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Secondary intracerebral blastomycosis with giant yeast forms

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Abstract

Secondary central nervous system (CNS) blastomycosis is an unusual manifestation of blastomycosis. We report a case of recurrent intracerebral blastomycosis that presented histopathologically with giant yeast-like cells and multinucleation that mimicked *Coccidioides immitis*. The yeast forms of *Blastomyces dermatitidis* usually range in size from 8 to 20 μm in diameter. Large or giant yeast forms (20–40 μm) are rare. The four cases previously reported in the literature involving giant yeast cell forms of *B. dermatitidis* are reviewed here. Intracerebral blastomycosis should be suspected in patients with signs and symptoms of CNS lesions and histories of primary blastomycosis, or treatment with corticosteroids, or comprised immune systems. The diagnosis should be confirmed by culture which presents typical biphasic microbiologic features.

Key words: *Blastomyces dermatitidis*, *Coccidioides immitis,* giant yeast form, intracerebral blastomycosis

Introduction

Blastomyces dermatitidis causes blastomycosis, which is an acute pulmonary, chronic pulmonary, or multisystem infection characterized by suppurative and granulomatous lesions [1, 2]. Blastomycosis is endemic around the Great Lakes and the Ohio River and Mississippi River valleys in North America, and in parts of India and Africa [1, 3, 4]. The infection ordinarily begins in the lungs and may disseminate to other organs [5, 6]. Central nervous system (CNS) involvement is a secondary manifestation of this disease and one of the rarest complications of systemic infection [7]. When secondary blastomycosis is suspected, surgery or biopsy with culture should be the first choice for diagnosis, and corticosteroids or immunosuppressive drugs should be avoided in these patients [8, 9].

Typical yeast-phase cells of *B. dermatitidis* have a characteristic appearance in tissue sections. They are multinucleated, relatively uniform in size (8–18 μm), and have thick walls with single broad-based (i.e., 4–5 μm) buds. When typical cells are present in sufficient numbers, a definitive diagnosis of *B. dermatiditis* infection can be made with confidence based on the histopathological examination of Hematoxylin & Eosin stained tissue sections [10, 11]. The unusual finding of giant, thin-walled, yeast-like cells with multiple nuclei and a pleomorphic appearance may lead to confusion with *Coccidioides immitis*. When giant yeast cell forms mimicking *C. immitis* are observed in the tissues, the distinctive morphology of *B. dermatiditis* in culture at 37 °C is diagnostic. We are reporting here a case of secondary intracerebral blastomycosis with giant yeast form. Three cases previously reported are reviewed.

Case report

A 56-year-old African American male presented with an episode of seizure and syncope in July,

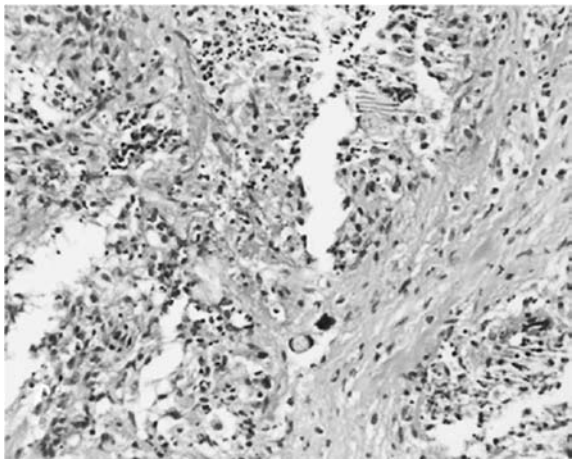

Figure 1. Acute and chronic inflammatory cells with mixed sizes of *B. dermatitidis*, two small cells on the left upper part, one big on the middle right with thick wall, hematoxylin and eosin (H & E) stain (20×).

2002. General physical and neurologic examinations were normal, but an MRI of the brain showed a right frontal heterogeneously enhancing mass measuring 1.5 cm. The patient had been diagnosed with pulmonary blastomycosis in 1999. At that time, the disease course was complicated by acute respiratory distress syndrome. The patient had been intubated and given high-dose intravenous liposomal amphotericin B for several months. The patient was a retired police officer who worked part-time in telecommunications. He denied intravenous drug abuse and he was negative for HIV antibodies on two occasions. Other past medical history included occasional sinusitis and obstructive sleep apnea. Stereotactic-guided biopsy of the right frontal mass revealed mild nonspecific changes, including gliosis and mild chronic inflammation. Gram and Gomori methenamine silver stains were negative for bacteria or fungi, respectively. Specific monoclonal antibody-based tissue stains directed against herpes simplex virus (HSV) type 1, HSV type 2 and cytomegalovirus (Dako, Inc., Carpinteria, CA) were negative. No biopsy specimens were submitted for culture at that time. The patient was sent home on phenytoin, famotidine, and dexamethasone. The patient remained asymptomatic and a follow-up MRI of the brain three months later showed that the right frontal lobe mass had slightly increased in size. The patient was re-admitted for stereotactic guided right frontal craniotomy and resection of the mass.

Results

Pathology

On gross examination, the excised lesion was a 2.5-cm encapsulated cystic mass containing greenish pus. Representative sections of mass were fixed in formalin and stained with hematoxylin and eosin (H & E). Microscopically, the lesion showed chronic inflammation, with giant cells and focal acute necrotizing inflammation. Some yeast like cells of various sizes were also noted (Figure 1). The largest fungal cells measured about 40 μm with thick walls (Figure 2) and multiple nuclei (Figure 3). Some fungal cells were found within the giant cells (Figures 3 & 4a), however, the budding yeasts were not clearly appreciated on the H&E-stained stained sections (Figure 4a). Based on the larger size, the thick walls, and the predominantly multinucleated fungal cells that resembled endosporulating spherules of *C. immitis*, a diagnosis of CNS coccidioidomycosis was reported by the surgical pathology laboratory.

Microbiology

A specimen of the pus from the cystic CNS mass was also submitted to the microbiology laboratory for culture. The specimen was inoculated onto inhibitory mould agar and brain heart infusion agar with 5% sheep blood. The plates were incubated aerobically at 25–30 °C with increased humidity. After nine days of incubation, downy, white colonial growth was noted on both plates. A scotch-tape prepara-

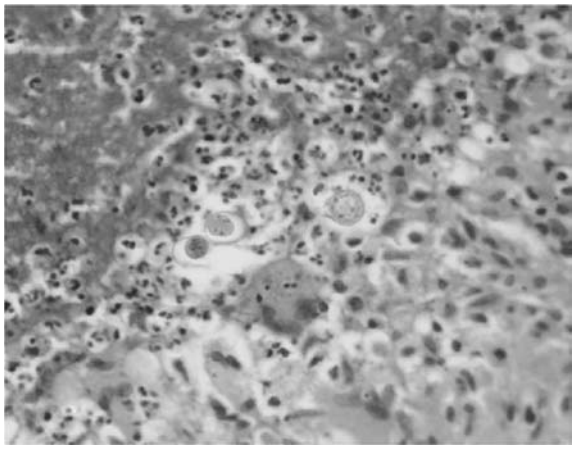

Figure 2. Different sizes of *B. dermatitidis* measuring from 25–30 μm on the left to 40 μm on the right, H & E stain (40×).

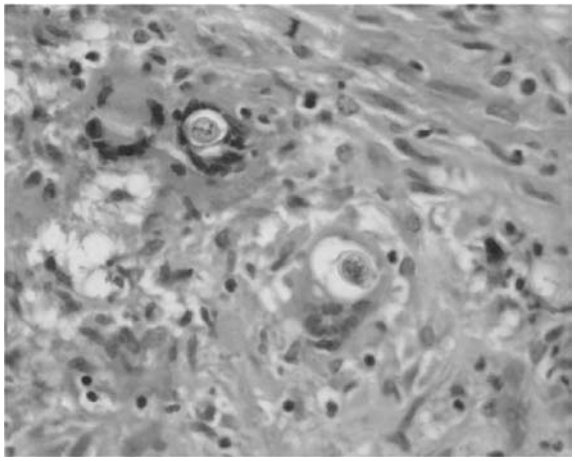

Figure 3. Multinucleated *B. dermatitidis* yeast forms within giant cells, H & E stain (40×).

tion from this growth showed delicate septate hyphae and conidiophores bearing single, lollypop-shaped conidia. This morphology was judged to be typical of the mycelial form of *B. dermatitidis*. Conversion of the mould to the yeast form by subculture and incubation at 35–37 °C was not attempted. The mould was submitted to the Microbiology Laboratory of the Illinois Department of Public Health and was subsequently confirmed as *B. dermatiditis* by the exoantigen test.

Immunohistology

A Gomori methenamine silver (GMS) stain of the tissue section revealed yeast-like cells of the same sizes that were observed on the H&E-stained sections. However, rare budding cells with broad bases (4–5 μm wide) and thick, double-contoured walls (Figure 4b) were also observed. This histopathological finding was morphologically consistent with *B. dermatiditis* and also confirmed the microbiological findings of the culture.

Follow-up

This patient was begun on therapy with intravenous liposomal amphotericin B (Ambisome, Gilead Corporation, California, 575 mg [5 mg/kg/day]). The following day his renal and hepatic functions began to deteriorate and, after hydration and discontinuation of the amphotericin B formulation, renal and hepatic functions improved. However, the patient developed a sudden onset of shortness of breath and was diagnosed with a pulmonary embolism by echocardiogram. Despite aggressive treatment with intravenous heparin, the patient expired. An autopsy revealed massive pulmonary thromboembolization as the immediate cause of death. A GMS stain of fibrotic lung tissue was negative for fungi, and fungal cultures of the site of the previously excised intracerebral mass were also negative.

Discussion

Blastomycosis is caused by the dimorphic fungus *B. dermatitidis*, which exists in nature in the mycelial phase and converts to a yeast phase at body temperature [12]. Yeast cells of *B. dermatiditis* are usually anywhere from 8 to 20 μm in diameter, contain multiple nuclei, and have a refractile double-contoured cell wall [2]. When budding is present, the bud is attached to the mother cell by a broad base [13]. In contrast, developing spherules of *C. immitis* usually are about 10–80 μm in diameter and display no reproductive buds. Mature spherules may actually be quite large, ranging from 100 μm to as large as 300 μm in diameter. Endospores within the spherules generally measure 2–5 μm in size. Spherules that are in the 8-to-20 micron size range may be mistaken for non-budding yeast forms of *B. dermatitidis*. Variability in the typical morphology of *B. dermatiditis* in tissue has been reported rarely in

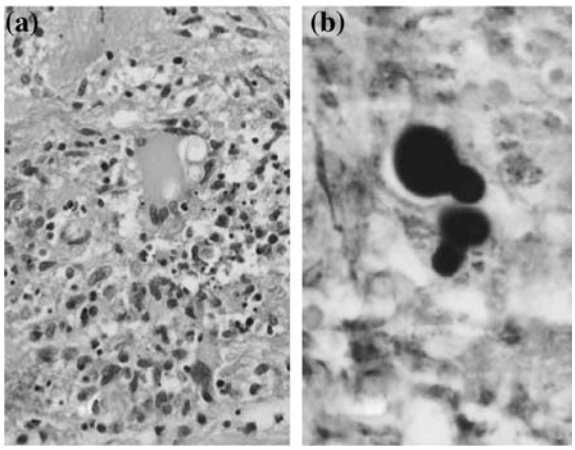

Figure 4. (a) Giant cell with two yeast like cells which indicate budding of *B. dermatitidis*, H & E stain (40×). (b) Typical yeast like cells with broad based blastoconidium, gomori methenamine silver (GMS) stain (60×).

Table 1. Four cases reported with giant yeast form of *Blastomyces dermatitidis*

Case	Author	Size (μm) giant yeast	TSF[d]	SU[e]	IM[c]	Age (yo)	Sex	UD[b]	Primary Blasto-mycosis	Out-come	COD[f]	Typical yeast form	G[g]
1	Watts	40	Lung	Y	N	49	F	SLE	Lung	Died	PB	Rare	N
2	Hussain	30–35	Lung	Y	N	65	M	COPD	Lung	Died	PB	Some	N
3	Walker	40	Skin	Y	Y	14	F	Heart Transplant	Lung	Died	PB, CB	Rare	N/A
4	Jay	28–35	Brain	Y	N	56	M	Cerebral Glioma	Lung	Died	PB	Rare	Y
5	Wu[a]	40	Brain	Y	N	56	M	None	Lung	Died	PE	Rare	Y

[a] Current case.
[b] UD = underlying disease; SLE = Systemic lupus erythematosus; COPD = Chromic obstructive pulmonary disease.
[c] IM = Immunosuppressive medication.
[d] TSF = Tissue sectioned from.
[e] SU = steroids used; Y = yes; N = No.
[f] COD = Cause of death; PB = Pulmonary Blastomycosis; CB = Cutaneous Blastomycosis; PE = Pulmonary Embolism.
[g] G = Granuloma; Y = yes; N = No; N/A = not available.

the literature [11, 14–17] (Table 1). The largest yeast cell size in these case reports was 40 μm, falling well within the size range of *C. immitis* spherules. Variations in yeast cell size in tissue may be due to strain variation or differential growth in host tissue. Small and atypical forms of *Blastomyces* have also been reported [18]. In the case reports cited in Table 1, all patients were also treated with corticosteroids. Whether corticosteroid therapy plays a role as the genesis of the giant yeast-like cells is not clear. Patients in all five reports were immunocompromised due to chronic disease and/or treatment of with immunosuppresive therapies. In our case, steroids were administered to the patient for three months for treatment for seizures after the first intracerebral mass biopsy. In two of the four previously reported cases, no granulomas were observed, one case with granuloma, and, the other one case, the formation of granulomas was not specifically addressed. The present case clearly showed granulomatous inflammation. In these case reports, all of the patients died of blastomycosis, but, in the current case, death was due to pulmonary embolism. Diffuse pulmonary thromboembolism associated with blastomycosis has been reported in a dog with pulmonary mycotic infection [19]. In our case, the pulmonary blastomycosis had apparently been eradicated, since no yeast forms were observed on GMS-stained lung tissue at autopsy. Unfortunately, autosy material was not submitted for fungal cultures. The patient's pulmonary embolism may have been associated with the recent surgical procedure and immobilization.

Secondary CNS blastomycosis is very rare [2]. In patients with diagnoses of previous pulmonary blastomycosis and current CNS lesions, secondary blastomycosis should be highly suspected [8, 20]. When surgical specimen is taken for histologic evaluation, culture should also be performed which remains the most valuable approach for diagnosis.

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