

Blastomycosis in Quebec (1981-90): Report of 23 cases and review of published cases from Quebec

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G ST-GERMAIN, G MURRAY, R DUPERVAL. Blastomycosis in Quebec (1981-90): Report of 23 cases and review of published cases from Quebec. Can J Infect Dis 1993;4(2):89-94. Twenty-three cases of blastomycosis were reported in a survey conducted in the province of Quebec from 1981-90. Thirteen patients resided south of the St Lawrence River and the other 10, north. Two small geographical clusters were apparent in and around the cities of Sherbrooke and Quebec. The male to female ratio was 1.6:1 and the median age was 47 years (range 26 to 77). Lung involvement was observed in 19 cases and was the only site involved in 11. Cutaneous manifestations were reported in 11 cases while bone infection (three cases) and central nervous system (CNS) infections were also noted. Diagnosis was confirmed by culture in 21 cases and by histopathology in two cases. Of the 21 culture-positive cases, 12 strains of *Blastomyces dermatitidis* were isolated from lungs, nine from skin, and one each from bone and brain. Serodiagnostic tests by immunodiffusion or complement fixation were positive for only one of the 10 patients known to have been tested. Ten patients were treated with amphotericin B, 11 with ketoconazole, one with fluconazole and eight underwent surgery. While amphotericin B was used in eight of the 10 earliest treated cases, ketoconazole was administered in 10 of the 13 more recent cases. Of the patients for whom follow-up data have been obtained, 21 are reported cured (one of whom was not treated) and one patient died of another cause. This survey confirms that blastomycosis is a rare disease in this endemic area and that patterns of therapy are changing.

Key Words: Blastomyces dermatitidis, Blastomycosis, Quebec

La blastomycose au Québec (1981-90): rapport de 23 cas et revue des cas publiés provenant du Québec

RÉSUMÉ: De 1981 à 1990, 23 cas de blastomycose nous ont été signalés dans le cadre d'une enquête menée au Québec. Treize patients résident au sud du fleuve St-Laurent et 10 au nord. On remarque deux petits foyers dans les régions de Sherbrooke et Québec. Le ratio homme-femme est de 1.6:1 et l'âge médian de 47 ans, variant de 26 à 77 ans. Une atteinte des poumons est observée dans 19 cas et pour 11 de ceux-ci, il s'agit du seul site impliqué. On signale 11 atteintes cutanées, trois osseuses et une du système nerveux central. Le diagnostic est confirmé par culture dans 21 cas et par histopathologie pour les deux autres cas. Des 21 cas cultivés, *Blastomyces dermatitidis* est isolé 12 fois des poumons, neuf fois de la peau et une fois des os et du cerveau. Les tests de sérodiagnostic par immunodiffusion ou fixation du complément sont

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négatifs pour les 10 patients chez lesquels on rapporte avoir effectué ces épreuves. Dix patients ont été traités avec l'amphotéricine B, 11 avec le kétoconazole et un avec le fluconazole. Dans huit cas, on a eu recours à la chirurgie. Alors que l'amphotéricine B est utilisée pour le traitement de huit des 10 cas les plus anciens, le kétoconazole a été administré dans 10 des 13 cas les plus récents. Parmi les patients pour lesquels nous avons obtenu un suivi, 21 sont rapportés guéris, dont 1 sans traitement; un patient est décédé d'autres causes. Cette enquête confirme que la blastomycose est une maladie rare dans cette région endémique et qu'un changement important s'est opéré dans le choix du traitement.

BLASTOMYCOSIS IS A SYSTEMIC INFECTION CAUSED BY THE dimorphic fungus *Blastomyces dermatitidis*. Primary infection presumably occurs following inhalation of conidia into the lungs. The spectrum of illness that can result is variable and ranges from asymptomatic or self-limited pulmonary infection to chronic or rapidly fatal illness involving multiple organ systems (1,2). In nature, the organism appears to be a soil saprophyte; the conidia apparently become airborne when the soil is disturbed. A few outbreaks, mostly associated with outdoor activities, have provided clues to the natural habitat of the organism, but many enigmas remain to be solved concerning growth and sporulation of *B dermatitidis* in the environment (3,4).

Cases of blastomycosis have been reported from all continents but are mostly prevalent in endemic areas of the United States, such as the Mississippi river basin, the south central and south eastern regions, and the Great Lakes area. The disease also is found in Canada where most cases have been reported from Quebec, Ontario and Manitoba (5,6). The authors describe 23

cases of blastomycosis diagnosed in Quebec from 1981-90. A review of cases published from Quebec also is presented.

MATERIALS AND METHODS

Survey: A survey was undertaken to estimate the number of cases of blastomycosis diagnosed in Quebec from 1981-90. During that period, 20 strains/cases of *B dermatitidis* were received for confirmation at the Quebec Public Health Laboratory. To obtain demographic and clinical data for each of these cases, questionnaires were mailed to the 12 hospital laboratories that had sent these strains. The information requested included age, sex, residence, clinical manifestations, microbiology, serology, histopathology and radiology results, treatment and outcome. Infectious disease physicians from these hospitals (and from teaching hospitals throughout the province) were asked to inform the authors of any other cases of blastomycosis diagnosed during the study period. A confirmed case of blastomycosis was defined by either a positive culture of the organism from

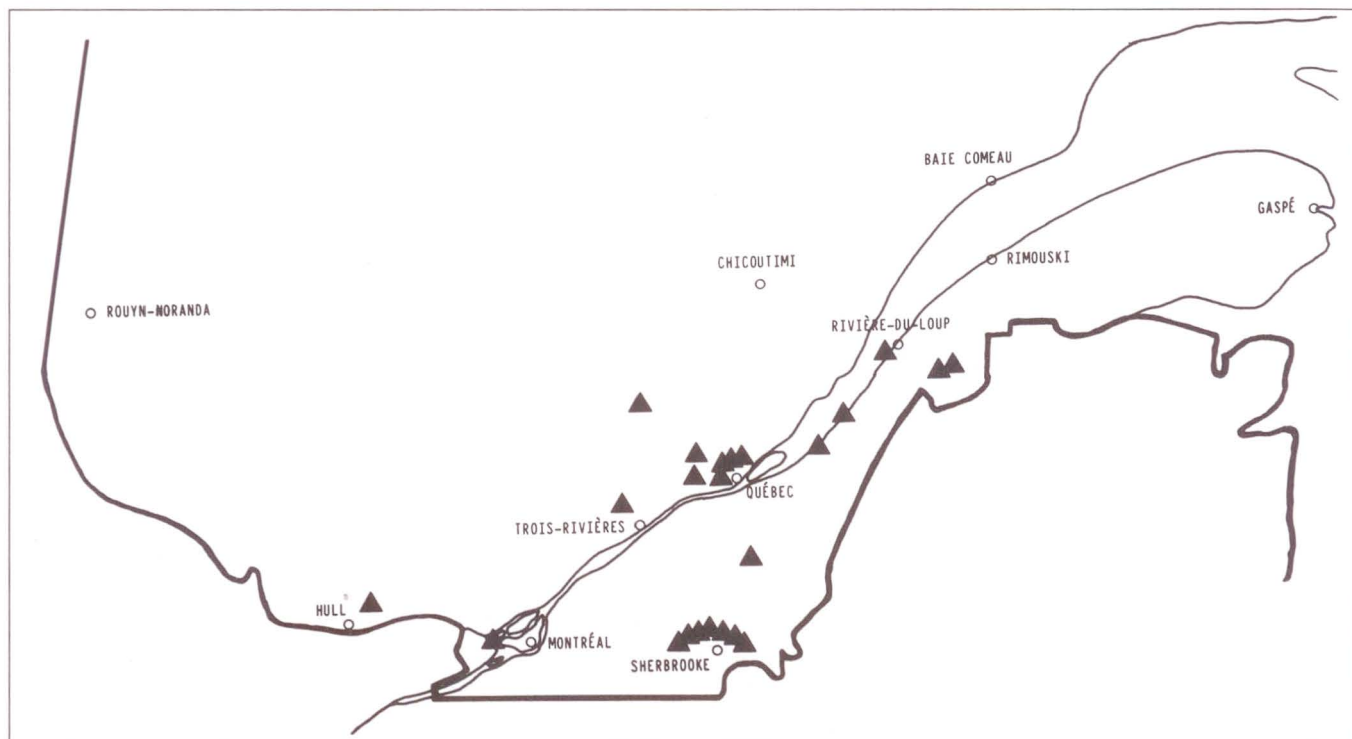


Figure 1) Geographical distribution of 23 cases of blastomycosis diagnosed in Quebec from 1981 to 1990. ▲ Individual cases

TABLE 1
Cases of blastomycosis diagnosed in Quebec from 1981 to 1990

Year	Age (sex)	Clinical manifestations	Isolation sites	Treatment	Outcome
1981	77 (Male)	P,C	NC	A,S	Cu
1982	36 (Male)	P	P	S	Cu
1982	58 (Male)	P	P	A	D
1983	64 (Male)	C	C	K	Cu
1983	44 (Female)	C	C	A	Cu
1983	63 (Female)	P,C	C	A,S	Cu
1983	45 (Male)	P	P	A	Cu
1984	57 (Male)	P	P	A,S	Cu
1984	29 (Female)	P	P	A	Cu
1985	56 (Male)	P	P	A	Cu
1986	53 (Male)	P	P	*	*
1986	42 (Male)	P	P	K,S	Cu
1988	43 (Male)	P,C,O	C,O	K,S	Cu
1988	53 (Female)	P	P	K	Cu
1988	46 (Female)	P	P	None	Cu
1988	47 (Female)	P,C,O	C	K	Cu
1988	45 (Male)	P,C,O	C	A,K	Cu
1989	76 (Male)	CNS	CNS	A,F,S	Cu
1989	71 (Female)	P,C	P,C	K,S	Cu
1990	44 (Male)	P,C	C	K	Cu
1990	47 (Female)	P,C	P	K	Cu
1990	26 (Female)	C	C	K	Cu
1990	33 (Male)	P	NC	K	Cu

*Unknown; A Amphotericin B; C Cutaneous; CNS Central nervous system; Cu Cured; D Deceased; F Fluconazole; K Ketoconazole; NC Not cultured; O Osseous; P Pulmonary; S Surgery

a clinical specimen or by histopathological tissue demonstration.

Identification of strains: Sporulation of the mold form was observed on modified Sabouraud dextrose agar at 25°C, and conversion to the yeast phase was performed on brain-heart infusion agar and blood agar at 37°C. Strains were also tested with exoantigen reagents (Nolan; Scott Biological Laboratories Inc, Georgia) and a molecular probe (GenProbe Inc, California). These reagents were used according to manufacturers' instructions.

Review of Quebec publications: Case reports published from Quebec were sought through Medline and the indexes of local medical journals. A case was considered valid when the description of the organism isolated or seen in tissue was compatible with *B dermatitidis*.

RESULTS

Twenty-three confirmed cases of blastomycosis were identified. Median age of patients was 47 years (range 26 to 77), with a male to female ratio of 1.6:1. Geographical distribution is shown in Figure 1. Demographic and clinical data for individual patients are presented in Table 1. Of the 21 culture-positive cases, *B dermatitidis* was isolated 12 times from lungs, nine

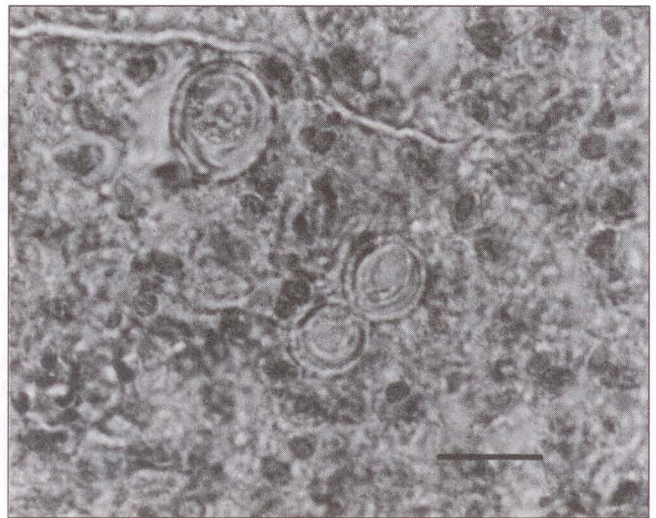


Figure 2) Hematoxylin-eosin stained skin biopsy specimen from the first case (1981). Typical broad-based budding yeast cells of *Blastomyces dermatitidis* are shown. Bar is 10 µm

times from skin, and once each from bones and brain. Overall, histopathological proof was found in 19 cases and suggestive radiological findings in 16. The complement fixation and/or immunodiffusion tests had been performed for 10 patients; only one positive complement fixation result was obtained. In this series, the prognosis was good with no deaths nor relapses reported. One patient died of another cause.

Typical mold and yeast forms (2) were observed for all 20 strains identified at the Quebec Public Health Laboratory. The exoantigen test was positive for each of these strains, but up to 60% of strains, initially grown on agar media, required repeated testing or culture in broth to obtain a positive test. On the other hand, all 20 strains were rapidly and accurately identified by molecular probe. In the two cases in which the disease was diagnosed by histopathology only, the organism was readily identified by its distinctive thick-walled yeast cells producing broad-based buds (Figure 2).

The results of the literature search for case reports from Quebec and their rating are presented in Table 2. Of the 48 cases found, 13 were considered questionable.

DISCUSSION

Blastomycosis was first described by Gilchrist in 1897. The first Canadian case report was published by Primrose (7) in 1906 and the first report from Quebec was written by Shepherd and Rhea (8) in 1911. From 1911-40, case reports were published by McKenty (9), Gaumond (10), Beregoff-Gillow (11) and Nadeau (12). As pointed out by Starrs (13), many of these earlier reports were, at best, questionable because they lacked sufficient evidence to establish a proven or a presumptive diagnosis - indeed, some were based on clinical information only. As the disease became better known

TABLE 2
Blastomycosis case reports from Quebec (1911-80)

Author (reference)	Year	Patient (age in years)	Sex	Year diagnosed	Clinical manifestations	Diagnosis by: culture	histology	Outcome	Case report rating
Shepherd (8)	1911	MM (25)	Male	1910	C	Yes	Yes	D	A
McKenty (9)	1915	AV (48)	Male	NG	C	No	Yes	NG	Q
McKenty (9)	1915	JO (63)	Male	NG	C	No	Yes	Cu	Q
McKenty (9)	1915	NG (43)	Male	1910	C,O	Yes	Yes	D	Q
McKenty (9)	1915	D (32)	Female	NG	C	No	Yes	NG	Q
Gaumond (10)	1933	AD (11)	Male	1931	P,C	Yes	No	D	Q
Beregoff-Gillow (11)	1936	NG (NG)	Female	NG	P	Yes	Yes	NG	Q
Nadeau (12)	1940	ZL (26)	Male	1940	CNS	Yes	Yes	NG	Q
Lamoureux (14)	1948	RSt-G (60)	Female	1947	O	No	Yes	NG	A
Simard (15)	1953	NG (52)	Male	1950	P,O	Yes	Yes	D	A
Simard (15)	1953	M (41)	Male	1950	C	Yes	Yes	NG	A
Simard (15)	1953	MM (30)	Male	1951	C,P	Yes	Yes	NG	A
Leduc (16)	1953	idem Simard 1953							
Leduc (17)	1953	NG (54)	Female	1951	C	Yes	Yes	Cu	A
Gaumond (18)	1953	MNL (51)	Male	1940	C	No	Yes	NG	Q
Gaumond (18)	1953	G-EG (30)	Female	1943	C	Yes	Yes	Cu	A
Gaumond (18)	1953	FL (48)	Male	1943	C	No	Yes	NG	Q
Gaumond (18)	1953	AQ (43)	Male	1943	C	Yes	Yes	Cu	A
Gaumond (18)	1953	EP (55)	Male	1945	C	No	Yes	Cu	Q
Gaumond (18)	1953	AL (34)	Male	1945	C	Yes	Yes	NG	A
Gaumond (18)	1953	RSt-P (30)	Male	1946	C	No	Yes	Cu	Q
Gaumond (18)	1953	GG (31)	Male	1947	C	No	Yes	Cu	Q
Gaumond (18)	1953	AB (50)	Male	1949	C	Yes	Yes	Cu	A
Gaumond (18)	1953	MAR (52)	Male	1951	C	Yes	Yes	NG	A
Giroux (19)	1955	AB (52)	Male	1954	P,O	Yes	Yes	D	A
Poirier (20)	1955	PC (46)	Male	1946	C	Yes	No	Cu	Q
Doray (21)	1957	PD (37)	Male	1954	P	Yes	Yes	Cu	A
Grandbois (22)	1957	TPE (53)	Male	1956	P,O	No	Yes	Cu	A
Grandbois (22)	1957	RP (36)	Male	1957	P	Yes	Yes	Cu	A
Watson (23)	1958	NG (40)	Male	1957	P,C,GU	Yes	Yes	D	A
Grandbois (24)	1958	RB (44)	Male	1955	C,O,GU	Yes	Yes	Cu	A
Grandbois (25)	1963	PT (36)	Male	1957	P,C,O	No	Yes	Cu	A
Grandbois (25)	1963	JD (73)	Male	1961	P,C,GU	Yes	Yes	Cu	A
Grandbois (25)	1963	AL (34)	Male	1961	P	No	Yes	NG	A
Boulet (26)	1980	* (21 to 62)	Male	1957-78	P(15), C(6), O(3)	Yes (3)	Yes (15)	Cu (15)	A

*Fifteen cases reported but not on an individual basis (all patients were male, average age was 42 years); Numbers in square brackets refer to number of cases; A Accepted; C Cutaneous; CNS Central nervous system; Cu Cured; D Deceased; GU Genito-urinary; Q Questionable; NG Not given; O Osseous; P Pulmonary

and laboratory expertise more readily available, more complete information was provided in case reports. In establishing the number and validity of these cases, some difficulties were encountered as most reports were published in local medical journals not listed in Index Medicus. Furthermore, some individual cases were reported in as many as three different journals. Of the 48 cases listed in Table 2, 27% were found questionable. Among the 35 cases with a conclusive diagnosis, the male to female ratio was 10.7:1 and the average age was 43.7 years.

In this 1981-90 survey, two geographical clusters of cases were found in and around the Quebec City and Sherbrooke areas (along with Montreal, they are the most densely populated areas in the province). The

1986 census in Canada established the population of the province at 6,500,000. Only one case was reported from the Montreal area (which has 45% of the population of the province). Although *B dermatitidis* has never been isolated from the environment in Quebec, it is apparent that the fungus is more prevalent in the wooded or rural areas in the vicinity of the first two locations. It is worth mentioning also that five cases were found in patients residing in the low density populated area in between Quebec City and Rivière-du-Loup (along the south shore of the St Lawrence River), indicating the presence of the fungus in that region.

Blastomycosis was previously thought to occur more often in males than in females. The male to female ratio derived from the 1911-80 review of case reports from

Quebec is 10.7:1. However, the 1981-90 survey produced a ratio of 1.4:1 indicating, as other recent studies have done, that occupation and outdoor activities were mainly responsible for the differences observed previously (3,4).

Clinical manifestations in the presented 23 patients are similar to those described in cases reported from the more highly endemic areas of North America, with pulmonary infections occurring most often, followed by cutaneous involvement (1). Serodiagnostic tests are not known to play an important role in the diagnosis of blastomycosis (1,27). Although the immunodiffusion test is reported to be highly specific, it lacks sensitivity. The complement fixation test lacks sensitivity and specificity. In this series, neither of these tests were found to be useful – only one patient out of 10 tested positive. Radiological findings were often useful but diagnosis was obtained mainly by culture and histopathology.

Although identification of *B dermatitidis* usually is obtained readily by conversion of the mold form to the yeast form, the fungus can also be identified by an exoantigen test or a molecular probe. The authors' experience with exoantigen testing indicates a lack of sensitivity with strains grown on agar slopes compared with broth cultures. The molecular probe was highly sensitive. Both of these tests are reported to be very specific, although the probe is known to cross-react with *Paracoccidioides brasiliensis*.

Clinical trials for the treatment of blastomycosis with

ketoconazole performed in the early 1980s showed that this drug is a viable alternative to amphotericin B to treat mild to moderate forms of blastomycosis (28,29). The drug was released on the Canadian market in December 1984. Not surprisingly, this survey shows that amphotericin B was used in eight of the 10 earliest treated cases whereas ketoconazole was administered in nine of the 10 more recent ones. Although ketoconazole has now been used for many years to treat moderate forms of blastomycosis, amphotericin B therapy still remains necessary for patients with life-threatening or CNS diseases, as well as for patients who do not respond to ketoconazole treatment or who cannot tolerate the drug (1). In case 18 (infection of the CNS was diagnosed), amphotericin B was used in combination with fluconazole, resulting in cure. Studies are ongoing to assess the efficacy of this latter drug and others such as itraconazole (30,31). As these drugs are reputedly less toxic than ketoconazole, it is likely that recommendations for treatment will change again in the '90s. Indeed, some clinicians now consider itraconazole as the drug of choice (32).

CONCLUSIONS

Blastomycosis is a rare disease in Quebec (where it is found mainly in the Quebec City and Sherbrooke areas), averaging two to four cases per year. Although early reported cases were treated with amphotericin B, more recently reported cases were treated with ketoconazole.

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