Central Nervous System Abscesses Due to Coccidioides Species

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Meningitis occurs in one-third to one-half of patients with disseminated coccidioidomycosis, but mass lesions have rarely been described; these lesions are usually found at autopsy. We report six cases of disseminated coccidioidomycosis with central nervous system (CNS) abscesses. Four patients had cerebellar involvement, and two had spinal cord involvement. Four patients were diabetic, and two subsequently died. Review of the literature on CNS coccidioidomycosis indicated that parenchymal brain involvement occurs in 1%-33% of cases, and <40 cases with mass lesions have been reported since 1905. Almost all patients were male and had other active disseminated foci of coccidioidomycosis. In approximately one-third of all cases, meningitis was absent. Brain lesions may be superficial or deep and multiple or single. In the absence of meningitis, serology of cerebrospinal fluid is negative. Hematogenous origin appears to be more common than direct extension from the meninges. Spinal cord involvement is rare. Diabetes was present in several cases, thus suggesting a vascular predisposition. We hope our experience will increase awareness of this entity, which appears to be more common than previously appreciated, and will facilitate diagnosis.

Coccidioidomycosis can disseminate widely, and meningitis, which is frequently the only site of extrapulmonary involvement, occurs in one-third to one-half of all patients with dissemination [1]. Meningitis usually involves the basilar portions of the brain (favoring the sulci), and a thick opaque membrane is formed. This membrane frequently obstructs CSF flow or blocks CSF resorption, thereby resulting in often fatal hydrocephalus.

Parenchymal brain involvement occurs less commonly than meningeal infection. In 1936 Abbott and Cutler [2] reported on cranial and intracranial lesions associated with systemic infections and noted three subgroups of lesions: cranial osteomyelitis with associated abscesses and meningitis, leptomeningitis with no other cranial or intracranial lesions, and subcortical lesions. According to Kelly [3] in 1980, the frequency of cerebral lesions varied from 1% to 29% in four case series [2– 6]. In 1984 Sobel et al. [7] noted four histopathologic patterns of CNS lesions: leptomeningitis alone (most frequent), leptomeningitis with cerebritis, leptomeningitis with cerebritis and infarcts, and disseminated miliary granulomas (unusual). Hypodense lesions in periventricular areas, both focal and diffuse, have also been reported; these lesions are possibly the result of vascular events but are poorly understood [8]. Vasculitis can also be a complication of coccidioidal infections of the CNS [9]. Mischel and Vinters [10] recently reported a review of the neuropathological as well as vasculopathic manifestations of CNS coccidioidomycosis. These authors demonstrated that it is common for coccidioidomycosis to extend into the brain and spinal cord as microscopic foci of disease, although it is uncommon for discrete CNS mass lesions to develop.

We report six cases of CNS mass lesions and review the literature on parenchymal brain involvement with mass lesions in patients with coccidioidomycosis.

Case Reports

Case 1

A 45-year-old Hispanic man with type I diabetes mellitus (DM) presented in April 1982 in San Jose, California, with diabetic ketoacidosis; a 2-month history of headache, vertigo, and neck pain; a 3-month history of worsening left-leg weakness; and a 3-year history of ataxia and left-upper-extremity and left-lower-extremity weakness with left-lower-extremity paresthesia. He was previously employed as a migrant farm worker in California's Central Valley.

Neurological examination revealed left-upper-extremity and left-lower-extremity weakness with left-leg sensory deficit and left cerebellar signs with intact cranial nerves. A chest roentgenogram showed a left-upper-lobe infiltrate. Skin testing demonstrated anergy. A head CT revealed a low-density 3-cm left cerebellar mass with contrast rim enhancement and an area of central lucency; no evidence of meningitis was noted. At the

Received 21 February 1995; revised 6 September 1995.

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Figure 1. An axial T1-weighted MRI of the head of a patient with a CNS abscess due to *Coccidioides* species (case 2) after introduction of gadolinium. This image demonstrates ring-enhancing contiguous collections of fluid in the right cerebellar hemisphere (*short arrows*) that are consistent with abscess formation.

time of open thoracotomy, examination of a 3-cm nodule resected from the left upper lobe showed fungal elements and confluent caseating granulomata strongly suggestive of coccidioidomycosis. Analysis of CSF obtained by lumbar puncture revealed clear fluid with a WBC count of 10/mm³ (10% neutrophils, 90% lymphocytes), a protein level of 45 mg/dL, and a glucose level of 35 mg/dL (peripheral glucose level, 116 mg/ dL); stains and cultures of CSF were negative, as was a CSF titer of CF antibodies to *Coccidioides* species. A serum titer of CF antibodies to *Coccidioides* species was 1:2.

Craniotomy revealed normal meninges with a deep left cerebellar mass; the mass was resected, and spherules consistent with *Coccidioides* species were found. Cultures of a lung specimen and a cerebellar mass specimen confirmed the presence of *Coccidioides* species. A bone scan showed increased uptake at multiple sites. A repeated head CT after the operation no longer demonstrated the cerebellar mass. The patient was treated with iv and intrathecal amphotericin B and had a good response.

The patient discontinued therapy and was admitted to the hospital 4 months later because of recurrence of his left cerebellar abscess; he presented with diplopia, left ptosis, confusion, urinary incontinence, and evidence of meningitis. Physical examination revealed a left-third-cranial-nerve palsy with left cerebellar signs and positive Brudzinski's and Kernig's signs. Analysis of CSF obtained by lumbar puncture showed a WBC count of 292/mm³ (47% neutrophils, 44% lymphocytes, 7% monocytes, 1% eosinophils, and 1% basophils) and a positive CSF titer of CF antibodies to Coccidioides of 1:8. A serum titer of CF antibodies to Coccidioides was also positive at 1:8. A head CT showed an area of enhancement at the left cerebellopontine angle in the area of the previous coccidioidal involvement and a fluid collection in the defect produced by craniotomy. An Ommaya reservoir was placed, and therapy with intraventricular amphotericin B was started.

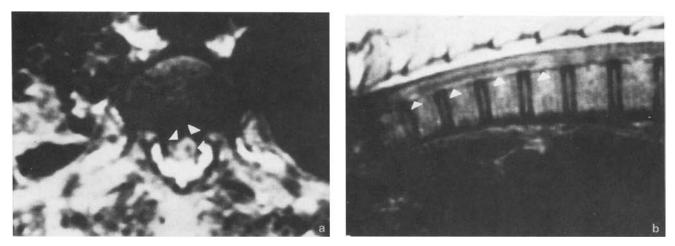


Figure 2. a: An axial T1-weighted MRI of the thoracic spine of a patient with a CNS abscess due to *Coccidioides* species (case 2) after introduction of gadolinium. This image demonstrates enhancement of the upper thoracic spinal cord (*arrowheads*) at the T3 level. b: A sagittal T1-weighted MRI of the same thoracic spine after gadolinium introduction. This image demonstrates serpiginous enhancement of the upper thoracic spinal cord (*arrowheads*) from approximately the T3 level through the T7 level; although these findings are nonspecific, they are commonly seen in cases of spinal cord inflammatory processes.

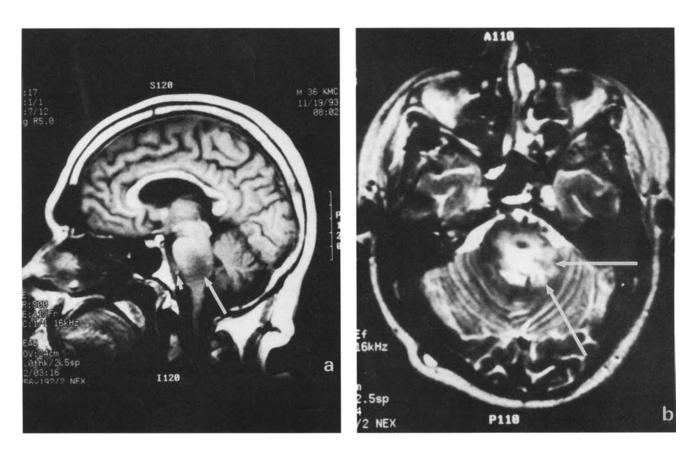


Figure 3. a: A sagittal T1-weighted MRI of the brain of a patient with a CNS abscess due to *Coccidioides* species (case 3). This image demonstrates pontine enlargement with amorphous signal changes in the central pontomedullary region (*long arrow*). This abnormal signal extends anteriorly to the prepontine cistern (*short arrow*). b: An axial T1-weighted MRI of the same brain after introduction of gadolinium. This image demonstrates an irregular ringlike enhancement (*long arrows*) in the left dorsal medial pons that is consistent with an abscess.

Ten weeks later the patient died of complications due to bronchopneumonia. Autopsy showed thickening over the base of the brain with residual meningitis. There was necrosis of the internal capsule and a 2×1 -cm area in the left cerebellum; there was no evidence of fungus. A right-frontal-lobe leptomeningeal infiltrate with giant cells and *Coccidioides immitis* spherules was identified.

Case 2

A 21-year-old white man with type I DM presented in Visalia, California, in December 1993 with a 4-day history of rightelbow pain and inflammation and mild diabetic ketoacidosis; he had no respiratory symptoms. Physical examination revealed a temperature of 100.7°F and right-elbow inflammation with marked limitation of his range of motion. A right-elbow roentgenogram showed no bony abnormalities, and a chest roentgenogram demonstrated bilateral fibronodular markings throughout with possible cavitation in the upper lobes. Skin tests showed an anergic response.

Therapy with intravenous antibacterial agents and oral fluconazole, isoniazid, rifampin, and pyrazinamide was started. Bronchoscopy was performed when his respiratory status deteriorated. Examination of a gram-stained preparation, an acidfast smear, and a KOH preparation of bronchial washings did not reveal any organisms. Deterioration of his mental status occurred on hospital day 3, and a head CT demonstrated a 1.5cm low-density lesion in the posterior portion of the right cerebellar hemisphere. A brain MRI revealed a 2.5-cm grapelike cluster of ring-enhancing lesions in the right cerebellar hemisphere with a mild mass effect (figure 1). Craniectomy of the posterior fossa was performed with evacuation of a right cerebellar abscess; 3 mL of purulent material was removed. Examination of KOH preparation of the material demonstrated *C. immitis*, as did cultures of bronchial washings and a rightelbow aspirate.

The patient also had a soft-tissue infection in the posterior superior aspect of the neck. Serology of specimens obtained on hospital day 2 was positive for IgM precipitin to *Coccidioides*, and a serum titer of CF antibodies to *Coccidioides* was positive at 1:8. After the operation the patient had paraplegia, and an MRI of the thoracic spine showed no focal abnormalities initially. The patient was believed to have an anterior spinal artery syndrome at the T8 level. Therapy with iv amphotericin B was started preoperatively, and iv fluconazole was added to the therapeutic regimen after the operation. Analysis of ventric-

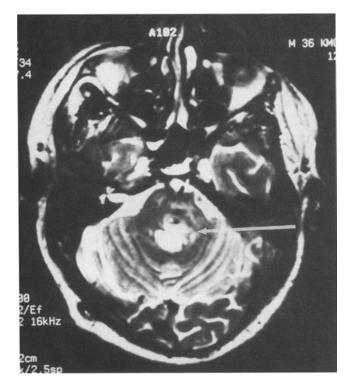


Figure 4. An axial T1-weighted MRI of the brain of a patient with a CNS abscess due to *Coccidioides* species (case 3) following introduction of gadolinium 1 month after treatment. This image demonstrates resolution of the left dorsal pontine abscess in figure 3b; there is a small residual area of enhancement (*long arrow*).

ular spinal fluid showed a WBC count of $5/\text{mm}^3$ (100% lymphocytes), a protein level of 31 mg/dL, and a glucose level of 145 mg/dL (blood glucose level, 280 mg/dL). At no time was there any clinical evidence of meningitis. The patient received amphotericin B therapy through an Ommaya reservoir with the distal end in the cisterna magna, and a ventricular shunt was placed. Fluconazole therapy was changed from iv administration to oral administration. Histopathologic studies and cultures of a specimen from the brain abscess confirmed that *C. immitis* was the only pathogen present.

On hospital day 21 an MRI of the thoracic spine showed a new enhancing lesion within the thoracic spinal cord at the T6–T7 level. A repeated scan on day 41 revealed enhancement of the thoracic spinal cord at the T3 level and enhancement of the anterior spinal cord in the midline from the T3 level to the T6 level, findings consistent with spinal cord infarction (fig-ure 2).

As of May 1995 the patient is paraplegic but otherwise asymptomatic; he is receiving fluconazole therapy (400 mg/d). There has been no recurrence of the cerebellar abscess, and clinical follow-up studies (including periodic lumbar punctures) have not shown evidence of meningitis. All other sites of dissemination are clinically quiescent.

Case 3

A 36-year-old Hispanic man from Bakersfield, California, who had a 10-year history of coccidioidal meningitis had been

previously treated with placement of a ventriculoperitoneal shunt and amphotericin B via the cisterna magna. For 2 years his only treatment had been oral fluconazole (400 mg/d). In November 1993 he presented with a 1-week history of rightsided numbness and weakness and a 2-day history of shortness of breath with fatigue, difficulty in swallowing, loss of urinary continence, and "fullness" in the head in the right parietal area.

Physical examination showed a left-lateral-rectus palsy with a left facial droop, left ptosis, and mild right hemiparesis. A brain MRI revealed an ill-defined amorphous abnormal signal within the brain stem centered in the pons that extended superiorly to the left cerebellum and inferiorly to the medulla (figure 3a). After introduction of an iv contrast medium, an irregular ringlike enhancement in the left dorsal medial pons that was consistent with an abscess was seen (figure 3b). The patient's condition clinically improved 1 month later (figure 4) after therapy with an increased dose of fluconazole (800-1,200mg/d) and a short course of dexamethasone. His cerebral infarct was attributed to vasculitis. As of February 1995 he continues to receive therapy but has stable neurological defects.

Case 4

A 42-year-old Laotian man living in Modesto, California, presented in January 1994 with a 2-year history of weakness; a 5-month history of ataxia; a 2-month history of headache, nausea, vomiting, and seizures; and a 24-hour history of vertigo and worsened ataxia, nausea, and vomiting. Physical examination showed ataxia. A head CT revealed hydrocephalus. Analysis of CSF obtained by lumbar puncture demonstrated a WBC count of 100/mm³ (99% lymphocytes, 1% neutrophils), a protein level of 1,000 mg/dL, and a glucose level of 56 mg/dL. A head MRI showed a thin anterior extramedullary intradural lesion extending from the midpoint of the C4 level to the foramen magnum contiguous with the anterior medulla, pons, and mesencephalon and a small nodule of enhancing material at the outlet of the fourth ventricle with associated ventricular dilatation (figure 5). A chest roentgenogram was unremarkable. CSF and serum titers of CF antibodies to Coccidioides were positive at 1:16 and 1:8, respectively.

Craniectomy was performed; a milky discolored arachnoid was found from the C1 level to the C4 level, and the C1 level was firm and adherent by granulation reaction to the cervical spinal cord. Biopsy of the thickened arachnoid and the tissue beneath the arachnoid dorsal to the spinal cord at the C1 level and to the right of the C4 level was performed. Histopathologic examination of the biopsy specimens showed a dense fibro-connective tissue with granulomas and spherules consistent with *C. immitis*. He was treated with fluconazole and intraventricular amphotericin B via an Ommaya reservoir. Headaches and ataxia recurred 2 months later with increasing hydrocephalus, and a ventricular shunt was placed in March 1994. In May 1994 the CSF titer of CF antibodies to *Coccidioides* increased to 1:64, and the serum titer remained unchanged. A repeated

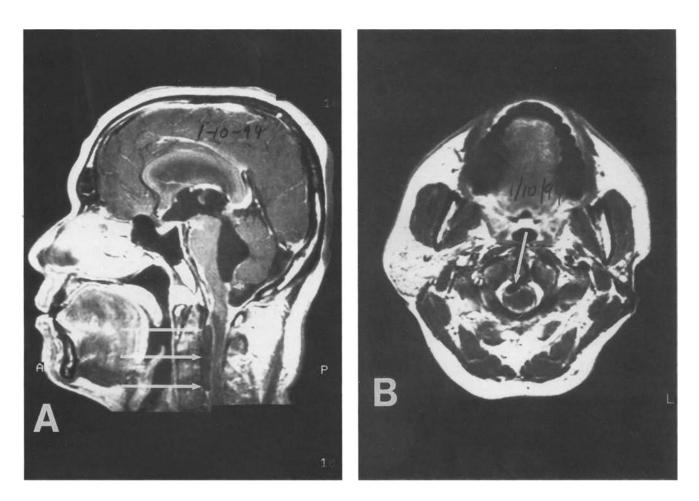


Figure 5. *a*: A sagittal T1-weighted MRI of the brain of a patient with a CNS abscess due to *Coccidioides* species (case 4) after introduction of gadolinium. This image demonstrates moderate hydrocephalus secondary to enhancing lesions in the preportine region and the foramen of Magendie (*short arrow*). A prominent anterior extramedullary intradural mass extending from the foramen magnum down to the C4 level is also noted (*long arrows*). *b*: An axial T1-weighted MRI of the same brain after gadolinium introduction. The spinal cord is displaced posterolaterally by an anterior rim-enhancing mass (*long arrow*).

MRI of the brain in May 1994 (figure 6) continued to show enhancement surrounding the spinal cord with cord edema and enlargement of the fourth ventricle that continued through at least July 1994.

As of May 1995 the patient is clinically stable and is tolerating therapy with 800 mg of fluconazole daily; however, he complains of generalized aching and syncope. A CSF titer of CF antibodies to *Coccidioides* in January 1995 was decreased at 1:4, as was a serum titer in February 1995 at 1:2.

Case 5

A 63-year-old white man from New York who had insulindependent DM for 20 years with diabetic retinopathy and nephropathy as well as chronic renal failure for 2 years was admitted to the hospital in June 1994 with a 1-month history of nausea, vomiting, weakness with headaches, and staggering when standing up. His medical history was significant for coccidioidomycosis in 1975 while he was living in Arizona; he had been a construction worker in that state for 5 years. The specifics regarding the hospitalization were unobtainable, but he thought he had had meningitis and "fluid around heart and lungs." He was treated with medication for 45 days and recovered; at the time of discharge, he was not receiving any medications and had no further related problems.

At the time of this admission in June 1994, he was found to be in acute renal failure, and dialysis was started. Physical examination revealed intact cranial nerves with good coordination and a slow but steady gait. His chest roentgenogram was unremarkable. Shortly after dialysis was started, an ataxic gait developed. A head MRI showed a prominent mass in the right posterior fossa that projected 3 cm inferiorly from the tentorium and had transverse dimensions of 4×4.5 cm; surrounding edema was also noted. There was peripheral irregular enhancement with a nonenhancing central component. The right cerebellum was compressed inferiorly, and the inferior pons and medulla were rotated and displaced toward the left with some upward herniation through the tentorial notch. The fourth ven-

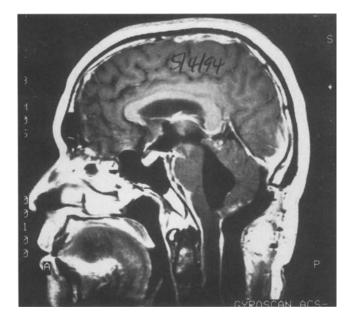


Figure 6. A sagittal T1-weighted MRI of the brain of a patient with a CNS abscess due to *Coccidioides* species (case 4) after an operation. This image demonstrates continued enlargement of the fourth ventricle with increasing meningeal enhancement extending from the basilar cisterns to the upper cervical region. The spinal cord mass is no longer present.

tricle was compressed and displaced toward the left, the third ventricle was slightly prominent and midline, and the lateral ventricles were normal (figure 7). An MRI of the lumbosacral spine was unremarkable.

Dexamethasone therapy for a presumed brain tumor was started, and his gait improved. An intracranial biopsy was scheduled; however, a repeated chest roentgenogram showed multiple diffuse bilateral pulmonary nodules that had not been present 3 weeks previously. The nodules were confirmed by chest CT. A lung biopsy was unrevealing. The titer of CF antibodies to Coccidioides was 1:16. No CSF values were available. The patient was treated with iv amphotericin B and iv fluconazole but died 6 weeks after his initial presentation. During autopsy disseminated coccidioidomycosis was found in the liver, spleen, prostate, and thyroid. Examination of the lungs revealed diffuse nodules containing spherules and endospores consistent with C. immitis and hilar nodes with focal abscesses. Analysis of the brain showed a right-posterior-fossa abscess due to Coccidioides, apparently involving the right cerebellum, that was adherent to the dural and petrous portion of the temporal bone.

Case 6

A 50-year-old Hispanic man with a history of insulin-dependent DM and hepatitis C-induced cirrhosis of the liver underwent orthotopic liver transplantation in April 1994 and was given immunosuppressive therapy with azathioprine, prednisone, and tacrolimus. The patient was born in San Jose but had traveled to Mexico and Los Angeles via the Central Valley of California.

In March 1995 the patient presented with a 2-week history of fever, chills, nausea, vomiting, abdominal pain, headache, and photophobia. Physical examination revealed a temperature of 39.6°C and right-upper-quadrant tenderness of the abdomen. There was no neck stiffness and no focal neurological abnormalities. A chest roentgenogram demonstrated a left pleural effusion. An abdominal CT showed a thickened loop of the small bowel. At the time of exploratory laparotomy, peritonitis was discovered (WBC count, 2,178/mm³), but bacterial culture of the peritoneal fluid was sterile.

Mental confusion and persistent headache prompted a lumbar puncture; analysis of CSF revealed an opening pressure of 39 cm, a WBC count of 2,360/mm³ (77% neutrophils, 17% lymphocytes, 6% monocytes), a protein level of 265 mg/dL, and a glucose level of 71 mg/dL (serum glucose level, 265 mg/dL). Culture of CSF yielded 20 colonies of mold, which was confirmed as *C. immitis* by gene probe. An immunodiffusion test of serum was positive for *C. immitis;* the serum titer of CF antibodies to *Coccidioides* was positive at 1:8, and a CF test of CSF was positive only with an undiluted specimen. An MRI of the brain demonstrated multiple small enhancing lesions within the cerebral parenchyma and a larger 1×3 -cm ring-enhancing lesion in the right posterior parietal region at the gray matter white matter junction (figure 8). A bone scan showed increased uptake of the radionuclide in the ribs and the pelvis.

The patient was initially treated with iv amphotericin B and iv fluconazole. Because of relative resistance to amphotericin B in vitro, this treatment was discontinued in April 1995 after he had received a total of 1.3 g, and his fluconazole dose was increased. As of May 1995 he is receiving 1.2 g of oral fluconazole daily. Left hemiparesis developed, and imaging studies suggested an ischemic lesion in the basal ganglia that was possibly due to vasculitis. The combined nephrotoxic effects of amphotericin B and immunosuppressive agents, such as tacrolimus, and the potential hepatotoxic effect of fluconazole make antifungal treatment of patients with liver transplants difficult.

Literature Review

Ophüls [11] reported the first case of coccidioidal meningitis in 1905, but it was not until 1928 that Jacobson [12] reported the first intraparenchymal brain lesion. This lesion occurred in a 31-year-old Filipino man with disseminated disease (but no meningitis) and a 4-mm caseous area within the "right optic thalamus."

In 1931 Beck [13] reported 286 cases of coccidioidomycosis from California, including 21 involving the CNS, 4 involving the "brain" as opposed to the "meninges," and 1 involving the brain and meninges. In 1936 Abbott and Cutler [2] reviewed the literature on chronic coccidioidal meningitis; they noted

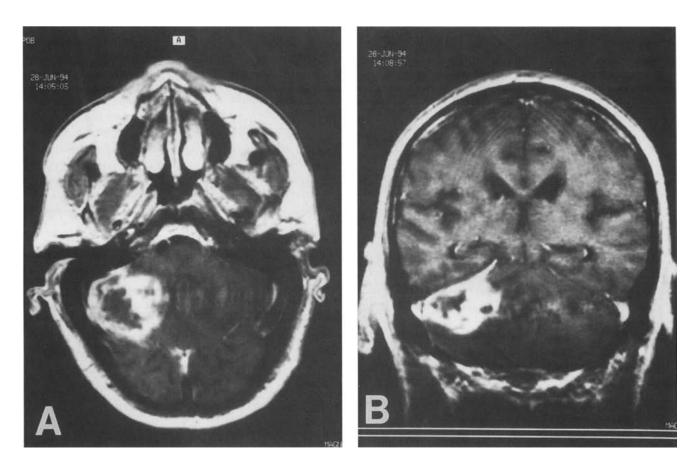


Figure 7. A: An axial T1-weighted MRI of the brain of a patient with a CNS abscess due to Coccidioides species (case 5) after introduction of gadopentetate. This image demonstrates a right cerebellar mass (4×4.5 cm in size) with predominant rim enhancement and a low-signal-intensity cavity consistent with an abscess. There is surrounding edema. The fourth ventricle is compressed and slightly displaced toward the left. B: A coronal T1-weighted MRI of the same brain after gadopentetate introduction. The right cerebellar mass with enhancement is present with no other areas of brain involvement. The adjacent mastoid sinus is normal.

that about 25% of patients with the acute form of this disease have brain lesions, and they described two patients with brain involvement (including a 3-year-old Mexican boy with meningitis who had one small nodule in the right hemisphere and the patient described by Jacobson [12]). In 1938 Courville and Abbott [5] reviewed the pathology of coccidioidomycosis in the CNS and described a 39-year-old white man with a "small area in superficial cortex involved" and a 28-year-old white man with chronic meningitis who had two small lesions in the cortex. The two patients described previously by Abbott and Cutler in 1936 were also included. It was noted that lesions arise in the nervous tissues "very rarely" and that secondary invasion of the cortex beneath accumulations of exudate in the subarachnoid space occurs more commonly.

In 1941 Craig and Dockerty [14] described a case of a left cerebellar abscess at a depth of 2 cm in a 49-year-old man; the abscess was resected, and *C. immitis* spherules were noted. Four weeks later, during autopsy, a 1-cm left cerebellar abscess and a purulent exudate around the cerebellum and lining the fourth ventricle were found, as were cerebral edema and hydrocephalus.

Both lungs contained coccidioidal nodules. This case marked the first attempt to resect a coccidioidal abscess in the brain.

In 1945 Schlumberger [6] reviewed 23 autopsied cases of coccidioidomycosis at the Army Institute of Pathology (Washington, DC); the brain and meninges had been examined in these cases. Thirteen patients had basilar meningitis, and three of these patients had brain involvement. There were two other patients with intracerebral lesions who did not have accompanying meningitis; one of these patients had only a single spherule in the medulla. A case report cited in Schlumberger's article described disseminated coccidioidomycosis with meningitis and focal lesions; 5- to 15-mm nodules were present in the cerebellum and midbrain and were lining the lateral ventricles and cerebral hemispheres.

In a case report by Rhoden [15] in 1946, a 16-year-old diabetic white man with a coccidioidal brain abscess that almost replaced the left cerebellar hemisphere was described. Analysis of CSF obtained by lumbar puncture revealed clear fluid and a WBC count of 214/mm³ (89% lymphocytes). During autopsy basilar meningitis with hydrocephalus and a midline shift was

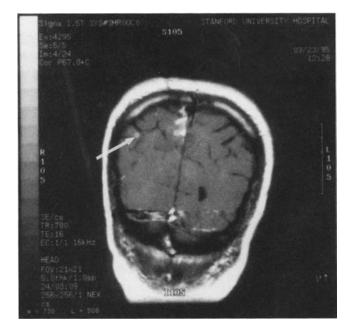


Figure 8. A coronal T1-weighted MRI of the brain of a patient with CNS abscesses due to *Coccidioides* species (case 6) after introduction of gadolinium. This image shows an area of enhancement in the right parietococcipital region near the midline as well as a smaller area in the brain parenchyma in the lateral aspect of the right parietal lobe (*long arrow*).

found. The lungs were the only other organs with coccidioidal lesions.

In 1946 Forbus and Bestebreurtje [16] described 12 patients with "brain" lesions; seven of the brain lesions were reported as "gross" and the other five were reported as "microscopic" (five patients were previously described by Schlumberger [6]). No identifying data were provided, but the authors did state the following: "solitary granulomas of considerable size (2–3 cm) have been observed and are like those that develop in other tissues. It is important to note however that these lesions develop both superficially and deeply in the brain."

In 1967 Huntington et al. [4] reported on 142 autopsied cases of coccidioidomycosis from 1947 to 1965 in the southern San Joaquin Valley in California; there were 82 cases of meningitis and one case of brain involvement (a 39-year-old black man with disseminated disease who had a microabscess within the brain but no meningitis).

In a 1977 review of amphotericin B and survival of patients with coccidioidal meningitis, Pappagianis and Crane [17] described a 32-year-old with disseminated disease and a cerebral abscess who died 1 month after the onset of meningitis. In 1977 Buchsbaum [18] described a 47-year-old woman with Hodgkin's disease who was receiving immunosuppressive therapy; this woman had disseminated coccidioidomycosis and a pituitary abscess with meningitis and cerebral vasculitis.

In 1978 Rodríguez et al. [19] studied the role of CTs in the diagnosis and treatment of brain inflammatory lesions and parasitic lesions in Mexico; of 617 abnormal head CTs, they found one case of a coccidioidal granuloma in the brain that was confirmed by biopsy (frequency, 0.16%). Multiple hypodense lesions, primarily supratentorial, were observed; these lesions were intensely enhanced with contrast.

In 1980 Dublin and Phillips [20] evaluated 15 cases of disseminated cerebral coccidioidomycosis that were confirmed by CSF serology or culture. Six patients had white matter lesions (two each had diffuse, focal, and mixed lesions); two of these six patients also had gray matter lesions. However, only one patient "demonstrated a sharply demarcated, enhanced nodule in the region of the cerebello pontine-angle cistern; whether this was intra- or extra-axial is uncertain, but it may represent a focal cerebellar granuloma."

In 1981 Bouza et al. [21] retrospectively analyzed 31 cases of coccidioidal meningitis from 1964 to 1976 and reviewed 114 cases from the literature; they found one patient with brain involvement (a 37-year-old diabetic white man with meningitis and hydrocephalus). Autopsy of this patient showed widespread dissemination with a coccidioidal granuloma in the left internal capsule and spherules in the basal ganglia and brain stem.

In 1983 Nakazawa et al. [22] reported the radiological results of case 1 in this presentation. In 1984 Sobel et al. [7] reported 32 cases of CNS coccidioidomycosis. There was CNS parenchymal involvement in 28 cases: 25 with extension of the inflammatory process from the meninges (resulting in cerebritis) and 3 with miliary granulomas in histologically normal brain parenchyma (separated from meningeal and ependymal surfaces) in association with widely disseminated disease. Necrotizing myelitis, endarteritis, and infarcts were also common.

In 1988 Jarvik et al. [23] reported the first case of HIVassociated brain abscess. An MRI revealed that a patient with AIDS-related complex had a 5-mm lesion in the substantia nigra of the midbrain; initial laboratory studies of CSF showed relatively normal results. He died 16 months after initial presentation with disseminated coccidioidomycosis despite oral ketoconazole therapy. Autopsy confirmed a 5-mm abscess in the midbrain that contained coccidioidal spherules and meningeal opacification and thickening, which were most prominent at the base of the brain.

In 1991 Scanarini et al. [24] described a 68-year-old immunocompetent woman in Italy who presented with left unilateral ophthalmoplegia and ptosis, severe headache, diplopia, and progressive visual loss. A pituitary mass was diagnosed radiologically. Prolactin levels were elevated, but other hormone levels were lower than normal. Transsphenoidal exploration of the sella turcica revealed a large cyst with a thick capsule that flattened the pituitary. Histopathologic examination showed inflammation, necrosis, some normal pituitary tissue, and structures consistent with endosporulating spherules of *C. immitis*. Cultures were not performed. No epidemiologic information was provided that explained how the patient may have been exposed. No disease was evident elsewhere, and serology was said to be negative; however, no details were provided. Abatement of symptoms was noted after surgery and ketoconazole

 Table 1. Findings for 39 patients with brain masses due to coccidioidomycosis since 1905.

[Reference] year	Location of brain involvement	Age (y)/sex, ethnicity	Meningitis	Remarks
[12] 1928	"Right optic thalamus" (4-mm caseous area)	31/M, F		Disseminated disease: lungs, nodes, subcutaneous and retroperitoneal abscesses, spleen, ostcomyelitis; CSF values normal; 5-mo duration of illness
[13] 1931	Left occipital	41/M, B		Disseminated disease
[13] 1931	?	21/F, W	-	Disseminated
[13] 1931	?	28/M, W	+	Brain, lung only
[13] 1931	?	31/F, W	_	Disseminated
[13] 1931	?	23/M, H	_	Disseminated
[2] 1936	Small nodule in right hemisphere	3/M, H	+	Disseminated disease; probably related to skin focus over right frontal bone and secondary erosion; 6-mo duration of illness
[5] 1938	Superficial cortex	39/M, W	+	Disseminated disease: skin, soft tissue, viscera, endocarditis
[5] 1938	Two small lesions in cortex	28/M, W	+	Disseminated: skin, lungs
[14] 1941	1-cm abscess in left cerebellum	49/M, ?	+	Brain, lung only; 2-mo duration of illness
[6] 1945	Miliary lesion in substantia nigra	22/M, W	+	Disseminated disease; 4-mo duration of illness
[6] 1945	Direct extension from meninges to brain	25/M, B	+	Disseminated; 3.5-mo duration of illness
[6] 1945	Miliary nodules in cerebrum, medulla, and cerebellum	21/M, B	_	Disseminated; 3-mo duration of illness
[6] 1945	Direct extension and miliary nodules in cerebrum (5 mm), cerebellum (two, 1.3 cm), midbrain (1.5 cm), and lateral ventricle lining	23/M, W	+	Disseminated
[15] 1946	Left cerebellar abscess	16/M, W	+	Brain, lung only; diabetes
[16] 1946	?	?/?, ?	?	Seven new cases; no identifying information
[17] 1977	Cerebral abscess	32/F, W	+	Disseminated disease; died 1 mo after onset of meningitis
[18] 1977	Pituitary abscess	47/F, ?	+	Hodgkin's disease during immunosuppressive therapy; disseminated coccidioidomycosis with cerebral vasculitis; nonreactive CSF serology
[19] 1978	Multiple cerebral nodular lesions	?/?, H(?)	-	CT revealed multiple hypodense lesions that were enhanced with a contrast medium
[20] 1980	Focal granuloma in cerebellum	37/M, W	+	Lung involvement for 8 y; dissemination to nodes, spine; hydrocephalus
[21] 1981	Left-internal-capsule coccidioidoma; granulomas in basal ganglia and brain stem	37/M, W	+	Disseminated disease; diabetes
[22] 1983*	3-cm mass in left cerebellum	45/M, H	_	Diabetes; lung and bone involvement, negative CSF serology, serum titer of CF antibodies to <i>Coccidioides</i> of 1:2; died of complications 10 mo later
[7] 1984	Miliary granulomas, including pituitary	2/M, W	+	Dissemination: lung, lymph nodes, kidney, liver, thyroid
[7] 1984	Miliary granulomas	27/M, W	÷	Dissemination: lung, heart, liver (massive), pancreas, kidney, spleen, bone marrow; died of hepatic failure
[7] 1984	Miliary granulomas	56/M, B	+	Dissemination: lung, liver, spleen, skin, adrenal, thyroid, pituitary; hydrocephalus
[23] 1988	5-mm abscess in substantia nigra of right midbrain	26/M, ?	+	HIV-positive; dissemination; died 16 mo after presentation; initial serum titer of CF antibodies to <i>Coccidioides</i> of 1:128; chronic meningitis at autopsy
[25] 1993	Cerebral mass	?/?, ?	+	HIV-positive; cerebral mass biopsy positive for <i>Coccidioides immitis</i> after 25 mo of treatment; lung involvement
[26] 1994	Right frontal lobe	19/M, H	_	Lung cavity and nodules; bone scan positive; normal CSF values; serum titer of CF antibodies to <i>Coccidioides</i> of 1:8; CSF titer negative
[PR] 1996	2.5-cm right cerebellar abscess	21/M, W	-	Diabetes; paraplegia; T8 anterior spinal artery syndrome; bone involvement

Table 1. (Continued)

[Reference] year	Location of brain involvement	Age (y)/sex, ethnicity	Meningitis	Remarks
[PR] 1996	Left pons	36/M, H	+	Coccidioidal meningitis for 10 y; ringlike enhancement in left pons
[PR] 1996	Outlet of fourth ventricle; C4 level to foramen magnum	42/M, L	+	Obstructive lesion in fourth ventricle; hydrocephalus; CSF titer of CF antibodies to <i>Coccidioides</i> of 1:16; normal chest radiograph
[PR] 1996	4-cm right cerebellar abscess	63/M, W	-	Diabetes; renal failure; CSF titer of CF antibodies to <i>Coccidioides</i> of 1:16; dissemination: lung, liver, spleen, prostate, thyroid; died 6 w after initial presentation
[PR] 1996	Multiple enhancing lesions	50/M, H	+	Diabetes; liver transplant; serum titer of CF antibodies to <i>Coccidioides</i> of 1:8 and CF test of CSF positive only with undiluted specimen; dissemination: peritonitis, bone involvement

NOTE. B = black; F = Filipino; H = Hispanic; L = Laotian; W = white; - = absent; + = present; ? = unknown.

* Case 1 in our study.

therapy (400 mg daily for 30 days); resolution of symptoms and improvement in visual acuity were found 2 years later when the case was reported.

In 1993 Galgiani et al. [25] reported a study on fluconazole therapy for coccidioidal meningitis. They described one HIVinfected patient with lung involvement and a focal cerebral mass (proven by biopsy to be coccidioidomycosis) that developed after 25 months of treatment.

In 1994 Mendel et al. [26] described the most recent case of brain coccidioidomycosis in a 19-year-old immunocompetent Latino man from Los Angeles who had a generalized seizure. An MRI revealed a 2×3 -cm intraaxial multiloculated ringenhancing cystic lesion in the medial and upper portion of the right frontal lobe with associated edema. CSF values were normal; the CSF titer of CF antibodies to Coccidioides was negative, but the serum titer was positive at 1:8. A chest roentgenogram demonstrated nodules and a right-lung cavitary lesion, and a bone scan showed abnormalities at multiple sites. A culture of bronchoalveolar lavage fluid yielded C. immitis. The patient was treated with fluconazole and amphotericin B. Craniotomy was performed with incision and drainage; cultures of the drainage yielded C. immitis. After resection, serial MRIs revealed that an initial small area of enhancement gradually resolved. These authors erroneously stated that their case was the first brain abscess due to Coccidioides in an immunocompetent patient.

In a recent neuropathological study [10], a patient with AIDS and CNS coccidioidomycosis was described, and a series of 15 autopsied cases of disseminated coccidioidomycosis was reported; CNS involvement occurred in eight of these 15 cases. All eight of these patients and the patient with AIDS had meningitis, and microscopic parenchymal involvement with granulomas and focal microabscesses were described in five of the eight patients and the patient with AIDS. Focal arteritis was present in one-half of the patients.

Discussion

CNS coccidioidomycosis usually involves the meninges, but as reviewed here, it can present as a mass lesion in brain parenchyma. The literature contains many cases with microscopic brain involvement, usually local extension from the meninges; this involvement can be quite common. In our review of all the literature on CNS coccidioidomycosis, we attempted to include only definitive brain lesions, such as distinct granulomas or abscesses, as described by the authors. The frequency of brain lesions varied from <1% to 33% in all the various case series of CNS coccidioidomycosis. A total of 39 cases (33 cases from the literature and our six cases) of brain coccidioidomycosis have been reported since 1905 (table 1).

Lesions can be multiple or single, can be superficial or deep, and can be found throughout the brain. Of note, however, cerebellar involvement occurred in four of our cases. True abscesses seem to be rare. It appears from the anatomic location that most discrete granulomas or abscesses are not due to direct invasion from the meninges but rather are caused by hematogenous spread from a lung or an infected meningeal source. Review of all cases, including our cases, indicated that approximately one-third (11 of 32 with pertinent information) of cases occurred when meningitis was absent. Disseminated disease was present in most cases, but there were some with brain and lung involvement only. Spinal cord involvement is rare, but this involvement was found in two of our cases. In the absence of meningitis, CSF serology appears to be negative. There was a strong male predominance, and no racial preference was noted. Vasculitic infarcts may underlay the formation of abscesses. Diabetes was noted in several cases, thus suggesting that vascular abnormalities (such as diabetic vasculopathy) may predispose to this complication. Immunosuppression associated with HIV disease was noted in two cases; Hodgkin's disease and organ transplantation were described in one case each.

Diagnosis of brain coccidioidomycosis in the era before CT and MRI was made at autopsy. With the availability of noninvasive brain imaging, more cases will be discovered. This technology probably explains why we have noted five cases in the last year, whereas only 33 cases were noted from 1905 to 1984. A contrast-enhancing mass on a brain CT or brain MRI with evidence of pulmonary coccidioidomycosis and a high clinical suspicion may suggest the diagnosis; the diagnosis will be confirmed by histologic examination or culture of a biopsy specimen. However, it should be noted that one of our patients had a normal chest roentgenogram and no respiratory symptoms. Serology may be useful for the diagnosis. Any case of coccidioidal meningitis or of disseminated disease with neurological symptoms (even with normal CSF values) should warrant brain imaging, although it should be noted that headache is a common symptom during the primary infection.

Optimal treatment of brain coccidioidomycosis is unknown at the present time, but three of our patients have remained in remission while receiving oral fluconazole therapy. Whether resection and treatment with intrathecal amphotericin B and/ or triazole antifungal agents will accomplish a cure remains to be evaluated. Prolonged treatment, perhaps indefinitely, should be considered because of the high rate of recurrence. We hope our series and literature review will increase awareness of this disease and facilitate diagnosis.

Acknowledgments

The authors thank Dr. Andrew Koo (Department of Diagnostic Imaging, Santa Clara Valley Medical Center, San Jose, CA) for his assistance, Sandra Pieper and Luis Gonzalez for their photographic expertise, and Marcia Vierra for preparing the manuscript.

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