Central Nervous System Abscesses Due to *Coccidioides* Species

Alfonso F. Bañuelos, Paul L. Williams, Royce H. Johnson, Salah Bibi, David N. Fredricks, Shelley A. Gilroy, Sana U. Bhatti, Jaime Aguet, and David A. Stevens

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, leptomenigitis 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: leptomenigitis alone (most frequent), leptomenigitis with cerebritis, leptomenigitis 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
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 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.

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.
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 x 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 right-elbow 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 cavitary 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 acid-fast 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 1.5-cm low-density lesion in the posterior portion of the right cerebellar hemisphere. A brain MRI revealed a 2.5-cm grape-like cluster of ring-enhancing lesions in the right cerebellar hemisphere with a mild mass effect (Figure 1). Cranietomy 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 right-elbow 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/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 (figure 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 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/mm$^3$ (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 fibroconnective 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
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 insulin-dependent 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 $4 \times 4.5$ 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-
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; 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. 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**

Ophuls [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...
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 parietooccipital 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 Buchbaum [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 Rodriguez 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 HIV-associated 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.

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

**Location of brain involvement:**
- Right optic thalamus
- Left occipital
- Two small lesions in cortex
- 1-cm abscess in left cerebellum
- Miliary lesion in substantia nigra
- Direct extension from meninges to brain
- Miliary nodules in cerebrum, medulla, and cerebellum
- Direct extension and miliary nodules in cerebrum (5 mm), cerebellum (two, 1.3 cm), midbrain (1.5 cm), and lateral ventricle lining
- Left cerebellar abscess
- Cerebral abscess
- Pituitary abscess
- Multiple cerebral nodular lesions
- Focal granuloma in cerebellum
- Left-internal-capule coccidioidoma; granulomas in basal ganglia and brain stem
- 3-cm mass in left cerebellum
- Miliary granulomas, including pituitary
- Miliary granulomas
- Miliary granulomas
- 5-mm abscess in substantia nigra of right midbrain
- Cerebral mass
- Right frontal lobe
- 2.5-cm right cerebellar abscess
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 HIV-infected 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 x 3-cm intraaxial multiloculated ring-enhancing 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...

Table 1. (Continued)

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

NOTE. B = black; F = Filipino; H = Hispanic; L = Laotian; W = white; - = absent; + = present; ? = unknown.
* Case 1 in our study.
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.

References