NORTH AMERICAN BLASTOMYCOSIS IN IOWA
REVIEW OF 34 CASES*

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INTRODUCTION

North American blastomycosis is one of the most fascinating but poorly recognized systemic fungal diseases. Its etiological agent, Blastomyces dermatitides, is dimorphic, occurring in yeast form in tissues and mycelial form in laboratory culture. The organisms were first recognized as the cause of the cutaneous form of the disease by Gilchrist and Stokes in 1896 [1, 2]. Initially, the pathogenesis of the cutaneous and systemic forms of blastomycosis was thought to be secondary to different portals of entry, i.e. the skin and lung. It has only been since 1951 that Schwartz and Baum’s [3] hypothesis that fungus is first inhaled, then spread to the other parts of the body, including the skin and bones, by lymphatic and hematogenous dissemination, has been accepted. Isolation of the fungus from the soil by Ajello [4] in 1956 was instrumental in the subsequent understanding of the epidemiology of the disease.

Blastomycosis has been commonly seen in North America in the northern part of the Mississippi and Ohio Valleys, Mid-Atlantic states, parts of the Midwest, and according to some reports, a few cases in eastern Iowa [5–12]. There have been case reports from other parts of the world—Rhodesia [13], the Congo [14] and other parts of Africa [15].

We report here 34 cases of Blastomycosis seen at the University of Iowa Hospitals between 1937 and 1971, a period of time during which no therapy was available, followed by the availability of modern treatment with Amphotericin B and dihydroxy-stilbamidine.

METHODS

Thirty-four cases of blastomycosis seen at the University Hospitals from 1937–1971 were reviewed. Marginal punch cards [16] were used in reviewing the records. Diagnosis was made by microscopic examination of stained tissue sections showing typical B. dermatitides, or direct microscopic examination of exudates with 10 per cent potassium

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hydroxide or by both culture and direct examination methods. Follow-up has been done by contacting patients or relatives or their physicians, or both, as well as checking hospital records in their local hospitals. Population distribution and geographic factors (altitude, valley, etc.) have been considered. There appears to be no significant relationship to these factors. However, altitude, topography, and climate do not vary widely throughout Iowa.

FINDINGS

(a) Incidence and distribution

Thirty-four patients (29 males and 5 females) were seen from 1937–1971. Patients ranged in age from 19 to 78 yr.

Blastomycosis is primarily a disease of the adult working male. Fifty per cent of our patients were in the 19–50 yr age group; males outnumbered females 5:1. Age and sex distribution are almost identical to reports from other states [3, 6, 12, 20].

Blastomycosis generally is a rare disease, but more cases are being reported in the United States, especially in the mid-Atlantic and Midwestern states, and along the Mississippi and Ohio River basins. Furcolow's [11] report on cases included only 17 from Iowa.

Figure 1 shows the map of Iowa and locations of patients at the onset of illness. Distribution appears quite uniform throughout the state. Only one case came from a
neighboring state (Illinois). Nineteen patients came from sites near rivers or lakes, and five from areas 1-2 miles from a body of water.

(b) Occupation

Of those patients indicating occupation, 14 had jobs with exposure to soil, i.e. farming, construction, foundry work, truck driving and carpentry. The remainder had non-soil related jobs. Although occupation was unknown in one-third of our patients, in more than half with known occupations exposure to soil appeared to be a contributing factor. The relationship of age, sex and occupation [5, 6], the natural occurrence of the disease in dogs [10, 17, 21, 22], and the fact that soil is the environmental source of B. dermatitides is now fairly well accepted since Ajello [4].

(c) Underlying predisposing conditions

Eighteen of 34 patients had underlying conditions; accidents were most common. Ten had accidents prior to the onset of blastomycosis, including auto accidents, fractures, or ulcerations. Cardiovascular disease, diabetes mellitus and respiratory disease were infrequent. Sixteen patients reported no underlying conditions.

(d) Clinical aspects of blastomycosis

Onset and symptoms (Table 1). Onset of illness ranged from 4 months to 1 yr before being seen in our hospital. Some had the onset of illness only a few weeks prior to being seen, others as long as 7 yr.

<table>
<thead>
<tr>
<th>TABLE 1. Blastomycosis in Iowa—onset and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of symptoms</td>
</tr>
<tr>
<td><em>Before diagnosis</em></td>
</tr>
<tr>
<td>Under 1 month</td>
</tr>
<tr>
<td>1-3 months</td>
</tr>
<tr>
<td>4-12 months</td>
</tr>
<tr>
<td>Over 1 yr</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Symptoms</td>
</tr>
<tr>
<td>Fever (101-104°F)</td>
</tr>
<tr>
<td>Weight loss</td>
</tr>
<tr>
<td>Night sweats</td>
</tr>
<tr>
<td>Skin lesions</td>
</tr>
<tr>
<td>Dysuria</td>
</tr>
<tr>
<td>Cough</td>
</tr>
</tbody>
</table>

Presenting symptoms or complaints varied. Table 2 lists the anatomical sites commonly involved. The most frequent complaint was involvement of the skin (29 patients); half of these had only cutaneous blastomycosis, mainly on the extremities (11 patients), head and neck (9 patients), and chest (2 patients). Six patients had multiple sites. Lesions varied from pimples, micro-abscesses and verrucous lesions to ulcerating and crusty lesions. Five patients had subcutaneous swelling with draining sinuses. It is interesting to note that 3 patients with lung lesions and 2 with genitourinary blastomycosis had no known skin lesions. Figure 2 shows a case (F.N.) of chronic cutaneous blastomycosis with a verrucous type rash over the ankle. Figure 3 (R.M.) shows
another type of cutaneous blastomycosis involving the nose but is a dry and crusty lesion; this patient was treated over 45 days with dihydroxystilbamidine (total of 4.725 g) and showed progressive improvement.

<table>
<thead>
<tr>
<th>Site</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>29</td>
</tr>
<tr>
<td>(Only cutaneous)</td>
<td>15</td>
</tr>
<tr>
<td>Lungs</td>
<td>12</td>
</tr>
<tr>
<td>Musculo-skeletal</td>
<td>10</td>
</tr>
<tr>
<td>Lymph Nodes</td>
<td>7</td>
</tr>
<tr>
<td>Genito-urinary</td>
<td>3</td>
</tr>
<tr>
<td>Disseminated</td>
<td>11</td>
</tr>
</tbody>
</table>

Ten patients had osseous blastomycosis; 5 of these had multiple bone and joint involvement. Common sites were feet, elbows and skull. Incidence of each site is indicated in Fig. 4. This differs from many reports where the common sites are the lumbar and thoracic vertebrae, pelvis, skull, ribs and long bones [12, 20, 24, 25, 36].

Fig. 4. Skeletal involvement of blastomycosis.
Fig. 2. Blastomycosis of skin verrucous type (F.N.) involving the lower extremity.

Fig. 3. Blastomycosis of skin, dry and crusty type of lesion involving the nose (W.R.).
FIG. 5. Blastomycosis of skeletal system. No bony or joint abnormalities were noted in right ankle on admission.

FIG. 6. The same patient three weeks later; there is a well defined area of bony erosion at the posterior aspect of the os calcis. The rest of the metacarpal bones show generalized osteoporosis due to disuse.
Fig. 7. The same patient after treatment 3 months later. There is residual loss of bone in the posterior aspect of the os calcis. The bony margin is sharp and there is a cortical margin to the area of the defect, indicating healing of the infection.

Fig. 8. Blastomycosis of the lung (R.P.).

FIG. 10. Biopsy from prostate (R.H.) showing the single-budding organism *B. dermatitides* (arrow).
There was no vertebral involvement in our series. Although patients may complain of tenderness, pain and limitation of motion, initial X-ray may not reveal any abnormality. Blastomycosis spreads to the bones by the bloodstream. Lesions in short and long bones are focal or diffuse osteomyelitis with sclerotic margins and in flat bones there is erosion. Bone X-rays showed periostitis, soft tissue swellings and osteolytic lesions. Fig. 5 is an X-ray of the ankle of a 21-yr-old (J.R.) male who was admitted with disseminated blastomycosis; initially he had no demonstrable bone lesion, although he complained of tenderness and pain over the right heel. Within 3 weeks, while on Amphotericin B, he had progressive bone lesions as shown in Fig. 6, with soft tissue swellings, periostitis, and osteolytic lesions. Three months after treatment he improved (Fig. 7).

Pulmonary blastomycosis was seen in 12 cases. All had positive sputum cultures or smear or both. Seven had cough (5 with hemoptysis) and 3 had associated chest wall lesions. Three had isolated lung lesions and underwent lobectomy for suspected carcinoma. Chest X-rays were taken in 21 of 34 patients; 15 were abnormal. Unfortunately, we cannot tell whether the others (without chest X-ray) had primary blastomycosis in the lungs as would be expected in most. These showed fibrosis in 3, fibronodular and diffuse infiltrate in 9 (2 of these had hilar adenopathy, one with miliary distribution and one with cavity). Fig. 8 represents a 23-yr-old female (B.P.) who was admitted because of cough, pleuritic chest pain, and weight loss. She had diffuse infiltrates in both lung fields with collapse of the right upper lobe with cavity and osteomyelitis of the ribs. She was treated with Amphotericin B (1.45 g over 2 months) and showed significant improvement. Fig. 9 (W.H.) is one of three patients who underwent lobectomy.

Genito-urinary blastomycosis was seen in 3 patients with involvement of the prostate and epididymis; one of these was previously reported by Bunge and Harness [18] from this institution. There were no cases of female GU blastomycosis in this series although conjugal blastomycosis has been reported [26].

Disseminated blastomycosis in 11 patients involved the skin, lymph nodes, lungs and bones, and a few other organs (Table 3). In one patient who died of disseminated blastomycosis, the organism was identified by tissue stain examination or culture, or both, from spleen, liver, arachnoid, large bowel, eyes (ciliary bodies) and adrenals. Cultures were positive in all cases. Three had tissue biopsy stain; all were positive showing the single-budding organisms (Fig. 10).

Central nervous system blastomycosis with meningoencephalitis or meningitis has been reported [27-31], but there was only one case in this series with involvement of arachnoid (detected at postmortem). The patient had no clinical evidence of central nervous system disease. This is also true for gastrointestinal involvement; only one patient had lesions of blastomycosis in the rectum as part of his extensive disease.

(c) Diagnosis of blastomycosis

In 41 per cent of the patients, detailed work-up for blastomycosis was not done (cultures, serology, skin tests, X-rays, and genito-urinary evaluations). Patients with cutaneous blastomycosis had no systemic symptoms and were diagnosed by positive smears with 10 per cent potassium hydroxide. We agree that the direct smear with 10 per cent potassium hydroxide is not conclusive for diagnosis of blastomycosis; how-
<table>
<thead>
<tr>
<th>Case</th>
<th>Year seen</th>
<th>Anat. site</th>
<th>Duration of onset of illness</th>
<th>Smear with KOH</th>
<th>Culture</th>
<th>Total dose</th>
<th>Other disease</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS (60 M)*</td>
<td>1941</td>
<td>skin, bones, lungs, rectum</td>
<td>18 mo.</td>
<td>√</td>
<td>√</td>
<td>KI</td>
<td>coronary heart disease and stroke</td>
<td>Died of disease during admission</td>
</tr>
<tr>
<td>JR (21 M)</td>
<td>1971</td>
<td>skin, bones, lungs</td>
<td>3 mo.</td>
<td>√</td>
<td>√</td>
<td>Amphotericin, 2g</td>
<td></td>
<td>Improved</td>
</tr>
<tr>
<td>ES (59 F)</td>
<td>1954</td>
<td>skin, probably lungs</td>
<td>6 mo.</td>
<td>√</td>
<td>√</td>
<td>KI and dihydroxystilbamidine, 5 and 9 g</td>
<td>diabetes TB of lung</td>
<td></td>
</tr>
<tr>
<td>CR (65 M)</td>
<td>1959</td>
<td>epididymus, skin, LN</td>
<td>6 mo.</td>
<td>√</td>
<td>√</td>
<td>dihydroxystilbamidine, 4.05 g</td>
<td>latent syphilis asthma</td>
<td>Died: 3 yr later of CHF and emphysema</td>
</tr>
<tr>
<td>RH (64 M)</td>
<td>1949</td>
<td>prostate, skin, lungs, adrenals</td>
<td>4 wk.</td>
<td>√</td>
<td>√</td>
<td>KI for 6 yr</td>
<td></td>
<td>Recurred 2 times (chest skin, epididymus). Died of blastomycosis after 7 yr</td>
</tr>
<tr>
<td>RK (47 M)</td>
<td>1953</td>
<td>lungs, spleen, liver, arachnoid</td>
<td>3 yr.</td>
<td>√</td>
<td>√</td>
<td>lymphatic leukemia, chemotherapy (N2H, radiation)</td>
<td>Died of lymphoma and blastomycosis post finding</td>
<td></td>
</tr>
<tr>
<td>JC (34 M)</td>
<td>1952</td>
<td>lungs, LN's</td>
<td>3 wk.</td>
<td>√</td>
<td></td>
<td>KI</td>
<td></td>
<td>Lobectomy, no follow-up</td>
</tr>
<tr>
<td>DS (22 M)</td>
<td>1968</td>
<td>skin, lungs, bones, LN's</td>
<td>4 mo.</td>
<td>√</td>
<td>√</td>
<td>Amphotericin, 1-5 g (8 wk.)</td>
<td></td>
<td>Doing well</td>
</tr>
<tr>
<td>BP (23 F)</td>
<td>1970</td>
<td>lungs, bones</td>
<td>1 mo.</td>
<td>√</td>
<td>√</td>
<td>Amphotericin, 1.45 gm (8 wk.)</td>
<td></td>
<td>Improved, doing well</td>
</tr>
<tr>
<td>ML (59 F)</td>
<td>1941</td>
<td>skin, lungs, LN's</td>
<td>1 yr.</td>
<td>√</td>
<td>√</td>
<td>KI</td>
<td>miliary TB, CHF</td>
<td>Died of CHF and miliary TB</td>
</tr>
<tr>
<td>RS (36 M)</td>
<td>1938</td>
<td>skin, bones, lungs</td>
<td>3 mo.</td>
<td>√</td>
<td>√</td>
<td>KI</td>
<td></td>
<td>No information since June, 1940</td>
</tr>
</tbody>
</table>

*Items within parentheses are age and sex.
†Congestive heart failure.
ever, histological examination of skin biopsy was done in 6 of 14 cutaneous cases, and all were positive. Biopsy stain reveals characteristic simple budding organisms [5, 33].

Diagnosis was made in 33 cases with positive smear with 10 per cent potassium hydroxide (in one patient no smear was done) and in 13 patients by positive culture in Sabouraud's glucose agar as well. Positive smears were seen in 24 micro-abscesses, 5 from bones and joints, 1 from sputum, and 6 from other organs (prostate, etc.). Of 20 cultures taken from 16 patients, 17 were positive; all positive cultures were isolated from 13 patients. Positive cultures were obtained from 5 skin micro-abscesses, 2 sputa, 3 bone lesions, 3 urines and 5 from other tissues (lungs, spleen, liver, large intestine).

Serologic tests for blastomycosis by complement fixation were done in 2 patients; one was negative, the other had 4+ at 1:16, 2+ at 1:32 and negative at 1:64. Skin tests were done in 4 patients; 2 had positive reactions. Diagnosis of blastomycosis by immunological techniques remains unreliable; the antigens used are inadequate and non-specific [34, 35], and there is cross-reaction with histoplasmosis and false negatives for blastomycosis [37].

Other laboratory tests were not significant. Low hemoglobin (< 10 g%) was encountered in 5 of 20 patients. Nine of 22 patients had an elevated leukocyte count (> 12,000/cm), the highest 26,000.

Dual fungal infection is an interesting clinical problem and there are reports on histoplasmosis and blastomycosis occurring simultaneously in patients [38, 39], including one example in this series [44]. However, it is important to keep this possibility in mind. Histoplasmosis is common in this area of the country and may occur in patients receiving hormonal or immunosuppressive treatment.

(f) Treatment of blastomycosis

Management of blastomycosis has been reported extensively by Lockwood et al. [40] and Utz [41].

From 1937–1950, patients were treated with potassium iodide by mouth (a few received sodium iodide). Twenty were treated with this regimen and all but 3 with disseminated disease (2 died of blastomycosis) had cutaneous or osseous blastomycosis. Side effects were seen in 3 who developed acne-like lesions, pruritis and rhinitis. Iodide treatment was used for prolonged periods, ranging from a few months to 3+ yr. Surgical treatment was not used extensively. The skin lesion of one patient was excised erroneously as an epidermoid cancer.

From early 1950 to 1971, dihydroxystilbamidine [19] was used in 7 patients, 2 with disseminated disease. All showed significant improvement; 2 had mild side effects with chills, fever and thrombophlebitis. Dosage was 225 mg, i.v., in D.W., 3–4 times per week for 4–6 weeks. Total dose ranged from 4.05 to 15 g.

Amphotericin B has been used since 1960 in 4 cases, 3 with disseminated blastomycosis. All showed significant improvement. Side effects were encountered in 2 patients who had transient azotemia, decrease in creatinine clearance (down to 4–56 ml/min), and mild hypokalemia. All reversed to normal gradually. Three patients had nausea, vomiting and fever. The total dose used was 1.45 – 2 g.

(g) Follow-up of patients with blastomycosis

Follow-up information is available in 29 of 34 cases (85.6 per cent). Thirteen died (38.2 per cent), 3 due to blastomycosis (8.8 per cent). One patient had lymphocytic
leukemia and blastomycosis was a postmortem finding. The remainder died of different causes: renal failure, unrelated to blastomycosis or its treatment (2 patients); congestive heart failure (5 patients); and unknown cause (3 patients). Two patients who died of blastomycosis were treated with potassium iodide. None treated with dihydroxystilbamidine or Amphotericin B died.

Blastomycosis recurred in 5 patients, 4 on potassium iodide and one on dihydroxystilbamidine (5.4 g). Three of the former were re-treated with potassium iodide, the other with dihydroxystilbamidine. Surgical treatment only by lobectomy of the lung was done in 3 patients. They have been followed 1 yr, 20 months and 16 yr without further treatment.

(h) Prognosis

Mortality due to blastomycosis was previously more than 90 per cent [20]. However, in the last two decades since the use of dihydroxystilbamidine and Amphotericin B, fatality has decreased to 27 and 20 per cent [6, 42]. In our series, fatality due to blastomycosis was 8.8 per cent of all cases, or 23 per cent of the patients with disseminated blastomycosis. Ten patients (29.4 per cent) died of other causes and overall mortality was 38 per cent. None of the patients treated with Amphotericin B and dihydroxystilbamidine died due to blastomycosis. The recurrence rate was 14.7 per cent overall, 9.09 per cent in those treated with Amphotericin B or dihydroxystilbamidine, and 20 per cent without this treatment.

SUMMARY

We have reviewed 34 patients with blastomycosis seen from 1937–1971 at the University of Iowa Hospitals, 29 men and 5 women, ages 19–78; 86 per cent of our patients were followed to death or for 5 or more years after hospitalization. Thirty-six per cent had a probable occupational soil exposure. A majority of patients had symptoms for 4–12 months before diagnosis. Fever was unusual and symptoms varied according to the anatomical site involved. The disease has been analyzed in patients with cutaneous, pulmonary, osseous, genito–urinary and disseminated blastomycosis. The disease should be diagnosed by culture, but the presence of round, thick-walled, single-budding yeast in KOH skin scraping preparations is highly suggestive. Treatment with dihydroxystilbamidine or Amphotericin B has reduced the recurrence rate from 20 per cent to 9 per cent and the death rate from 8 per cent to zero. Surgical treatment by lobectomy was done in 3 patients.

REFERENCES