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The Differential Diagnosis of Pulmonary Blastomycosis Using Case Vignettes: A Wisconsin Network for Health Research (WiNHR) Study

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Abstract

Purpose—Pulmonary blastomycosis is an uncommon but serious fungal infection endemic in Wisconsin. Clinician awareness of the protean presentations of this disease may reduce diagnostic delay. This study addressed the diagnostic accuracy of physicians responding to case vignettes of pulmonary blastomycosis and the primary care differential diagnosis of this disease.

Methods—Eight pulmonary blastomycosis cases were developed from case files. From these, 2 vignettes were randomly selected and mailed to primary care physicians in the Wisconsin Network for Health Research. Respondents were asked to list the 3 most likely diagnoses for each case.

Results—Respondents listed Blastomycosis as the most likely diagnosis for 37/227 (16%) case vignettes, and 1 of the 3 most likely diagnoses for 43/227 (19%). When vignettes included patient activity in counties with an annual incidence rate of blastomycosis greater than 2/100,000, compared to counties with lower incidence rates, diagnosis was more accurate (28/61 [46%] vs 15/166 [9%]; $P < 0.001$). Physicians with practice locations in counties with annual blastomycosis incidence rates >2/100,000 listed blastomycosis more commonly than physicians from other counties (16/36 [44%] vs 27/177 [15%]; $P < 0.001$). This difference in accurate diagnosis remained significant in a multivariate model of practice demographics. Based on responses to the vignettes, pneumonia, cancer, non-infectious pulmonary disease, and tuberculosis emerged as the most-frequently noted diagnosis in the differential diagnosis of blastomycosis.

Conclusion—Blastomycosis was not listed as 1 of 3 primary diagnoses in a majority of cases when Wisconsin primary care physicians considered case vignettes of actual pulmonary blastomycosis cases. Diagnosis was more accurate if the patient vignette listed exposure to a higher incidence county, or if the physician practiced in a higher incidence county. In Wisconsin, failure to include blastomycosis in the differential diagnoses of illnesses associated with a wide variety of pulmonary symptoms suspected to represent infectious or non-infectious pulmonary,

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Editor's Note: See appendix on page 73 for the complete text of 3 case vignettes. The text of all 8 vignettes used in this study is available online at www.wmjonline.org/_WMS/publications/wmj/pdf/110/2/68vignettes.pdf.

cardiac, or neoplastic disease, regardless of geographic exposure, could result in excess morbidity or mortality.

Introduction

Blastomycosis is an uncommon but serious infection caused by the dimorphic fungus, *Blastomyces dermatitidis*, which primarily affects the lungs and skin.[1] Infected individuals may present with variable symptoms, ranging from no symptoms, mild-severe respiratory problems, to progressive illness involving multiple organ systems or acute fulminating pulmonary infection.[2] Pulmonary blastomycosis can clinically be divided into 4 broad categories: (1) asymptomatic, associated with only serological evidence of prior infection or granulomas, often in the lung, which can be confused with other lung nodules; (2) acute localized pneumonia; (3) severe acute respiratory distress syndrome (ARDS), seen in 2 of our cases, often confused with congestive heart failure, pulmonary emboli, or other causes of ARDS; (4) subacute to chronic infiltrates and/or cavitary disease, confused with cancer, tuberculosis, bacterial abscess, and Wegener's granulomatosis. In addition, acute or chronic dissemination of *B dermatitidis* to skin, brain, genitourinary (GU) system, or bone, including illnesses that mimic psoriasis, lung cancer with metastases, or other malignancies, may occur at any stage of any category.

In highly endemic areas of Wisconsin (generally northern and north central Wisconsin), where clinicians more commonly encounter blastomycosis,[3,4] a large proportion of cases are discovered in the earlier pulmonary stage. Even in these areas, significant delay may occur between onset of pulmonary symptoms and diagnosis and treatment.[5] This disease may mimic a variety of pulmonary, infectious, or malignant diseases.[1,6,7] Delay in diagnosis of blastomycosis is well described in the literature,[6,8] and can often be fatal in patients with delayed diagnosis.[9,10] One review[8] states, “Improving the awareness of clinicians to the possibility of *B dermatitidis* infection is a key step to resolving the problem of delayed diagnosis.” Therefore, it is essential to obtain a better understanding of how primary care physicians initially diagnose the various clinical presentations of blastomycosis.

The purpose of this study was to determine the rate at which clinicians currently practicing medicine in distinct geographic regions of Wisconsin correctly diagnose *B dermatitidis* infection when given brief descriptions of actual cases.

Methods

During March and April 2010, primary care physicians affiliated with the Wisconsin Network for Health Research (WiNHR)[11] (N=1064) were mailed a survey to be completed anonymously and returned using an enclosed metered, preaddressed envelope. The survey packet invited the recipient to participate in “a research study of the differential diagnosis of pulmonary disease,” and contained questions regarding the county of practice, gender, specialty, and years in practice of the respondent; and 1 of 28 possible fixed combinations of 2 clinical case vignettes selected from a set of brief descriptions of 8 pulmonary blastomycosis cases on a rotating basis. The vignette pairs were always ordered the same, but identified by fictitious numbers from 1 to 56. The vignettes were described in the cover letter as “2 randomly selected (actual) clinical case histories that resulted in the diagnosis of a pulmonary condition.” The letters were sent on behalf of WiNHR by the third author (EG), and the name of a specific person involved in the research program at the particular institution was included in the cover letter (for questions concerning the study). Participants were not informed of the names of the 2 primary authors as their identity, based on reputation, may have biased responses toward blastomycosis (DJB) or influenza or anthrax (JLT).

De-identified vignettes were selected from a case series of blastomycosis from eastern Wisconsin. The case series was a continuation of a recently published study[12] that used the same methods. The cases (Table 1) were chosen to represent the variety of patient presentations, ages, and geographic areas of exposure in the case series. The demographic, geographic, clinical, laboratory, and radiologic data were those obtained and considered at the time of each presentation, according to the medical record. Patients with the case illnesses were initially examined between January and August 2009. The only information excluded was the clinician impressions and the nature and result of the definitive diagnostic test. A summary of the 8 case vignettes is included in Table 1; details are available at www.wmjonline.org/_WMS/publications/wmj/pdf/110/2/68vignettes.pdf. For each case, respondents were asked to write down their 3 most likely diagnoses, in order, based on their experience and the clinical vignette. Similar methods have been used by one of the principal investigators to study the differential diagnosis of anthrax.[13]

Diagnostic responses were coded by one of the physician authors (DJB) into 1 of 11 categories (Table 2). Counties of respondent practice location and case vignette residence and exposure were placed into 5 ranked categories based on blastomycosis incidence rates as published for 1999 - 2003 by the Wisconsin Division of Public Health.[14] MINITAB statistical software (State College, Penn) was used for data analysis. Categorical data was analyzed using chi-square tests, or Fisher exact test, as appropriate. Multivariate analysis was performed using binary logistic regression models.

For Aurora Health Care, Marshfield Clinic Research Foundation, and University of Wisconsin, the project was reviewed and approved by the Wisconsin IRB Consortium. The project was exempted from oversight by the Gundersen Lutheran Medical Foundation review board.

Results

The survey had an 11% response rate, with 227 case vignette surveys returned by 114 physicians. Sixty-six percent were male (compared to 63% in the survey mailing, $P = 0.7$), and included 147 (65%) family medicine, 63 (28%) general internal medicine, 9 (4%) internal medicine/pediatrics and 6 (3%) hospitalist physicians (1 physician did not identify specialty). Thirteen percent of respondents had been in practice less than 5 years, 11% for 5 to 10 years, 31% for 11 to 20 years and 46% for 21 years or more.

Respondent practice locations included 30 of the 72 Wisconsin counties. Survey responses, by county, could not be compared to the mailing distribution due to extensive use of non-clinic addresses. However, survey response by county of practice regarding blastomycosis incidence rate categories 1 - 5, as listed in Table 1, is similar to the population distribution (US Census 2006 estimate) of counties in these categories, respectively (3%/10%/4%/75%/8% vs 1%/9%/5%/73%/13%, $P = 0.7$, actual vs expected).

Overall, blastomycosis was listed as the most likely diagnosis for 37/227 (16%) case vignettes, and 1 of the 3 most likely diagnoses for 43/227 (19%). There was, however, considerable variation in accuracy of diagnosis between vignettes (Table 1) and between respondents. Vignettes 1 and 2 that described patient residence or exposure within 1 of the 20 counties with higher annual incidence rates (> 2/100,000) of blastomycosis[14] much more commonly included blastomycosis as 1 of the 3 most likely diagnoses (28/61 [46%] vs 15/166 [9%] for counties with annual incidence rates < 2/100,000; $P = 0.001$). Physicians with practice locations in the higher incidence counties listed blastomycosis more commonly as a potential diagnosis than did those from other counties (16/36 [44%] vs 27/177 [15%]; *P*

< 0.001). Physicians with >20 years in practice were associated with increased blastomycosis diagnosis on univariate analysis (26/103 [25%] vs 17/122 [14%]; $P = 0.05$).

In multivariate analysis with blastomycosis listed in top 3 diagnoses as outcome, and clinician gender, internal medicine vs family medicine specialty, practice > 20 years and practice location in higher incidence county as predictors, practice location was significantly associated with blastomycosis diagnosis ($P < 0.001$) as was internal medicine specialty ($P < 0.04$).

When "blastomycosis" and "fungal pneumonia" were combined, these diagnoses were listed in the top 3 suggested diagnoses for 78/227 (34%) case vignettes; associations with highincidence case and respondent county of exposure or practice, respectively, remained similar to blastomycosis alone (internal medicine specialty was no longer significant). Only 4/227 (2%) respondent vignette results listed both "blastomycosis" and "fungal disease" for the top 3 diagnoses. Responses for 97/227 vignettes (43%) listed either "blastomycosis," "fungal disease," or a specifically named fungus, eg, *Histoplasma* (proposed diagnoses that may have resulted in a blastomycosis diagnosis if a non-specific test such as fungal stain and culture were ordered in actual clinical practice).

When only vignettes 1 and 2 (which together included blastomycosis as 1 of the 3 most likely diagnoses in 28/61 [46%] of cases) are considered, blastomycosis was listed in only 1/10 (10%) instances when these vignettes were paired with each other, compared to 27/51 (53%) instances when vignette 1 or 2 was paired with any of vignettes 3 through 8 ($P < 0.02$). When only vignettes 1 and 2 were considered, blastomycosis was listed as a top 3 diagnosis by 7/10 (70%) physicians from high incidence counties, compared to 21/48 (44%) by physicians from low incidence counties, but this difference was not significant ($P = 0.17$).

Table 1 includes the top 3 listed diagnoses for each scenario. Table 2 summarizes all diagnoses, by category, for all vignettes combined (total suggested diagnoses = 657; some listed fewer than 3).

Discussion

When confronted with masked cases of diagnosed blastomycosis, Wisconsin physicians provided a very wide constellation of diagnoses. Pneumonia, cancers, noninfectious pulmonary disease, and tuberculosis accounted for 69% of diagnoses offered compared to 19% with a fungal diagnosis considered and 6% with blastomycosis specifically listed. Accordingly, the primary care differential diagnosis for blastomycosis is quite broad and diverse, features that are likely to contribute to difficulty in an accurate clinical diagnosis.

The diagnosis of an uncommon infectious disease relies on high clinical suspicion, which can be enhanced through experiential or educational exposure. Low recognition of blastomycosis as seen in our study can contribute to delayed diagnosis and may result in poor outcome, similar to the delayed recognition of inhalational anthrax in 2001.[15]

Clinical clues and experience can contribute to higher recognition. In this study, geographic location played such a role in recognition. This was seen in that vignettes involving patients residing in or with activities in Wisconsin counties with high blastomycosis incidence were significantly more likely to have correct diagnoses than vignettes that detailed other locations. Physicians working in high incidence counties had significantly higher rates of correctly diagnosing blastomycosis than did peers from lower incidence counties. In a study of the differential diagnosis of inhalational anthrax, Lyme disease appeared in the

differential of inhalational anthrax cases of upper Midwest physicians while hantavirus pulmonary syndrome was included by physicians in the 4 corners area of the southwest.[13]

This study was limited by the low rate of response to the survey; however, the gender and geographic distribution of responses appear to be representative of Wisconsin primary care practices, and the number of responses to clinical vignettes yielded a robust differential diagnosis. Nonetheless, the estimate of likelihood of correct diagnosis is suspect. One could surmise that clinicians more interested in pulmonary or infectious disease would be more inclined to respond, which could bias this estimate upward. In addition, specific case scenarios may have biased the differential diagnosis (ie, history of rheumatoid arthritis and sarcoidosis, respectively, in the 3rd and 4th case listed in Table 1). As evidenced by our data, respondents may have been unwilling to name blastomycosis for both case scenarios, disbelieving that both would be the same. Considering that blastomycosis is an uncommon disease with protean manifestations, it is perhaps not surprising to find it infrequently listed as a potential diagnosis in a case vignette when the physician is limited to 3 diagnoses.

Strengths include the broad geographic and demographic representation of respondents and an adequate number of responses per case that facilitates “saturation” of diagnostic possibilities. This study used a master of public health student as the corresponding investigator with the respondents since this limited any bias toward infectious agents that may have resulted if the primary authors had sent the contact letter.

Despite limitations, this study indicates that blastomycosis is frequently not included in the differential diagnosis by clinicians seeing patients with pulmonary disease. Undoubtedly, this is because of the infrequency of blastomycosis among pulmonary diseases, even in Wisconsin. Despite this rarity, blastomycosis should be considered, as it is a curable infection. In addition, if this diagnosis is not considered in a case in which steroid therapy is initiated, catastrophic complications could occur. In absolute numbers, urban-origin cases contribute significantly to the burden of blastomycosis in Wisconsin. For example, while Vilas County[14] has a much higher reported annual incidence rate than Milwaukee County[12] (approximately 38 vs 1/100,000) the much larger Milwaukee County population leads to similar numbers of cases (approximately 9) per year. Despite this, physicians in urban areas are much less likely to correctly diagnose blastomycosis.

Increased awareness of the protean manifestations and complete geographic distribution of pulmonary blastomycosis should increase the frequency with which blastomycosis is properly considered in the differential diagnosis of respiratory illness throughout Wisconsin.

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Appendix. Actual case vignettes sent to surveyed physicians (listed in order of appearance in Table 1)

Case 1

A 42-year-old male presented to urgent care in August with a 1-month history of cough, sore throat, chest congestion and some shortness of breath. A week ago he experienced a syncopal episode due to an intractable cough. Chest x-ray revealed an abnormal opacity near the right cardiac border. A week later his symptoms worsened. His cough persisted, was worse with activity and after waking up in the morning, and was associated with scant phlegm, chest discomfort, tickles in throat, low-grade fever and occasional sweats. A repeat chest x-ray showed an increase in the right lung middle lobe infiltrate. He was started on levofloxacin. Ten days later he returned to urgent care again with complaints of continuous cough, which made it difficult to breathe or laugh, a decrease in activity and appetite. He was fatigued and felt as if something was stuck in his throat. In the past few weeks, he had lost 5 to 6 pounds and had a constant dull chest pain, which was aggravated by coughing.

The patient has never been a smoker and drinks rarely. He had a history of gastroesophageal reflux disease (GERD). He went canoeing and camping in Spooner and Northern Wisconsin around mid-July for a week, and a week or two later developed this cough. He also mentioned inhaling some dust while cleaning his computer. He lives in the Fox Valley and does computer-imaging/editing, and owns a pet snake, dog, and cat.

Physical examination revealed a temperature of 99.4°F, blood pressure of 122/72, pulse 100, respiratory rate 20. Lungs revealed decreased breath sounds in the right axillary area and lower right posterior chest. Bronchophony was detected on the right posterior chest at the bases and in the axillary area on the right.

Case 2

A 31-year-old male presented in May with an 11-week history of worsening cough, left-sided rib and back discomfort. Six weeks into his illness he was seen in the emergency department for left mid-back pain radiating to left axilla, shortness of breath and nonproductive cough. He denied any fevers or chills. A chest x-ray taken at that time revealed a left middle lobe infiltrate. He was given hydro-codone/acetaminophen, oral azithromycin and IM ceftriaxone. A month later his cough was now mostly nonproductive, except in the mornings it appeared brownish. He recently lost approximately 15 pounds of weight, and stated that he normally loses weight in spring when he starts working full-time as a painter. Several weeks prior to becoming ill he was exposed to “pipes with molds” at work. He had a lump on his left cheek and occasionally experienced wheezing and shortness of breath. He denied any nausea, vomiting, diarrhea, chills, fever, skin lesions, and rashes but had night sweats.

He is single and lives with his parents in a small settlement near a river in Manitowoc County. He enjoys fishing and hunting. He had not traveled outside the country but went to Northern Wisconsin in January for bow hunting. Patient admitted to smoking 1 pack per day and drinking alcohol.

Physical examination revealed a temperature of 98.6°F, blood pressure of 104/68, heart rate of 81, pulse oximetry 98% on room air. Lungs had coarse rhonchi noted posteriorly throughout and bronchial vascular sounds were heard over the left mid-zone.

Chest x-ray now revealed consolidation of the superior segment of the lower lobe of the left lung.

Case 3

A 54-year-old morbidly obese woman presented to the emergency department in July with a 3-week history of nonproductive cough, night sweats, shortness of breath, and fatigue. She had a fever which resolved in the first 2 weeks but in the past 4 to 5 days she had increased shortness of breath along with marked swelling in her lower extremities and pain in her knees. She experienced nausea and vomiting with eating. She had a rash on her body, mainly on the torso.

The patient had a history of rheumatoid arthritis (RA) and had undergone cholecystectomy, appendectomy and fibroid surgery in the past. She had been taking prednisone and methotrexate for her RA and was allergic to penicillin. She had a greater than 10 packs per year smoking history but had quit smoking. She denied any alcohol and drug use. She lived in a house in a subdivision in Racine.

Physical examination revealed a temperature of 101°F, blood pressure 125/59, pulse of 110-120, and respirations of 20-30. She was profoundly hypoxic, saturation range 60%. Bilaterally diffuse rhonchi and tubular breath sounds were detected. There were erythematous pustules and lesions on her face, forehead, legs, and nares, and an indurated abscess on her back. She had 2+ pitting edema in her lower extremities.

Laboratory data included WBC count of 20,000 (absolute neutrophils 19,000), sedimentation rate 48, hemoglobin 11.0, platelets 537,000, sodium 138, potassium 5.4, CO2 24, BUN 25 and creatinine 0.8. Liver function test revealed elevated alkaline phosphatase level of 224, AST 220, ALT 66, myoglobin 102, C-reactive protein 1.6, and lactic acid levels of 5.6. Chest x-ray revealed bilateral fluffy infiltrates, right greater than left. Large bacteria were found in the urine.

Additional case vignettes are available online at www.wmjonline.org/_WMS/publications/wmj/pdf/110/2/68vignettes.pdf.

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Table 1

summary of Descriptions of Blastomycosis Case Vignettes, Percentage of Respondent Wisconsin Primary Care Physicians Diagnosing Blastomycosis, and Top 3 Diagnoses suggested for each Vignette

Patient Characteristics							
Age	**Gender**	**County of Residence[a]**	**Other Counties Visited[a]**	**Case Scenario in Brief**	**Blastomycosis Clinical Category[b]**	**Respondents Diagnosing Blastomycosis[c]**	**Top 3 Diagnoses**
42	M	"Fox Valley" (1-4)	Washburn (3) "northern Wisconsin" (1-4)	1 month cough, sore throat, dyspnea, chest congestion, low-grade fever, weight loss; RML infiltrate; computer technician; camping, canoeing and pets	2	13/26 (50%)	Pneumonia, cancer, blastomycosis
31	M	Manitowoc (4)	"Northern Wisconsin" (1-4)	11 weeks of cough and rib/back pain, weight loss, no fever; smoker; painter; mold exposure; hunting and fishing; LLL consolidation	4	15/35 (43%)	Pneumonia, blastomycosis, "fungal"
54	F	Racine (4)	None mentioned	3 weeks of cough, febrile, night sweats, dyspnea, fatigue; obesity; rheumatoid arthritis on prednisone/methotrexate; unemployed; became hypoxemic, had signs of ARDs	3	3/25 (12%)	Pneumonia; noninfectious, nonmalignant pulmonary process; complication of non pulmonary disease
56	M	Milwaukee (4)	None mentioned	Skin lesions and progressive dyspnea, cough, chills, weight loss; no fever; history of sarcoidosis; truck driver, no recent outdoor activities; LuL mass, mediastinal adenopathy	4, D	2/26 (8%)	Noninfectious, nonmalignant pulmonary process; cancer; pneumonia
31	M	Kewaunee (5)	None mentioned	2-3 weeks of cough, hemoptysis, dyspnea, chest/ back discomfort, fatigue, weight loss; works outdoors as welder; fume exposure; LML/LLL infiltrates	2	5/36 (14%)	Pneumonia; cancer; noninfectious, nonmalignant pulmonary process
29	M	Milwaukee (4)	None mentioned	Pleuritic chest, back and scapular pain, productive cough, night sweats; afebrile; machine tool and steel fabricator; LuL mass	4	2/25 (8%)	Cancer, pneumonia, tuberculosis/mycobacterium
48	M	Kenosha (4)	None mentioned	2 months of cough, low-grade fever, chest congestion, weight loss; then night sweats, chills, hemoptysis; engineer, works indoors; lung abscess, pulmonic process and hemoptysis	4	3/31 (10%)	Pneumonia. tuberculosis/mycobacterium. cancer
47	M	Milwaukee (4)	None mentioned	4 days of dyspnea, cough; diabetes, hypertension, hyperlipidemia; computer technician; bilateral lung infiltrates, increased pulmonary vascular congestion with normal heart size	3	0/23 (0%)	Cardiac disease; pneumonia; noninfectious, nonmalignant pulmonary process

Abbreviations: LUL, left upper lobe; LML, left middle lobe; LLL, left lower lobe; RML, right middle lobe; ARDS, acute respiratory distress syndrome

[a] Categories of county specific mean annual reported blastomyosis incidence per 100,000 population adapted from reference 14: Category 1 county incidence is > 20 cases/100,000 population; category 2 is > 5 to 20; category 3 is > 2 to 5; category 4 is <2; category 5 is no cases.

[b] Clinical category of blastomycosis corresponding to illness presented in the vignette. Blastomycosis clinical categories: category 1 – Asymptomatic (no vignettes sent in this category); category 2 – Acute localized pneumonia; category 3 – ARDS; category 4 – Subacute to chronic infiltrate and/or cavitary disease; D – Dissemination from lungs to other organs, bone, or skin.

[c] Number of respondents who included blastomycosis as a diagnosis for this vignette divided by the number of reviews of this vignette (%).

Table 2

Differential Diagnosis of Pulmonary Blastomycosis Based on the 3 Diagnoses Provided by Respondent Wisconsin Primary Care Physicians for each of the 227 Reviews of Clinical Vignettes

Disease category	Number of respondent diagnoses
Pneumonia	186
Viral etiology listed	4
Cancer	108
Noninfectious pulmonary	83
Sarcoidosis	28
Hypersensitivity/autoimmune	11
Tuberculosis/mycobacteria	78
Blastomycosis	43
Other specific fungal/fungal-like	42
Aspergillosis	15
Histoplasmosis	11
Pneumocystis	6
“Fungal disease”	39
Cardiac disease	33
Congestive heart failure	14
Complication of systemic process	19
Sepsis	12
Trauma/toxin	14
Pulmonary embolism	13

Total suggested diagnoses = 657.

Diagnoses are grouped into 11 disease categories.