Case Reports

Central Nervous System and Genitourinary Blastomycosis: Confusion With Tuberculosis

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INFECTION WITH the dimorphic fungus *Blastomyces dermatitidis* causes a wide spectrum of disease, ranging from asymptomatic pulmonary infection to a fatal systemic illness. Although effective antifungal therapy is available, the difficulty in establishing an early diagnosis hampers management of the disease.

We describe a fatal case of blastomycosis occurring in a nonendemic area that illustrates the difficulties in distinguishing blastomycosis from tuberculosis. Furthermore, this report shows the importance of carefully searching for evidence of blastomycosis elsewhere than the central nervous system when there is unexplained chronic meningitis. In addition, blastomycosis as a cause of hypothalamic-pituitary dysfunction, as described in this case, has only infrequently been reported.[1]

Report of a Case

The patient, a 54-year-old heavy equipment operator, first presented to the Portland Veterans Administration Medical Center on August 10, 1981, because of urinary frequency and hesitancy. On examination he had a tender prostate and analysis of urine showed 20 leukocytes per high power field without visible bacteria. Empiric treatment with trimethoprim-sulfamethoxazole resulted in symptomatic improvement. Culture of a urine specimen obtained before therapy was negative for bacteria.

First Admission, September 1, 1981

Three weeks later he was admitted to hospital because of shortness of breath, cough, night sweats, polyuria, polydipsia and a 6.8-kg (15-lb) weight loss. There was no history of recent travel outside of Oregon though the patient had traveled widely in the 1950s while in the service. He had also worked for three years in a tuberculosis sanatorium in the 1940s. Findings on physical examination were unremarkable. A chest roentgenogram showed infiltrates of both apices and posterior upper lobes (Figure 1). Gram's stain of an expectorated sputum specimen showed numerous polymorphonuclear leukocytes, rare epithelial cells and predominant Gram-positive diplococci. Stains for acid-fast bacilli were negative on three occasions. Analysis of urine again showed 20 leukocytes per high power field and bacterial cultures were negative. A tuberculin skin test (5 tuberculin units) was positive with 18 mm of induration. Screening tests of blood chemistries and complete blood count were normal. A pyelogram with dye given intravenously showed mild bladder outlet obstruction and prostatic hypertrophy but no evidence of upper urinary tract disease. The patient was diagnosed as having pneumococcal pneumonia and possible active pulmonary and renal tuberculosis. Treatment with procaine penicillin, isoniazid and rifampin was begun. The patient reported symptomatic improvement and was discharged on a regimen of antituberculous therapy after completing a ten-day course of penicillin.

Second Admission, September 14, 1981

Readmission three days later was prompted by lethargy and orthostatic dizziness. Despite clinical evidence of volume depletion, he was noted to be polyuric. Results of water deprivation tests were suggestive of partial central diabetes insipidus (Table 1).[2] Further evaluation of the patient's hypothalamic-pituitary axis showed the following values: follicle-stimulating hormone, 7.6 mIU per ml (normal, 5 to 20); luteinizing hormone, 3.0 mIU per ml (normal, 5 to 20); testosterone, 76 ng per dl (normal, 300 to 1,100); adjusted thyroxine, 2.4 ng per dl (normal, 4 to 10.5); thyroid-stimulating hormone, 2.3 IU per ml (normal, less than 5.8), and prolactin, 35 ng per ml (normal, 2 to 18). Plasma cortisol levels before and 30 minutes after intravenous administration of 0.25 mg cosyntropin (Cortrosyn) were 5.3 μg per dl and 12.9 μg per dl, respectively. The results were considered typical of hypothalamic dysfunction and replacement therapy with hydrocortisone, levothyroxine and vasopressin was begun. A computerized tomographic (CT) scan of the head showed enhancing lesions in the suprasellar region, left cerebellum and right caudate nucleus (Figure 2). A low-density lesion in the left temporal area was felt most suggestive of an arachnoid cyst. Lumbar puncture done September 30, 1981, showed an opening pressure of 260 mm of water. Cerebrospinal fluid studies are recorded in Table 2. Results of Gram's stain; fluorochrome, india ink, cryptococcal antigen and VDRL tests; cytology examination, and bacterial and fungal

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ABBREVIATIONS USED IN TEXT

CF=complement-fixation
CT=computerized tomography

cultures were negative. Four-vessel cerebral angiography showed left ophthalmic artery and anterior communicating artery aneurysms and the left temporal lesion that again was felt to be an arachnoid cyst. Though tuberculous meningitis was the likely diagnosis, cultures of urine, sputum and cerebrospinal fluid specimens were all negative for mycobacteria at six weeks. Diagnostic bronchoscopy with transbronchial biopsy, brushing and washing specimens was done with cytologic examination, cultures, fluorochrome, Gram's stain and potassium hydroxide preparation. These did not result in a diagnosis. Biopsy specimens of the upper lobes of the lung showed chronic inflammation without organisms or granulomata.

The patient improved symptomatically with rehydration and was discharged receiving isoniazid, rifampin, hydrocortisone, desmopressin acetate and levothyroxine. Two weeks after discharge he was seen in the outpatient clinic and remained improved.

Third Admission, October 24, 1981

The patient was admitted because of confusion, lethargy and pronounced orthostatic hypotension. Neurologic examination showed meningism, ataxic gait and a mild left hemiparesis. Findings on a chest roentgenogram and CT scan of the head were unchanged. Lumbar puncture was repeated October 26, 1981 (Table 2). A large volume cisternal tap showed similar values and smears, cultures and cytologic studies were also negative. Serologic tests of serum showed the following titers: coccidioidomycosis complement-fixing (CF) of 1:8, blastomycosis CF 1:8, histoplasmosis CF 1:32 and cryptococcal antigen test negative. Cerebrospinal fluid electrophoresis showed a polyclonal increase in immunoglobulin G. Culture of expressed prostatic secretions grew an organism initially identified as a *Chrysosporium* and felt to be a contaminant. The culture was sent to the Centers for Disease Control for further identification. A bone marrow biopsy specimen showed no organisms or granulomata.

TABLE 1.—*Water Deprivation Test, Second Admission (September 14, 1981)*

Urine volume for 24 hrs	4,450-5,750 ml
Dehydration period	7 hrs
Maximum urinary osmolality on dehydration	252 mosm/kg water
Urinary osmolality after vasopressin therapy	286 mosm/kg water
Change in urinary osmolality	+34 mosm/kg water (+13.5%)
Plasma osmolality before vasopressin	283 mosm/kg water
Weight change on dehydration	1.4 kg

Recurrent episodes of somnolence were attributed to rising serum sodium content and volume depletion. Vasopressin tannate was given subcutaneously and fluids intravenously to maintain intravascular volume. Ten days after admission, the patient became severely obtunded and an acute right hemiparesis and central hyperventilation developed. A CT scan of the head

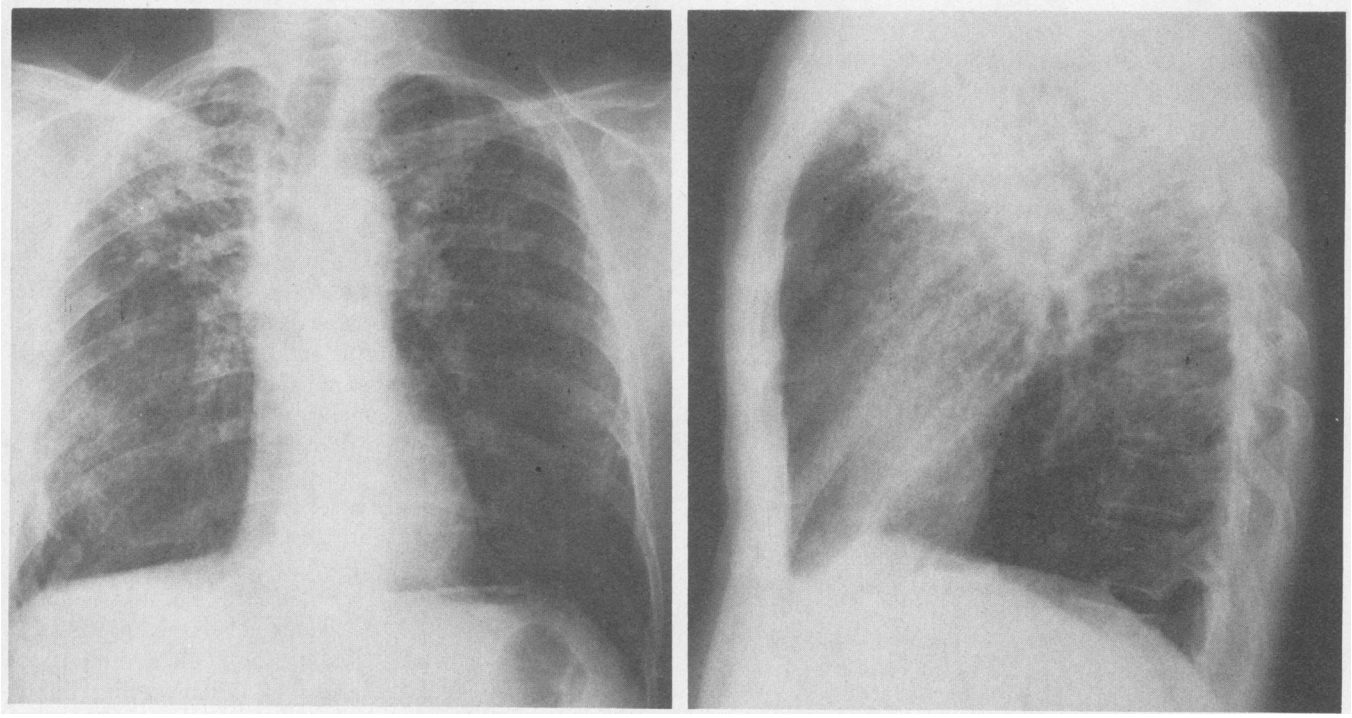

Figure 1.—Posteroanterior **(left)** and lateral **(right)** chest films done on first admission (September 1, 1981) showing infiltrates in both apices and posterior upper lobes.

showed no change. Progressive obtundation and respiratory depression necessitated mechanical ventilation. Lumbar puncture was repeated November 6, 1981 (Table 2). Serologic studies of a cerebrospinal fluid specimen for fungus showed histoplasmosis CF titer 1:8, blastomycosis CF titer 1:2 and cryptococcal antigen test negative.

Because of a failure to respond to antituberculous therapy, an uncertain diagnosis and a severely worsening clinical condition, amphotericin B therapy was begun on November 6, 1981, for the possibility that fungal meningitis might be present. Diagnostic craniotomy was done after three days of amphotericin B administration, with biopsy specimens of brain and meninges showing nonspecific inflammation. No microorganisms or malignant cells were identified but the presence of a benign arachnoid cyst was confirmed. A follow-up CT scan showed decreased enhancement of the suprasellar lesion. Over the next several weeks the patient's mental state improved gradually but never returned to baseline. Five weeks after beginning amphotericin B therapy, a repeat lumbar puncture showed a return to normal of cerebrospinal fluid values (Table 2). Subsequently, bacteremia and bilateral lower lobe

TABLE 2.—*Cerebrospinal Fluid Measurements*

Date	Glucose mg/dl	Protein mg/dl	Leukocytes	Neutrophils Percent
9/30/81	37	111	610	44
10/26/81	14 (86)*	310	450	49
11/ 6/81†	20 (92)	253	1,285	83
12/12/81	82 (128)	51	15	0

*Simultaneous serum glucose values in parentheses.
†Amphotericin B therapy was begun on November 6, 1981.

aspiration pneumonia developed due to *Staphylococcus aureus*. Following profound and prolonged hypotension, the patient became decerebrate and a CT scan showed decreased density in the entire left hemisphere and a large midline shift, indicating a left cerebrovascular accident. A nuclear brain scan showed no perfusion of either hemisphere. An electroencephalogram showed no cerebral electrical activity and mechanical ventilation was discontinued.

Postmortem Findings

Serologic studies for fungi done on a cerebrospinal fluid specimen obtained just before death showed no change in histoplasmosis, blastomycosis, cryptococcal

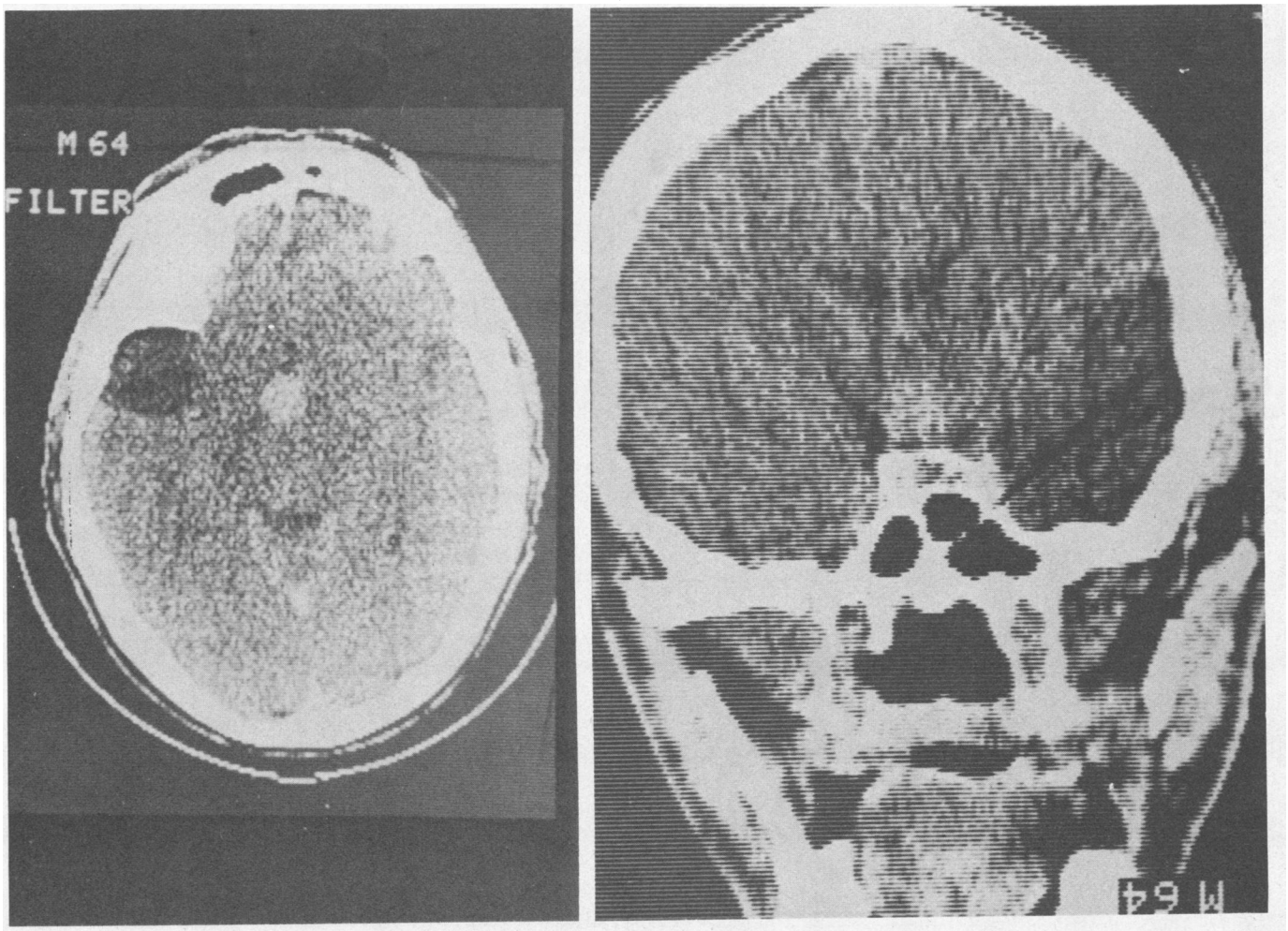

Figure 2.—Computerized tomographic scan of head, axial **(left)** and coronal **(right)** sections, on second admission (September 14, 1981) showing lesions in the suprasellar region, left cerebellum and right caudate nucleus.

or coccidioidomycosis antibody titers. Four weeks after the patient died, culture of the expressed prostatic secretions taken nine weeks before his death was reported by the Centers for Disease Control to be growing *Blastomyces dermatitidis*. Postmortem examination showed extensive central nervous system and prostatic involvement with budding yeast forms on periodic acid-Schiff staining, morphologically typical of *B dermatitidis* (see photomicrographs, Figures 3 and 4). Organisms were identified in both lobes of the pituitary gland, in the pituitary stalk and in the leptomeninges at the base of the hypothalamus. A diffuse perivascular mononuclear cell infiltration associated with budding yeast was found in vessels from the circle of Willis. A recent left hemispheric infarction was present. The remainder of the brain including the hypothalamic region was not sufficiently preserved for accurate pathologic diagnosis. The lungs showed apical scarring and fibrosis without active disease and pneumonia of both lower lobes was found. Acid-fast and periodic acid-Schiff stains showed no organisms in pulmonary tissue. Fungal culture of specimens taken at autopsy from lung, brain and prostate were negative.

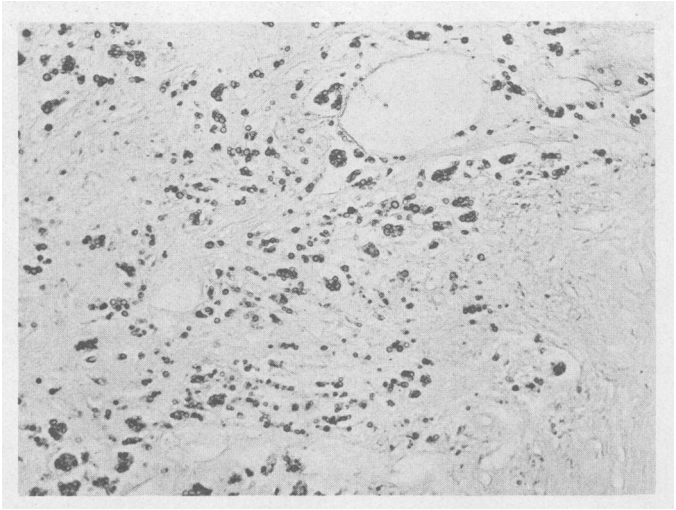

Figure 3.—Secretion of prostate shows numerous budding yeast forms. (Methenamine silver stain, reduced from magnification ×100.)

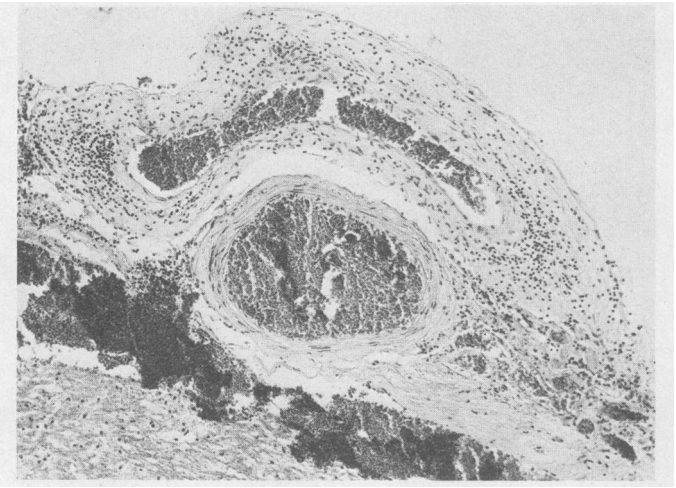

Figure 4.—Section of nutrient branches of basilar artery, with upper vessel showing vasculitis. (Hematoxylin and eosin stain, reduced from magnification ×100.)

Comments

Although originally felt to be a disease limited to North America, blastomycosis is now recognized to have a worldwide distribution. Endemic areas in North America, as defined by case reporting, include the southeastern and south central United States, as well as the Great Lakes region of the United States and Canada. The disease appears to be distinctly less prevalent west of the Rocky Mountains, though cases have been reported sporadically.[3,4] The precise epidemiology of blastomycosis has yet to be defined. Occupational or recreational exposure to soil enriched with avian excreta has been suggested as a potential source of infection; attempts to culture the organism from soil, however, have usually failed.[4] Our patient's occupation (heavy equipment operator) is likely to have provided ample opportunity for such exposure. No related cases in humans or dogs that would suggest a common source of exposure could be identified.

Pulmonary infection due to *B dermatitidis* can present as acute pneumonia but more often results in minimally symptomatic or asymptomatic pneumonitis. Spontaneous healing and late endogenous reactivation have been observed.[4] The findings on chest roentgenograms in cases of pulmonary blastomycosis are not distinctive, with changes varying from a consolidated lobar pneumonia to multiple diffuse infiltrations. Hilar adenopathy is common but cavitation is rare.[5,6] Our patient's chest roentgenogram showed changes typical of granulomatous disease but without prior films for comparison the activity of disease could not be assessed. Because of a positive tuberculin skin test, the abnormalities were initially considered due to tuberculosis. No evidence of active pulmonary blastomycosis or tuberculosis was found on repeated cultures or histopathologic examination of the lungs either before or after death. Whether the roentgenographic abnormality represented healed blastomycosis or tuberculosis or both cannot be determined.

Central nervous system involvement with blastomycosis is estimated to occur in 3% to 10% of cases. Estimates are as high as 33% in autopsy series.[7] Central nervous system disease presents clinically as chronic meningitis or as intracranial or spinal mass lesions. A similarity between blastomycotic and tuberculous meningitis has been stressed in recent reviews[7,8] and, indeed, the two diseases are indistinguishable on clinical grounds. Serodiagnosis of blastomycosis is insensitive and cross-reaction with *Histoplasma capsulatum* can occur.[4,9] Although a complement-fixation titer of 1:32 or higher should encourage aggressive attempts to diagnose blastomycosis, no single titer is diagnostic of active disease. Skin tests are of no value in diagnosis and are no longer commercially available. More than 90% of reported cases of central nervous system blastomycosis have had culture-negative lumbar cere-

brospinal fluid. Cisternal or ventricular fluid sampling has been considered more sensitive than lumbar puncture,[7,8] but in the current case a large-volume cisternal tap was negative for fungi by both smear and culture despite extensive central nervous system involvement proved at autopsy. Likewise, meningeal and brain biopsy studies showed no abnormalities, although specimens were not obtained from the basal meninges, the area found at autopsy to have the richest fungal invasion. Gonyea[7] has stressed the importance of a vigorous diagnostic search for extraneural disease and that testing should include cutaneous and subcutaneous lesions, joint effusions, large volume urine culture, smear and culture of prostatic secretions or prostatic biopsy. A needle biopsy of the prostate would likely have provided an earlier diagnosis in our patient. Vasculitic response to deep mycotic infection has been well described in cases of histoplasmosis and coccidioidomycosis,[1] but to our knowledge has not been described in those of blastomycosis. Vasculitis may have contributed to our patient's recurrent focal neurologic events.

The male genitourinary tract is involved in 20% to 30% of cases of blastomycosis. Presentation with prostatitis or urinary retention is well documented.[10,11] The importance of aggressive evaluation of a slowly resolving case of prostatitis, including fungal culture of prostatic secretions and a biopsy study, cannot be overemphasized. Culture of expressed prostatic secretions eventually led to a correct diagnosis in our patient but delay in doing this caused a delay in instituting appropriate therapy. Because *B dermatitidis* may require two to three weeks for isolation and identification, histopathologic examination of biopsy material potentially provides a more rapid diagnosis.

Endocrine syndromes caused by blastomycosis have included primary adrenal insufficiency due to adrenal involvement,[12] hyperprolactinemia due to chronic pleural disease[13] and, recently, diabetes insipidus of unclear cause.[14] Pathologic series have described thyroid and pituitary involvement but no clinical data are provided.[1] To our knowledge this is the first reported case of hypopituitarism due to blastomycosis with pathologic correlation. Pathogenesis of this syndrome is evident from the necropsy findings; fungal organisms were found in both lobes of the pituitary and in the stalk. In addition, the area of richest meningeal involvement was that of the median eminence. Hypothalamic invasion was suspected clinically on the basis of an enhancing suprasellar mass on CT scan that diminished in size during amphotericin B therapy. Endocrine evaluation also suggested hypothalamic dysfunction (elevated prolactin level with depressed luteinizing hormone, testosterone, thyroid-stimulating hormone and thyroxine levels). Hypothalamic tissue was not sufficiently preserved at autopsy to show destruction by fungi. The patient's endocrine dysfunction likely resulted from patchy involvement of both the pituitary and the hypothalamus with blastomycosis.

Finally, the differential diagnosis between tuberculosis and blastomycosis deserves comment. These infections can be clinically indistinguishable and, in fact, have been reported to occur simultaneously.[15,16] Our patient's presenting symptoms of fever, night sweats and weight loss, coupled with a positive tuberculin skin test and findings on a chest roentgenogram typical of tuberculosis, led to the empiric administration of antituberculous therapy while awaiting culture confirmation. Chronic meningitis, sterile pyuria and hypothalamic dysfunction are all well described in cases of tuberculosis; however, several aspects of this case suggested a cause other than mycobacteria. Abnormal upper urinary tracts on a pyelogram with dye given intravenously are seen in more than 90% of patients with genitourinary tuberculosis[17]; therefore, the normal findings on our patient's pyelogram should have prompted search for an alternate cause of sterile pyuria. Of the deep mycoses only blastomycosis commonly involves the lower genitourinary tract.[11] Prostatic biopsy would likely have provided an earlier diagnosis and avoided more invasive diagnostic procedures. Second, his failure to respond to empiric antituberculous therapy and the development of progressive chronic meningitis while receiving therapy would be unusual for tuberculosis. Failure to show improvement by cerebrospinal fluid measurements after eight weeks of isoniazid and rifampin therapy should prompt search for other causes of chronic meningitis.[18,19] Ventricular fluid sampling and brain and meningeal biopsy studies, although unrewarding in this case, may be indicated in the search for a specific diagnosis. Blastomycosis should be considered in the differential diagnosis of any systemic illness resembling tuberculosis, even when it occurs outside the usual endemic areas.

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