridocorneal angle are sequelae to severe ocular inflammation that can be seen histopathologically.[13] Culture is not recommended as it is time consuming and presents an occupational hazard to laboratory personnel.[1,2]

Due to the nature of *B. dermatitidis,* thoracic radiographs should be evaluated in patients with or without respiratory signs. A diffuse interstitial (“snowstorm”) or nodular interstitial pulmonary pattern is characteristic of blastomycosis. Intrathoracic lymphadenopathy is also a common finding and can be suggestive of dissemination to other organs.[1,2,4,5]

Urine *Blastomyces* antigen testing is an acceptable, non-invasive method of diagnosing systemic blastomycosis. This test detects galactomannan in the fungal cell wall, and it is reported to have a high sensitivity during initial diagnosis and treatment.[15] Urine antigen concentration decreases with treatment, which makes this test valuable for monitoring response to therapy. However, it is recommended to consider the patient’s clinical condition and thoracic imaging in combination with urine antigen testing when making decisions regarding therapy.[12,15]

Hematologic evaluation may be supportive of systemic blastomycosis. Complete blood count abnormalities may include a mild nonregenerative anemia, mature neutrophilia, or neutrophilia with a left shift. Serum biochemical profile results are often within normal limits, but hypoalbuminemia and hyperglobulinemia may be present.[1,2] Hypercalcemia is suggestive of extensive dissemination of the organism.[9]

Serum antibody tests for blastomycosis, such as agar gel immunodiffusion and radioimmunoassay, are available. However, these tests are based on antibody response to fungal antigens, and false negative results can occur with early infection, immunosuppression, or advanced disease.[1,5] Serologic examination should be interpreted as supportive of blastomycosis and should not be used as the sole diagnostic test.[4] Additionally, titers are variable following treatment, and the results cannot be used to monitor response to therapy.[4,12]

Treatment and Management Options

Dogs with clinical blastomycosis will not clear the organism spontaneously and require therapeutic intervention to treat the disease.[2] In cases of ocular blastomycosis, a combination of ophthalmic and systemic treatment is indicated.[1,3,4] Appropriate supportive care should also be administered.

Specific medications used in ocular therapy vary depending on the clinical signs, but the goals of therapy remain the same: vision preservation and pain elimination.[4] Treatment with a topical steroid (0.1% dexamethasone or 1.0% prednisolone acetate) should be used 4-6 times per day to treat uveitis and to control anterior segment inflammation. Topical 1% atropine can be used to effect for miosis, but its use is contraindicated in secondary glaucoma. Topical

administration of a beta-blocker (0.5% timolol) or carbonic anhydrase inhibitor (2.0% dorzolamide) is indicated in secondary glaucoma.[4]

Systemic prednisone (1mg/kg, PO, q12-24h) should be given when posterior segment inflammation is severe or when retinal lesions do not show improvement with antifungal treatment alone. As lesions improve, the dose should be slowly tapered.[4] In one retrospective study, the use of systemic corticosteroids was shown to positively affect vision and did not negatively affect the survival rate in the group of dogs.[10] Painful, glaucomatous globes that do not respond to medical therapy should be enucleated but only when the patient is clinically stable enough for anesthesia.[4] Enucleation may also aid in the clearance of *B. dermatitidis* if the eye is unable to clear the infection.[1]

Itraconazole is the antifungal of choice for treatment of systemic blastomycosis in dogs because of its safety and efficacy.[2] The recommended dose is 5mg/kg given orally with food every 24 hours for 60-90 days and one month past the resolution of clinical signs.[10,16,17] Possible side effects of itraconazole include hepatotoxicity and gastrointestinal upset. Although itraconazole does not penetrate the blood-ocular barrier of a normal eye, it is thought to reach sufficient levels to treat *B. dermatitidis* in eyes with inflammation.[16,17] Studies show that itraconazole is less toxic and equally as effective as amphotericin B, the previously preferred treatment. Less monitoring requirements and oral administration make itraconazole a convenient treatment option.[1,17]

Fluconazole is similar but less expensive than itraconazole. It has been used successfully in treatment of systemic blastomycosis at an empiric dose of 5-10mg/kg orally every 24 hours.[9,16] Fluconazole's ability to cross the blood-ocular, blood-brain, and blood-prostate barriers better than itraconazole make it a reasonable treatment option for ocular, CNS, and urogenital *B.*

dermatitidis infections.[1,4] Like itraconazole, hepatotoxicity is a possible side effect of fluconazole.

Amphotericin B and ketoconazole are additional antifungal medications used in the treatment of blastomycosis. Because amphotericin B is cumulatively nephrotoxic, evaluation of serum creatinine, blood urea nitrogen, and urine specific gravity can be useful in assessing the patient's renal health prior to administration.[16,17] To reduce the risk of nephrotoxicity, concurrent administration of intravenous fluids should be considered as well as the use of lipid-complexed amphotericin B, which is less nephrotoxic. As with the previously mentioned azoles, gastrointestinal upset and hepatotoxicity can also be seen with ketoconazole administration.[16]

Monitoring

When using systemic antifungal medications, it is important to monitor the patient for adverse effects as well as response to therapy. A serum biochemical profile should be assessed periodically for elevations in hepatocellular enzymes (alanine transferase and alkaline phosphatase) or renal values (creatinine and blood urea nitrogen).[16,17] Response to therapy can be monitored by physical examination as well as serial thoracic radiographs, fundic examinations, and urine antigen testing. Improvement of clinical signs and radiographic pulmonary pattern, resolution of fundic lesions, and a decreasing urine antigen concentration are indicators of a positive response to therapy.

Treatment of systemic blastomycosis should only be discontinued when a negative or weakly positive (<1ng/mL) urinary antigen concentration is achieved in conjunction with normal findings on physical examination, fundic evaluation, and thoracic radiographs.[15]

Expected Outcome and Prognosis

During the first 5 days of treatment of systemic blastomycosis, clinical signs and ocular inflammation may worsen due to an inflammatory response from sudden death of the fungal organisms. During this time, failure of treatment is more likely for dogs with severe respiratory disease or infection of multiple body systems.[2] Treatment response depends on the affected tissues, degree of dissemination throughout the body, the clinical status of the patient, and the selected treatment protocol.[1]

In general, the prognosis for recovery is good (70-75%) in dogs with systemic blastomycosis. Unfortunately, the prognosis significantly worsens for patients with severe pulmonary disease or CNS involvement.[1] Prognosis for vision depends on the severity of ocular involvement. Dogs with low-grade aqueous flare and chorioretinal lesions with intact retinas have the best ocular prognosis. Patients presenting with advanced stages of ocular disease, including secondary glaucoma, endophthalmitis, or blindness, have a guarded ocular prognosis and often require enucleation.[1,3, 4,5,6] In one study, the addition of systemic corticosteroids may have helped to maintain vision in dogs.[10]

The recurrence rate of blastomycosis is approximately 20% following systemic antifungal therapy.[5,9,17] If relapse of disease occurs, the previously prescribed treatment should be repeated.[5] It has not been determined whether blind eyes due to ocular blastomycosis serve as a nidus of infection or contribute to disease recurrence.[3] One retrospective study showed that *B. dermatitidis* can be present in cases of severe endophthalmitis even following appropriate treatment.[18] Enucleation may be required to eliminate the organism in persistently inflamed eyes; however, quiet, non-painful eyes may not require enucleation.[3,4,18]

Public Health Considerations

Because they are more prone to developing blastomycosis, dogs serve as a sentinel for human disease.[4,8,9] Although a “point source” exposure could result in infection of both dogs and humans, aerosol transmission of *B. dermatitidis* yeast forms from infected dogs to humans is not possible. However, there are reports of cutaneous inoculation of organisms via contaminated needles and the bite of an infected dog.[1,4] Human infection is also possible following exposure to contaminated bandages, infected tissues, and positive fungal cultures.[1,5] Appropriate precautions should be taken when handling these materials.[2]

Conclusion

Systemic blastomycosis occurs following inhalation and hematogenous spread of *B. dermatitidis* organisms. Diagnosis is based on clinical signs, appearance of the organism, thoracic radiographs, and urine antigen testing. The mainstay of treatment is systemic antifungal therapy and supportive care, and prognosis depends on the affected tissues and severity. Ocular blastomycosis is a relatively common manifestation of systemic blastomycosis. A complete ophthalmic examination should be performed in every patient with diagnosed or suspected blastomycosis, as ocular findings can be useful in diagnosing disease, directing therapy, determining prognosis, and monitoring response to treatment.[3,4]

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