

A Deadly Dimorph: What You Need to Know About *Blastomyces spp.*

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Introduction

Maxx had just returned from spending a holiday weekend at a camp near Geraldton, Ontario when his owners noticed he just “wasn’t himself.” He began coughing and then “started licking his paws a lot.” When his paws began to bleed, that was enough for Maxx to be taken to the vet. He had symptoms of fever, swollen lymph nodes, high white blood cell counts, lesions over his entire body – “including inside his adorable ears” - swelling limbs and paws. These symptoms, along with a positive fungal spore test confirmed a diagnosis: Blastomycosis. Things progressed quickly, too quickly it seemed. Maxx was put on aggressive antifungal therapy. Shortly after his visits to the vet, his right eye became swollen, and Maxx returned to the vet, who confirmed that *Blastomyces spp.* was spreading to his eye. Even after three days of eye drops and aggressive oral drugs, his right eye became so cloudy and painful that it had to be surgically removed.

Maxx’s story, adapted from the local daily newspaper in Thunder Bay, Ontario, is familiar among dog owners. Blastomycosis infection rates for dogs are ten times higher than humans; they are the second most common host of this deadly fungal pathogen. Working as a medical laboratory technologist and supervisor of the Mycology Department at Public Health Ontario Laboratories (PHOL) in Thunder Bay, Ontario, I see approximately 1800 human specimens requesting fungus culture testing yearly. Anywhere between 30 and 50 of those are typically new patients diagnosed with *Blastomyces dermatitidis* or *Blastomyces gilchristii* (*Blastomyces spp.*). Since I began working at PHOL in June of 2000, I have taken an interest in the Mycology Department and enjoy working with fungal cultures. My interest peaked in 2005 when the Thunder Bay District Health Unit (TBDHU) requested us to spike soil samples with

cultures of *Blastomyces spp.* for anonymous trial testing at another laboratory that performed the Polymerase Chain Reaction (PCR) test. The TBDHU wanted a method to test soil samples in and around the Thunder Bay area. Fewer than three years later, the investigation was “unearthed.” Of the 45 soil samples collected, 12 tested positive for the fungus (Dunn, 2008). It was then that my passion for the research of this and other deadly human fungal pathogens began.

This literature review is a summarization of the progression of research from the discovery of the species *Blastomyces dermatitidis* through to our current understanding of the disease blastomycosis and the organisms involved in this potentially deadly infection, *Blastomyces spp.* For more than a century, many dedicated researchers have added to the current knowledge of this pathogen. Building from this knowledge, four significant areas are contributing to our present understanding of *Blastomyces spp.* These areas involve the diagnosis, prognosis, treatment and prevention of blastomycosis. Each of these areas link to the four sections of this literature review: The tasks of the laboratory, the infection in the host, the monitoring by the physician and veterinarian, and the health unit’s public awareness. From these sections, the review will conclude with a discussion of where the future lies with this deadly Risk Group 3 (RG3) (Public Health Agency of Canada, 2015, Chapter 2.3.1.3) fungal pathogen.

Definitions

The following words used in the text are defined in terms of how they are used in the field. They are provided here for quick reference and convenience.

- Antibody – produced by the host as part of a defence mechanism when infected with a pathogen.
- Antigen – a foreign body (e.g. a pathogen) to the host that can cause antibody production.

- Dimorphic – having two forms.
- Direct specimen – an unaltered sample of body fluid or tissue from the host.
- Filamentous (mould) form – composed of lengthy thread-like structures.
- Hematogenous – distributed via the bloodstream.
- Immunocompetent – no known compromising health issues that may affect the immune system.
- Immunocompromised – having other existing health issues that affect the natural immune system.
- Macrophages – the first line of defence in the immune system.
- Media – a substance used for the growth of organisms in the laboratory.
- Sensitivity – how well a test can find positives.
- Specificity – how well a test can eliminate false positives.
- Spores – the form an organism produces for protection against adverse environmental conditions.
- T-lymphocytes – blood cells that are alerted by macrophages (other blood cells) to fight infection.
- Virulence – a pathogen's ability to infect its host.
- Yeast form – round or oval, usually budding.

The Laboratory

The knowledge, procedures and protocols developed in microbiological laboratories over the past 200 years has played a significant role in diagnosing human pathogenic fungal infections. This section will discuss the laboratory's contribution throughout the organism's discovery, investigation and methods of identification.

The Discovery

Blastomyces dermatitidis (*B. dermatitidis*) was first isolated in 1894, when the English-American dermatologist, Thomas Casper Gilchrist (Figure 1.), attempted to classify a previously unknown organism found in a skin lesion initially diagnosed as Scrofuloderma (an infection caused by tuberculous bacilli). Initially, Gilchrist (1896) thought it was a protozoan, but upon further examination of subsequent specimens, decided on fungal:

In reporting the case before the American Dermatological Society I expressed the opinion that these bodies in all probability would be found to belong to plant rather than to animal life, and further examination appeared to verify the conclusion that they might be classed as Blastomycetes. (p. 271)

Since then, many scientists have investigated this organism for its properties relating to disease. Meece et al. (2011) noted the genus *B. dermatitidis* had two genetically distinct forms and so put them in two different Groups, speculating that each may influence virulence and pathogenicity. Brown et al. (2013) have shown through genetic analysis that these two Groups were, in fact, two distinct species: “Our analyses provide evidence for the existence of two genetically distinct monophyletic clades within *B. dermatitidis*, which we use to describe a novel cryptic species, *Blastomyces gilchristii*” (p. 2) in honour of Gilchrist, the 1894 discoverer. Before genetic analysis, a characteristically similar disease was noted from Africa



Figure 1. The English-American dermatologist, Thomas Casper Gilchrist (1862-1927) (Borroni, Cananzi, & Vassallo, 2004) .

but found to be more closely related to the genus *Emmonsia* (McTaggart, Brown, & Richardson, 2016). This pathogen was examined one year later by Dukik et al. (2017) and found to be

phylogenetically closer to the genus *Blastomyces* and so gave it the name *Blastomyces percursus* (*B. percursus*). *B. percursus* however, differs in appearance microscopically in both its yeast and mould forms whereas *B. dermatitidis* and *Blastomyces gilchristii* (*B. gilchristii*) are indistinguishable. Further examination of *Blastomyces spp.* led to a key physical characteristic, placing them in a group with other potentially fatal fungal pathogens known colloquially among mycologists as the “dimorphs.”

Dimorphism

Fungi are normally seen as one of two main physical forms, yeast and filamentous. The yeasts are round or oval and budding, and usually appear creamy on laboratory media. The filamentous or mould, taken from the Norse “mowlde” for fuzzy (Mycoses Study Group Education and Research Consortium, 2018) form consists of string-like hyphae with various types of spores or conidia and usually appear fuzzy on laboratory media. Gilchrist (1896) recognized these two forms, thus giving the newly isolated fungus a descriptive name: Blastomycetes, which are noted as “a class of pathogenic imperfect fungi that typically grow like yeasts by budding but sometimes form a mycelium and conidia on artificial media” (Merriam-Webster, 2018). Most fungi exist as one form or the other. However, some species exhibit both forms depending on environmental factors. This phenomenon, as seen in the genus *Blastomyces* and a few other human pathogenic fungi, is termed dimorphism (two bodies or forms). Although *Blastomyces spp.* had been influenced to exhibit these two forms using special media alone (Kane, 1984), Levine and Ordal (1946) determined an optimal temperature of each form. Thus the term thermal dimorphism was later fashioned by Nickerson and Edwards (1949).

As deadly a fungus as *Blastomyces spp.* can be, they are of high curiosity and study in the mycology laboratory for their diagnostic forms and dimorphic nature (Scherr & Weaver, 1953).

The function of each of these forms was described by Marty et al. (2015), as the yeast form facilitating immune evasion and the mould form generating transmissible spores, promoting survival in the environment and sexual reproduction. Baumgardner (2016) explains why the mould to yeast transition facilitates the fungus' ability to infect so successfully: "The resultant yeast cell is too large to be ingested by polymorphonuclear neutrophils (PMNs), unlike the smaller infectious conidia particles (spores)" (p. 61). Gauthier (2017) explains precisely that "the morphologic switch to yeast is associated with the upregulation of specific virulence factors that promote adhesion to host tissues, growth in and lysis of macrophages, blunt proper cytokine responses, and impair cell-mediated immunity" (p. 5). The dimorphic nature of *Blastomyces spp.* allows it to successfully infect its mammalian host. Researchers questioned where the organism resides prior to inoculation, ultimately discovering its ecological niche to be the soil.

Identification in Soil

As early as 1902, the diagnosis was made microscopically on a direct specimen, and was later speculated by Brayton (1902) that the organism originated in soil "Those affected ... are people in contact with the soil and its products; they are laborers, carpenters, etc" (p. 315). Gilchrist (year) appropriately named the disease "blastomycetic dermatitis" as it was initially diagnosed from an infection of the skin. However, Schwarz and Baum (1951) noted in a case study that most patients with skin lesions from *Blastomyces spp.*, also showed a positive disease in the lungs. They speculated that "this lends strong weight to the belief that the primary lesion in blastomycosis is in the lung and that almost all skin lesions are the result of hematogenous spread from this primary lesion" (Schwarz & Baum, 1951, p. 1022).

This gave credence to the speculation of a course of infection from soil to host. In the organism's mould phase at the lower environmental temperature, the spores produced are easily

dispersed if disturbed, creating the ability to be inhaled into the host lung causing disease (Klein et al., 1986). It was not proven as a soil organism until Denton and DiSalvo (1964), by “the intravenous inoculation of soil suspensions in the tail vein of mice...recovered [*Blastomyces spp.*] from 10 of 356 samples collected in an endemic area at Augusta, GA” (p. 716). In 2006, Burgess, Schwan, and Volk (2006) developed a specific assay via PCR, to test soil samples for the detection of *Blastomyces spp.* Use of this method led to the investigation of positive soil samples and speculation that “the ability of *B. dermatitidis* to survive and grow in organic carbon-poor, high ammonia microenvironments may be important to the competitive success of this fungus” (Baumgardner, 2009, p. 745). How then did the organism travel from soil to host?

Identification in the Host

Proving soil origin of *Blastomyces spp.*, it was then speculated that the disturbance of the soil, whether by the influence of the weather (such as by temperature variations and windy conditions) or host involvement (physical manipulation of the earth), or both, liberates the spores into the air making them available for inhalation via the respiratory tract (Baumgardner, Bernhard, & Egan, 2015, pp. 30–31). This was supported by the fact that dogs, especially ones that love to dig in the soil, have been known to be up to 14 times more likely to be infected than humans, especially in endemic areas and near waterways (Baumgardner, Paretsky, Baeseman, & Schreiber, 2011).

Due to the pathogenicity of this potentially fatal fungus, the desire was to have a diagnostic test indicating positive exposure to *Blastomyces spp.* Researchers attempted to develop a test for blastomycosis, creating Blastomycin, an intradermal skin test (not unlike the tuberculin skin test for TB), but it was later found to be unreliable (Lancaster & Sprouse, 1976) and consequently there is no skin test currently in use. Immunological testing was then pursued

to identify antibodies produced by the host in response to the infection. Several methods were created including complement fixation, immunodiffusion and enzyme immunoassay but were found to have unacceptable sensitivity, specificity or both (Abuodeh, Chester, & Scalarone, 2004; Bradsher & Bariola, 2011). A better test proved to be the antigen itself: “By detecting antigens produced by the fungal organism instead of antibodies produced by the infected individual, a more rapid diagnosis may be made” (Shurley, Legendre, & Scalarone, 2005, p. 141). Physicians occasionally use antigen detection for blastomycosis. However, for identification and follow-up treatment, urine antigen testing is popular among veterinarians because of the ease of obtaining these samples in dogs (Foy, Trepanier, Kirsch, & Wheat, 2014).

Currently, the standard laboratory analysis for diagnosis in humans is growth in culture with confirmation by PCR, or conversion from the mould phase back to the characteristic yeast. When specimens are received in the laboratory, it can take more than two weeks for the organism to grow. Therefore a direct smear is performed on the sample for a more rapid report. *Blastomyces spp.* in a specimen presents in the diagnostic yeast form, thus with the expertise of a trained mycologist or pathologist, a preliminary report can inform the physician directly. With this initial result, along with travel history and typical signs and symptoms of the disease, it is possible for the physician to diagnose and begin treatment without undue delay.

The Host

Following inoculation of *Blastomyces spp.* in the host, the resulting infection produces a variety of signs and symptoms. However, it is the immune status of the patient and other influences that affect how the disease invades the body. This section outlines the development of infection of *Blastomyces spp.* in the mammalian host, from the time the organism enters the body to the final, possibly fatal, outcome of the disease.

Inoculation

As the name dermatitidis suggests, the skin was assumed to be the initial site of entry; it was then discovered that it was more likely the lungs via inhalation of spores from the soil. Since then, research and investigations have alluded to alternate ports of entry. There are five documented modes of infection described as: “(1) inhalation, (2) accidental inoculation, (3) dog bites (a form of inoculation), (4) conjugal, and (5) intrauterine transmission” (DiSalvo, 1992, p. 76). Farber, Leahy, and Meadows (1968) investigated a case of sexual transmission; however, this was a rare case and circumstances were unique. Panciera, Troy, and Purswell (2014) conducted a study on an infected pregnant dog and demonstrated the unlikelihood of transplacental infection. Currently, the most common port of entry for infection is through inhalation of spores, with consequent dissemination to the other organs including skin, kidney, bone, eyes and brain.

Further investigation from other interested researchers shows the intrigue behind this mysterious fungus. Varani, Baumgardner, Czuprynski, and Paretsky (2009) “failed to demonstrate asymptomatic nasal carriage of *B. dermatitidis* in a moderate sized sample of dogs from a highly endemic area” (p. 781), but suggests that the test they used may have been insensitive. The current consensus among researchers and physicians was first presented by Schwarz and Baum (1951) who revealed evidence “that cutaneous blastomycosis is most frequently secondary to a primary pulmonary infection” (p. 1026). In detailing specific case studies, both Emer and Spear (2009) and Kumar and Kumar (2015) proposed that a direct inoculum of the skin had disseminated to the lungs, the opposite to what is suggested by previous research. Mason, Cortes, Cook, Maize, and Thiers (2008) discussed the difficulties understanding the disease, arguing that the determination whether a dermal infection begins as a

direct inoculation or is secondary to a subclinical lung infection can be difficult without proper specimens, reliable laboratory testing and chest radiographs. Regardless of the portal of entry, once *Blastomyces spp.* enters and invades the host, the indicators of infection in the body can be ambiguous.

Progression

Following inoculation, the progression of *Blastomyces spp.* ranges from asymptomatic to the development of a painful and debilitating illness requiring aggressive medical treatment. The usual pathogenesis of the organism begins after the spores enter the respiratory tract, well described by Klein, Aizenstein, and Hogan (1997): “Upon transformation into the pathogenic yeast phase, *B. dermatitidis* multiplies within the lung and disseminates via the bloodstream and lymphatics to cause disease in the skin, bone, genitourinary tract, and brain” (p. 1505).

Regardless of how it enters and where it ends up inside the body, the organs it ultimately chooses to infect result in varied signs and symptoms of the disease.

The following three descriptions relay just how destructive and painful this potentially fatal fungal pathogen can be to its host. First, Brayton (1902) quite descriptively illustrates the symptoms of ulcers caused by blastomycetic dermatitis:

The symptoms are heat, redness, swelling and pain—a gnawing, burning and persistent pain, intensified at night, preventing sleep, leading to the use of opiates, and only relieved by the destruction of the invaded margins with caustic, or the actual cautery, or by the knife. (p. 314)

Second, Kurtz and Sharpnack (1969) described a case history of the dissemination of *Blastomyces spp.* to the central nervous system (CNS): “Blastomycotic meningoencephalitis in a dog was characterized by granulomas, which occurred most frequently in the gray matter of the cerebrum and the granular layer of the cerebellum” (p. 376). Third, a description by Abuodeh et al. (2004) conveyed the seriousness of the infection: “[*Blastomyces spp.*] can produce severe

disease ranging from a severe tuberculosis-like infection to a more fatal disseminative form that can involve multiple organ systems such as the bone, skin, and central nervous system” (p. 143). It is evident that this organism is quite invasive. Consequently, almost all specimen sources, from easy to obtain sputa or urine to the more invasive brain or lung tissue, are accepted for fungus culture in the laboratory. As in many cases of infection, however, it is the host's natural defence mechanism that can determine the individual's outcome of the disease.

Host Immunity

Most fungal pathogens opportunistically infect an immunocompromised host, however few, such as *Blastomyces spp.* and other dimorphs can infect a healthy (immunocompetent) one. The characteristics of dimorphic fungi are significant factors in the ability of the organism to cause infection. Datta and Hamad (2015) explain that the cell wall of fungi “not only serves as a structural barrier, but also protects against complement-mediated damage and osmotic lysis” (p. 738). Evidenced by Sugar and Picard (1991), the mould phase of *Blastomyces spp.* does not have the ability to cause disease and the organism must convert to the yeast phase for pathogenicity to occur. After studying the unique ability of this type of fungus, Medoff, Painter, and Kobayashi (1987) detailed the stages of transition when converting from mould to yeast forms, the first of which is triggered by the change in temperature to 37 °C, when the organism enters the body of the mammalian host. Once inside the host the thick capsule of the yeast (Figure 2.) form, “is very difficult for phagocytes to ingest and kill [and]

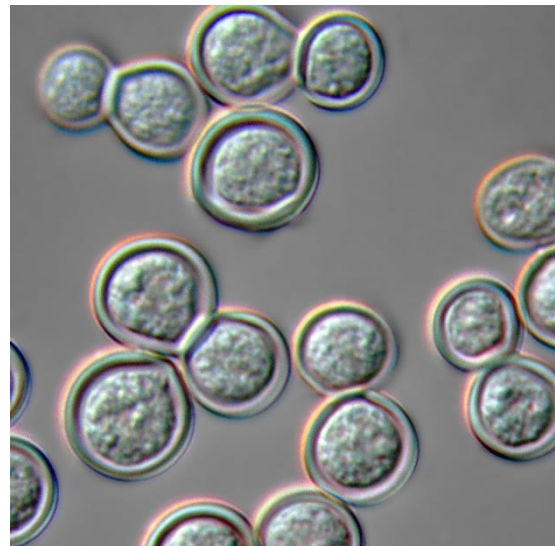


Figure 2. *Blastomyces dermatitidis*, showing the thick capsule of the yeast form (Rodriguez, 2018).

PMN's, which handle inhaled conidia better than macrophages, are relatively ineffective ... thus humoral immune responses do not play a significant role in host defense against *B. dermatitidis*" (Saccente & Woods, 2010, p. 369).

Chang et al. (2000) claim that "humans infected with the dimorphic fungus *Blastomyces dermatitidis* develop strong T-lymphocyte responses" (p. 502). Therefore, the hosts with compromised immune systems may have a more difficult prognosis. In 2008, the United States' Food and Drug Administration (FDA) issued a warning to immunocompromised individuals, listing *B. dermatitidis* as one of the organisms that may cause a severe and possibly fatal infection (FDA, 2018). Researchers continue to analyze the capability of *Blastomyces spp.* to invade so prolifically and efficiently. More recently, Gauthier (2017) highlighted how "the morphologic switch to yeast is associated with the upregulation of specific virulence factors that promote adhesion to host tissues, growth in and lysis of macrophages" (p. 5), giving the organism the ability to survive and thrive, resulting in a possibly fatal prognosis for the host.

Prognosis

Considering the many varied factors that are involved in infection, blastomycosis has a vague prognosis. With an indefinite incubation period of 21-106 days with a median of 43 days (Ministry of Health and Long-Term Care Government of Ontario, 2018) the likelihood of survival depends on many factors, especially the timeliness of diagnosis. It has been speculated that some infections "spontaneously" recover (Recht, Philips, Eckman, & Sarosi, 1979; Sarosi, Davies, & Phillips, 1986) while others cause a swift and debilitating death, with "immunocompromised hosts [having a] higher rate of ICU admission, development of [Acute Respiratory Distress Syndrome] ARDS and mortality" (Prueksaritanond et al., 2016, p. 1).

Following the discovery of the second distinct species of *Blastomyces*, there was speculation of pathogenic differences in virulence between the two organisms: *B. dermatitidis* and *B. gilchristii* (McTaggart et al., 2016). Brömel and Sykes (2005) found that the prognosis of the disease in some areas had worsened, suggesting “this may be related to geographic variations in strain virulence” (p. 237). More recently, Dalcin, Rothstein, Spinato, Escott, and Kus (2016) demonstrated in a case study, that *B. gilchristii* was responsible for a fatal infection, resulting in ARDS and causing death. However, the patient had a history of drug abuse and diabetes and was therefore considered immunocompromised, weakening their ability to fight the infection. If there are differences in strain virulence that result in a more predictable prognosis, it would have a significant and valuable influence on diagnosis, aiding the physician’s ability to treat the disease. The following section will detail some of the challenges faced by the physician when presented with an infected patient.

The Physician and Veterinarian

When a patient becomes infected with *Blastomyces spp.* and first presents to their physician, the clinical appearance along with the physician’s familiarity with blastomycosis will determine the diagnosis, treatment and final prognosis of the disease. In this section, the development of the disease is described through the eyes of the treating physician or veterinarian, from the initial visit through to a cure or termination of life.

Presentation

Some of the factors that influence the status of the patient at presentation are age and species of the host (the majority being dogs and humans), underlying health (immune status), the pathway and foci of infection and how long they have had symptoms. The age of the patient, however, should not rule out treatment; from very young children to mature adults, the disease

has been known to strike all age groups, as well as all genders and ethnicities (Crampton et al., 2002; Fanella, Skinner, Trepman, & Embil, 2011; Saccente & Woods, 2010). Dogs, especially ones of the hunting and sporting breeds, are ten times more likely than humans to become infected by *Blastomyces spp.* (Armstrong et al., 1987; Pfaller & Dickema, 2010). Whether the host has a healthy immune system at the time of infection or not, the degree of pulmonary infiltration and dissemination to other areas of the body can be slight to severe, even expediting death (Chu, Feudtner, Heydon, Walsh, & Zaoutis, 2006; Lemos, Baliga, & Guo, 2001; Meyer, McManus, & Maki, 1993).

While Gilchrist first diagnosed the disease as a skin infection, Brayton (1902), to assist other dermatologists, gave a descriptive account of a typical cutaneous infection (Figure 3.):

The edges of these ragged and irregular ulcers are in a constant state of inflammation, extending perhaps from one-fourth to one-half an inch into the skin not yet breaking down. ... Therefore the occurrence of multiple acneoid pustules in close proximity to each other occurring in unusual localities, unsymmetrically distributed and followed by necrosis and punctiform excavated ulcers, should call attention to the probability of blastomycosis. (p. 314-315)

Presently, the patient typically first appears with unresolved pneumonia and a travel history to an endemic area, optimistically before dissemination to other organs. Physicians in endemic areas will consistently order



Figure 3. Cutaneous blastomycosis (Chima-Okereke, 2015).

tuberculosis and fungus culture concurrently as blastomycosis and tuberculosis are similar in their presentation.

Diagnosis

Local physicians from endemic areas are familiar with the varied symptoms of blastomycosis and its similarity to other infections; however in non-endemic areas, if the patient's travel history is not considered, it may take longer for diagnosis, which can prove fatal (Brown et al., 2018; Chu et al., 2006; Pfaff, Agger, & Volk, 2014). Therefore, it is best to rule out *Blastomyces spp.* in endemic areas if the patient is not responding to conventional antimicrobial therapy (Sutcliffe, 2017). Turning to canine infections, Brömel and Sykes (2005) give an account of what signs the veterinarian might expect for diagnosis:

Clinical signs range from nonspecific (lethargy, weakness, anorexia, and weight loss) to more specific signs including cough, increased respiratory rate, lameness, or reluctance to walk. ... Other clinical signs include localized soft tissue or bony swellings, blindness, seizures or other neurological signs, hemoptysis, hematemesis, melena, polyuria, polydipsia, and lumbar pain.... Common findings on physical examination are fever, peripheral lymphadenopathy, dyspnea or tachypnea ... increased breath or lung sounds, and subcutaneous abscesses, or ulcerative draining lesions of the skin (e.g., muzzle, digits, body wall). (p. 234)

Although it is not ideal for the animal to be suffering, if the disease has progressed to the point of dissemination to the skin, “cutaneous involvement by blastomycosis helps the clinicians to reach the correct diagnosis” (Lemos, Guo, & Baliga, 2000, p. 201). In cases where organs are severely compromised, surgery is performed along with antimicrobial therapy as in the decision to remove Maxx's right eye.

With its many modes of infection, and the multitude of organs it is capable of infecting, the difficulty the veterinarian or physician has in diagnosing blastomycosis can be daunting. Malignancy, other fungal pathogens, and especially pneumonia and tuberculosis have similar disease spectra, increasing the chance of misdiagnosis (Fanella et al., 2011; Lemos et al., 2000;

Saccante & Woods, 2010). Even in endemic areas, trying to rule out blastomycosis may be challenging for the physician when fungus cultures come back negative, due to the difficulty in obtaining a suitable specimen. (e.g. some patients have a difficult time producing a productive sputum sample). Lyou, Longoria, and Davoudi (2017), presented a case to illustrate this:

A 48-year-old immunocompetent male presented with a subacute history of generalized fatigue, and an acute presentation of severe neck pain, headache, and gait instability [the patient underwent extensive diagnostic workup including repeat cerebral spinal fluid examinations, serology, and brain biopsies which were non-diagnostic. Computed tomography (CT) chest was performed, which was notable for mild mediastinal and bilateral hilar lymphadenopathy. Flexible bronchoscopy with endobronchial ultrasound and transbronchial needle aspiration of the mediastinal lymph nodes confirmed the presence of lymphocytes and rare multinucleated giant cells. Ultimately, a mediastinoscopy and lymph node resection revealed broad-based budding yeast, favoring blastomycosis against a background of extensive necrotizing granulomas. (p. 1)

For the veterinarian, urine is the most convenient sample to obtain, however, “diagnosis is best made through cytological identification on aspirates, biopsy, or bronchoalveolar lavage” (Lavelly & Lipsitz, 2005, p. 216). For more difficult diagnoses in areas such as the CNS, where specimens can be difficult to obtain, a magnetic resonance imaging (MRI) may be considered (Bariola et al., 2010). Nevertheless, of the many possible tests from specimens such as tissues, abscess fluids, sputa and urine, the “visualization of characteristic yeast forms or growth of the fungus in culture is necessary to diagnose blastomycosis definitively” (Saccante & Woods, 2010, p. 372). Typically, treatment does not begin unless blastomycosis is confirmed due to the aggressive nature and sometimes severe side effects of the anti-fungal drugs necessary to fight this infection.

Treatment

Blastomycosis “is almost invariably fatal without treatment” (Harasen & Randall, 1986, p. 1). Prior to antifungal drugs and before the disease was known to infect the lungs, it was common to debride the affected area and use iodides empirically as antibiotics were not effective

(Schwarz & Baum, 1951). Brayton (1902) vividly describes how blastomycetic dermatitis was treated in the early 1900's:

The knife, the hot iron, the application of carbolic acid followed by the concentrated acid nitrate of mercury, gives immediate relief, or at least as soon as the pain of the burning has been subdued by appropriate dressings ... with the further growth of the organism on one side or the other of the primary lesion, the intolerable pain again begins and the patient is willing to submit to a repetition of the destructive process, even begging to have the affected member amputated. (p. 314)

Currently, of all the antifungal agents, Amphotericin B and many of the azoles are commonly effective in eradicating *Blastomyces spp.* Factors such as cost, effectiveness, drug-drug interactions and tolerability all play a role in the choice of treatment (Lavelly & Lipsitz, 2005; Pappas et al., 1997; Saccente & Woods, 2010; Tyler, DeVier, Carpenter, Carr, & Trabue, 2013; Wiebe & Karriker, 2005), but in itself, Amphotericin B remains “the ‘gold standard’ by which all subsequent antifungals were compared because of its broad spectrum of activity against diverse fungi and the ability to cure otherwise recalcitrant life-threatening fungal infections” (Hector, 2005, p. 42).

Often, the challenge for the physician as well as the veterinarian is not the decision of “which drug to use, but rather, how much drug to use and for how long” (Hector, 2005, p. 247). In the canine community, “Itraconazole is the treatment of choice for blastomycosis in dogs because it produces fewer adverse effects, it is easier to administer, and its cost is similar to that of Amphotericin B treatment” (Legendre et al., 1996, p. 371). As it was with Maxx, the dog mentioned in the Introduction, “a combination of topical and systemic therapy is indicated in dogs with ocular blastomycosis” (Brömel & Sykes, 2005, p. 237). For humans, according to the Ministry of Health and Long Term Care (MOHLTC, 2018), most of those infected “will require treatment ...[and this] is indicated for all patients with progressive pulmonary or extrapulmonary diseases as well as those patients who are immunocompromised” (para. 18). Overall, if

diagnosed early, treated promptly, and with the cooperation of the patient, or dog owner, faithfully taking the prescribed medication, a good recovery is expected (Bariola et al., 2010; Meyer et al., 1993; Seitz, Adjemian, Steiner, & Prevots, 2015).

Prognosis

In a study done by Pappas et al. (1997) it was found that for a successful prognosis, the median length of time for antifungal therapy was eight months, with a range of 2 to 24 months. It was noted by Brömel and Sykes (2005) that “the success of treatment depends on the tissues involved, the degree of dissemination, the condition of the patient and the treatment regimen” (pp. 236-237). Bradsher and Bariola (2011) implore physicians that “careful follow-up for several years is mandatory in patients with acute pneumonia who do not receive antifungal therapy to ensure that there is no recrudescence of infection” (p. 344). A patient’s lack of symptoms may indicate that the infection enters a subclinical, asymptomatic or dormant stage and is not eradicated (Light et al., 2008). The immunocompetence of the host and the strength of the organism’s virulence (as suggested between the two species of *Blastomyces*) may be a factor in the reason for the suggestion of spontaneous recovery and other differential diagnoses (Lemos et al., 2001).

Antifungal therapy is typically necessary to eradicate fungal pathogens, especially severe pulmonary and chronic skin infections. However, they come with a price. Patients must be carefully monitored while on antifungal drugs as commonly there are minor side effects including nausea, vomiting and diarrhea, but severe adverse effects can occur (i.e. liver toxicity and blood disorders) (Kukanich, 2008; Saccente & Woods, 2010). By only losing his right eye, Maxx was lucky as “most dogs with brain involvement will die, but aggressive treatment with Amphotericin B, Fluconazole, or Voriconazole may occasionally be effective” (Gaunt & Taylor,

2009, p. 255). In most clinical cases, even if the physician chooses the right drug, dose and length of treatment, they “still rely on the host’s immune response to ultimately clear any residual fungal burden” (Hector, 2005, pp. 240–241). The physician is faced with the fact that blastomycosis, not unlike other endemic fungal infections, at 90 days after diagnosis, has a mortality rate of 9.5% (Baddley et al., 2011). With such a deadly and invasive pathogen that is successfully treated if diagnosed early, awareness and prevention are justifiably warranted. The next section discusses the health unit’s challenge to educate the community about this deadly dimorph through public awareness, protection and prevention.

The Health Unit

The health unit’s (HU’s) primary role in the Ontario health system is to promote the well-being of individuals in their districts. This can be accomplished through education programs and the awareness of strategies for protection from disease. When a disease is deemed “reportable,” the diagnosing physician must inform the HU for investigation and tracking purposes. The HU’s responsibility increases when a disease outbreak occurs; however it is preferred, through awareness and protection measures, that the spread of disease is prevented. The TBDHU is one of 36 Public Health Units in Ontario. The following section summarizes how blastomycosis has increased in awareness, influenced research, and will direct future studies, especially in the district of Thunder Bay, where blastomycosis cases are on the rise.

Awareness

Reportable disease of an RG3 organism. In Canada, *B. dermatitidis* is designated as an RG3 organism (Public Health Agency of Canada, 2011). This designation means it is a pathogen that is “likely to cause serious disease in a human or animal ... effective treatment and preventive measures are usually available and the risk of spread of disease ... is low for the

public” (Public Health Agency of Canada, 2015, Section 2.3.1.3). In Ontario, in 1989, *B. dermatitidis* was removed from the reportable list of organisms that require mandatory reporting to the local HU. Researchers and physicians, knowing the severity of the disease, were frustrated by the difficulties in tracking and investigating the organism. There have been repeated requests that blastomycosis cases become reportable once again (Brown et al., 2018; DiSalvo, 1992; Morris et al., 2006). These concerns were finally heard; as of May 1, 2018, *Blastomyces spp.* (both *B. dermatitidis* and *B. gilchristii*), have been designated reportable and blastomycosis was named a disease of public health significance in Ontario (MOHLTC, 2018). This designation will allow local health units to monitor the number of cases officially and potentially track where the fungus is most prevalent.

Incidence. In some endemic areas of the United States, where blastomycosis remained reportable, records were reviewed to determine why there was generally a ten times higher risk for dogs to contract the disease over humans; it was noted that the dog’s desire to “sniff the ground” may be the reason for the higher number of canine cases (Harasen & Randall, 1986; Pfaller & Diekema, 2010). Neighbouring Northern Ontario, “in highly endemic Northern Wisconsin, USA, per-capita dog cases of blastomycosis occur at a rate 14-fold higher than that of humans” (Baumgardner et al., 2011, p. 49). In the United States, MacDonald, Langley, Gerkin, Torok, and MacCormack (2006) studied incidence rates in states where the disease remained reportable and found the rates to be 1.3-1.4 cases per 100,000 people. However, in hyperendemic areas, it climaxed at 41.9 cases per 100,000 people and is on the rise, likely influenced by environmental conditions. Even though the disease had not been reportable in Ontario, researchers have been estimating the prevalence of blastomycosis, but it is difficult to know where areas of increased incidence are occurring. Crampton et al. (2002) estimated “the

incidence rate for the Kenora district [in Northern Ontario], as 7.11 cases per 100,000 population” (p. 1311). However, Morris et al. (2006) state that the true incidence is likely more than was predicted, and will increase when physicians and the community are more aware of the disease. The question remains; since blastomycosis is now reportable, will increased awareness of the disease be effective in reducing the number of cases in Ontario through prevention strategies? One Sault Ste Marie, Ontario, veterinarian, Dr. Poitras, does not think so, as he feels it cannot be eliminated from the soil in the environment (Ougler, 2017). Baddley et al. (2011) argue, however, that “knowledge of areas of increased incidence may improve diagnostic or prevention measures in older adults at risk for endemic mycoses, including those receiving immunosuppressive medications or with new environmental exposures” (p. 1668). By making the disease reportable, and thus increasing knowledge and awareness, the health unit will have a better chance at improving the healthcare of their residents through the education of protection and prevention procedures.

Protection

Avoidance prevention. One of the reasons blastomycosis was no longer considered a reportable disease in Ontario was that it was deemed not transmissible from person to person or even animal to person (unless bitten or by direct inoculation) (Schwarz & Baum, 1951). The search for how it becomes infective revealed *Blastomyces spp.* to be a soil organism, able to survive relative drought and high ammonia levels, inhabiting sandy soils, and along waterways with periods of intermittent moisture (Baumgardner, 2009, 2015; Baumgardner et al., 2011; McTaggart et al., 2016). Due to the severity of the disease once infected, and the toxicity of antifungal drug use, Burgess et al. (2006) felt PCR testing might best be used to confirm positive soil samples in endemic areas but still maintains the best practice is to use prevention measures

to avoid contracting the disease. Many attempts have been made to investigate environmental temperature and seasonal variations related to presentation, the type of infection (localized versus disseminated) and the prognosis of *Blastomyces spp.* in humans (Baumgardner, 2015; Baumgardner et al., 2011; Light et al., 2008) with only equivocal results. In his latest study of environmental exposure of the disease, Baumgardner et al. (2015) concludes that his research “illustrates the complexities involved in acquisition of this disease, likely a combination of environmental and temporal factors, host susceptibility and opportunity for exposure to the ecological niche of the involved fungus” (p. 31). For this reason, it is not surprising that the MOHLTC (2018) made the statement: “Decontamination of sites of exposure is not possible, and soil testing is not reliable [thus] early diagnosis and treatment of disease are therefore important control strategies” (p. 5). As a dedicated researcher of pathogenic fungi (including *Blastomyces spp.*) and someone who is interested in promoting prevention strategies, Baumgardner (2016), outlines general household routine measures to prevent accumulation of any mould indoors, from maintaining below 60% relative humidity to installing proper HVAC systems, in hopes of educating the community.

Immunity. Many dedicated researchers are working hard to create a vaccine against *Blastomyces spp.* (Chang et al., 2000; Datta & Hamad, 2015; Scorzoni et al., 2017). Vaccines were considered a good option for blastomycosis, as it affects immunocompetent hosts – those with the ability to respond to vaccines – thus making them valuable (Spellberg, 2011). However, Spellberg (2011) outlines three barriers to the effectiveness of vaccines:

First, vaccination would target the general population living in endemic areas and would require prolonged—or lifelong—immunity to be maintained.... A second barrier ... is that, although the number of invasive infections per year caused by the endemic mycoses is quite large, these infections occur only in limited geographical areas, and [third,] the number of patients who develop significant sequelae from infection represents a small fraction of the total infected population. (p. 5)

Deepe, Wüthrich, and Klein (2005) added that the “lack of epidemiological data regarding incidence and prevalence of infection” is another barrier to the development of vaccines (p. 381). Due to the severity of fungal pathogens and the difficulty in diagnosis and treatment of blastomycosis, it is hoped through education and awareness that the clinical development of an efficient vaccine will be possible (Spellberg, 2011). Reaching out to the community for assistance in tracking this deadly disease will not only increase awareness through education, and promote the necessary precautionary measures, but will additionally assist in obtaining the data needed for researchers to identify endemic areas.

Prevention

Epidemiology. At the beginning of the 20th century, Brayton (1902) astutely suspected that the disease was contracted from the soil by observing a higher number of infections in occupations that worked in these areas, but did not pursue this as a possibility. Schwarz and Baum (1951) suggested the acquisition of the disease came from animals as they produced evidence of “the failure to demonstrate transmission from man to man” (p. 1021). In the following decade, Denton and DiSalvo (1964), discovered: “that *B. dermatitidis* is a self-sufficient saprophyte, capable of surviving and thriving in nature, and that it infects man only rarely by accident” (p. 716). Increasing awareness developed as endemic areas grew in the Northwestern Ontario area (Kane, Righter, Krajden, & Lester, 1983). A prospective case series by Nicolle, Rotstein, Bourgault, St-Germain, and Garber (1998) revealed a misleadingly high provincial incidence of blastomycosis in Manitoba as “the large unexposed population in southern Ontario decrease[d] the Ontario provincial incidence” (p. 351), thereby skewing the results. As the awareness grew, the desire and importance of epidemiological studies became realized; not just for knowledge of the ecological niche of the organism but for surveillance of

the area and for the sake of prevention and public health awareness within and outside of the endemic areas (Benedict, Thompson, Deresinski, & Chiller, 2015; Burgess et al., 2006; Crampton et al., 2002; DiSalvo, 1992; MOHLTC, 2018).

Studies that rely on retrospective data can limit the availability of information, thus restricting the ability to uncover specific locations of *Blastomyces spp.* in the soil (Baumgardner et al., 2011; Litvinjenko & Lunny, 2017; Pfaff et al., 2014). There is a need to design studies going forward to create survey information regarding travel history (humans) or soil contact information (dogs) and even species identifications and local weather conditions so risk factors can be determined (Chen, Legendre, Bass, Mays, & Odoi, 2008; Reed, Meece, Archer, & Peterson, 2008). Due to the natural inclination of dogs and their attraction to the typical niche of *Blastomyces spp.*, they represent an excellent sentinel to create an epidemiological map. Baumgardner et al. (2015) noted that “dogs have long been considered harbingers of human blastomycosis, and in this area, there have been a mixed human and dog outbreak, same-household cases over time, and similar geographic distributions of human and dog cases” (p. 30). Randhawa et al. (2013) suggested the “applications of PCR assays for rapid detection of *B. dermatitidis* in clinical and soil samples is highly promising for more rewarding future epidemiologic studies” (p. 190-191) and would also be useful in the confirmation and identification between the two *Blastomyces spp.* in endemic areas.

Communication. As research progresses, the success in educating the community lies in the hands of the HU and knowledge mobilization techniques. There is a desire to communicate current information about this potentially fatal pathogen to the public that needs to know, and the physicians that need to treat infected patients (Baumgardner et al., 2015). Effective communication of well-researched information can “bridge the gap” between researchers and the

public, including physicians, veterinarians and health inspectors, and assist in putting the information into active use. Currently, the MOHLTC (2018) recommends that “public health units may consider periodic education reminders to health care providers ahead of the peak occurrence of blastomycosis in October-December” (p. 5). However, if there were constant reminders in physician and veterinarian offices, such as posters or pamphlets, and the completion of surveys from affected people and their pets (Figure 4.), it can not only increase awareness but also assist researchers, the medical community and health inspectors in their fight against this deadly dimorph.



Figure 4. Panophthalmitis (inflammation of all layers of the eye) of a dog infected with ocular blastomycosis (Gaunt & Taylor, 2009).

Conclusion

Maxx was a lucky dog. His owners made sure he had the care he needed to survive. The veterinarian bills, which exceeded \$4000, were subsidized by a caring friend telling their story on social media and a “gofundme” page. Without this help, the owner’s upcoming wedding was going to be put on hold. Maxx is currently on the road to recovery with another six months of vet visits and medication. It is still unknown where he had contracted the fungus; *Blastomyces spp.* typically has a three-week incubation period and the symptoms began within days of him returning home from a camping trip. Other than walks in the dog park, Maxx stays at his home. If Maxx did not live in Thunder Bay where veterinarians are cognizant of the symptoms of blastomycosis and thus sent the spores for testing, Maxx might not have survived.

Blastomyces spp. are not the only dimorphic fungi that can be fatal in otherwise healthy hosts, particularly when they disseminate to other organs. Histoplasmosis and Coccidioidomycosis are also among the few known deadly dimorphic fungal infections. Even though dimorphic fungi can be lethal if untreated, infections are rare, which is a disadvantage when it comes to research funding for vaccines, advanced testing protocols and antifungal treatments. The onus lies in the hands of health units to identify areas of potential infection, and to mobilize the valuable researched information to the public for awareness and prevention.

The best way to minimize the impact of this rare but often fatal pathogen is for everyone to work together. The laboratory, especially in endemic areas, should be well trained to identify the pathogen in the initial microscopic examination, to give the fastest turn-around time in reporting the disease to the physician. The patient, if aware of the condition and their possible exposure, can alert the examining physician with characteristic symptoms and travel history. The physician and veterinarians should be well educated on the latest research regarding diagnosis and treatment, especially in or near endemic areas. Finally, the health unit has the responsibility to mobilize the latest researched information to all parties, raising awareness. All four roles can work together in unearthing the high-risk areas of infection so that a continually updated epidemiological map can be created for the ongoing monitoring of the endemic regions of this fungus.

As dogs are such great harbingers of this infection, it could be of benefit to use them as a guide to address the many unanswered questions about the epidemiology of *Blastomyces spp.*, the main one being: Where is this organism found? In Ontario, *Blastomyces* is once again a reportable pathogen for humans, for both microscopic and culture results. This is a step in the right direction, but to get even more precise and current information, it is necessary to utilize the

data from canine cases. With the cooperation of dog owners, veterinarians can send specimens to the laboratory for diagnosis. The laboratory would alert the health unit of positive cases which can then immediately deliver detailed surveys to the dog owner and collect valuable evidence (e.g. home location or recent travel history before the first signs of illness). This information can track not only possible locations of infection but the virulence of the organism. An increase in canine case numbers can alert the health unit, physicians and the public and may predict or even prevent future outbreaks. Cultures collected by the laboratory with detailed survey information can be invaluable to researchers in future investigations and bring awareness to all parties concerned. Currently, it is not until a case like Maxx's is detailed on social media that the seriousness of this deadly dimorph is realized, and public awareness is initiated.

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