Epidemiology and Clinical Spectrum of Blastomycosis Diagnosed at Manitoba Hospitals

Tracy L. Crampton, R. Bruce Light, Greg M. Berg, Michael P. Meyers, Gary C. Schroeder, Earl S. Hershfield, and John M. Embil

Departments of Medicine, Radiology, and Radiation Oncology, and Sections of Infectious Diseases and Respiratory Medicine, Department of Medicine, University of Manitoba, Winnipeg, Canada

Blastomyces dermatitidis is a dimorphic fungus endemic to Canada and the United States. Few reports regarding blastomycosis in Canada have been published. We retrospectively reviewed the medical charts of 143 patients with confirmed cases of blastomycosis diagnosed in hospitals in Manitoba, Canada, from 1988 through 1999. The annual incidence rate of blastomycosis in Manitoba was 0.62 cases per 100,000 population, compared with 7.11 cases per 100,000 population in the Kenora, Ontario district. The average age of patients was 38.0 years, and males accounted for 65.0% of cases. An increased incidence of blastomycosis was observed in the Aboriginal subpopulation. Organ systems involved were as follows: respiratory system (93.0% of cases), skin (21.0%), bone (13.3%), genitourinary tract (1.4%), and the central nervous system (1.4%); 6.3% of patients died, and death was associated with a short clinical course. This study provides a summary of the current status of blastomycosis in this area of endemicity in Canada.

Blastomycosis is an uncommon granulomatous infection caused by the thermally dimorphic fungus Blastomyces dermatitidis which exists in a mycelial form in the soil of warm, moist, wooded areas that are rich in organic debris [1–6]. When mycelia are disturbed, conidia are inhaled and, at body temperature, convert to thick-walled budding yeast [7, 8]. Hematogenous dissemination may result in extrapulmonary blastomycosis. Cases of primary cutaneous blastomycosis have been reported [9].

Determination of the incidence and epidemiology of blastomycosis has been hindered by the difficulty of isolating B. dermatitidis from natural reservoirs and by the lack of a sensitive and specific skin or serologic test to confirm infection or exposure [10]. Molecular epidemiological studies of B. dermatitidis isolates have shown that isolates from Canada and the upper midwestern United States are genetically related [11]. Cases of blastomycosis are currently classified as reportable diseases in Wisconsin (since 1984) [12], and in Manitoba and northwestern Ontario (since 1 June 2000). Blastomycosis was reportable in Ontario until 1989, when it was removed from the reportable diseases list. Study of sporadic cases and outbreaks indicates that the area of endemicity for B. dermatitidis in North America includes the Ohio and Mississippi River basins as well as the Canadian provinces and American states that border the Great Lakes [13]. Studies performed during outbreaks indicate that infection occurs in a high percentage of persons exposed, but symptomatic disease occurs in <50%; the median incubation period ranges from 30 to 45 days [14, 15]. In persons who develop...
symptomatic disease, the clinical presentations are diverse, including pulmonary and extrapulmonary manifestations. Pulmonary disease can be acute or chronic, and dissemination most commonly involves skin, bone, and the genitourinary system [15].

There have been few reports from Canadian regions of endemicity; the majority of data are from Ontario and Quebec [5, 16–21]. Cases have been reported in New Brunswick [18, 22, 23], Nova Scotia [18, 24], Saskatchewan [25], and Alberta [19]. The 3 reports regarding blastomycosis in Manitoba and northern Ontario include a review of 36 cases that occurred in 1960–1970 [16], a review of 15 cases that occurred in 1992–1994 [18], and, most recently, a 16-month retrospective study summarizing 61 cases that occurred in the Kenora, Ontario, catchment region [17]. Current data regarding the status of blastomycosis in Manitoba are lacking.

The objectives of this study were (1) to define the epidemiology and clinical spectrum of blastomycosis in patients who presented at hospitals in Manitoba and (2) to determine whether there are differences in the demographic characteristics of and epidemiology associated with Aboriginal and non-Aboriginal patients who have received a diagnosis of blastomycosis.

METHODS

We retrospectively reviewed the medical charts of patients with confirmed cases of blastomycosis that were diagnosed at Manitoba hospitals with >200 beds during the 12-year period from 1 January 1988 through December 31, 1999. A patient with a confirmed case of blastomycosis was defined as a patient with a clinically compatible illness (e.g., subacute pneumonia or characteristic skin lesions) from whom B. dermatitidis was isolated by culture or visualized (as a characteristic broad-based budding yeast) in a clinical specimen [12].

From each patient’s chart, we abstracted the following data: demographic characteristics, occupation (classified into 23 categories using a modified Standard Occupation Classification system [26]), hospital of admission, date of symptom onset, date of diagnosis, clinical features, patterns observed on chest radiograph obtained at the time of admission to the hospital, therapy administered, and outcome. Population characteristics, according to census divisions (i.e., districts used in the census) and demographic classifications for Manitoba and Ontario, were obtained from Statistics Canada [27]. We used the term “Aboriginal” to refer to the indigenous inhabitants of Canada; it includes the Aboriginal and Metis people, without regard to their separate origins and political or cultural identities [28]. Approval for this study was granted by the Research Ethics Board, Faculty of Medicine, University of Manitoba (Winnipeg); the ethics review boards of the specific facilities where records were reviewed; and the Access and Confidentiality Committee of Manitoba Health.

RESULTS

Distribution of case patients. During the 12-year period from 1988 through 1999, B. dermatitidis was isolated from or visualized in clinical specimens from 161 patients. Of these 161 patients, 5 were evaluated at Manitoba hospitals with <200 beds, and the records of 13 could not be located; therefore, 143 patients with confirmed cases of blastomycosis had their records identified and reviewed. The mean number of cases (±SD) diagnosed per year was 11.9 ± 3.9 (range, 7–18 cases). The number of cases diagnosed had a cyclical pattern, peaking in 1990, 1992, and 1996, and increasing again in 1999. Cases of blastomycosis were diagnosed and patients became symptomatic in all months of the year; a slightly higher proportion of patients became symptomatic from October through March (59.3% of patients).

Of the 143 patients with confirmed cases, 84 (58.7%) were residents of Manitoba and 59 (41.3%) were residents of Ontario. A travel history was available for only 57 (67.9%) of 84 patients from Manitoba; 23 (40.4%) of these 57 had a history of travel to northwestern Ontario. The mean annual incidence (±SD) of blastomycosis for patients residing in Manitoba was 0.62 ± 0.25 cases per 100,000 population (range, 0.26–1.00 cases per 100,000). The annual incidence per 100,000 population was specified for Statistics Canada census divisions in Manitoba and for the 3 Ontario census divisions (the Kenora, Rainy River, and Thunder Bay districts) in which the patients who were evaluated at a Winnipeg or Brandon facility resided (figure 1). At least 1 case of blastomycosis was identified in 18 of the 23 Manitoba census divisions. The highest annual incidence rates were reported among patients residing in the southern half of Manitoba, with the exception of the southeastern section. The incidence rate for the Kenora district (7.11 cases per 100,000 population) was the highest for all the districts in both Manitoba and Ontario.

Demographic characteristics of patients. The mean age (±SD) of the 143 patients at the time of diagnosis was 38.0 ± 19.9 (range, 0–79) years. No difference was observed in the mean age at the time of presentation for residents of Ontario (37.3 ± 20.7 years) and Manitoba (38.4 ± 19.4 years; P = .727). Cases were identified that occurred in all decades included in the study (table 1). The highest percentage of cases in the Kenora, Rainy River, and Thunder Bay districts occurred in patients aged 30–39 years (18.6% of cases), whereas, in Manitoba, the highest percentage occurred in patients aged 20–29 years (17.9% of cases). The highest incidence rates for patients from Manitoba and from the Kenora, Rainy River, and Thunder Bay districts of Ontario occurred among those aged 50–59 years (Manitoba, 0.96 cases per 100,000 population; Ontario, 2.91 cases per 100,000 population) and 60–69 years (Manitoba, 0.87 cases per 100,000 population; Ontario, 3.07 cases per 100,000 population).

Overall, 93 case patients (65.0%) were male. A difference in
the sex distribution was not observed between patients in Ontario (61.0% male) and Manitoba (68.0% male; \( P = .396 \)). The annual incidence among male residents of Manitoba was 0.87 cases per 100,000 population; among female residents, it was 0.40 cases per 100,000 population. The annual incidence among male residents of the Kenora, Rainy River, and Thunder Bay districts was 2.46 cases per 100,000 population; among female residents, it was 1.57 cases per 100,000 population. The mean age (±SD) of male patients at presentation (40.2 ± 19.8 years) did not differ from that of female patients (33.7 ± 19.6 years; \( P = .061 \)).

Race was specified for 122 case patients (85.3%); the highest percentage of patients were white (72 patients [59.0%]; table 2). Forty-three cases (35.2%) occurred in Aboriginal patients and 7 cases (5.7%) in patients of another race. For residents of Ontario, race was specified for 48 of the 59 case patients (81.4%). Thirty-one patients (64.6%) were Aboriginal, 16 patients (33.3%) were white, and 1 patient (2.1%) was of another race. Information on race was available for 74 (88.1%) of the 84 Manitoba patients. Fifty-six (75.7%) patients were white, 12 patients (16.2%) were Aboriginal, and 6 patients (8.1%) were of another nationality. Grouping together patients who were white or of another race as "non-Aboriginal" patients revealed that a significantly higher proportion of patients from Ontario were of Aboriginal origin, compared with patients from Manitoba \( (P < .0001) \). The annual incidence of blastomycosis in the Aboriginal population of Manitoba was 0.78 cases per 100,000 population, compared with 0.53 cases per 100,000 population in the non-Aboriginal population. In the Kenora, Rainy River, and Thunder Bay districts, the annual incidence of blastomycosis in the Aboriginal population was 7.42 cases per 100,000 population, compared with 0.68 cases per 100,000 population in the non-Aboriginal population. The mean age at presentation for the Aboriginal population (31.6 ± 20.5 years) was significantly younger than it was for the non-Aboriginal population (41.2 ± 19.2 years; \( P = .012 \)). Annual incidence per decade of life could not be calculated for the Aboriginal and non-Aboriginal populations, because demographic data classified according to decade of life were unavailable. A difference was not observed in the sex ratio of the patients in the Aboriginal population (56 males [70.9%]) and the non-Aboriginal population (26 males [60.5%]; \( P = .477 \)).

Information on occupation was available for 138 patients (96.5%). Outdoor occupations were noted for 18 patients (13.0%); construction had the greatest representation (8 patients [5.8%]). Job-specific incidences could not be calculated,
Table 1. Age distribution, by decade of life, of patients with blastomycosis who were residents of Ontario or Manitoba and the corresponding annual incidence.

<table>
<thead>
<tr>
<th>Patient age range, years</th>
<th>Total no. (%) of patients (n = 143)</th>
<th>Ontario residents with blastomycosis (n = 59)</th>
<th>Manitoba residents with blastomycosis (n = 84)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>Annual incidence&lt;sup&gt;a&lt;/sup,b</td>
<td>No. (%)</td>
</tr>
<tr>
<td>0–9</td>
<td>12 (8.4)</td>
<td>7 (11.9)</td>
<td>1.64</td>
</tr>
<tr>
<td>10–19</td>
<td>20 (14.0)</td>
<td>8 (13.6)</td>
<td>1.85</td>
</tr>
<tr>
<td>20–29</td>
<td>20 (14.0)</td>
<td>5 (8.5)</td>
<td>2.26</td>
</tr>
<tr>
<td>30–39</td>
<td>24 (16.8)</td>
<td>11 (18.6)</td>
<td>2.32</td>
</tr>
<tr>
<td>40–49</td>
<td>23 (16.1)</td>
<td>10 (16.9)</td>
<td>2.91</td>
</tr>
<tr>
<td>50–59</td>
<td>20 (14.0)</td>
<td>8 (13.6)</td>
<td>3.07</td>
</tr>
<tr>
<td>60–69</td>
<td>16 (11.2)</td>
<td>7 (11.9)</td>
<td>3.07</td>
</tr>
<tr>
<td>70–79</td>
<td>8 (5.6)</td>
<td>3 (5.1)</td>
<td>1.78</td>
</tr>
</tbody>
</table>

<sup>a</sup> Per 100,000 population.

<sup>b</sup> Patients from the Kenora, Rainy River, and Thunder Bay, Ontario census divisions.

because this demographic information was unavailable. There was no association between being Aboriginal and having an outdoor occupation (P = .4980).

**Clinical characteristics.** A total of 133 patients (93.0%) had lung involvement, 30 patients (21.0%) had skin involvement, 19 patients (13.3%) had bone involvement, 2 patients (1.4%) had genitourinary system involvement, and 2 patients (1.4%) had CNS involvement. Pulmonary disease was an isolated finding in 100 (69.9%) of the 143 patients. Extrapulmonary disease was observed in 43 patients (30.1%); in 33 patients (23.1%) it occurred in conjunction with lung involvement, and, in 10 patients (7.0%), it occurred in isolation. In 35 patients (81.4%) with extrapulmonary involvement, multiple-organ disease was present.

Thirteen patients (9.1%) were asymptomatic. In symptomatic patients, the presenting symptoms reflected the high rate of occurrence of pulmonary involvement with cough (in 96 patients [73.8%]), sputum production (in 56 patients [43.1%]), chest pain (in 53 patients [40.8%]), dyspnea (in 54 patients [41.5%]), and hemoptysis (in 25 patients [19.2%]). The most frequently noted systemic manifestations were fever (in 72 patients [55.4%]), weight loss (in 51 patients [39.2%]), and night sweats (in 46 patients [35.4%]).

Sixty-seven patients (46.9%) had underlying medical conditions; the most commonly encountered conditions were diabetes mellitus (in 15 patients [10.5%]), hypertension (in 13 patients [9.1%]), asthma (in 12 patients [8.4%]), and heart disease (in 11 patients [7.7%]). Two patients (1.4%) infected with HIV were identified. One of the patients was pregnant and her fetus was presumably affected via maternal-fetal transmission.

Temporal data were available for 123 patients. The mean duration (±SD) of symptoms at the time of diagnosis was 67.5 ± 81.4 days. Patients with a longer duration of symptoms at diagnosis were more likely to have extrapulmonary involvement (P = .022).

**Patients who died.** Nine patients died of complications of blastomycosis, for a mortality rate of 6.3%. All of these patients had a diagnosis of blastomycosis established at the time of death. Three of these patients died of respiratory failure, 4 died of cardiac arrest, 1 patient had life support discontinued secondary to status epilepticus, and 1 patient was declared to have brain death. For patients who died, the mean duration (±SD) of symptoms before diagnosis (25.8 ± 10.5 days) was significantly shorter than for patients who survived (70.0 ± 83.2 days; P < .0001). Patients who died and patients who survived did not differ with respect to age (P = .120), sex (P = .549), ethnicity (P = .837), and province of residence (P = .450). Extrapulmonary involvement was not significantly associated with death (P = .090). Three patients died of unrelated causes while in the hospital.

**DISCUSSION**

During the 12-year study period, a mean of 11.9 cases of blastomycosis were diagnosed each year in Manitoba. A previous report describing 26 cases found that a mean of 3.1 cases were diagnosed per year at the University of Manitoba teaching hospitals [16]. Although this increase in the number of cases diagnosed per year may be due in part to the smaller number of hospitals reviewed in the previous report, 76.9% of the cases reviewed in our series were seen at the same hospitals (for a
mean incidence of 9.2 cases per year). It therefore appears that the number of cases of blastomycosis diagnosed per year in Manitoba has increased. Furthermore, a greater proportion of the patients in our study were residents of Ontario than were patients in the previous study (41.9% vs. 25%) [16]. The incidence of blastomycosis in Manitoba is strongly influenced by its proximity to the region of Kenora, Ontario, where the disease is hyperendemic [17]. In addition to the increasing number of case patients referred to Manitoba hospitals from this area, many patients from Manitoba travel to this area, resulting in potential exposure to B. dermatitidis.

The annual incidence rate of blastomycosis among Manitoba residents (0.62 cases per 100,000 population) has not previously been reported. This rate is less than one-half the annual incidence rate reported for other areas of endemicity, such as Wisconsin (1.4 cases per 100,000 population) [12] and Mississippi (1.3 cases per 100,000 population) [29]. The annual incidence rate of 7.11 cases per 100,000 population reported for the Kenora, Ontario district is 4 times greater than the next-highest rate reported for other Ontario or Manitoba census divisions. The incidence rates calculated for the Ontario census divisions likely exceed those reported, because not all patients with blastomycosis who reside in these areas were evaluated at a Manitoba hospital. Frequently, diagnostic dilemmas or seriously ill patients from northwestern Ontario are referred to Manitoba hospitals for assessment and management. Although we calculated the incidence rate according to place of residence, this may not indicate the place of acquisition. A recent study from the area of hyperendemicity in the Kenora catchment region has reported an annual incidence rate of 117.2 cases per 100,000 population [17].

Seasonal variation in the occurrence of blastomycosis has been difficult to establish, because blastomycosis often has a chronic course and diagnosis is often delayed. Several studies have reported seasonal peaks during the winter months [17], but other studies have not noted a seasonal prevalence [30]. In the present study, it was observed that symptoms began and cases were diagnosed in all months of the year, although a slightly higher percentage of patients (59.3%) became symptomatic during October–April.

The patients in our series presented at a slightly younger age (mean, 38.0 ± 19.9 years) than the ages reported for patients in other areas of endemicity (52 years [30], and 46.0 years [29]). The mean age of presentation for patients from the Kenora, Ontario region is the most similar to that in our study (41.9 years) [17]. When we analyzed the annual incidence according to decade of life, we found that the highest annual incidences were among patients aged 50–59 and 60–69 years. A similar finding was reported in Mississippi [29]. It has been proposed that this increased risk of infection in older patients is due to decreased cellular immunity that results in an increased susceptibility to primary infection or reactivation of dormant infection [29]. In previous studies, increasing age was a risk factor for death [29]. In our study, however, death due to complications of blastomycosis was not associated with age.

Earlier studies reported that male sex and employment in outdoor occupations were associated with blastomycosis [16, 20, 31]. The proportion of men among the patients in our study (65.0%) is similar to the proportions reported in recent studies from other areas of endemicity, which show a more equal distribution between the sexes [12, 17, 29, 30] than was previously reported [16, 20, 31]. Similarly, an outdoor occupation was noted for only 13% of case patients in our study; in an earlier report of cases diagnosed in Manitoba, some form of outdoor occupation or activity was indicated for 60% of patients [16]. A review of outbreaks that have occurred to date revealed that neither sex nor age is associated with blastomycosis. The higher proportion of men and of patients employed in outdoor occupations reported in studies of sporadic cases of blastomycosis is likely due to increased risk of exposure through work or recreational activities. It appears that the increased risk associated with male sex and outdoor occupation is becoming a less important risk factor for blastomycosis. Because this study was a retrospective chart review, we were unable

<table>
<thead>
<tr>
<th>Race</th>
<th>Total no. (%) of patients (n = 122)</th>
<th>Ontario residents with blastomycosis (n = 48)</th>
<th>Manitoba residents with blastomycosis (n = 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aboriginal</td>
<td>43 (35.2)</td>
<td>31 (64.6)</td>
<td>12 (16.2)</td>
</tr>
<tr>
<td>White</td>
<td>72 (59.0)</td>
<td>16 (33.3)</td>
<td>56 (75.7)</td>
</tr>
<tr>
<td>Other nationality</td>
<td>7 (5.7)</td>
<td>1 (2.1)</td>
<td>6 (8.1)</td>
</tr>
</tbody>
</table>

* * *

**Table 2.** Distribution according to the race of patients with blastomycosis who were residents of Ontario or Manitoba and the corresponding annual incidence.

* Per 100,000 population.
  b Patients from the Kenora, Rainy River, and Thunder Bay, Ontario census divisions.
to determine whether patients were exposed to soil through recreational activities, and, therefore, we could not determine the risk associated with recreational exposure.

It has been proposed that the incidence of blastomycosis appears to be higher among Aboriginal people [16]. Our findings concur with this suggestion: we found a higher annual incidence rate among Aboriginal people than among non-Aboriginal people. Similarly, the report from the Kenora catchment region noted a significantly higher incidence of blastomycosis in the Aboriginal population [17]. Although the cause of this higher incidence could not be determined, it is speculated that it is due to an increased environmental exposure to B. dermatitidis, because race has never been associated with an increased incidence of blastomycosis. Aboriginal patients in our series presented at a younger age (mean ± SD, 31.6 ± 20.5 years) than did non-Aboriginal patients (mean ± SD, 41.2 ± 19.2 years). This finding was also observed in the report from the Kenora catchment region [17]. Although age-specific incidences for Aboriginal and non-Aboriginal patients could not be calculated, it is speculated that the younger age at presentation among the Aboriginal population is the result of the younger age of this population.

The clinical manifestations of blastomycosis have been described previously, in reports of sporadic cases [12, 16, 29] and outbreaks [14]. Dissemination was reported to occur in up to two-thirds of patients, in earlier reports [16, 31]; however, the rate that we found (30.1% of patients) is consistent with recently reported dissemination rates of ∼25% [12, 29, 30]. As awareness of blastomycosis increases and diagnosis is made earlier in the course of disease, it is possible that extrapulmonary disease is being observed with less frequency. As might be expected, patients with prolonged duration of symptoms at the time of diagnosis are more likely to have extrapulmonary involvement, because the time for dissemination to occur is greater. The most frequent sites of extrapulmonary involvement observed in this series agree with those previously reported (i.e., skin, bone, genitourinary system, and CNS) [15]. Extrapulmonary disease rarely involved a single organ. In Manitoba and northwestern Ontario, blastomycosis is entertained in the differential diagnosis of many pulmonary, skin, and bone infections; however, we are aware that visitors to this area and residents who have become infected present to care providers outside of the area of endemicity who are unfamiliar with this condition. A knowledge of the local epidemiology is therefore important in preventing delays in diagnosis and treatment [32].

The characteristics of the patients who died were very similar to those of the patients who survived. The only characteristic significantly associated with death was a shorter duration of symptoms at the time of diagnosis. The observed mortality rate was 6.3%, which was less than that reported in other studies [29, 30].

CONCLUSION

This study provides valuable results that form the foundation for a prospective laboratory-based surveillance system to evaluate the epidemiology of blastomycosis in Manitoba and northwestern Ontario. It is anticipated that this study will provide significant insights into a condition with important clinical and public health implications for these geographic regions.

Acknowledgments

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References