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BRIEF REPORT

Diagnostic Delay and Antibiotic Overuse in Acute Pulmonary Blastomycosis

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The diagnosis of blastomycosis is often delayed. We identified 28 cases of pulmonary blastomycosis in a retrospective chart review. Most patients received multiple antibiotic courses before being diagnosed, and the sputum KOH smear was rarely used. Diagnostic delay can be decreased with higher suspicion for pulmonary blastomycosis and early use of the sputum KOH smear.

Keywords. pulmonary blastomycosis; fungal infection; antibiotic overuse; diagnostic delay.

Blastomyces dermatitidis is a temperature-dependent dimorphic fungus endemic to the Ohio and Mississippi River basins, the regions bordering the Great Lakes, and the Arkansas and Mississippi delta region [1, 2]. Inhalation is the usual mechanism of initial infection [1, 3]. Pulmonary disease is the most common manifestation of blastomycosis, ranging in severity from a mild self-limited illness to multi-lobar pneumonia with acute respiratory distress syndrome (ARDS) [4]. As compared to other dimorphic fungi, most cases require treatment due to high rates of disseminated disease. In endemic regions, blastomycosis should be considered when a patient presents with community-acquired pneumonia (CAP), particularly after failing initial antibiotic treatment.

Establishing blastomycosis as the cause of pneumonia may be difficult. Culture is gold standard, with a sensitivity ranging from 67%–86%, but fungal growth is slow and may take up to 5 weeks [5, 6]. The *Blastomyces dermatitidis* antigen enzyme immunoassay (EIA) detection method has a higher sensitivity ranging from 85%–93% but requires a reference laboratory, delaying results [7]. Further, the Blastomyces EIA, targets a galactomannan in the fungal cell wall and cross-reacts with *Histoplasma capsulatum*, *Paracoccidioides brasilienses*, and *Penicillium marneffei* [8]. In addition, low suspicion for blastomycosis and its ability to mimic other pulmonary processes contribute to diagnostic delay. Shortening the time to diagnosis may improve outcomes [6].

One rapid and inexpensive way of diagnosing pulmonary blastomycosis is direct visualization of the *Blastomyces dermatitidis* yeast from respiratory specimens via the potassium hydroxide (KOH) fungal smear with or without calcofluor white staining [9]. The KOH smear takes 15–30 minutes but sensitivity is variable (50%–90%) [6]. Obtaining early KOH smears in patients presenting with CAP could lead to early diagnosis and improved clinical outcomes.

In this study, we sought to determine if (1) obtaining early KOH sputum smears or (2) making an early diagnosis of pulmonary blastomycosis, was associated with reduced clinical complications, hospital length of stay (LOS), ICU admissions, and antibiotic usage.

METHODS

We conducted a multi-center, retrospective chart review of patients diagnosed with pulmonary blastomycosis within a large, integrated healthcare system in Minnesota and western Wisconsin between 1 January 2000 and 30 April 2015. A case was defined as the presence of pneumonia, empyema, or mediastinal lymphadenitis with *Blastomyces* species identified by KOH smear microscopy, culture, and/or histopathology from a clinical specimen. Time to diagnosis was stratified into "diagnosis made at first visit to healthcare" and "diagnosis made after the first visit to healthcare". Cases of extra-pulmonary blastomycosis were excluded.

Cases were identified using ICD-9 codes. Charts were reviewed to obtain demographic information, clinical presentation, course of illness, time to diagnosis, presence or absence of immunosuppression, and mortality. Complications were defined as respiratory failure requiring intubation, ARDS, or formation of empyema/abscess requiring drainage. The institutional review board at HealthPartners approved this study.

Data were described as medians with interquartile range for numerical outcomes and percent having the outcome. We compared clinical outcomes of those diagnosed at the first healthcare encounter to those diagnosed after the first healthcare

Received 16 February 2016; accepted 13 April 2016.

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DOI: 10.1093/ofid/ofw078

Table 1. Clinical Characteristic of 28 Pulmonary Blastomycosis Patients

Clinical outcome	N (%)	Median (IQR)
Diagnosis made on first healthcare visit	5 (19)[a]	
Antecedent healthcare visits prior to diagnosis		2 (1–4)
Antibiotic courses		2.5 (1.5–4.5)
Days from initial healthcare visit to diagnosis		23 (8–36)
Hospitalized	13 (46)	
Duration of Hospitalization, days[b]		10 (8–19)
Intensive Care Unit (ICU) stay	4 (14)	
Duration of ICU stay, days		12 (9.5–24.5)
Complications[c]	6 (21)	
Mortality	0 (0)	

[a] Denominator of 27, due to limited information for one participant.

[b] Duration among those hospitalized.

[c] Complications included: respiratory failure requiring intubation, acute respiratory distress syndrome (ARDS), or formation of empyema/abscess requiring drainage.

encounter using a Wilcoxon-two sample test for numerical outcomes, and Fischer's exact Chi-square for categorical outcomes. SAS version 9.3 (SAS Institute Inc, Cary, NC) was used.

RESULTS

Seventy four possible cases occurring between 1 January 2000 and 30 April 2015 were identified. Forty-six cases were excluded: 39 due to incorrect diagnosis related to coding errors; two cases due to inadequate information available in the medical chart; and five cases were excluded due to skin (n = 2) and other extra-pulmonary disease presentations (n = 3). Twenty-eight cases were included in the study. The median age at time of diagnosis was 43 (IQR: 31–54, maximum: 78) years with 61% aged <50 years. The majority of patients were men (n = 21, 75%) and immunocompetent (n = 25, 89%). In one case, a patient's dog was also infected with blastomycosis. Seven persons (25%) had known outdoor activity prior to the onset of symptoms.

Clinical outcomes are summarized in Table 1**.** Eighty-one percent (22/28) of patients were diagnosed after at least two visits to the healthcare system. The median number of healthcare visits required to make a diagnosis was 2 (IQR: 1–4, maximum: 7), encompassing a median of 23 (IQR: 8–36, maximum: 100) days from the initial presentation to a healthcare facility. A median of 2.5 (IQR: 1.5–4.5, maximum: 9) antibiotic courses were prescribed prior to the diagnosis of pulmonary blastomycosis.

Approximately half of patients required hospitalization (n = 13, 46%), and of those hospitalized, the median length of stay was 10 days (IQR: 8–19, maximum 44). Four patients (14%) required treatment in the intensive care unit (ICU), all of who required intubation with mechanical ventilation. Six complications (21%) occurred, which included respiratory failure requiring intubation (n = 2), ARDS (n = 2), procedure-related pneumothorax (n = 1), and empyema (n = 1). There were no deaths.

Most patients were diagnosed by bronchoscopy with bronchoalveolar lavage (n = 16, 57%), followed by CT-guided lung biopsy with fine needle aspirate (n = 8, 29%), and open thoracotomy (n = 3, 11%). A KOH sputum smear with culture was sent in 18% (n = 5) of cases. Of the KOH sputum smears, one was smear positive, another was culture positive but smear negative, and three were smear/culture negative. Adequate sputum was collected for Gram's stain and bacterial culture in 12 persons.

Time to diagnosis as a measure of clinical outcome is summarized in Table 2. A diagnosis made after the first visit to the healthcare system was associated with more antibiotic courses used (median 3, IQR: 2–6) as compared to a diagnosis made on the first visit (median 0, IQR: 0–2) ($P = .033$). Visit number was not associated with difference in ICU days or complications.

DISCUSSION

In this retrospective study, delays in the diagnosis of pulmonary blastomycosis were common and use of the KOH smear for early diagnosis was rare. Delayed diagnosis was associated with multiple empiric antibiotic courses and healthcare visits. We found that pulmonary blastomycosis remains under-recognized by clinicians resulting in significant diagnostic delays [10–12]. Healthcare providers had difficulty expanding their differential diagnosis beyond common bacterial causes of CAP, even after their patients had multiple visits to the healthcare system and failed to improve with initial antibiotics.

Most patients received multiple antibiotics courses (median 2.5, IQR: 1.5–4.5) before a diagnosis of pulmonary blastomycosis was made. The practice of prescribing a second or third course of antibiotics despite a lack of improvement with the first, is common [13]. Failure to respond to the initial antibiotic regimen should prompt clinicians to consider alternative

Table 2. The Effect of Time to Diagnosis on Clinical Outcomes

Characteristic	Diagnosed at First Healthcare Visit (n = 5)	Diagnosed After ≥2 Visits (n = 22)	*P* Value
Diagnostic Delay in Days, median (IQR)	10 (7–23)	26 (10–39)	.67
Antibiotic Courses, median (IQR)	0 (0–2)	3 (2–6)	.03
Required Hospitalization, n (%)	4 (80)	9 (41)	.16
Duration of Hospitalization in days, median (IQR)	10 (4–14)	12 (8–22)	.43
Required ICU, n (%)	0 (0)	4 (18)	.56
Complications	1 (20%)	5 (23%)	.99

diagnoses, including fungal infections in geographically endemic areas. Yet blastomycosis is often not included in the differential diagnosis of CAP [14], and is not listed in the Infectious Disease Society of America (IDSA) guidelines [15].

Early diagnosis of pulmonary blastomycosis may improve outcomes in patients who develop ARDS and shock, which carries a high mortality rate (50%–90%) [7]. Yet little is known about the effect of early diagnosis on other clinically important outcomes. We found that when more than one healthcare visit was required for diagnosis, there was a statistically significant association with use of additional antibiotic courses as compared to diagnoses made at the first visit. This finding is not unexpected, and re-affirms the notion that clinicians become anchored to the diagnosis of bacterial pneumonia, and are slow to consider alternative diagnoses.

We found that the sputum KOH smear with culture was underutilized. It was sent only five times (18%) in our study, and 50% of cases had a sputum sample sent for Gram's stain and culture, suggesting that inability to obtain sputum was not the reason a sputum KOH smear was not sent in most cases.

More commonly, invasive techniques were the method of diagnosis, such as bronchoscopy, CT-guided lung biopsy, or thoracotomy. Due to variable sensitivity, a negative initial sputum KOH smear should not deter the clinician from pursuing more definitive diagnostic methods. However, we would posit that in addition to considering the use of invasive diagnostic techniques, sputum sample testing including both a Gram's stain and a KOH smear should also be performed. While only 20% of the KOH sputum smears that were sent resulted in a positive smear, a positive KOH smear obtained early in the course of illness may reduce antibiotic usage and improve hospital length of stay, ICU days, cost, morbidity and mortality.

This study has several limitations. Case determination was made using ICD-9 codes. Cases may have been missed due to variable coding methods. Because case descriptions were made by retrospective chart review, important clinical details may have been incomplete. Due to a low sample size, the study was underpowered to detect some associations. Finally, confounding variables may have been missed as this study was observational.

In conclusion, we found that the diagnosis of pulmonary blastomycosis was often delayed in routine care. Most patients received multiple antibiotic courses before being diagnosed, and use of sputum KOH smear was underutilized. Diagnostic delay in pulmonary blastomycosis can be decreased if there is higher suspicion for the disease and early use of the sputum KOH smear, especially if a patient has failed a course of antibiotics.

Notes

Acknowledgements. J. D. A. had full access to the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. J. D. A. participated in data acquisition, study design, data interpretation, and manuscript writing. N. C. B. participated in data interpretation and manuscript writing. G. V. B. participated in data analysis. D. R. B. participated in study design, data interpretation, and manuscript writing. JSS participated in study design, data interpretation, and manuscript writing. G. A. S. participated in study design, data interpretation, and manuscript writing. The authors thank Ann Hanson for assistance with ICD-9 review.

Funding. This work was supported by HealthPartners GME Resident Research Grant (to J. D. A.); National Institute of Allergy and Infectious Disease (T32AI055433 to N. C. B.).

Conflicts of Interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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