Case Reports

Coccidioidomycotic Brain Abscess in an HIV-Infected Man

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PRIMARY COCCIDIOIDOMYCOSIS is a pulmonary infection caused by the soil fungus *Coccidioides immitis.* "[When] primary pulmonary infection fails to heal, either chronic pulmonary lesions, or dissemination supervenes. . . . Dissemination via the bloodstream occurs in 0.1% of Caucasians, and in up to . . . 10% of Filipinos and Orientals."[1] While more than a dozen cases of disseminated infection have been reported in patients with the acquired immunodeficiency syndrome (AIDS),[2-10] there has not been a description of a brain abscess due to *C immitis.* We report a fatal case of disseminated coccidioidomycosis in a homosexual man with AIDS-related complex who during life had a focal lesion in the brain stem localized by magnetic resonance (MR) imaging that at autopsy proved to be a brain abscess containing *C immitis* sporangia, spherules, and hyphae.

Report of a Case

The patient, a 26-year-old sexually active gay man, had a history of prostatitis and chronic perianal problems including candidiasis, rectal condylomata, and herpes simplex. He presented with myalgias, arthralgias, fatigue, a low-grade fever of 37 to 38°C (99 to 100°F), and a slightly productive cough and was given a course of trimethoprim/sulfamethoxazole that transiently reduced his symptoms.

Within six weeks of his initial presentation, the patient again was seen complaining of fatigue, with abdominal cramping and diarrhea. Two of two stool specimens contained *Giardia lamblia* cysts. Treatment was begun with the administration of quinacrine hydrochloride, followed by metronidazole hydrochloride, resulting in the resolution of his diarrhea and nausea. Subsequent stool cultures and multiple evaluations for parasites were negative. Despite normalization of his temperature over the next several weeks, his fatigue continued and he reported occasional night sweats. At that time, a chemistry panel, thyroxine level, and urinalysis were normal, and tests for hepatitis B surface antigen and antibody and a rapid plasma reagin test were negative. His leukocyte count was 7,800 per μl with 22% lymphocytes.

Five months after his initial presentation, the patient began having daily morning headaches and nightly temperature elevations to 38°C (101°F). Examination at this time revealed palpable, rubbery supraclavicular nodes and an 8-kg (18-lb) weight loss.

His chest x-ray film showed a right-sided mediastinal prominence. A computed tomographic (CT) scan of the chest confirmed the presence of a right and left paratracheal adenopathy and mild splenomegaly. Blood cultures were negative, the erythrocyte sedimentation rate (Westergren) was 90 mm per hour, and an arterial blood gas determination with the patient breathing room air showed a partial oxygen pressure of 81 torr and a partial carbon dioxide pressure of 33 torr. Repeated complete blood cell counts, quantitative immunoglobulin G analysis, cryptococcal antigen titers, cytomegalovirus (CMV) titers, barium enema, sigmoidoscopy, and bronchoscopy with transbronchial biopsies were all normal. A bone marrow biopsy specimen showed nonspecific hyperplasia. The T-cell helper/suppressor ratio was low at 0.1 (normal 0.9 to 3.5). An initial complement fixation serologic test for *Coccidioides immitis* was positive at a titer of 1:128. The patient refused a superficial lymph node biopsy.

The patient's daily headaches gradually increased, requiring oral and intravenously given narcotic analgesics. A CT scan of the head showed a discrete 4-mm midbrain lesion without evidence of a mass effect (Figure 1). No other abnormality was seen. A lumbar puncture was done and showed a normal opening pressure, normal protein and glucose contents, a cell count consisting of two monocytes, and normal india ink and acid-fast bacilli (AFB) stains. There was no growth on cerebrospinal fluid cultures for bacteria, AFB, CMV, or fungi. Because the patient refused treatment with amphotericin B, he was started on a regimen of oral ketoconazole, 400 mg daily, which resulted in the resolution of his fever. Repeat complement fixation titers for *Coccidioides* at one and three months after the initial 1:128 titer were greater than 1:512. Human immunodeficiency virus (HIV) antigen was detected in his serum at this time.

An MR scan of the head showed a single, high-signal focus in the right midbrain substantia nigra. It measured 5 mm in diameter and was heterogeneous with indistinct margins. There was also a mild increase in the size of the sulci, indicating some brain volume loss (Figure 2).

He was observed for five months further while receiving oral ketoconazole and increasingly stronger doses of narcotics daily for severe, generalized headaches. The condition of the patient remained unchanged, without the development of nuchal rigidity or increased peripheral adenopathy. A low-grade fever was well documented in the range of 37.8 to 38.3°C (100 to 101°F). Further spinal fluid evaluation was refused by the patient, and intrathecal antifungal therapy was not initiated.

The patient was admitted to hospital 16 months after his initial presentation for rehydration and control of pain and nausea. On the morning of his death, he was noted to be confused, with a right-sided coarse tremor and athetosis. The right pupil was enlarged to a diameter of 6 mm with the left pupil 3 mm in diameter. Respirations and pulse rate were regular. He was found by the nursing staff to be unresponsive.

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ABBREVIATIONS USED IN TEXT

AFB = acid-fast bacilli
AIDS = acquired immunodeficiency syndrome
CMV = cytomegalovirus
CNS = central nervous system
CT = computed tomography/ic
HIV = human immunodeficiency virus
MR = magnetic resonance

Neuropathology

The patient's corpse was refrigerated, and an autopsy was done 28 hours postmortem. The brain weighed 1,700 grams and showed diffuse cerebral edema. The meninges appeared opacified and thickened, most prominently at the base of the brain, where there was softening of the brain stem and cerebellar cortices. The cerebral hemispheres were symmetric and without evidence of herniation. Coronal sectioning revealed smooth ventricles of normal caliber. There was no gross evidence of infarction, hemorrhage, or other focal lesion, except for a minute parenchymal cavitation in the right midbrain.

Microscopic sections from the meninges at the base of the brain showed abundant sporangia and spherules of *C immitis* with acute and chronic inflammation, focal necrosis, and focal granulomatous inflammatory reaction. The fungal organisms included characteristic spherules containing endospores and abundant immature spherules. Occasional spherules were identified within multinucleated giant cells (Figure 3). One focus of hyphal elements was noted, including some focal, barrel-shaped arthrospores characteristic of *Coccidioides* hyphae, which were admixed with immature spherule forms (Figure 4). There were perivascular chronic inflammation and focal necrosis of the brain-stem parenchyma (pons) adjacent to areas of meningeal infection.

Sections from the minute cavitary lesion in the right midbrain showed an abscess, 5 mm in diameter, containing spherules of *C immitis,* with focal necrosis of parenchyma and chronic inflammatory reaction.

Sections from the brain stem showed focal microglial nodules, some of which contained large cells with eosinophilic intranuclear inclusions consistent with cytomegalovirus. No spongiform change or multinucleated giant cells suggestive of HIV were identified.

Discussion

Coccidioides immitis is a dimorphic fungus that is endemic to the arid regions of the southwestern United States, Mexico, and Central and South America. After the arthrospores are inhaled, cell-mediated immunity restricts the infection to the lung and prevents dissemination.[1]

Because patients with AIDS have severely compromised cell-mediated immunity, they are at high risk for disseminated fungal infections. Levy and co-workers reviewed 315 cases of AIDS patients with central nervous system (CNS) involvement.[2] Although the most common infection was toxoplasmosis (103 cases), *Cryptococcus neoformans* was the most frequent fungal infection (41 cases). They reported only one case of coccidioidomycosis. In a second series, Anders and colleagues found CMV to be the most frequent CNS infection (14.4%), followed by *Toxoplasma* (13.4%), with *Cryptococcus* again being the most common fungal infection (8.7%) and no cases of CNS *C immitis.*[11]

To date there have been fewer than 20 reported cases of coccidioidomycosis in AIDS patients. None of the individual reports of disseminated coccidioidomycosis in AIDS patients[3-9] described CNS involvement. The case of disseminated coccidioidomycosis in the series of Levy and associates had *C immitis* meningitis with microabscesses containing spherules throughout the cerebellum found at autopsy.[2] Most recently, Bronnimann and co-workers reported seven cases of coccidioidomycosis in AIDS patients, one of whom had spherules found in the brain stem.[10]

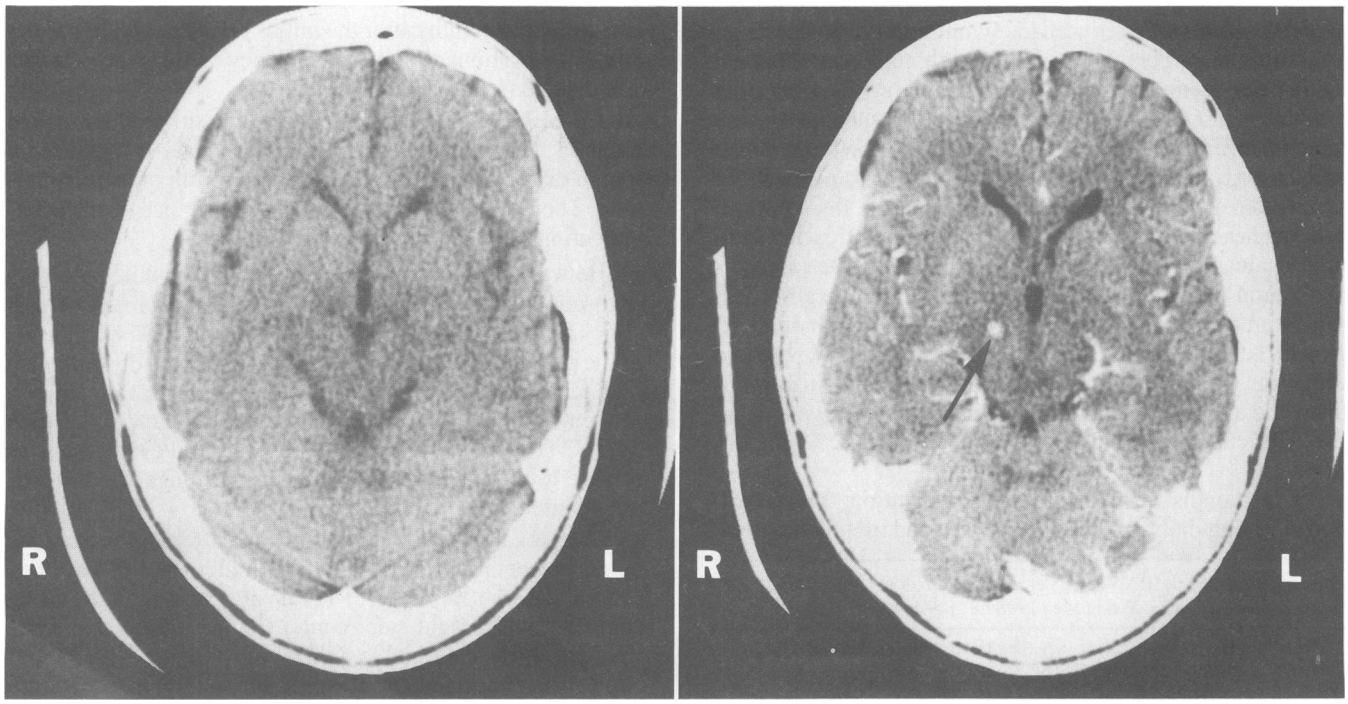

Figure 1.—Plain **(left)** and contrast-enhanced **(right)** computed tomographic scans show a discrete 4-mm midbrain lesion **(arrow)** that enhances with contrast.

The spectrum of lesions reported for *C immitis* meningitis includes leptomeningitis, cerebritis, infarcts, and, less commonly, miliary granulomata.[12] A CT scan usually shows ventricular dilatation indicating a noncommunicating hydrocephalus, but it may also show cisternal obliteration, cisternal enhancement, ependymal enhancement, and hypodense white matter lesions, presumably due to vasculitis and subsequent infarction.[13]

The MR scan on our patient showed a single, 5-mm midbrain lesion with distinct margins and a low-signal center, without evidence of ventricular enlargement. Although magnetic resonance has been shown to be more sensitive,[14] its specificity is still about equal to that of computed tomography.[15] In our patient there is nothing specific about the lesion's appearance to distinguish it from other focal infectious processes or tumor.

The pathogenesis of the *C immitis* abscess is probably similar to that of abscesses caused by other fungal infections. The most likely scenario is that the meninges were hematogenously seeded by a focus outside of the CNS, in this case from the lungs, and subsequently the fungus spread deep into the midbrain through the cerebrospinal fluid by following the Virchow-Robin space.

Conclusions

C immitis brain abscess must now be added to the long list of complications that can occur in patients infected with HIV. Although coccidioidomycosis is still relatively uncommon among AIDS patients and CNS infection by *C immitis* is even rarer, the rapidly accumulating case reports[2-10] suggest that *C immitis* will be an increasingly important pathogen. Moreover, as the incidence of AIDS increases in the Ohio and Mississippi river valleys, the frequency of disseminated *Histoplasma capsulatum* infection, which has already been well documented,[16-19] will undoubtedly also increase. Whereas complement fixing antibody testing may be helpful in diagnosing *C immitis* infection in immunocompromised patients, serology cannot precisely diagnose specific CNS lesions. This is a particularly important point in AIDS patients because they are likely to have multiple infec-

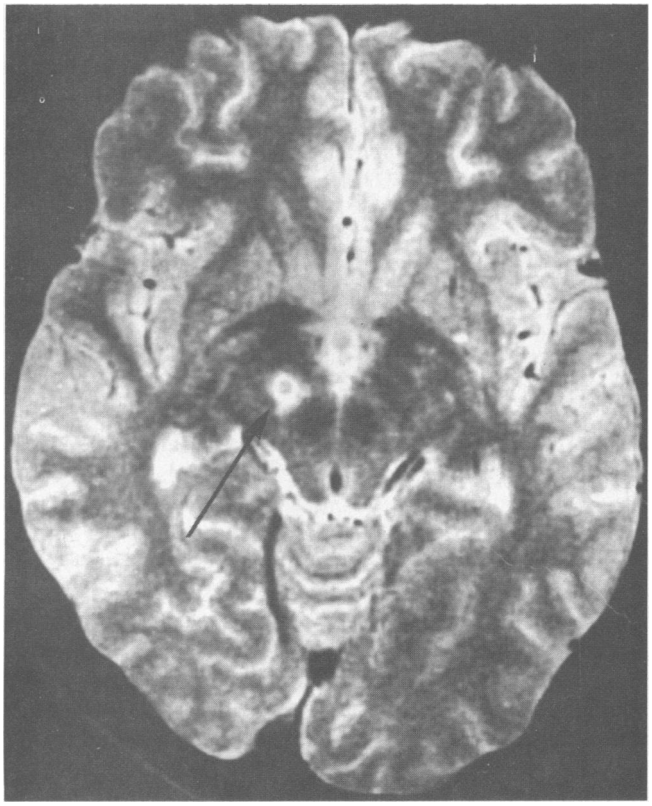

Figure 2.—A magnetic resonance scan (TR 2,000 ms, TE 70 ms) shows a heterogeneous, 5 mm in diameter, high-signal focus **(arrow)** with indistinct margins in the right midbrain. There is also a mild increase in the size of the sulci, indicating some brain volume loss.

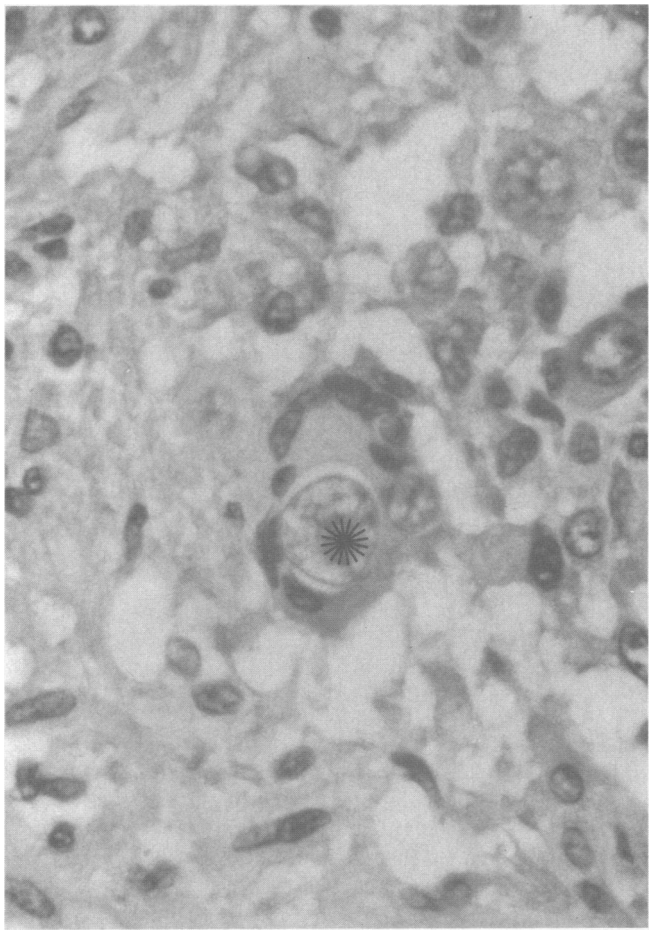

Figure 3.—A hematoxylin and eosin-stained paraffin section from the midbrain shows a *Coccidioides* spherule **(asterisk)** within a multinucleated giant cell (original magnification × 200).

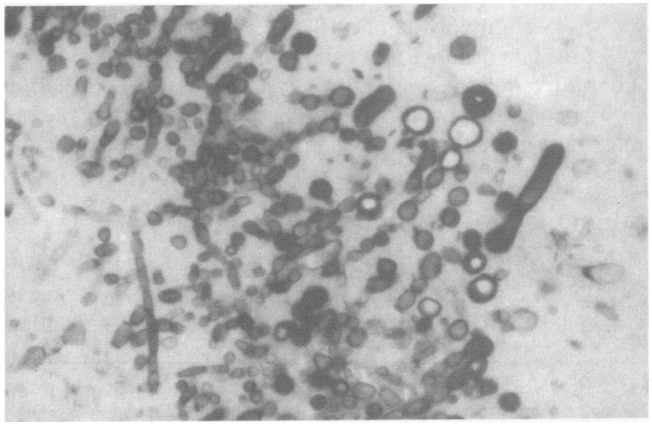

Figure 4.—A silver methenamine-stained paraffin section of the midbrain shows barrel-shaped arthrospores characteristic of *Coccidioides immitis* hyphae admixed with immature spherule forms (original magnification × 200).

tious and neoplastic processes. Unfortunately, neither CT nor MR is sufficiently specific for the precise diagnosis of the various possible brain lesions in AIDS. Because early appropriate therapy is of paramount importance in the immunosuppressed, our description of a CNS mass lesion due to *C immitis* emphasizes the importance of doing a biopsy of an accessible brain lesion in a patient with AIDS.

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Congestive Heart Failure and Sudden Death in a Young Woman With Thyrotoxicosis

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THE EXISTENCE OF "hyperthyroid heart disease" with resultant congestive heart failure has been a matter of controversy for a number of years. Some clinicians feel that thyrotoxicosis merely overstresses a heart with valvular, coronary, or other preexisting organic disease.[1] Other clinicians have reported congestive heart failure in patients in whom a careful search failed to reveal any other cause of heart disease and that resolved when the patients' thyrotoxicosis was treated.[1-11] Few postmortem evaluations of hearts of patients with presumed thyrotoxic congestive heart failure have been done to definitively confirm the absence of other significant disease. The death of this young thyrotoxic patient, who had congestive heart failure in the absence of atrial fibrillation, provided an opportunity to do anatomic, histologic, and biochemical evaluations of human myocardial tissue in this syndrome.

Methods

Clinical Testing

Thyroid function tests during the patient's early course were done at Consolidated Medical Laboratories, Highland Park, Illinois. Clinical tests during her final month were done at Michael Reese Hospital and Medical Center, Chicago. Thyroid-stimulating hormone (TSH) levels were determined using the Gammadab Kit (Travenol-Genetec Diagnostics, Cambridge, Mass).

Electron Microscopy of Myocardial Tissue

Myocardial tissue was taken at autopsy about 19 hours after death. Tissue for electron microscopy was fixed in 2.5% glutaraldehyde, postfixed in osmium tetroxide, dehydrated in graded alcohols, and embedded in epon. Sections were stained with uranyl acetate and lead citrate and were examined in a Philips 300 electron microscope.

Biochemical Characterization of Cardiac Myosin

Ventricular myosin was prepared as described by Offer and co-workers[12] with slight modifications used by Lompre and associates.[13] Myosin was prepared from this patient and from three human hearts from patients without thyrotoxicosis to serve as controls. The control patients had no history of heart disease, were not taking cardiac drugs, and their hearts had no evidence of significant disease. Myosin isotype composition was evaluated by a solution phase radioimmunoassay analysis using a monoclonal antibody to V3 cardiac myosin, as previously described.[14] Purified rat V1 and V3 isomyosins served as control standards. Rat V3 isomyosin was iodinated with sodium iodide I 125 by the lactoperoxidase procedure, and each myosin was evaluated for its ability to compete for antibody binding relative to the labeled rat V3. Logit transforms of combined data from two to four competition curves of each specimen were evaluated by linear regression analysis.

Results

Report of a Case

This 34-year-old woman had been generally well until January 1984, when she began having tremulousness, ner-

(Magner JA, Clark W, Allenby P: Congestive heart failure and sudden death in a young woman with thyrotoxicosis. West J Med 1988 Jul; 149:86-91)

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