ORIGINAL RESEARCH

Symptoms of Pulmonary Blastomycosis: Northern Wisconsin, United States

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Objective.—Pulmonary disease is the most common manifestation of the systemic fungal infection, blastomycosis. This study examines symptoms of pulmonary blastomycosis and possible age and gender differences in a 22-year case series.

Methods.—Laboratory-confirmed cases of blastomycosis were identified from mandatory reports to the Vilas County Health Department (1984–2001) and from hospital records and case contacts before mandated reports (November 1979–1983). Symptoms were ascertained by interviews of respondent cases (or next of kin) by using a standard form. Proportions were compared with the chi-square test or Fisher exact test.

Results.—One hundred seventy cases of blastomycosis (mean age 44, 56% male) were identified and pulmonary manifestations were present in 154 (91%). Of the 118 interviewed cases, the following symptoms were common: cough (90%), fever (75%), night sweats (68%), weight loss (66%), chest pain (63%), dyspnea (54%), and aches (50%). Hemoptysis occurred in 18%, and nearly all queried patients had fatigue. The dyad of cough and fever occurred in 73%, and triads of fever–cough–night sweats, fever–cough–weight loss, and fever–cough–chest pain occurred in 58%, 57%, and 51%, respectively. Among men, fever ($P = .03$), cough and fever ($P = .03$), fever–cough–weight loss ($P = .03$), and fever–cough–night sweats ($P = .03$) were less common in those 50 years of age and older. Symptoms did not vary by duration of illness.

Conclusions.—Cough, fever, night sweats, weight loss, chest pain, dyspnea, and aches are common symptoms of pulmonary blastomycosis. Symptom constellations that included fever were less common in men 50 years of age and older. There was no apparent difference in symptoms between acute and chronic blastomycosis.

Key words: blastomycosis, lung infections, mycoses

Introduction

Blastomycosis, caused by the dimorphic fungus *Blastomyces dermatitidis*, is a potentially fatal systemic and cutaneous infection of humans, dogs, and other animals.^{1–3} It is endemic in an expanding region of eastern North America and parts of India and Africa. The precise environmental niche of *B dermatitidis* is unknown but is thought to occur near or in soil.^{4,5} The few en-

vironmental isolations have occurred at sites typically involving decaying wood, other organic materials, and animal excrements.⁶ Risk factors for disease acquisition include exposure to highly endemic areas near waterways and excavation but generally not specific outdoor occupations or activities.^{4,7–15} Except for rare inoculation cases,¹⁶ disease follows inhalation of infectious *B dermatitidis* conidia released by the fungus, presumably after mechanical disruption of the soil or other organic material or by moisture, sometimes as part of a point-source outbreak.^{17–24} Thus, the lungs are the portals of entry in nearly all infections. The resulting pulmonary disease may be asymptomatic or take the form of a mild to moderate pneumonia or a fulminating, life-threatening illness including the adult respiratory distress syndrome.^{3,25} Dissemination of the fungus from the lungs

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may affect any organ system, and the disease may be particularly devastating in patients who are immunocompromised.^{2,26,27} Older case series and reviews indicate an approximately equal distribution of pulmonary and skin disease. Bone or joint, central nervous system, and prostate involvement^{28–30} are less common. Our 1992 report⁹ and those subsequent to it^{10,14,31–34} document a predominance of pulmonary manifestations. This is presumably because of earlier diagnosis and effective treatment of lung disease (before dissemination) and proper diagnosis of mild cases, which may have been previously undetected.

Current textbooks^{2,35,36} differentiate acute from chronic pneumonia of blastomycosis. Fever, cough, myalgias, and chest pain^{2,35,37} are considered typical symptoms of acute infection; cough, weight loss,^{2,35,36} chest pain, and sometimes fever^{2,35,37} and hemoptysis are typical symptoms of chronic pneumonia. Symptom constellations and gender differences in symptomatology have not been reported. Our original case series⁹ and follow-up¹⁰ are inadequately powered to explore issues of gender or symptom duration. We report a 22-year series of blastomycosis cases from highly endemic northern Wisconsin, United States, and explore possible age and gender differences in pulmonary symptomatology and the delineation of acute vs chronic pulmonary syndromes.

Methods

A retrospective review was performed on 170 cases of blastomycosis to evaluate for the presence of pulmonary symptoms. All cases were laboratory confirmed by culture, direct microscopy, or histologic evidence of *B dermatitidis*, and all cases occurred in residents or seasonal visitors to Vilas County or adjacent counties in northern Wisconsin in the years 1979–2001. One hundred twenty cases had been included in 2 previously published case series (1979–1990⁹ and 1991–1996¹⁰) that focused on epidemiological aspects of the disease. Aggregate data on 7 single pulmonary symptoms were presented in the first paper,⁹ and pulmonary symptomatology was not reported in the second.¹⁰ Records from 50 additional cases from the years 1997–2001 were also reviewed. Altogether, these cases represent all state-mandated blastomycosis disease reports to the Vilas County Health Department from the onset of mandatory reporting in 1984 through 2001. In addition, before 1991, case findings had also occurred through the 3 Vilas County hospitals and patient interviews. These case records were also filed at the Health Department. Mandatory reports were found to capture 96% of county residents with blastomycosis^{9,10} and were therefore used as the sole source

of case identification for the period 1992–2001. This study was done in conjunction with the Vilas County Health Department. This investigation was considered by the Aurora Health Care human subjects committee to be exempt from review, and written informed consent was not required.

After case identification, all available patients (or next of kin, if deceased or unable to be interviewed) were contacted by telephone for telephone or in-person interviews by one of the authors (D.J.B. or G.E.) or a health department nurse. A standardized questionnaire was used as previously reported.^{9,10} Interviews from 1988 to 2001 were conducted as soon as possible after diagnosis (1 day–6 months). Cases before 1988 were interviewed in 1989. To maximize recall consistency in the older cases, all 24 interviewed patients were interviewed personally by the first author, and medical records were obtained and used to confirm reported symptoms for 20 of 24 patients. These 24 cases were included in the analysis because they were similar to those cases from 1988 to 2001 regarding gender, mean age ($P > .5$), and 4 of 8 queried symptoms (weight loss, night sweats, dyspnea, and myalgias were reported less often). Data were entered into an Excel spreadsheet and tabulated. Symptom duration was calculated from the onset of the first symptom until the day of diagnosis and treatment (if any). Proportions were compared with the χ^2 test with Yates correction or Fisher exact test by using Epi-Info software. P values less than .05 were considered significant.

Results

One hundred seventy cases of blastomycosis (mean age 44 years, range 3–86 years, 56% male) related to Vilas County, WI, were identified over the 22-year period of this report. Pulmonary manifestations occurred in 154 cases (91%), of which 118 were available for interview. The mean age of the interviewed population was 43 years (SD = 18; female, 45 years, SD = 17; male, 42 years, SD = 19), and 63 (53%) were male (parameters not significantly different from the total series or all pulmonary cases).

Among the 118 interviewed patients, cough (90%) was the most common symptom among patients with pulmonary blastomycosis, followed by fever (75%), night sweats (68%), weight loss (68%), chest pain (63%), dyspnea (54%), aches or myalgias (50%), and hemoptysis (18%). The most recent 66 patients were queried regarding fatigue, which was present in 63 cases (95%). Among single pulmonary symptoms, no significant differences were found between genders (Figure 1). Similarly, no differences were noted in age, or age and gender combined, for symptoms of cough, night sweats,

Figure 1. Pulmonary symptoms of blastomycosis, by gender.

weight loss, chest pain, dyspnea, aches, or hemoptysis. Fever was less common (64% vs 83%, $P = .03$) among patients 50 years of age and older when compared with younger patients. There was also a difference in fever (57% vs 85%, $P = .03$) among men 50 years of age and older when compared with younger males. No significant difference was found in fever (71% vs 82%, $P = .58$) among women 50 years of age and older when compared with younger females.

The symptom dyad of cough and fever occurred in 73% of all cases. The triads of fever–cough–night sweats (58%), fever–cough–weight loss (57%), and fever–cough–chest pain (51%) were less common. Among males, 3 symptom constellations were less common in those 50 years of age and older: cough–fever (52% vs 82%, $P = .03$), cough–fever–night sweats (35% vs 67%, $P = 0.03$), and cough–fever–weight loss (35% vs 67%, $P = 0.03$). No significant age differences were seen in the prevalence of these constellations among women.

Information on symptom duration was available for 109 of the cases. The overall mean duration of symptoms was 6.2 weeks (median = 4, SD = 7). The distribution of pulmonary blastomycosis cases by weeks of

total symptom duration is shown in Figure 2. No significant differences were found in mean or median symptom duration by gender or age. There were also no significant differences in pulmonary symptom prevalence in cases of longer or shorter total symptom duration. This was true at various weekly time intervals (data not shown). Regarding the potential acute symptom triad of cough–fever–chest pain,^{2,35,37} the mean and median symptom duration in patients with this triad (5.8 weeks and 4 weeks, respectively) and without this triad (6.6 weeks and 4 weeks, respectively) did not differ. Overall, no characteristic features of acute vs chronic pulmonary blastomycosis were found when looking at age, gender, symptoms, or symptom duration.

Discussion

Pulmonary manifestations occurred in 91% of patients in this large case series. This proportion of pulmonary cases agrees quite well with other recent case series (Table).^{14,31–33} No single symptom was universally present in all cases of pulmonary blastomycosis; however, cough was a predominant symptom in recent reports (Table).

Figure 2. Distribution of pulmonary blastomycosis cases by symptom duration.

Differences in symptom percentages, where present, likely reflect differences in data collection or degree of overall case severity caused by differences in case sources among the studies. One study identified cases from all Manitoba hospitals³³ and the other 3 from selected hospitals and laboratories.^{14,31,32}

Symptom constellations did not present in more than three quarters of pulmonary cases of this disease. Cough and fever occurred in 73%, but symptom triads occurred approximately half of the time or less. Therefore, no pathognomonic symptom constellation appears to exist for this disease. In fact, blastomycosis presents in a fashion similar to many community and occupationally acquired pulmonary processes^{2,3,34} and also manifests a variety of chest radiologic findings that mimic other bacterial and fungal pneumonias.³⁸ In a tertiary hospital-based study,³⁴ for example, only 18% of 123 patients with blastomycosis had their illness correctly suspected at the time of presentation. Other pneumonias (40%),

malignancies (16%), and tuberculosis (14%) were the most common misdiagnoses. In the 78 pulmonary-only cases, only 5% were correctly diagnosed at presentation. Symptoms of pulmonary blastomycosis are heterogeneous and difficult to discern from other illnesses in children as well as in adults³⁹ and may be potentially difficult to confirm.⁴⁰ Even in endemic areas with a higher rate of physician awareness of blastomycosis, a delay in diagnosis is common. In the study by Chapman et al,¹⁴ for example, 43% of cases required more than 1 month for diagnosis.

Diagnosis should also not depend on residence in a known endemic area, because this disease is acquired in previously nonendemic areas.⁴¹ Laboratory diagnosis is generally successful if a quality sputum, lesion drainage, or tissue sample is obtained; however, rapid diagnosis by direct microscopy of wet preparations is less sensitive (49%) than cytology (69%) when both are compared with the standard—fungal culture.¹⁴

Blastomycosis: pulmonary symptoms in recent studies

	<i>Chapman et al,¹⁴ Mississippi</i>	<i>Vasquez et al,³¹ northeast Tennessee</i>	<i>Dwight et al,³² Kenora, Ontario, Canada</i>	<i>Crampton et al,³³ Manitoba, Canada</i>	<i>Current Study, Vilas County, WI</i>
Year reported	1997	1998	2000	2002	2004
N	326*	61	61*	143*	118
Pulmonary, %	91	85	...	93	91
Cough, %	73	75	93	67	90
Fatigue, %	...	...	82	...	95
Dyspnea, %	38	46	77	38	54
Fever, %	54	49	73	50	75
Weight loss, %	37	57	68	36	66
Chest pain, %	41	31	58	37	63
Night sweats, %	31	26	68	32	68
Hemoptysis, %	23	23	...	17	18
Asymptomatic, %	...	...	...	9	2
Mean age, y*	46	52	42	38	44
Male, %*	64	69	53	65	56

*All cases (pulmonary cases not segregated).

Overall, the presence or absence of underlying disease is not a helpful diagnostic clue for blastomycosis. Lemos et al³⁴ found a disproportionate percentage of immunodepression and underlying disease in the series of 123 patients; however, this is likely explained by their case finding in a tertiary-hospital setting. Our previous study⁹ and that of Chapman et al,¹⁴ which include additional nonhospital sources of case identification, revealed rates of underlying comorbidities similar to the general population.

This study also suggests that older individuals are less likely to report fever as part of their symptom constellation and that men 50 years of age and older report comparatively fewer febrile symptom constellations with pulmonary blastomycosis. Particular care must be taken to include pulmonary blastomycosis in the differential diagnosis of older men with exposure to an endemic area.

We found no clear delineation between acute and chronic or indolent pulmonary blastomycosis based on individual symptoms, symptom constellations, or symptom duration. Davies and Sarosi³ divide the clinical presentations of pulmonary blastomycosis into the following: 1) asymptomatic disease; 2) brief, self-limited flu-like illness, likely rarely diagnosed outside of outbreaks; 3) acute illness (high fever, productive cough, pleuritic chest pain); 4) subacute or chronic illness (low-grade fever, productive or chronic cough, night sweats, weight loss); and 5) fulminant infectious adult respiratory distress syndrome. Our study does not refute this useful classification scheme, but it does suggest a less distinct

gradation between acute and subacute or chronic pulmonary disease.

Limitations of this study include the retrospective design. In addition, information on symptom duration was obtained for only the total duration of any symptomatology rather than the duration of each specific symptom. Such specific information may have allowed a better differentiation of acute vs chronic forms of pulmonary blastomycosis; however, it is striking that the symptom profile of these cases did not vary significantly over a wide distribution of illness durations. A significant strength of our study is case findings based on mandatory reports from physicians and laboratories in addition to hospitals, which resulted in data from a spectrum of outpatient and inpatient illnesses likely most reflective of the spectrum of the natural history of blastomycosis.

Clinicians should be aware that the geographic area endemic for blastomycosis is expanding.^{33,41} Risk factors include exposure to waterways and moist environments,^{4,5,8,12,13,17} soil-disturbing activities,^{8,19-24} and exposure to animal droppings or burrows.^{4,6,7,22,41} Alternatively, the disease may occur in healthy persons without significant outdoor exposure^{1-3,9,10,15} or after a period of drought.²⁴ Individuals exposed to soil-disturbing or other high-risk activities in areas endemic for blastomycosis may be partially protected by use of N-95 respirator masks and protective covering⁴¹; however, this has not been studied. Patients with blastomycosis frequently present to primary care providers. An awareness of this disease and its nonspecific clinical features is important for timely diagnosis.

Conclusion

Cough, fever, night sweats, weight loss, chest pain, and, to a lesser extent, dyspnea and myalgias are common symptoms of pulmonary blastomycosis. Symptom constellations are also sometimes manifested. Overall, this is a heterogenous disease with respect to symptomatology, severity, and duration of symptoms at time of diagnosis. It may be confused with a variety of infectious, malignant, and inflammatory processes. Including blastomycosis in the differential diagnosis of pulmonary symptoms and having a higher index of suspicion leading to appropriate testing are the keys to proper diagnosis.

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