



Incidental findings of blastomycosis lung nodules in five asymptomatic patients



Jennifer L. Anderson^a, Matthew C. Hall^b, Jennifer K. Meece^{a,*}

^a Marshfield Clinic Research Institute, Marshfield Clinic, Marshfield, WI USA

^b Department of Infectious Diseases, Marshfield Clinic, Marshfield, WI USA

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ABSTRACT

Asymptomatic blastomycosis infections are rarely identified or described in the literature, but are believed to comprise 50% of cases. In this report we describe five sporadic cases of blastomycosis in asymptomatic patients. All of these cases were initially identified as incidental findings of lung nodules on CXR or CT. To our knowledge, these are the first detailed descriptions of asymptomatic blastomycosis, occurring as sporadic disease, in the literature.

1. Introduction

Human blastomycosis is caused by three distinct species within the *Blastomyces* genus. *B. dermatitidis* and *B. gilchristii* cause infections mostly in North America, whereas *B. percursorus* has been found in South Africa and Israel [1,2]. The symptoms of blastomycosis range from asymptomatic infection to fulminant respiratory failure with acute respiratory distress syndrome and/or dissemination to skin, bone, and other organs. *B. percursorus* has only recently been re-categorized based on genome sequencing and therefore knowledge regarding the range of clinical manifestations is limited. Alternatively, the other two species vary in virulence with *B. gilchristii* being more often associated with pulmonary-only disease and *B. dermatitidis* being more likely to disseminate and occur in older patients with comorbidities [3].

Asymptomatic infections are rarely described in the literature. They are most often identified during outbreak investigations due to heightened awareness and testing of potentially exposed individuals regardless of whether they have symptoms. Based on previous outbreak investigations, asymptomatic infections are believed to comprise 50% of total blastomycosis cases [4,5]. Study of these cases could provide insight into pathogenesis, host immune response, and future vaccine development.

In this report we describe five sporadic cases of blastomycosis in asymptomatic patients. All of these cases were initially identified as incidental findings of lung nodules on chest x-ray (CXR) or computed tomography (CT) chest scan and subsequently diagnosed by histopathology, fungal culture, or both. To our knowledge, these are the first detailed descriptions of asymptomatic blastomycosis, occurring as

sporadic disease, in the literature.

2. Cases

For all cases described in this series, day 0 is the date that lung nodules were identified by CXR or CT in each patient.

2.1. Patient 1

A 73 year old male smoker with coronary artery disease, COPD, and stage IV chronic renal disease was hospitalized for radical cystectomy for bladder cancer. A CXR revealed a right lower lobe lung nodule not present one month earlier (day 0). The patient had no evidence or symptoms of any lung infections in the previous twelve months. At a follow up appointment, (day +38) the patient denied fever and chills. Due to multiple hospitalizations for *Clostridium difficile* infection, a kidney stone, and nephrostomy tube placement, follow up on the patient's pulmonary nodule was delayed. On day +95, a CT scan revealed that the right lung nodule was significantly larger. On day +112, the patient continued to deny fever, chills, shortness of breath, and chest pain. An abnormal positron emission tomography (PET) chest scan was obtained (day +122) and on day +127 a CT guided lung biopsy was positive for *Blastomyces* by Grocott-Gomori's methenamine silver (GMS) stain, with observation of budding yeast forms. Culture confirmation was not performed on the biopsy specimen. Treatment with itraconazole was initiated (200 mg three times daily for 2 days, then twice daily) and the patient completed two months of treatment. Treatment was discontinued on day +188, due to declining health, and he died

* Corresponding author.

E-mail address: meece.jennifer@MarshfieldResearch.org (J.K. Meece).

from bowel cancer (day +245). The patient was noted to engage in wood working, gardening, and composting on his property and had a dog that died from blastomycosis.

2.2. Patient 2

A 66 year old overweight (BMI = 30.7 kg/m²) male smoker with diabetes, hypercholesterolemia, and hypertension presented with complaints of unintentional weight and appetite loss. The patient denied chest pain and shortness of breath. As part of a medical workup, a CXR revealed a nodular mass-like opacity at the right lung base (day 0). The patient had no evidence of any lung infection or symptoms in the previous twelve months. A CT image confirmed the presence of a mass within the lateral basal segment of the right lower lobe. At a pulmonology consult (day +18), the patient reported a cough, but denied fever, chills, and night sweats. Bronchoscopy was performed and histopathology was positive for *Blastomyces* by GMS stain, with observation of broad-based budding yeasts. Culture of both induced sputum and bronchial wash were positive using standard methods, which included culture of the mold form on brain-heart infusion agar with blood at 25°C and conversion to the characteristic broad-based budding yeast when incubated in Middlebrook 7H9 broth at 35°C in 10% CO₂. Urine *Blastomyces* antigen was later reported as positive. Itraconazole treatment of 200 mg, three times daily was initiated (day +24) and then lowered to twice daily (day +27). On day +31, the patient denied that he ever had any cough, fever, chills, or night sweats. The physician documented that the patient was “asymptomatic”. The patient completed eight months of treatment and on day +224, his CXR was stable with minimal scarring. The cultured clinical specimen was previously bio-banked and available for pathogen genetic analysis. DNA was extracted from the clinical specimen and species-typed by sequencing a portion of the ITS2 rDNA as previously described [6]. Bi-directional sequencing of the PCR product yielded 308 bp of sequence. BLAST alignment showed 100% coverage and identity match with a previously sequenced isolate, accession JN562151.1. The isolate was determined to be *B. dermatitidis*, based on a fixed nucleotide difference between *B. dermatitidis* and *B. gilchristii* at position 19 [6]. Two years and nine months later, a CT showed left sided mediastinal adenopathy and recurrence of pulmonary nodules, which were not diagnosed or treated due to the patient's deteriorating health and decision by his power of attorney for health care. On the most recent imaging, the adenopathy was stable and the nodular densities have shown improvement.

2.3. Patient 3

A 76 year old obese (BMI = 31.8 kg/m²) male with a history of smoking, prostate cancer, and hypertension had an abnormal CXR at a pre-operative physical for prostate seed implantation (day 0). A CT confirmed a pulmonary nodule in the superior segment of the left lower lobe. The patient had no evidence or symptoms of any lung infections in the previous twelve months. On day +9, a PET scan was suspicious for malignancy. At a pulmonology consult (day +23), the patient denied cough, chest congestion, fevers, chills, and fatigue. Left thoracotomy and wedge resection of the superior segment were performed on day +30 and histopathology was positive for fungal organisms consistent with *Blastomyces* using GMS stain. Follow up culture of lung biopsy was later positive for *Blastomyces* using standard methods described above. Itraconazole treatment of 200 mg once daily was initiated and switched to 400 mg of fluconazole daily due to the cost of itraconazole (day +35). Urine *Blastomyces* antigen was not detected (day +45). On day +52, CXR and CT revealed moderate level hydropneumothorax, increase soft tissue emphysema, and small air-fluid level in the chest wall were noted on the patient's chest CXR and chest tube placement was performed. CXRs were obtained to monitor progress, the air leak resolved and chest tubes were removed on day +58 and pneumothorax was resolved on day +65. A CT scan obtained on day +252 showed

no pulmonary nodules. The patient completed seven months of treatment and has no evidence of recurrence over the last three years. The cultured clinical specimen was species-typed as described above. Bi-directional sequencing of the PCR product yielded 295 bp of sequence. BLAST alignment showed 100% coverage and identity match with a previously sequenced isolate, accession JN562151.1. The isolate was determined to be *B. dermatitidis* [6].

2.4. Patient 4

A 58 year old obese (BMI = 34 kg/m²) male with hypertension, coronary artery disease, and diabetes was found to have right upper lung nodules on CXR performed for amiodarone monitoring (day 0). The patient had no evidence or symptoms of any lung infections in the previous twelve months. A CXR six months prior did not show nodules. He denied fever, unintentional weight loss, cough, or chest pain. The physician noted that the patient was “asymptomatic and his labs are unremarkable.” On day +18, a CT scan confirmed the pulmonary nodules. A CT-guided needle biopsy, was performed +45 days after the abnormal CXR. Histopathology was abnormal on GMS stain with fungal organisms consistent with *Blastomyces* being present. Culture confirmation of the biopsy specimen was not performed and urine *Blastomyces* antigen was not detected. Treatment was determined necessary but delayed until amiodarone was cleared based on blood levels. On day +91, the patient continued to be symptom free without treatment and a follow up CXR found moderate resolution of the nodules. Itraconazole treatment of 400 mg once daily was initiated on day +108. Itraconazole level was obtained (day +155) and was found to be within the recommended range (2.4 mcg/mL). A CXR obtained on day +216 showed interval improvement with mild scarring. The patient completed six months of treatment and follow up CXR's over the next three years have not found any evidence of recurrence of nodules. The patient was noted to be an avid outdoorsman.

2.5. Patient 5

A 43-year old obese (BMI = 46 kg/m²) male with a history of smoking, hypertension, and high cholesterol presented with leg swelling, abdominal pain, and shortness of breath. The patient had no evidence or symptoms of any lung infections in the previous twelve months. CXR and CT revealed a left upper lobe nodular density (day 0). The patient denied cough, fever, chills, and chest pain. An abnormal PET scan was obtained on day +7. Lobectomy was recommended but delayed due to insurance issues. The patient eventually underwent wedge resection on day +57 and histopathology was positive for *Blastomyces* using GMS stain showing broad-based budding yeasts. Follow up culture of lung biopsy was later positive for *Blastomyces* using standard methods described above. Itraconazole treatment of 200 mg of twice daily was initiated. Itraconazole serum levels were monitored at day +70, day +92, and day +126 with all levels being within the recommended range (0.5 mcg/mL, 1.4 mcg/mL, and 0.9 mcg/mL, respectively). On day +156, the patient was instructed to continue itraconazole treatment for 2 more months, but the patient did not comply and completed only 4 months of treatment. The patient has no evidence of recurrence over the last fifteen months. The cultured clinical specimen was species-typed as described above. Bi-directional sequencing of the PCR product yielded 278 bp of sequence. BLAST alignment showed 100% coverage and identity match with a previously sequenced isolate, accession JN562106.1. The isolate was determined to be *B. gilchristii* [6]. The patient was noted to work for a lawn care business.

3. Discussion

Although infection with *Blastomyces* can result in fulminant sepsis with acute respiratory distress syndrome and death, it is suspected that

asymptomatic infections comprise 50% of cases. We report five sporadic cases of blastomycosis in asymptomatic patients with all cases being initially identified as incidental findings of lung nodules on CXR or CT scan.

Case patients 1, 3, and 4 are consistently documented as denying any classic symptoms of blastomycosis, with the first and fourth case patients being notable for remaining asymptomatic for three months between diagnosis and treatment. The second patient presented with poor appetite associated with unintentional weight loss and there was some question of whether he had a cough but this was not consistently documented and as a smoker, occasional cough might be expected. His attending physician considered the infection “asymptomatic” and documented it in his medical record. The fifth patient reported shortness of breath, but he is an obese smoker, making it difficult to determine whether this is due to blastomycosis infection.

None of these patients had evidence of medically attended respiratory disease in the twelve months prior to diagnosis of pulmonary nodules, though many patients do not seek care for mild self-limited respiratory illnesses. Moreover, in only one case can we make an estimate of infection onset due to a clear CXR one month prior to identification of the pulmonary nodule. Thus, we have no way of accurately knowing how long these patients were infected and asymptomatic. In fact, these patients were likely diagnosed due to frequent care seeking for their underlying medical conditions. We have no way of knowing if these infections would have self-resolved, progressed to acute respiratory failure, or disseminated to other organs systems. Interestingly, patient 2 had a recurrence of pulmonary nodules of unknown etiology 2 years and 9 months after complete resolution of blastomycosis. We have no way of knowing the cause of these, but cancer seems unlikely given the recent evidence of improvement without treatment. Relapse or recurrence of blastomycosis is rare, but has been documented in the literature [7].

We have several hypotheses regarding why these, and an estimated 50% of cases, remain asymptomatic when medically attended disease can be quite severe with hospitalization rates of 59% [3,] and mortality rates of 4–9% [3,8]. It is possible that these cases were identified very early in the course of disease and treatment was initiated prior to the presentation of symptoms, although this seems unlikely in case patients 1 and 4, where treatment was delayed for 3 months. Alternatively, underlying medical conditions could play a role. These patients had a significant number of underlying medical conditions which may have limited their ability to mount a robust response to infection. Or their underlying medical conditions may have masked the symptoms of their new disease or prevented their doctors from considering etiologies other than the preexisting diseases [9,10]. However, we believe in the cases presented here, it is more likely that frequent care for underlying medical conditions lead to diagnosis of the disease instead of delaying it. The atypical disease presentation of isolated pulmonary nodules [11], in these cases, could partially explain the lack of classic symptoms. Whether due to host factors or pathogen virulence, these infections were seemingly contained to a very small area in the lungs and did not cause a systemic immune response. Acquired immunity may be another explanation for asymptomatic infections, as it is likely that previous exposure provides future protection against blastomycosis [12,13]. Exposure is not always associated with residence, but review of these cases showed that all the patients lived and were regularly seeking health care within endemic areas for blastomycosis, and therefore could have been previously exposed. In addition, disease severity is presumed to depend partly on exposure inoculum and therefore asymptomatic infections could be the result of inhalation of only a

small number of *Blastomyces* spores.

The number of days from identification of a pulmonary nodule to diagnosis varied greatly between the patients (18–127 days, mean 56.6). Cancer was considered in the diagnostic differential for all the cases presented here, with it being considered highly likely in four of the five cases. Blastomycosis can resemble lung cancer on CXR and CT imaging [14] and distinguishing it from lung cancer remains challenging for physicians, especially in the absence of classic symptomatology. These cases illustrate that physicians serving in endemic areas should maintain a high degree of clinical suspicion for pulmonary blastomycosis when lung nodules are identified on CXR or CT.

In this report we describe sporadic blastomycosis in 5 asymptomatic patients, initially identified as incidental findings of lung nodules on CXR or CT. Further genetic analysis of these *Blastomyces* isolates and future genetic studies of asymptomatic patients in these unique cases could provide much insight into pathogenesis and host immune response and contribute to future vaccine development.

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Conflict of interest

There are no conflicts of interest.

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