Case Report

Blastomycosis in a South Indian patient after visiting an endemic area in USA

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We describe a case of blastomycosis in a diabetic patient from South India who had visited Milwaukee, Wisconsin, an endemic area for blastomycosis in the USA. After his return to Bangalore, India, the patient developed intermittent fever of moderate to high grade, cough, loss of weight and appetite, and abscesses in the left cubital fossa and thigh regions. Systemic examination at our hospital revealed that he had dullness to percussion over the chest region and decreased breath sounds. Direct examination of Gram-stained smears of the pus from an abscess showed many broad-based budding yeast cells and culture yielded a dimorphic fungus later identified as Blastomyces dermatitidis. Histologic examination of the curettage tissue slides stained with hematoxylin and eosin, periodic acid Schiff’s reagent, and Gomori’s methenamine silver stain procedures showed many broad-based budding cells characteristic of B. dermatitidis. The patient was successfully treated, initially with amphotericin B, followed by oral itraconazole for a period of 6 months. Blastomycosis cases in India are reviewed and the likely source of infection in this patient is discussed.

Keywords blastomycosis in India, Blastomyces dermatitidis

Introduction

Systemic endemic mycoses such as blastomycosis, coccidioidomycosis, penicilliosis, and paracoccidioidomycosis have been reported as health risks among travelers who visit or reside in an endemic area for a short period and often acquire such diseases. The risk of acquiring such an endemic mycotic infection is higher among immunocompromised patients [1]. In India, autochthonous cases of blastomycosis in humans and animals have been reported mainly from the states of Uttar Pradesh and Madhya Pradesh in northern India (Fig. 1) [2–5]. To our knowledge, there has been only one case report of blastomycosis from the state of Tamil Nadu, in southern India [6]. However, the diagnosis was based on inadequate documentation and is thus questionable. We present the first case of blastomycosis from southern India in a diabetic patient from Bangalore, India, who recently visited the state of Wisconsin, USA, a known area of endemcity for Blastomyces dermatitidis.

Case report

A 41-year-old diabetic male patient was admitted on 15 March 2003 to St John’s Medical College and Hospital, Bangalore, India, with complaints of fever and cough of 3 months duration. His history revealed that he had been on a 1-month long trip to the US between the months of October–November 2002. Detailed history
of his travel to the US revealed that he had visited Milwaukee, Wisconsin – a known endemic area for *B. dermatitidis*, for 2 weeks followed by visits to Tampa, Florida, Wallingford, Connecticut, and Princeton, New Jersey. However, most of his time in Milwaukee was spent indoors doing office work. One weekend he visited Pewaukee Lake for a brief period of 1.0–1.5 h. Pewaukee Lake is in Waukesha county, and the estimated annual incidence of blastomycosis for that county from 1985–2003 is 0.9 per 100,000 according to Wisconsin Division of Health. According to a study of recent cases of blastomycosis in Milwaukee county (personal communication from Dr Dennis J. Baumgardner) the estimated annual incidence of blastomycosis is 0.96 per 100,000. However, some zip codes had no cases and incidence figures were as high as 3.25 per 100,000 for the highest incident zip code.

On his return to India, he was apparently healthy. About 2 weeks after his return in the month of December 2002, he suddenly developed Bell’s palsy for which he was treated with prednisolone. After about 4 weeks of treatment, his symptoms improved and prednisolone was discontinued. Two weeks later in mid-January 2003, he developed a dry cough, intermittent fever of moderate-to-high grade without chills or rigor. A viral infection was suspected and the patient was
initially treated symptomatically followed by a course of antibiotics. His clinical condition improved but symptoms persisted. Sputum examination was negative for tubercle bacilli, however, X-ray findings were suggestive of tuberculosis. Therefore, anti-tubercular treatment (ATT) was initiated with isoniazid, ethambutol, rifampicin, and pyrazinamide. During these 2 months, the patient had a weight loss of about 10 kg and a substantial decrease in his appetite. During this time, he also developed a swelling on his left knee. Fine needle aspiration cytology (FNAC) did not offer any positive findings.

The patient was admitted to our hospital on 15 March 2003, with the above-mentioned complaints. He had a swelling just below his left jaw. At the time of admission, his general physical condition was stable. Systemic examination revealed dullness to percussion over the chest region and decreased breath sounds in the left mammary and infra-mammary region. His ATT treatment was continued. During his stay in the hospital, the cough worsened with production of yellowish non-foul-smelling sputum that was occasionally blood-stained. He also developed abscesses in the left cubital fossa and thigh regions.

**Laboratory findings**

Routine hematological findings were as follows: total white blood cell count was 15,900 cells/μl, differential count had a neutrophilic predominance (neutrophils 84, lymphocytes 13, basophils 2, and bandforms 1), and platelet count was 4.5 l/μl. Initial biochemical investigations including fasting blood sugar, liver function tests, lipid profile, blood urea, creatinine and serum electrolytes were within normal limits. Other parameters such as bleeding time, clotting time, and prothrombin time were normal.

His chest X-ray and CT scan revealed a non-homogenous opacity in the right mid zone and left mid and lower zones. Abdominal scan revealed hepatosplenomegaly with the liver measuring 15.7 cm in the long axis and the spleen 14.2 cm. There were no focal lesions.

No bacterial pathogens were isolated from patient’s sputum, blood and urine cultures. The pus and the curettage from the abscess on the left cubital fossa were sent for microbiological and histopathological investigations. Direct examination of Gram-stained smears of the pus sample showed broad-based budding cells measuring 8–12 μ in diameter suggestive of *B. dermatitidis*. Similar broad-based budding cells were observed in the fibro-connective tissue from the curettage tissue sections stained by hematoxylin and eosin, periodic acid Schiff’s reagent, and Gomori’s methenamine silver stain procedures (Fig. 2). Similar characteristic budding cells were also observed in the FNAC examination of the submandibular abscess.

The pus and a portion of curettage tissue from the abscess were cultured on several media including Sabouraud dextrose agar containing chloramphenicol (Sab + C), blood agar, and biphasic brain heart infusion agar. Duplicate cultures were incubated at room temperature (25°–28°C) and at 37°C and were regularly observed for growth. White, moist to cottony colonies became visible after 3–4 weeks of incubation at room temperature. Examination of slide cultures prepared from one of the mycelial colonies on potato dextrose agar incubated at room temperature after 10 days showed hyaline, septate branching hyphae, many bearing lateral round, to pear-shaped 1-celled conidia on short stalks or directly on the hyphae. The isolate was converted to its yeast form after repeated subcultures on BHI agar at 37°C. Microscopic examination of the yeast-like growth showed globose to subglobose, budding cells with many showing broad-based buds characteristic of *B. dermatitidis*.

A subculture of the mycelial isolate (R-41) was sent to (AAP) at the Mycotic Diseases Branch, Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, for confirmation. The mycelial-yeast conversion was successfully achieved at the CDC on Kelley’s agar at 37°C and yeasts showed broad-based budding cells characteristic for *B. dermatitidis*. The isolate (R-41) has been deposited in the American Type Culture Collection (ATCC MYA-3235) and Centraalbureau voor Schimmelcultures, Utrecht, The Netherlands (CBS 114389).
Treatment

The patient was treated with amphotericin B (40 mg daily) based on mycological and histopathological reports. The patient received a total dose of 2.5 g of amphotericin B. During the treatment, his ATT was withdrawn. His blood sugar was maintained with insulin injections. The patient improved dramatically on completion of amphotericin B treatment. He was then treated with itraconazole (200 mg daily). The patient was discharged on 6 July 2003, and was advised to continue his treatment with itraconazole. He was then observed regularly in the out-patient department. After 6 months of treatment with itraconazole, his treatment was discontinued. The patient was observed on regular follow-up visits every fortnight for the first 3 months, and every 3 months for the next 6 months. He continues to come regularly to have his blood sugar checked and meet his chest physician. He has been free of infection up to the present time.

Discussion

The occurrence of *B. dermatitidis* in India was unknown until 1982 when Khan et al. isolated *B. dermatitidis* from the lungs of a bat, *Rhinopoma hardwickei* Gray, captured from an abandoned part of a school building in Delhi [2]. Before 1982, there were nine cases of blastomycosis reported from India. These cases were carefully reviewed by Randhawa et al. in 1961 [7] and later by Misra and Sandhu [8]. All of the nine reports were based on inadequate documentary evidence and thus were rejected. In 1983, Randhawa et al. [3] reported the first isolation of *B. dermatitidis* from a bronchial aspiration of a female asthmatic patient residing in a small town in Uttar Pradesh, about 250 km south-east of Delhi. Since 1983, 13 additional cases of human and animal blastomycosis have been described in India (Table 1). To our knowledge, of the 13 cases there has been only one case report describing blastomycosis from southern India from the state of Tamil Nadu [6]. However, the diagnosis was based on inadequate documentation and is thus questionable. In the present case, the patient had a history of travel to a known endemic area of blastomycosis in the USA. After his return to India he developed symptoms of the disease. The diagnosis was based on observing characteristic broad-based budding cells of *B. dermatitidis* in histopathologic examination of the biopsy tissue as well as isolation of *B. dermatitidis* from the affected tissue. Travelers who develop fungal diseases are often exposed to obvious or salient risk factors during a wide range of leisure and work activities. The infection in some instances, may have been acquired during a short trip (‘travel-related’ infection) or during a longer period of residence in an endemic area with subsequent migration to a region where infection is not endemic (migration-related infection) [1]. In many cases of travel-related fungal disease, individuals present with non-specific symptoms and signs of acute respiratory illness shortly after their return, as was the condition in the present case.

To assess the present status of blastomycosis in India, we critically reviewed 13 relevant case reports published from 1983–1997 (Table 1). Of these 13 cases reported from India, eight were human cases of blastomycosis [3,4,6,9–13] and five were case reports of blastomycosis in animals including bat, bird droppings, cattle, dog, and a monkey [5,14–17]. In none of the eight human case reports, was there any mention of travel outside India, thus the infection was claimed to have been acquired in India. The diagnosis in four of the eight cases was described as having been based on histological examination of the affected tissue and isolation of *B. dermatitidis* in culture. However, in only one case report out of these four reports [3], did the authors successfully convert their mycelial form culture to its yeast-form and provide convincing photomicrographs of the mycelial as well as yeast forms showing broad-based budding cells of *B. dermatitidis*. In the remaining three reports, only a brief mention was made of the isolation of ‘fluffy, white to tan colonies’ or ‘culture was positive’ assumed to be those of *B. dermatitidis*. No attempt was made to achieve mycelial-yeast conversion *in vitro* at 37°C to prove the dimorphic nature of the isolates. As a result, diagnosis in these three cases [6,9,11] was based mainly on histologic examination of the affected tissue observing yeast-like cells interpreted as being those of *B. dermatitidis*. In our opinion, diagnosis in these three cases is based on inadequate documentary evidence, especially as the photomicrographs of the histological slides were of poor quality. None of these photomicrographs showed clearly any characteristic broad-based yeast cells of *B. dermatitidis*. Additional tests such as serologic tests (immunodiffusion test, fluorescent antibody test using *B. dermatitidis* specific conjugate, or exoantigen test to confirm the identity of the culture) were done in only two of the eight human cases [3,4]. In both case reports, authors provided cultural and/or histological evidence with supporting photomicrographs of the yeast form cells showing characteristic broad-based budding, thus providing convincing diagnosis. Therefore, only these two of the eight case reports are acceptable as cases of blastomycosis. The case report from Mumbai (Bombay), India [4], is the
### Table 1 Summary of published case reports on blastomycosis from India (1983–1997)

<table>
<thead>
<tr>
<th>Case no. (Sex/Age)</th>
<th>Symptoms</th>
<th>Diagnosis based on</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Ref./State/Scientific authenticity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Human cases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 = F/40</td>
<td>Paroxysmal dyspnoea, cough, occasional low grade fever, asthmatic</td>
<td>Direct KOH exam., culture +, <em>in vitro</em> dimorphic nature +, serologic immuno-diffusion test +, exoantigen test +</td>
<td>Pulmonary symptoms resolved without antifungal therapy</td>
<td>Long term outcome not mentioned</td>
<td>[3]/Uttar Pradesh/Accepted</td>
</tr>
<tr>
<td>2 = M/40</td>
<td>Rt. side headaches, progressive proptosis, diminishing vision in rt. eye, paranasal sinus infection</td>
<td>Histopathology first biopsy neg., second biopsy tissue diagnosed as blasto.</td>
<td>Amphotericin B – total dose or other details not mentioned</td>
<td>Not mentioned</td>
<td>[9]/Maharashtra/Not accepted</td>
</tr>
<tr>
<td>3 = F/60</td>
<td>Swelling on forehead and jaw, proliferative, crusty, ulcerating lesion, osteolytic lesions of bony calvarium, mandible, fracture of left acromion, destruction of rt. ulna, left tibia, left fibula, paratracheal adenopathy, rt. midzone micro-calciﬁc nodules</td>
<td>Histopath. + for small-form B. dermatitidis. FA test for B. dermatitidis done at CDC was +</td>
<td>Amphotericin B total dose 1.9 g</td>
<td>Six month follow-up showed patient cured</td>
<td>[4]/Madhya Pradesh/Accepted</td>
</tr>
<tr>
<td>4 = F/38</td>
<td>Suspected ‘brucellar nodule’, hard ulcerating nodule under left arm</td>
<td>Direct exam of pus –, culture described as +, no culture details provided</td>
<td>Not mentioned</td>
<td>Unknown</td>
<td>[10]/Maharashtra/Not accepted</td>
</tr>
<tr>
<td>5 = F/15</td>
<td>Swelling of face, neck, breathlessness, cough, fever, trachea shifted to right</td>
<td>Large enhancing anterior foramen magnum tumor, histopath of excised tumor + for B. dermatitidis yeast cells (?), no culture, no serology</td>
<td>Surgical removal of tumor, amphotericin B (total dose 2.2 g)</td>
<td>Cured</td>
<td>[11]/Maharashtra/Not accepted</td>
</tr>
<tr>
<td>6 = F/25</td>
<td>Numness and weakness of left limbs, giddiness, neck pain, depressed palatal and gag reflexes, extra axial fungal granuloma</td>
<td>FNAC showed large spherical cell with broad-based budding?, Culture grew fluffy, tan colonies, no <em>in vitro</em> conversion done</td>
<td>Oral ketoconazole (400 mg/day) for 30 days, itraconazole (400 mg/day) for 48 days</td>
<td>Cured</td>
<td>[12]/Maharashtra/Not accepted</td>
</tr>
<tr>
<td>7 = M/19</td>
<td>Painless swelling of left eye, soft, ﬂuctuant, extending from medial canthus to left eye lower lid</td>
<td>Discharge from inguinal lesion KOH +, culture described as +, no culture details, no <em>in vitro</em> conversion</td>
<td>Ketoconazole (400 mg/day) for 3 months</td>
<td>Outcome unknown, patient lost to a follow-up</td>
<td>[13]/Not mentioned/Not accepted</td>
</tr>
<tr>
<td>8 = M/40</td>
<td>Cutaneous blasto? Non tender, firm inguinal lesion</td>
<td>Direct exam pus +, histopath of curettage tissue from abscess +, culture + for B. dermatitidis, <em>in vitro</em> conversion +, Gen Probe test +</td>
<td>Amphotericin B (total dose 2.5 g), itraconazole (200 mg/day) for 6 weeks</td>
<td>Cured</td>
<td>Present case/ endemic imported infection</td>
</tr>
<tr>
<td><strong>Present case = M/41</strong></td>
<td>Fever, cough, loss of appetite, weight loss, hepatosplomegaly, multiple abscesses left cubital fossa</td>
<td>Both mycelial and yeast forms well illustrated, mycelial-yeast conversion +, pathogenicity in mice +</td>
<td>None</td>
<td>Not applicable</td>
<td>[14]/New Delhi/Accepted</td>
</tr>
</tbody>
</table>

### Isolation from animal/saprobic sources

- **Lesser rat-tailed bat (Rhinopoma hardwickei hardwickei)** Of 627 bats examined *B. dermatitidis* isolated from liver of one apparently healthy bat Necropsy-nodular lesions in lungs

- **Mongrel dog found dead on campus** Necropsy-nodular lesions in lungs

- **Bird droppings of Aythya fuligata** Six of the 60 samples from nests of tufted pochard claimed to yield *B. dermatitidis* by direct culturing on Sabag

- **Cattle** Lungs from 8–12-year-old cattle from a slaughter house

- **Captive Nilgiri Langur Monkey** Caseated, irregular, firm nodules in lungs of one monkey
only case of disseminated blastomycosis in a 60-year-old female patient from Madhya Pradesh documenting occurrence of ‘small form’ *B. dermatitidis* yeast cells in the affected tissues. In the remaining six case reports of human blastomycosis [6,9–13], quality of the photomicrographs showing so-called yeast-form cells of *B. dermatitidis* is poor and unconvincing. Therefore, these case reports are based on equivocal evidence and are unacceptable as being cases of blastomycosis (Table 1).

Of the five case reports of blastomycosis in animals, only two case reports, namely, isolation of *B. dermatitidis* from the liver of one apparently healthy bat [14] is accepted because the authors have provided convincing proof that their isolate was indeed dimorphic by providing photomicrographs of the mycelial as well as yeast-form cells characteristic of *B. dermatitidis*. A subculture of their isolate was deposited in the American Type Culture Collection. The second case of *B. dermatitidis* infection in a dead mongrel dog [5] was diagnosed based on histopathological examination of nodular lung lesions which showed broad-based budding cells of *B. dermatitidis*. The photomicrographs of the lung tissue showed clearly the broad-based budding cells of *B. dermatitidis*. In the remaining three case reports of blastomycosis in cattle, a Langur monkey from a zoo and direct isolation of *B. dermatitidis* by directly cultivating bird droppings collected from the nests of *Aythya fuligata*, the evidence provided was based on inadequate documentation [15–17]. An especially suspect report is that of Rawal et al. [15] which described the isolation of *B. dermatitidis* by directly cultivating bird droppings collected from nests of *Aythya fuligata* on Sabouraud dextrose agar. In this context, it may be pointed out that *B. dermatitidis* has never been isolated by direct culture of any environmental samples. Successful isolation of *B. dermatitidis* from environmental samples requires inoculation of laboratory animals (including mice, gerbils, guinea pigs, dogs and cats) by the intravenous route. This is the only proven method for the successful recovery of *B. dermatitidis* from environmental samples [18]. Therefore, these three case reports [15–17] are rejected based on inadequate documentation.

In the majority of Indian case reports reviewed here, we found that brain heart infusion agar was used as a conversion medium. It is well known that the medium of choice for the conversion of the mycelial form of *B. dermatitidis* to its yeast form is Kelley’s agar – a cotton-seed-embryo-derived proteinaceous product marketed in the USA. Even though Kelley’s agar is not commercially available in India, 9% aqueous seed extract of any of the eight indigenously grown varieties of cotton in India provides an inexpensive but highly efficacious medium of choice for converting mycelial form *B. dermatitidis* to its characteristic yeast form at 37°C [19–21].

The present case raises an important question regarding the patient’s exposure to *B. dermatitidis*. Was he infected in the US during his stay in Milwaukee, Wisconsin, a known endemic area for blastomycosis, or in South India? It is estimated that the incubation period of blastomycosis acquired by inhalation varies from 6–8 weeks [18]. Our patient developed intermit-tent fever and dry cough 4 weeks after he returned from his visit of 1 month duration to the US that included two weeks in Milwaukee, Wisconsin. The exposure, however, did not involve any high risk activity such as camping, hiking, riverbank fishing, hunting etc. undertaken by the patient. The patient’s outdoor exposure while visiting Pewaukee Lake in Waukesha County was quite minimal. However, as evidenced by a beaver pond outbreak of blastomycosis [22], a brief chance exposure to *B. dermatitidis* in soil may result in infection.

The possibility that the patient may have been infected in South India cannot be excluded. The infection may represent what appears to be a reactiva-tion of dormant blastomycosis following the adminis-tration of steroid (prednisolone) when the patient suddenly developed Bell’s palsy 2 weeks after his return to India from the US. According to Dr Dennis J. Baumgardner (personal communication), he and his co-workers have observed what appeared to be reactiva-tion cases of dormant blastomycosis following ad-ministration of steroids to patients.

Our diabetic patient had a history of travel in the known endemic area for blastomycosis in the USA. Before his travel he manifested no symptoms of any disease. As is the case in many travel-related fungal diseases, the patient presented himself in the hospital with non-specific symptoms and signs of respiratory illness shortly after his return to India. The present case emphasizes the importance of a detailed travel history of the patient as well as using microbiological, serological and histological tests to establish a diagnosis of an endemic mycosis such as blastomycosis or coccidioidomycosis in non-endemic areas. It is equally important to isolate causative agents of systemic mycoses in pure cultures and deposit them in national and international culture collections so that dimorphic fungal cultures will be available for further studies by other researchers.

In India, blastomycosis is a rare disease. There is no well-defined endemic area of blastomycosis in India and based on a few human and animal cases of blastomycosis in India, it appears that *B. dermatitidis* occurs in the environment in microfoci. Even in the US,
environmental isolations of *B. dermatitidis* are few and incompletely defined. There is not a reliable skin test antigen available for blastomycosis. The majority of epidemiologic information, especially regarding the occurrence of *B. dermatitidis* in the environment, has come from several outbreaks of blastomycosis in the endemic areas in the US. Epidemiological studies of clustered cases and outbreaks have revealed that *B. dermatitidis* occurs in decaying wood and other organic materials including bird guano and animal excreta, forest or sandy soils, waterways, ponds and riverbanks [23]. No such studies have been conducted in India.

**Acknowledgements**

We wish to thank Professor Dennis J. Baumgardner, MD, Department of Family Medicine – Milwaukee Clinical Campus, University of Wisconsin Medical School, Milwaukee, for sharing his expertise, his advice and valuable suggestions in revising the manuscript.

**References**
