زانکۆی سەلاحەدین - هەولێر
Salahaddin University-Erbil

Blastomycosis

Submitted to the Department of (Biology) in partial fulfillment of the requirements for the degree of **BSc.** in **Biology** in (Salahaddin University).

By

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CERTIFICATE

This research project has been written under my supervision and has been submitted for the award of the **BSc.** degree in **Biology** with my approval as a supervisor.

Signature
Name:

Date: **April 10, 2021**

DEDICATION:

This effort I dedicate to Allah Almighty, my lord, my powerful foundation, my source of inspiration, wisdom, knowledge, and understanding.

ACKNOWLEDGMENTS:

To begin with, I thank (**Allah**) for His blessing, which made me able to complete and perform this study with success, the lord of the universe, blessing, and peace be on **Muhammad** (Allah's peace and prayers be upon him).

I want to say thanks to my supervisor **Dr. Rezhin ali** for helping me in writing this review article .Finally, I want to say thanks to all those I forgot them here to mention his/her name, who assisted me even by one useful scientific word directly or indirectly.

SUMMARY

This article illustrates a typical case of blastomycosis, which is caused by the dimorphic fungal pathogen *B. dermatitidis*. The organism may cause both pulmonary and extrapulmonary disease and is typically contracted through inhalation of infectious conidia found in the environment.These fungi can be found in moist soils, particularly in wooded areas and along waterways.and it can From the lungs, the fungus can spread to other areas of the body including your skin, bones, joints and central nervous system. This disease is rare and more commonly affects people involved with outdoor activities. Symptoms of blastomycosis usually appear between 3 weeks and 3 months after a person breathes in the fungal spores. test for blastomycosis by taking a blood sample or a urine sample and sending it to a laboratory. Healthcare providers may do imaging tests such as chest x-rays or CT scans of your lungs. There is no vaccine to prevent blastomycosis, and it may not be possible to completely avoid being exposed to the fungus that causes blastomycosis in areas where it is common in the environment. People who have weakened immune systems may want to consider avoiding activities that involve disrupting soil in these areas.

CONTETNTS

INTRODUCTION:

blastomycosis is a chronic granulomatous disease caused by the thermally dimorphic fungus *Blastomyces dermatitidis*. (Dismukes et al., 1992) a thermally dimorphic fungus that grows as a mold in the environment and as a yeast in tissues (Allison and Scalarone, 2012). Of the 3 major mycoses endemic in North America, blastomycosis was the only one originally recognized on this continent . Gilchristfirst described the illness in 1894 and speculated that it was caused by a protozoan. (Davies, 1979) Blastomycosis can be a subclinical illness with subsequent protection against progressive infection afforded by cellular immune mechanisms, but it may present with progressive disease with either pulmonary or extrapulmonary disease or both.airborne disease caused by the fungus *Blastomyces dermatitidis.*The infectious spores become airborne when soil in which the fungus is growing is disturbed.

Infection develops after the inhalation of spores into the lungs. Once established in lung tissue, the fungus undergoes a change into the characteristic “broad-necked” budding yeast which increases in number and can potentially spread to other organs of the body via the bloodstream. Based on outbreak investigations of blastomycosis infections in which likely sources of exposure to Blastomyces spores could be reliably fixed, incubation periods usually ranged from 30-90 days. This data may indicate that infections recognized late in the fall and winter months are typically associated withautumn exposures.The illness resulting from exposure to this organism is extremely variable.(archer)

common extrapulmonary site followed by bone, prostate, and central nervous system (CNS) manifestations. Diagnosis is made best by visualization of the yeast in smears or in tissue specimens or by culture. Because colonization does not occur, as with Candida or Aspergillus, identification of B dermatitidis provides a definitive diagnosis. Itraconazole has been shown to be the drug of choice for both infections, except in cases of life-threatening infection when amphotericin B should be used (Ferreira, 2018).

The Blastomyces spores that enter the lungs initially produce a lung infection called fungal pneumonia. Once the infection is established in the lungs, it can spread throughout the body. Common sits of infection are the eyes, bones, skin, and lymph nodes, but most tissues can become infected. Signs of blastomycosis depend on the sites of infection. Lung disease can cause an increased respiratory effort, exercise intolerance, and coughing. There may be loss of appetite, fever, and weight loss. Dogs with bone involvement are often lame. Blastomycosis of the skin results in raw, ulcerated lesions and draining abscesses. Infected eyes are usually red, painful, and have a discharge. Many of the changes are similar to bacterial infections but fungal infections do not improve with antibiotic treatment. In areas where blastomycosis is common, an infection unresponsive to antibiotics is suggestive of blastomycosis (Davies et al., 2013).

B. dermatitidis is categorized as one of the true systemic fungal pathogens. It is a dimorphic organism that grows as yeast or spherule forms in humans and culture at 37 °C, while producing a mold form in the external environment and culture at 25 °C to 30 °C. The fungus is capable of causing disseminated infection in immunocompetent hosts and is endemic to distinct geographic regions. In the United States,blastomycosis is mainly distributed throughout the Mississippi, Missouri, and Ohio River valleys in addition to North Carolina and the Great Lakes states.

Canada, Africa, and the Middle East are also endemic zones for the fungus. Blastomyces sp. has been recovered from soil and other natural environments, but correlation between environmental exposure and development of disease is often difficult.

Specific conditions support the organism's growth, including high temperatures and moist or wet soil enhanced by decaying vegetation. Other dimorphic fungal organisms include *Histoplasma capsulatum, Coccidioides immitis,* and *Paracoccidioides brasiliensis (Boswell and Aziz, 2004).*

Blatomycosis:

Blastomycosis is a severe systemic fungal disease due to *Blastomyces dermatitidis*, a spore-forming dimorphic saprophytic fungus that thrives in humid and acidic soil rich in decaying plant or animal waste(Rodríguez-Tovar et al., 2015)This organism grows as a mold in the environment and becomes yeast in host tissues (Kauffman and Miceli, 2015)The fungus is a primary pulmonary pathogen in humans and outdoor or hunting dogs and can sporadically affect cats (Brömel and Sykes, 2005) The environment is a reservoir of the spores. Zoonotic transmission is rare, but possible in humans through bites or through handling of infected tissues Typically, infection occurs by inhalation of infectious spores.In the pulmonary tract, the spores transform into yeasts, causing pyogranulomas (Bateman, 2002)However, yeasts can be transported from the lungs via the bloodstream or lymphatics and disseminate to other organs, like the skin and the brain. Blastomycosis is more prevalent in certain regions of United States and Canada and has been reported in Europe, Africa, and the Middle East. There are few human pulmonary blastomycosis cases reported in Mexico, but all of them were imported infections from other countries where the fungus is endemic (Salas-Alanis et al., 2013).

Figure 1. *Blastomyces dermatitidis* — conidia found in the mold form.

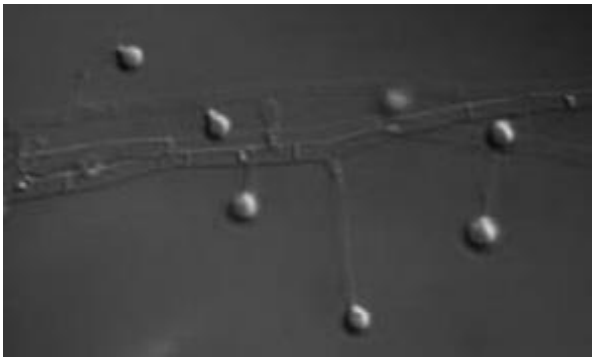

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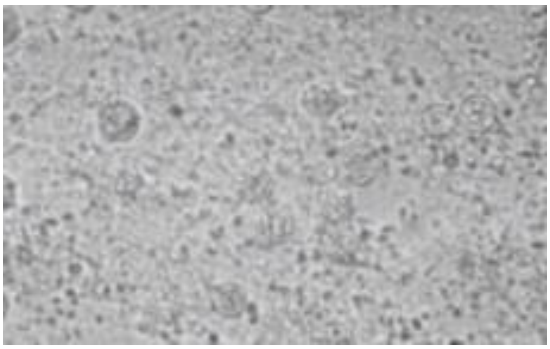
Figure 2. *Blastomyces dermatitidis* — thick-walled, budding yeast form.



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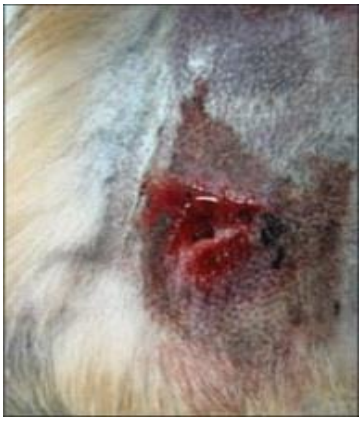
Blastomycosis in the Environment:

Although little is known about the ecology of *Blastomyces dermatitidis* in the environment, it is a fungus that appears to favor areas characterized by sandy, acidic soils with high organic content, abundant soil moisture, and decaying vegetation – all areas typically found along many Wisconsin waterways. Specific conditions of humidity, temperature and nutrition also appear to be contributing factors for growth and formation of spores by the fungus. While B. dermatitidis is widely distributed geographically, the actual area infected with the fungus is likely to be small and may be limited to one rotting log or several square yards of infected soil. Depending upon environmental conditions, the area may be infected for only a brief time. Environmental factors that increase the occurrence of *B. dermatitidis* remain a mystery. Without a more precise understanding of the ecology of Blastomyces in nature, it is extremely difficult to prevent recurrent (Blastomycosis, continued)> 10.0/100K 5.0 to 9.9/100K < 4.9/100K No Cases Top 10 Counties of Blastomycosis Infections in Wisconsin, 2005-2009 Incidence Rate per 100,000 population In spite of recent publicity, blastomycosis is a relatively uncommon disease with approximately 3 cases per 100,000 people.3 Lake Tides 35(2) illness or apply appropriate control measures. More effective skin and blood tests are needed to diagnose blastomycosis, and more individual surveys need to be conducted in areas where blastomycosis is suspected to occur. Through such surveys, high-risk areas in the environment could be identified, and hopefully, the necessary environmental conditions for the growth of B. dermatitidis could also be identified. Control efforts may then be possible. Despite thousands of attempts, the fungus has rarely been isolated in nature. Even repeated testing at specific locations where the organism was previously isolated yielded negative results. There are no standardized procedures currently available for environmental testing of soil samples.

PATHOGENIC AND CLINICAL PRESENTATION:

The 0rganism is primarily transmitted by inhalation of conidia that are in the mycelial phase .Ifection occurs when these conidia are deposited into the alveoli phagocytized by pulmonary macrophages and transported to pulmonary intrstitum. (Arceneaux et al., 1998) where normal body temperatures promot transformation to the yeast phase (Shurley et al., 2005).The disease may stay localized in the lungs or may spread hematoge-nously or limphatically to other body systems(Arceneaux et al., 1998).Dermal or lingual inoculation of the organism has also been reported, causing localized granlumatous disease;however, this from of transmission is uncommon. (Taylor and Gaunt, 2009)The infection is not transmissible between humans ,between , or from animals to humans and, therefore, is not considered contagious or zoonotic (Greene, 2006).A typical case presentation is a young , male, large –breed dog presenting with coughing, or dyspnea.skin lession that appear papular or plaque-like are commonly present , occasionally with draining cutaneous tract (Arceneaux et al., 1998, Rudmann et al., 1992).(FIGURE 4).Other common physical examination finding are lymphadenopathy, ocular abnormalities such as uveitis , and pyrexia . (Arceneaux et al., 1998).The disease is usually pulmonary in orgin and self-limiting.) (Rudmann et al., 1992).



(FIGURE 4)Draining tract on the lateral hock of a German shephered . *B.dermatitididis* organisms were confirmed on cytology.

Diagnosis:

The clinical presentation, physical exam, and the radiographic manifestations of blastomycosis are non-specific; therefore, a high index of suspicion is essential for prompt diagnosis. Delays in diagnosis are common, even in endemic areas, as few patients are correctly diagnosed at initial presentation and delays in diagnosis exceeding one month can occur in more than 40% of patients. (Chapman et al., 2008, Lemos et al., 2002, Vasquez et al., 1998). A detailed history to identify possible exposures and at-risk hosts can facilitate a diagnosis. In patients with pneumonia, medical histories should include place of residence, travel, outdoor activities (e.g., fishing, canoeing, rafting), hobbies, recent home remodeling, exposure to road construction, and use of a wood burning stove or community compost pile. Blastomycosis in a household pet, such as a dog, suggests a common source of exposure and can serve as a harbinger of human infection. (GEORGE A et al., 1979) In patients with concomitant pulmonary and cutaneous disease, blastomycosis must be considered in the differential diagnosis.

Microscopic and Culture-Based Diagnostics:

The most expeditious method to diagnose blastomycosis remains the examination of stained clinical specimens. While Blastomyces is not well visualized with Gram or hematoxylin and eosin (H&E) stains, sputum or tissue samples stained with 10% potassium hydroxide,calcofluor white, Gomori methenamine silver (GMS) or periodic acid-Schiff (PAS) can facilitate visualization of the characteristic Blastomyces yeast (Saccente and Woods, 2010). The discovery of the characteristic yeast forms (8 to 20 μM) with broad-based budding and a doubly refractile cell wall can lead to a presumptive diagnosis of blastomycosis before the results of culture and non-culture tests are available. In one case series, the use of appropriately stained clinical specimens identified nearly 80% of culture-confirmed cases (Patel et al., 2010). Despite the effectiveness of fungal-specific stains in diagnosis, this technique is often underutilized.

Even noninvasive methods including cultures from sputum, tracheal secretion or gastric washings yielded Blastomyces growth in 86% of samples. (Martynowicz

and Prakash, 2002) Specialized media including Sabouraud dextrose agar, potato dextrose agar, and brain-heart infusion media are required for growth.Incubator temperatures used in most clinical laboratories (25°C to 30°C) promote the growth of Blastomyces as a mold. Although highly specific, Blastomyces grows slow in culture. Fungal colonies take an average of 5 to 14 days to be visualized; however, when burden of infection is low, growth can take longer(Saccente and Woods, 2010)

Non-culture diagnostics:

Classic antibody testing by complement fixation (CF) or immunodiffusion (ID) is not clinically useful for the diagnosis of blastomycosis due to poor sensitivity and specificity. (Klein et al., 1987) A newer enzyme immunoassay (EIA) that uses microplates coated with BAD1 protein has enhanced sensitivity (87%) and specificity (94–99%); however, it is not yet commercially available As BAD1 is unique to Blastomyces, BAD1 assays can distinguish between histoplasmosis and blastomycosis. (Richer et al., 2014) An antigen assay that detects a galactomannan component in the cell wall of Blastomyces has supplanted CF and ID, and can be used to test urine, serum, BAL fluid, and CSF specimens. (Richer et al., 2014, Bariola et al., 2011). Sensitivity of antigenuria in patients with proven disease is 76.3 – 92.9% and specificity is 79.3%. (Bariola et al., 2011, Frost and Novicki, 2015). False-positives can occur in the setting of other fungal infections such as histoplasmosis, paracoccidioidomycosis and penicilliosis (talaromycosis). ((Richer et al., 2014). The clinical impact of a false positive test is often minimal because paracoccidioidomycosis and penicilliosis (talaromycosis) can be removed from the differential diagnosis if the patient has not traveled to Central and South America (paracoccidioidomycosis), or Southeast Asia and China (talaromycosis). Moreover, the treatment of blastomycosis is similar to histoplasmosis. Serial urine antigen concentrations can be used to monitor response to treatment.

Following initiation of therapy, a rise in antigenuria can occur (median of 11 days), which is followed by progressive decline in antigen titer with successful therapy. Initial post treatment increase in titer may be reflect increased urinary excretion of antigen due to fungal cell death.(Frost and Novicki, 2015)

Treatment:

Updated practice guidelines for the treatment of blastomycosis have been published by the Infectious Diseases Society of America (IDSA)All patients with blastomycosis, even those with a single cutaneous lesion, should be treated with an antifungal agent because of the high likelihood of progression or recurrence of the infection if not treated. In general, initial therapy for patients who have mild-to-moderate pulmonary or disseminated blastomycosis will be with an azole agent and for patients who have severe pulmonary or disseminated blastomycosis will be with an amphotericin B formulation. Immunosuppressed patients and those with central nervous system disease should be treated initially with an amphotericin B formulation.(Dismukes et al., 1992). The major changes that have been incorporated in the 2008 IDSA guidelines as compared with the 2000 IDSA guidelines are noted below.

Amphotericin B Therapy:

Lipid formulations of amphotericin B, either liposomal amphotericin B or lipid complex amphotericin B, are recommended as alternatives to amphotericin B deoxycholate, which was the only formulation recommended in 2000. There are no controlled trials proving the benefit of lipid formulations compared with standard amphotericin B deoxycholate, but in many institutions the lipid preparations are preferred for most indications that require amphotericin B therapy because they are clearly less nephrotoxic.

The dosage is 3 to 5 mg/kg daily for severe pulmonary or disseminated infection. The recommendation to use amphotericin B for the entire course of therapy has been changed to encourage step-down therapy to an azole when the patient has had a satisfactory clinical response to initial amphotericin B therapy . Chapman (Dismukes et al., 1992).

Azole Therapy:

Itraconazole remains the azole of choice for mild-to-moderate blastomycosis and for step-down therapy after initial amphotericin B treatment for severe blastomycosis (Dismukes et al., 1992) (Dismukes et al., 1992). Cure rates are as high as 95% for nonmeningeal mild-to-moderate disease.The usual dosage is 200 mg once or twice daily after an initial loading dose of 200 mg three times daily for 3 days. When the daily dosage of itraconazole is 400 mg, absorption is enhanced if the drug is given as 200 mg twice daily. The main drawbacks of itraconazole are the variability in absorption and the many drug–drug interactions. The preferred formulation is the oral suspension because absorption is more predictable with this formulation. The suspension is administered on an empty stomach; unfortunately, gastrointestinal upset is common and not all patients are able to tolerate this formulation. The capsule formulation of itraconazole requires both food and gastric acid for maximum absorption. Thus, acid-inhibiting drugs cannot be prescribed when the capsule formulation is used.Wide inter-patient variability of serum concentrations is evident with either formulation. Because of this, serum itraco nazole levels should be monitored. Itraconazole levels should be determined after approximately 2 weeks when steady state has been reached. A serum level greater than 1.0 mg/ml is recommended(Dismukes et al., 1992).

Central Nervous System Infection:

For patients with central nervous system blastomycosis, a lipid formulation of amphotericin B at a dosage of 5 mg/kg daily is recommended for 4 to 6 weeks, followed by therapy with an azole for a total of a least a year of antifungal therapy. The guidelines offer several options for azole step-down therapy, based entirely on anecdotal data(Dismukes et al., 1992).

Length of Therapy:

The length of therapy for pulmonary or disseminated forms of blastomycosis depends on the severity of the infection and the immune status of the host. Pulmonary blastomycosis and disseminated infection in patients who have mild to-moderate illness is usually treated for a total of 6 to 12 months (Chapman et al., 2008).

Can I avoid blastomycosis?

It is not possible to completely avoid exposure to blastomycosis spores. Even if you work, live or vacation in the geographical areas with moist, acidic soil, it is important to remember that blastomycosis is an uncommon illness and the risk of getting it islow. Testing soil for the presence of this fungus is difficult and not reliable. If you do come in contact with the fungus, it does not mean you will become ill. If your immune system is weakened, you may wish to avoid direct contact with the soil, especially in areas where the likelihood for fungal growth is higher. Little is known about the actual fungal locations at any particular time or the conditions that cause the fungus to grow or die out in the soil.It is reasonable to believe that wearing protective clothing and disposable filter dust masks may reduce exposure to blastomycosis spores.

However, it has not been shown that such preventive measures will reduce the risk of getting sick with blastomycosis. It is not considered practical at this time to recommend the wearing of masks in all settings in which exposure to blastomycosis spores could occur. There is no vaccine for blastomycosis.

CONCLUSION

Blastomycosis is a rarely reported fungal infection, but subclinical cases occur in areas where *B. dermatitidis* is endemic. Better understanding of the epidemiology of this infection is dependent on more reliable and more specific immunologic testing. Blastomycosis may mimic several other conditions, particularly neoplastic disease. Therefore,specimens for fungal cultures and smears, which allow a secure diagnosis, should be obtained during invasive procedures aimed at the diagnosis of cancer. Therapy for blastomycosis has been broadened.

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