Fulminant blastomycosis with blastomycotic infection of a cerebral glioma

Light microscopic and ultrastructural observations

V. Jay¹, N. Laperriere², and R. Perrin³

¹ Department of Pathology, Ontario Cancer Institute/Hospital for Sick Children, University of Toronto, 555 University Avenue, Toronto MSG 1X8, Ontario, Canada
² Department of Radiation Oncology, Ontario Cancer Institute, Toronto, Canada
³ Department of Neurosurgery, Wellesley Hospital, Toronto, Canada

Received June 20, 1991/Revised, accepted July 8, 1991

Summary. Except for isolated case reports, blastomycosis has not been identified as a significant problem in immunosuppressed patients. We describe an unusual case with blastomycotic infection of a cerebral glioma in a 56-year-old man who underwent radiotherapy for his tumor and died of fulminant blastomycotic pneumonia. This is believed to be the first reported case of *Blastomyces dermatitidis* infection of a cerebral glioma. The light microscopic and ultrastructural features of *B. dermatitidis*, the giant forms of which were encountered in our patient, are described, and the role of immunosuppression due to steroid therapy in the pathogenesis of this fulminant infection are reviewed.

Key words: Blastomycosis – North American Blastomycosis – Brain tumor – Opportunistic infection – Ultrastructure

Invasive fungal infections are common when the immune function is depressed [7]. The most common fungi encountered are Candida and Aspergillus species which rarely if ever cause invasive disease in a normal host. Except for a handful of individual case reports, blastomycosis has not been a significant problem in immunosuppressed patients [2, 5, 11, 22, 26, 31]. We describe presentation of blastomycosis as a fatal pneumonitis in a 56-year-old man who underwent radiation therapy for a cerebral glioblastoma multiforme. The unusual clinical and pathological findings with involvement of the tumorbed itself and the role of immunosuppression due to steroid therapy are discussed.

Case report

This 56-year-old white male, a business executive, presented to the Wellesley Hospital with a 3-month history of decreasing sensation in the right half of his body. There was no other significant past medical history. There was no history of drug abuse. He denied homosexual contact. The patient was a resident of Toronto and there was no history of recent travel.

Clinical examination revealed decreased sensation on the right side, visual field defect with a right inferior quadrantanopsia, and some difficulties in word finding. A CT scan of the head revealed an irregular enhancing mass deep in the left parietal lobe with surrounding edema (Fig. 1). A stereotactic biopsy revealed a
high-grade astrocytoma with necrosis and endothelial vascular hyperplasia, consistent with the diagnosis of glioblastoma multiforme.

The patient was started on Dexamethasone and Ranitidine and his condition stabilized. He underwent a radical course of cranial irradiation with isocentric high energy linear accelerator (25 megavolts) to a dose of 50 Gy in 25 daily fractions in 5 weeks via a parallel pair of fields to a regional volume incorporating the primary tumor plus a 3-cm margin. The patient tolerated this quite well and developed the expected side effects of alopecia and scalp erythema, and remained on dexamethasone 8 mg/day.

Approximately 8 months after his initial symptoms, the patient was admitted to hospital with a 1-week history of increasing dyspnea, mild fever, and generalized weakness. On examination, he appeared quite unwell and confused with a respiratory rate of 40/min, pulse 120/min and temperature of 37.5°C. He was disoriented to time and place. There was 2+ pedal edema. Examination of the chest revealed bronchial breathing in the left lower lung field with coarse crepitations bilaterally. There were no new neurological abnormalities as compared to the previous examinations.

A chest X-ray revealed bilateral pulmonary changes involving all lobes of the lungs with diffuse interstitial changes consisting of edema, nodules and interstitial infiltrates. Arterial blood gases revealed PO$_2$ 30 mmHg, PCO$_2$ 23 mmHg, pH 7.54, and HCO$_3$ 20 mmol/l. Oxygen and morphine were administered. There was no sputum production. Blood cultures for both aerobic and anaerobic bacteria were made and revealed no growth after 7 days. Empirically, the patient was started on intravenous Keflex, Tobramycin, Erythromycin, and Septra.

The patient’s condition continued to deteriorate and he died 36 h after admission to the hospital. The autopsy was limited to examination of the brain, liver and lungs.

**Pathological findings**

Both lungs were consolidated with a nodular hemorrhagic appearance, the right lung weighing 1080 g and the left lung weighing 1570 g. On cut section, all lobes of both lungs revealed extensive consolidation with firm nodules and multiple abscesses. Microscopic examination of lungs revealed a florid necrotizing pneumonia with abscess formation. Numerous *Blastomyces dermatitidis* organisms were seen within the alveolar spaces, which appeared packed with fungi (Fig. 2). They revealed the characteristic single broad based budding. The sizes were quite variable, being on average about 20 μm with many larger fungi in the range of 28–35 μm. The double-contoured cell walls and the cytoplasmic mass were stained by the periodic acid-Schiff (PAS) stain, with the cytoplasm being often retracted from the cell wall (Fig. 2b). Multiple nuclei were present. The cell walls were also stained by the Gomori methenamine silver stain but not by mucicarmine. There was also severe diffuse alveolar damage and severe edema. Hyperplastic type 2 pneumocytes with moderate nuclear hyperchromatism and atypia were present. The lungs were virtually replaced by fungal growth, with plugging of bronchi and bronchioles with fibrinous and mucoid material abounding in fungi. In rare blood vessels, intraluminal organisms were seen, indicating hematogenous dissemination. Fibrinopurulent pleuritis with *B. dermatitidis* organisms on the pleural surface was also observed. Focally, there was a

![Fig. 2. a Low-power micrograph of lung showing extensive fungal pneumonitis with alveoli packed with *Blastomyces dermatitidis* organisms. b High-power micrograph illustrating fungal morphology: note the variability in fungal size with giant forms. a, b PAS; a × 112; b × 560](image-url)
component of chronic inflammation with macrophages and plasma cells.

The liver was enlarged weighing 1600 g and grossly was not very remarkable except for occasional whitish specks on the cut surface. On microscopy, it was studded with microabscesses and fungal organisms could be identified within Kupffer cells. There was mild steatosis involving the hepatocytes. In a few portal tracts, a few macrophages and occasional plasma cells were present. Special stains did not demonstrate bacterial, fungal, or mycobacterial infection in sections of the lung and liver. Immunostaining for cytomegalovirus antigen revealed no immunopositivity in sections of the lung and the liver.

The brain weighed 1460 g. There was slight thickening and opacification of the leptomeninges, but no evidence of meningeal exudates. Coronal sections of the brain showed an irregular partially necrotic highly vascular tumor in the left temporal, parietal and occipital white matter with involvement of the thalamus and basal ganglia and extension to the ventricular surface. Microscopic examination revealed a high grade astrocytoma (glioblastoma multiforme) with extensive radiation necrosis and radiation vasculopathy. The tumor itself was composed of plump gemistocytic astrocytes with moderate nuclear pleomorphism. Extensive hemosiderin accumulation indicated old hemorrhage. Besides the radiation-associated changes, there were no other unusual features in the tumor which had relatively few mitoses.

The most noteworthy finding was that of B. dermatitidis organisms within the tumor (Fig. 3) and the brain. These were seen in several patterns: well-organized microabscesses with fungi, well-organized epithelioid granulomas with fungal forms within Langhan’s giant cells, microglial nodules or scattered phagocytes containing fungal organisms. In the cerebellum, focal meningeal involvement was noted; in one area, the microabscess was seen to rupture into the subarachnoid space with overlying meningeal inflammation. Fungi were not seen within reactive or neoplastic astrocytes, but rather within microglia or multinucleated giant cells. They were not identified in the pituitary, pineal, or choroidal plexus. There was evidence of recent hypoxic-ischemic encephalopathy with cosinophilic Purkinje cells in the cerebellum. There was no evidence of any other opportunistic infection in the brain and immunostaining of several sections failed to disclose cytomegaloviral infection.

Ultrastructural studies

Methods. Pieces of formalin-fixed tissue from the lung and liver were submitted for electron microscopic studies. Tissues were postfixed in 1% osmium tetroxide, dehydrated in ethanol, and embedded in Spurr’s embedding media. Ultrathin sections were stained with lead citrate and uranyl acetate and studied with a Zeiss 902 electron microscope.

EM findings. Both the lung and liver samples showed relatively well-preserved and viable fungal forms in contrast to the host tissues. Most organisms were extracellular; due to postmortem artifact and poor preservation of host tissues, the detailed morphological appearances of cells harboring the intracellular fungi could not be commented upon. The fungi had lamellated cells walls with two distinct layers separated by a relatively electron lucent intervening zone (Fig. 4). The outer aspect of the cell wall presented an irregular external surface. The thickness of the cell
isolation of the organism from other sites. Although, the
reported in the literature with regards to the size and
this pathogen. Our observations confirm the findings
with diameters measuring from 28 to 35 μm (normal
morphology was encountered with many giant forms
fluid (CSF) examination, CSF smears or cultures may be

Discussion

Blastomycosis is caused by *B. dermatitidis*, a dimorphic
fungus that dwells as a saprophyte in the soil worldwide,
but principally in the southeastern, south central, and
upper midwestern regions of the USA with new endemic
foci being uncovered in other geographical locations [13,
18, 29]. The organism enters the body via the lungs with
subsequent dissemination to other organs and patients
most often present with cutaneous or pulmonary com-
plaints, although the infection may be asymptomatic
[18, 29].

Blastomycosis involving the central nervous system
(CNS) has been reported infrequently in the literature
almost invariably in association with systemic infection
[1, 4, 10, 14, 15, 20, 21, 23–25, 27, 30]. The estimates of
CNS involvement range from 3%–10% in clinical studies and from 6%–33% in autopsy studies [4, 10, 27].

Patients with CNS blastomycosis may present with acute
or chronic meningitis or mass lesions of the brain or
spinal cord including multiple or single abscesses or
granulomas. A clinical diagnosis of CNS blastomycosis is
difficult, and in many of the cases a presumptive
diagnosis has been based on the identification or
isolation of the organism from other sites. Although, the
diagnosis has been made on the basis of cerebrospinal
fluid (CSF) examination, CSF smears or cultures may be
negative [15].

In our case, a variation from the typical fungal
morphology was encountered with many giant forms
with diameters measuring from 28 to 35 μm (normal
range 8–15 μm). Excellent preservation allowed for clear
documentation of the ultrastructural morphology, especi-
ally with reference to the budding characteristics of
this pathogen. Our observations confirm the findings
reported in the literature with regards to the size and
distribution of various organelles [6, 20]. In an ultra-
structural study of a cerebellar blastomycoma, Mirra et al.
[20], described fungi which were intracellular in
membrane-bound compartments within multinucleated
giant cells and macrophages. In our case, besides
organisms within macrophages in the liver, most yeasts
were extracellular, and in an excellent state of preser-
vation compared to the host tissues which were auto-
lyzed. Organisms in various stages of budding were
identified: it is apparent that the outermost layers of
the cell wall are sheared off at the initiation of this process
with contribution of the inner layers to the septum and
the new coat of the daughter cell. The most abundant
organelle was the mitochondrion. The mitochondria
showed well-preserved cristae and electron-dense particu-
late material reminiscent of calcium. The lamellated

walls was variable ranging from 0.3 to 0.8 μm. The organelles
included moderate numbers of mitochondria, glycogen and lipid
granules, a few freelying as well as membrane-bound structures
with electron-dense lamellated profiles, a few tubular structures,
and multiple nuclei (Fig. 4). The nuclei had one to two nuclei and
showed some heterochromatin condensations (Figs. 4, 5). A few
fungi contained numerous mitochondria. A number of cells in the
process of budding were encountered: the initiation of budding was
marked by a shearing of the outermost electron-dense lamellated
layers of the cell wall (Fig. 5). The inner layers of the cell wall
persisted over the protruding bud and covered the daughter cell
and the broad-based septum (Fig. 5). Scattered bacteria were also
found in the lung sample.

The tissue response to *B. dermatitidis* is a combined
granulomatous and suppurrative reaction as illustrated in our
case. Interestingly, despite extensive sampling, the
chronic inflammatory component was minimal in the
lungs which showed alveoli packed with organisms.
Fatal adult respiratory distress syndrome (ARDS) due to
*B. dermatitidis* has been described by Evans and collec-
tues in a report of two patients [9]. ARDS secondary to
blastomycosis has also been reported in pregnancy [19],
which has been considered to be related to the pregnan-
cy-related immunosuppression.

To our knowledge, this is the first reported case of
blastomycotic infection of a cerebral glioma. The tumor
itself showed no unusual features except the anticipated
radiation necrosis. The fungi occurred within microglial
nodules, epithelioid granulomas or microabscesses with-
in the tumor bed. They were either extracellular or
within macrophages and were not contained within the
tumor cells. This is in contrast to the report of Ho et al.
[12] of cytomegalovirus infection of a glioma in a patient
with the acquired immune deficiency syndrome [AIDS],
where virus-infected tumor cells were described.

The epidemiology and ecology of blastomycosis are
not fully elucidated [13, 18 29]. In this regard, it is of
interest that our patient was a city dweller and had no
occupational exposure to wood, soil, or animals. Immu-
nosuppression related to steroid therapy was presum-
bly the predisposing factor in our patient for develop-
ment of fulminant blastomycosis. Although the autopsy
was limited to examination of lungs, liver and brain only,
it is evident that the patient had hematogenous spread of
the disease, with fungal organisms demonstrable within
cells of the monocyte-macrophage system and also
within vascular spaces in the lungs. There were no visible
skin lesions in our patient, thus the portal of entry and
original infection is most likely the lung and this
fulminant infection perhaps represents endogenous
reactivation of a latent infection, which is a well-
recognized phenomenon [8, 16].

Blastomycosis is not a common infection associated
with immunosuppression. It is rarely reported as an
opportunistic pathogen in the immunocompromised
host usually in the setting of hematological malignancy
or steroid immunosuppression [2, 5, 22, 26]. Of 78 patients with blastomycosis, Recht et al. [26] found an underlying hematological malignancy in 3 cases and association with glucocorticoid therapy in 3 patients. The clinical picture in these 6 patients was similar to blastomycosis in immunocompromised patients with chronic pulmonary infiltrates or isolated skin ulcers. Blastomycosis complicating bone marrow transplantation has been described by Winston et al. [31].

The standard therapy advocated for this infection is amphotericin B and ketoconazole [3, 7, 28]. Ketoconazole, which has the advantages of oral adminisatability and less severe toxicity has the disadvantage of poor penetration of the blood-brain-barrier and treatment failures resulting in death of some patients with severe pulmonary blastomycosis. Pitrak et al. [23] described development of a cerebral mass lesion in a patient treated with oral ketoconazole for pulmonary blastomycosis, with resolution of the lesion after intravenous amphotericin therapy. Our patient did not have the benefit of therapy due to the rapidity of clinical course and death before definitive diagnosis of the nature of the pneumonitis.

In summary, a case of fulminant blastomycosis with fungal infection of a glioma is described. In our patient, besides steroid immunosuppression, there appears to be no other predisposing factor, although the rapidity of the clinical course precluded a detailed workup of the immunological status. Blastomycosis has been described in the setting of the AIDS [11, 17]; in our patient, there is no evidence to suggest this as a possible predisposing factor; furthermore, besides this uncommon fungal pathogen, no other opportunistic infections are identified.

References

1. Benzel EC, King JW, Mirakhraee M, West BC, Misra RP, Hadden TA (1986) Blastomycotic meningitis. Surg Neurol 26:192–196
2. Berger R, Kraman S (1981) Acute miliary blastomycosis after 'short-course' corticosteroid treatment. Arch Intern Med 141:1223–1225
3. Bradsher RW (1989) Blastomycosis: fungal infections of the lung update: 1989. Semin Respir Infect 5:105–110
4. Buechner HA, Clawson CM (1967) Blastomycosis of the central nervous system. II. A report of nine cases from the Veterans Administration Cooperative study. Am Rev Respir Dis 95:820–826
5. Chow S, Goldstein EJC, Brody N (1981) North American blastomycosis in an immunosuppressed patient. Cutis 28:572–574
6. Daniel WC, Nair SV, Blaustein J (1979) Light and electron microscopic observations of Blastomyces dermatitidis in spumum. Acta Cytol 23:222–226
7. Druet DI, Ed., (1989) Systemic fungal infections: diagnosis and treatment II. Infect Dis Clin North Am 3:1–133
8. Ehm W (1989) Endogenous reactivation in blastomycosis. Am J Med 86:831–832
9. Evans ME, Haynes JB, Atkinson JB, Delvaux TC, Kaiser AB (1982) Blastomyces dermatitidis and the adult respiratory distress syndrome. Case reports and review of the literature. Am Rev Respir Dis 126:1099–1102
10. Gonyea EF (1978) The spectrum of primary blastomycotic meningitis: a review of central nervous system blastomycosis. Ann Neurol 3:26–39
11. Herd AM, Greenfield SB, Thompson WS, Brunham RC (1990) Miliary blastomycosis and HIV infection. Can Med Assoc J 143:1329–1330
12. Ho KL, Gottlieb C, Zarbo RJ (1990) Cytomegalovirus infection of cerebral astrocytoma in an AIDS patient [Abstr]. J Neuropathol Exp Neurol 49:325
13. Kane J, Righter J, Kraiden S, Lester RS (1983) Blastomycosis: a new endemic focus in Canada. Can Med Assoc J 129:728–731
14. Krarup C, Davis CH, Symon L, Harding BN, Hay RJ (1984) Spinal blastomycosis: case report. J Neurol Neurosurg Psychiatry 47:217–218
15. Kravitz GR, Davies SF, Eckman MR, Sarosi GA (1981) Chronic blastomycotic meningitis. Am J Med 71:501–505
16. Laskey WK, Sarosi GA (1978) Endogenous activation in blastomycosis. Ann Intern Med 88:50–52
17. Lo HY, Notenboom RH (1990) A new enzyme immunoassay specific for blastomycosis. Am Rev Respir Dis 141:84–88
18. Logsdon MT, Jones HE (1979) North American blastomycosis: a review. Cutis 24:524–535
19. MacDonald D, Algire PC (1990) Adult respiratory distress syndrome due to blastomycosis during pregnancy. Chest 98:1527–1528
20. Mirra SS, Trombley IK, Miles ML (1980) Blastomycoma of the cerebellum. An ultrastructural study. Acta Neuropathol (Berl) 50:109–114
21. Morgan D, Young RF, Chow AW, Mehringer CM, Itabashi H (1979) Recurrent intracerebral blastomycotic granuloma: diagnosis and treatment. Neurosurgery 4:319–324
22. Onal E, Lopata M, Lourenço RV (1976) Disseminated pulmonary blastomycosis in an immunosuppressed patient. Diagnosis by fiberoptic bronchoscopy. Am Rev Respir Dis 113:83–86
23. Pitrak DL, Anderson BR (1989) Cerebral blastomycoma after ketoconazole therapy for respiratory tract blastomycosis. Am J Med 86:713–714
24. Raftopoulos C, Flament-Durand J, Coremans-Pelseneer J, Noterman J (1986) Intracerebellar blastomycosis abscess in an African man. Clin Neurol Neurosurg 88:209–212
25. Rainey RL, Harris TR (1966) Disseminated blastomycosis with meningeval involvement. Arch Intern Med 117:744–747
26. Recht LD, Davies SF, Eckman MR, Sarosi GA (1982) Blastomycosis in immunosuppressed patients. Am Rev Respir Dis 125:359–362
27. Roos KL, Bryan JP, Maggio WW, Jane JA, Scheld WM (1987) Intracranial blastomycoma. Medicine 66:224–235
28. Saag MS, Dismukes WE (1988) Treatment of histoplasmosis and blastomycosis. Chest 93:848–851
29. Sarosi GA, Davies SF (1979) Blastomycosis. Am Rev Respir Dis 120:911–938
30. Tang TT, Marsik FJ, Harb JM, Williams JE, Frommell GT, Dunn DK (1984) Cerebral blastomycosis: an immunodiagnostic study. Am J Clin Pathol 82:243–246
31. Winston DJ, Gale RF, Meyer DV, Young LS (1979) Infectious complications of human bone marrow transplantation. Medicine 58:1–31