

Blastomycosis: A Systematical Review

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Review Article

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ABSTRACT

Blastomycosis is a systemic mycotic infection which is frequently seen in North America. Any study about blastomycosis has not been encountered on veterinary field in our country. This disease affects especially humans and dogs; but it is also seen in cats, horses and the other mammals. Diagnosis of the blastomycosis can be overlooked because the disease affects multiple organs and systems and many different symptoms can be observed.

It is aimed to give information about Blastomycosis which is rarely known but tends to be confused with other diseases, causes life-threatening inflammations and can be observed in many different countries because of the owners travel with their pets.

INTRODUCTION

Blastomycosis is a systemic and cutaneous fungal disease caused by conidia of systemic mycose agent, *Blastomyces dermatitidis*. In some cases this systemic fungal disease can be fatal ^[1,2]. *Blastomyces dermatitidis* is a saphrophytic and dimorph fungal organism which can be found as mycelial form in the soil and as yeast form in the infected tissues ^[3,4]. Young large breed dogs and especially unneutered male dogs are the group of highest risk for dogs. Blastomycosis is most commonly observed in sporting dog breeds, hunting dog breeds and especially seen in Labrador Retrievers, Golden Retrievers and Doberman Pinschers ^[5]. Many bacteria excrete through feces, which can cause undesirable effects in health and environment ^[6-9].

Blastomyces dermatitidis is endemic in Canada, southcentral of United States and especially in North America. For example the number of Blastomycosis cases per 100,000 population is 0.62 in Canadian province of Manitoba, 7.11 in Ontario, 1.3 in Wisconsin, 1.4 in Mississippi are determined ^[4]. Epidemiological information has been derived primarily from investigations of outbreaks and case reports. Although a number of studies has been undertaken to define the incidence and prevalence of blastomycosis, determining these epidemiological parameters has been difficult because *B. dermatitidis* cannot be easily recovered from nature and there is no suitable, sensitive and specific skin or serological test to confirm infection; therefore, cases may be undetected or underdiagnosed ^[1,10]. Most epidemiological studies are based on growth of *B. dermatitidis* in cultures of clinical specimens or direct histological visualization to establish the diagnosis ^[1,11]. Although there are some case studies for human blastomycosis, but there aren't any studies in veterinary field in Turkey ^[12,13].

PATHOGENESIS

Infection with *B. dermatitidis* typically occurs when conidia is produced from the mycelial phase in soil or decaying matter are inhaled into the lungs ^[5,14]. Direct inoculation of the organism via skin puncture wounds is rarely seen. The increase in temperature within the body causes conversion from the spore phase to a large broad-based budding yeast cell. It is discovered that yeast exhibit enhanced growth in the presence of canine macrophages, and when yeasts reach into the lungs they cause

pyogranulomatous pneumonia. They cause granulomatous or pyogranulomatous inflammation in many organs via vascular or lymphatic system (lymph nodes, eyes, bones, central nervous system, kidneys, liver, spleen, skin, genitourinary system, heart, adrenal glands). It is determined that mostly effected tissues are respiratory system, lymphatic tissues, eyes, skin and bones [5,15].

CLINICAL EXAMINATION FINDINGS

It is reported that Blastomycosis can be seen as asymptomatic or diffuse form [15]. Clinical findings represent the multisystemic and inflammatory nature of the disease. Fever, weight loss and anorexia are the common nonspecific clinical signs of all cases [2,5]. Lymphadenopathy and hyperthermia (39.4 °C or higher) are detected in 40% - 60% of diseased dogs in some studies [2,16].

It is detected that because of the conidia's are majorly transmitted by inhalation, the disease primarily develops as pulmonary syndrome [15]. Pulmonary lesions occur 65% - 85% cases [17]. Disease may be clinically silent or, more often, associated with respiratory signs, including exercise intolerance, tachypnea and cough [18,19]. Cough, tachypnea and reluctance to walk are the clinical signs about respiratory system [5,17,20,21]. Otherwise; fever, peripheral lymphadenopathy, dyspnea or tachypnea, tachypnea, subcutaneous abscesses in mouth and on fingers and the other parts of the body, catarrhal ulcerative skin lesions and oral lesions can be seen. In a case report; it is reported that a 6 year old dog had respiratory stridor 1 month duration and two months prior to referral; the owner had noticed a remarkable change in phonation, exercise intolerance, partial anorexia and weight loss. The patient diagnosed as pharyngeal - laryngeal blastomycosis. At first clinical examination existence of hyperthermia (T = 39.9 °C), cyanosis in mucous membranes and dyspnea has been reported [22].

20% - 50% of the dogs have ocular invasion with or without concurrent pulmonary disease has been reported [2]. Clinical findings that can remind ocular invasion are ocular drainage, conjunctivitis, keratitis, chorioretinitis, uveitis, photophobia and impaired vision [5,17]. Endophthalmitis has been reported more oftenly in dogs with ocular blastomycosis. Posterior and anterior segment diseases have been rarely reported [23]. In the dogs with endophthalmitis, the most common anterior segment disorder is anterior uveitis, with changes including corneal edema, aqueous flare, miosis, iris bombe or synechia [5]. In a study based on dogs with endophthalmitis *B. dermatitidis* has been isolated from 31 of 33 cases [24].

It is reported that while some testicular blastomycosis cases had systemic signs as exercise intolerance, weight loss, peripheral lymphadenopathy, nonproductive cough; some cases had scrotal edema without systemic signs. Some cases also had mass in testes but the body temperature was detected in normal ranges. In prostatic blastomycosis; it is reported that patients have systemic signs like hyperthermia (T = 39.4 °C - 40 °C) and also had urogenital signs like dysuria and hematuria due to urethral obstruction [3]. In a study of blastomycosis including 115 dogs, the testes were affected in 17% of 58 intact male dogs and the prostate was affected 3% of 58 intact male dogs [20]. In the same study it is reported that 6% of 115 dogs had neurologic involvement with neurologic signs (hypermetry, abnormalities in postural reactions, timidity, pupiller light reflex decay, sensitivity on face, blindness, focal or generalized tremors, back pain, lethargia, depression, ataxy and tetraparesis) [5,20,25,26].

In some cases; reluctance to walk, lameness, localized soft tissue and bone swelling and back-lumbal pain have been reported. These symptoms are related with arthritis, periostitis, osteomyelitis and rarely hypertrophic osteopathy is caused by *B. dermatitidis* [5,27].

The other atypical clinical conditions are reported as diffuse pulmonary thromboembolism, thrombus, V. cava cranialis obstruction and granulomas that cause cheilothorax [5,18,28]. And also temporary calsinosis cutis after treatment with Amphotericin B or Amphotericin B lipid complex [5,29] and swelling on face due to osteomyelitis caused by *B. dermatitidis* in skull bones [5].

In a study including 571 cats [30]; only 41 of cats has been diagnosed as blastomycosis and 68% of them diagnosed in necropsy, 32% of cats had systemic form and 10% of all cats was diagnosed as FeLV positive. It is reported that affected tissues are similar with dogs and dyspnea, cough, anorexia, lethargy and weight loss are the clinical signs [5]. Peripheral lymphadenopathy, cutaneous nodules and lameness have been reported. It is detected that the neurological signs occurred as a result of pyogranulomatous inflammation caused by *B. dermatitidis* and depending on affected tissue, symptoms are similar to dogs [31,32].

DIAGNOSIS

Complete blood count and blood serum biochemical analysis

There are also abnormalities in blood parameters, including; nonregenerative anemia, neutrophil leukocytosis (mostly shift to the left), monocytosis, lymphopenia, hyperglobulinemia, hypoalbuminemia, hypercalcemia and hypoglisemia. That has been detected in some studies based on cat, although there isn't any common finding, in some cases anemia and lymphopenia can occur [2,3].

Cytology, histopathology, culture and serology

It is reported that the most successful methods in the way to diagnose blastomycosis are cytologic samples from the cutaneous lesions, peripheral lymph nodes, lungs, joints and bones collected with fine-needle aspiration biopsy and samples from cerebrospinal fluid and vitreous silica [1,2,5,12,13,22,29,33-35]. Histopathologic examination of tissue and bone biopsies have been revealed as a very successful method for diagnosing blastomycosis [5,22,25]. In some studies it is revealed that *B. dermatitidis*

can be isolated from bronchoalveolar, transtracheal and peritoneal lavage samples, urinary sediment and prostatic flush fluids [2,3,5]. It is reported that *B. dermatitidis* yeasts are round to oval, 10 µm - 20 µm in diameter, have a basophilic interior, thick and double-contoured walls and display broad-based budding. As revealed in some studies; special stains like periodic acid-Schiff, Gridley's fungal and Gomori's methenamine silver are useful for detecting organisms however microscopic identification may not be successful [2,5,22]. Fungal cultures of exudates from cutaneous lesions, fine-needle aspirates or biopsy materials from affected tissues may identify *B. dermatitidis* growth, but it is time-consuming and the safety of laboratory personnel is a concern [5].

A study of a Golden Retriever with osteomyelitis has been revealed that there was no growth detected in the culture of metacarpal bone biopsy, but in histopathological examination pyogranulomatous osteomyelitis due to blastomycosis had been determined. In this case *B. dermatitidis* has been determined with Gomori's methenamine silver stain and at the same time fungal osteomyelitis has been confirmed [33]. In a study including eight dogs with testicular and prostatic blastomycosis; However after the examination of urine samples, firstly *B. dermatitidis* couldn't be determined after the examination of urine samples but histopathological examination from testes and prostate revealed *B. dermatitidis* [3].

It is reported that organism may not be identified serologically because the blood serum may be concealed for fungal antibody titer. For this reason, serological diagnosis of blastomycosis is highly suspicious. Agar-gel immunodiffusion test (AGID) is reported to be a valuable adjunctive test with 41% sensitivity and 100% specificity for blastomycosis and its mechanism predicated on establishing the mycelial antigens of *B. dermatitidis* [5].

Diagnostic imaging techniques

It is reported that thorax radiographs of the animals that has been diagnosed with blastomycosis typically reveals diffuse or nodular interstitial or bronchointerstitial pulmonary pattern. Tracheobronchial lymphadenopathy can be also seen in thorax radiograph [2,5]. Pulmonary blastomycosis image has encountered in thorax radiographs of most cases with central nervous system, prostatic, testicular, pharyngeal-laryngeal blastomycosis [3,12,25]. It is also revealed that blastomycosis can be seen as osteomyelitis, osteolytic lesions typically seen on joints and distal of long bones at the same time [5,33]. Otherwise, pleural effusion and pulmonary mass lesions can be seen in cats [5].

It is reported that magnetic resonance imaging (MRI) and tomography (CT) are usable imaging techniques in dogs with central nervous system blastomycosis. These techniques facilitate to discover intracranial lesions related with blastomycosis, their sizes, locations, counts and contrasts [5]. In a study including 5 dogs with intracranial blastomycosis [34,35]; hydrocephalus, vasogenic brain edema, bone lesions, meningeal / chorioid plexus / ependymal contrast variations has displayed with these techniques.

TREATMENT

It is reported that success of therapy depends on affected tissues, transmission degree, patient's general health condition and treatment [36]. Amphotericin B is given intravenously (IV), alone at a dosage of 8-9 mg/kg or in combination ketoconazole, has been a common treatment for systemic fungal infections in dogs. However amphotericin B has been discovered as nephrotoxic [37]. It is reported that treatment with ketoconazole (10 mg/kg/day BW PO one time a day for 2 months) in combination with amphotericin B (4 mg/kg body weight before and 2 mg/kg body weight after ketoconazole) is as effective as amphotericin B alone and it is less nephrotoxic [37]. Ketoconazole alone at a dosage of 10 mg/kg/day BW one time a day for 2 months was not effective as amphotericin B alone. Amphotericin B lipid complex has reported as a safer and more effective alternative agent than amphotericin B. Amphotericin B lipid complex can be used at a dosage of 8 mg/kg - 12 mg/kg IV but it is more expensive than amphotericin B [5].

In a study of 115 dogs with blastomycosis [20], treatment with itraconazole has been detected as effective as treatment with a combination of amphotericin B and ketoconazole. Itraconazole at a dosage of 5 mg/kg one time a day with food for at least 4 - 6 months is the accepted treatment of choice for blastomycosis in dogs. Cats require 10 mg/kg itraconazole one time a day or divided dosage twice a day [34]. It is reported that itraconazole is less effective than amphotericin B, so it removes the necessity of controlling the kidney and liver functions during the therapy, otherwise itraconazole is safer and easier to apply because it is given orally [5,36]. In a case report it is reported that a 6-year-old Labrador retriever with pharyngeal - laryngeal blastomycosis treated with 100 mg itraconazole twice a day orally for 10 weeks. Patient progress is seen with surgical intervention and bronchointerstitial mass image was mended after 3 months [22]. Fluconazole appears to be less effective than itraconazole for the treatment of blastomycosis in dogs and cats and it is more expensive. It may be a more appropriate agent choice for urinary tract, prostatic and central nervous system infections, and it can be used at a dosage of 5.5 mg/kg - 22 mg/kg [34,38]. It is revealed that fluconazole and itraconazole are hepatotoxic on animals and patient's liver functions must be controlled during this therapy [39].

CONCLUSION

Blastomycosis is a very important disease which affects many tissues and organs and causes fatal lesions. Although there isn't any case reports of blastomycosis on veterinary field in our country, there can be unnoticed cases because of the difficulty to diagnose and miscibility with the other tissues and organ diseases. It shouldn't be forgotten that blastomycosis isn't seen very

often in our country, it can be transmitted with the animals that travels with their owners.

It must be considered that respiratory and ocular forms can be disguised in clinical approach and these cases must be also investigated for blastomycosis. It must be remembered that early diagnosis makes significant contribution to the treatment of animals with blastomycosis. Profile of blastomycosis in our country can be revealed more clearly with prospective prevalence studies.

REFERENCES

1. Choptiany M, et al. Risk factors for acquisition of endemic blastomycosis. *Can J Infect Dis Med Microbiol.* 2009;20:117-21.
2. McMillan CJ and Taylor SM. Transtracheal aspiration in the diagnosis of pulmonary blastomycosis (17 cases: 2000-2005). *Can Vet J.* 2008;49:53-5.
3. Totten AK, et al. *Blastomyces dermatitidis* prostatic and testicular infection in eight dogs 1992-2005. *J Am Hosp Assoc.* 2011;47:413-8.
4. Baumgardner DJ, et al. Effects of season and weather on blastomycosis in dogs. Northern Wisconsin, USA. *Med Mycol.* 2010;49:49-55.
5. Brömel C and Sykes JE. Epidemiology, diagnosis, and treatment of blastomycosis in dogs and cats. *Clin tech Small Anim Pract.* 2005;20:233-9.
6. Nandre, et al. Immunogenicity of a *Salmonella enteritidis* mutant as vaccine candidate and its protective efficacy against salmonellosis in chickens. *Veterinary Immunology Immunopathology.* 2011;144:299-311.
7. Nandre, et al. A genetically engineered derivative of *Salmonella Enteritidis* as a novel live vaccine candidate for salmonellosis in chickens. *Research in Veterinary Science.* 2012;93:596-603.
8. Nandre, et al. Adjuvant effect of *Escherichia coli* heat labile enterotoxin B subunit against internal egg contamination in domestic fowl immunised with a live *Salmonella enterica* serovar *enteritidis* vaccine. *Veterinary Journal.* 2013;197:861-7.
9. Nandre, et al. Construction of a recombinant-attenuated *Salmonella enteritidis* strain secreting *Escherichia coli* heat-labile enterotoxin B subunit protein and its immunogenicity and protection efficacy against salmonellosis in chickens. *Vaccine.* 2014;32:425-31.
10. Chapman SW. *Blastomyces dermatitidis*. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, Bennett's Principles and Practice of Infectious Diseases.* 6th edn. Elsevier, Philadelphia, USA; 2005.
11. Centers for Disease Control and Prevention (CDC). Blastomycosis - Wisconsin, 1986-1995. *MMWR Morb Mortal Wkly Rep.* 1996;45:601-3.
12. Durdu M, et al. More experiences with the Tzanck smear test: cytologic findings in cutaneous granulomatous disorders. *J Am Acad Dermatol.* 2009;61:441-50.
13. Güler N, et al. Progressive vertebral blastomycosis mimicking tuberculosis. *Pediatr Infect Dis J.* 1995;14:816-8.
14. MacDonald PD, et al. Human and canine pulmonary blastomycosis, North Carolina, *Emerg Infect Dis.* 2002;12:1242-4.
15. De Groote MA, et al. Expanding epidemiology of blastomycosis: Clinical features and investigation of 2 cases in Colorado. *Clin Infect Dis.* 2000;30:582-4.
16. Legendre AM. Blastomycosis. In: Greene CE, ed. *Infectious Diseases of the Dog and Cat.* 3rd edn. Elsevier Saunders, St. Louis, USA; 2006.
17. Davies SF and Sarosi GA. Epidemiologic and clinical features of pulmonary blastomycosis. *Semin Respir Inf.* 1997;12:206-18.
18. Howard J, et al. Blastomycosis granuloma involving the cranial vena cava associated with chylothorax and cranial vena caval syndrome in a dog. *J Am Anim Hosp Assoc.* 2000;36:159-61.
19. Kerl ME. Update on canine and feline fungal diseases. *Vet Clin North Am Small Anim Pract.* 2003;33:721-47.
20. Arceneaux KA, et al. Blastomycosis in dogs: 115 cases (1980-1995). *J Am Vet Med Assoc.* 1998;213:658-64.
21. Nielsen C, et al. Diagnostic peritoneal lavage for identification of blastomycosis in a dog with peritoneal involvement. *J Am Vet Med Assoc.* 2003;223:1623-7.
22. Salinardi BJ, et al. Pharyngeal - Laryngeal Blastomycosis in a Dog. *J Vet Dent.* 2003;20:146-7.
23. Bloom JD, et al. Ocular blastomycosis in dogs: 73 cases, 108 eyes (1985-1993). *J Am Vet Med Assoc.* 1996;209:1271-4.
24. Hendrix DV, et al. Comparison of histologic lesions of endophthalmitis induced by *Blastomyces dermatitidis* in untreated and treated dogs: 36 cases (1986-2001). *J Am Vet Med Assoc.* 2004;224:1317-22.
25. Gaunt MC, et al. Central nervous system blastomycosis in a dog. *Can Vet J.* 2009;50:959-962.

26. Nafe LA, et al. Central nervous system involvement of blastomycosis in the dog. *J Am Anim Hosp Assoc.* 1983;19:933-6.
27. Bone DL. Osteomyelitis due to canine blastomycosis. *J Vet Orthopedics.* 1984;3:15-20.
28. Mc Guire NC, et al. Pulmonary thromboembolism associated with *Blastomyces dermatitidis* in a dog. *J Am Anim Hosp Assoc.* 2002;38:425-30.
29. Gortel K, et al. Calsinozis cutis associated with systemic blastomycosis in three dogs. *J Am Anim Hosp Assoc.* 1999;35:368-74.
30. Davies C and Troy GC. Deep mycotic infections in cats. *J Am Anim Hosp Assoc.* 1996;32:380-91.
31. Breider MA, et al. Blastomycosis in cats: five cases (1979-1986). *J Am Vet Med Assoc.* 1988;193:570-2.
32. McEwen SA and Hulland TJ. Cerebral blastomycosis in a cat. *Can Vet J.* 1984;25:411-3.
33. De Lorimier LP and Fan TM. Delayed diagnosis of fungal osteomyelitis with early scintigraphic lesions in a dog. *Can Vet J.* 2010;51:1394-6.
34. Ettinger SJ and Feldman EC. *Textbook of Veterinary Internal Medicine.* Vol 1, 6th edn. Elsevier Saunders, St. Louis, USA; 2005.
35. Hect S, et al. Clinical and imaging findings in five dogs with intracranial blastomycosis (*Blastomyces dermatitidis*). *J Am Anim Hosp Assoc.* 1995;47:241-9.
36. Legendre AM, et al. Treatment of blastomycosis with itraconazole in 112 dogs. *J Vet Intern Med.* 1996;10:365-71.
37. Legendre AM, et al. Treatment of canine blastomycosis with amphotericin B and ketoconazole. *J Am Vet Med Assoc.* 1984;184:1249-54.
38. Mazepa ASW, et al. Retrospective Comparison of the Efficacy of Fluconazole or Itraconazole for the Treatment of Systemic Blastomycosis in Dogs. *J Vet Intern Med.* 2011;25:440-5.
39. Somchit N, et al. Hepatotoxicity induced by antifungal drugs itraconazole and fluconazole in rats: a comparative *in vivo* study. *Hum Exp Toxicol.* 2004;23:519-25.