

Disseminated Coccidioidomycosis Complicated by Vasculitis: A Cause of Fatal Subarachnoid Hemorrhage in Two Cases

William K. Erly, Enrique Labadie, Paul L. Williams, Darlene M. Lee, Raymond F. Carmody, and Joachim F. Seeger

Summary: We describe two cases of disseminated coccidioidomycosis that were complicated by fatal subarachnoid hemorrhage. In the first case, a left middle cerebral artery aneurysm and long-segment vasculitis occurred. In the second case, MR imaging revealed an enlarging coccidioidal granuloma at the tip of the basilar artery, and the artery subsequently ruptured. Fatal intracranial hemorrhage is a rare complication of disseminated coccidioidomycosis.

The fungus *Coccidioides immitis* resides in the topsoil of the Southwestern United States and Northern Mexico. There are an estimated 60,000 to 80,000 new cases of coccidioidomycosis every year, with disseminated disease occurring in less than 1% of the population (1). Although vasculitis may occur, it more commonly causes ischemia and not hemorrhage (2, 3). Fatal intracranial hemorrhage is rare and, to our knowledge, has been reported as occurring in only one patient (4). We describe two cases of fatal intracranial hemorrhage, one resulting from direct invasion of the basilar artery and the second from rupture of a mycotic aneurysm in a patient without meningitis.

Case Reports

Case 1

A 74-year-old man with a history of immunoglobulin M kappa chain monoclonal gammopathy (Waldenström's macroglobulinemia) had been receiving steroid therapy for 2 years before admission and intermittent chemotherapy for 5 years. Four months before the final admission, he developed emesis, chills, and fever. Five blood cultures obtained during the next 4 days grew *Coccidioides immitis*. Amphotericin B therapy was initiated and resulted in resolution of the symptoms. The administration of amphotericin was tapered, and oral ketoconazole therapy was started.

At the final admission, the patient presented with the abrupt onset of headache, fatigue, and sweating. The results of a lum-

bar puncture were negative for meningitis, and the results of fungal culture and coccidioides serology of the CSF were negative. Within 24 hours, the patient became aphasic, febrile, and confused. CT was performed (Fig 1A), which showed a large parenchymal and subarachnoid hemorrhage involving the left lentiform nuclei and sylvian fissure. Cerebral angiography showed vasospasm and a distal left middle cerebral artery aneurysm (Fig 1B).

The patient underwent a craniotomy, at which time a 3-cm vasculitic segment of the middle cerebral artery with a focal aneurysm was identified and resected. A pathologic examination of the vascular wall disclosed necrosis with an infiltrate of neutrophils and lymphocytes. Small granulomata, which contained coccidioides spherules, were seen throughout the wall (Fig 1C–D). The patient died 5 days after surgery. Autopsy revealed *Coccidioides immitis* spherules throughout the liver, spleen, and lungs.

Case 2

A 33-year-old otherwise healthy man was diagnosed with coccidioidal meningitis in September 1995. At that time, CSF analysis showed 396 WBC/HPF (52% neutrophils), decreased glucose (32 mg/dL), and elevated protein (93 mg/dL). The results of the remainder of the work-up, including contrast-enhanced MR imaging of the brain, were unremarkable. Oral fluconazole therapy was initiated.

Within 1 year, the patient developed worsening headache, which was treated with increasing doses of fluconazole. By April 1997, he complained of worsening right frontal headaches and diplopia. A repeat MR examination showed a focal area of inflammatory change in the prepontine cistern adjacent to the basilar artery and extending along cranial nerve III (Fig 2A). Despite the worsening MR findings, the CSF parameters had improved (WBC/HPF, 15; glucose, 52 mg/dL; and protein, 71 mg/dL). The fluconazole was increased with an initial favorable response. Within 3 months, however, the symptoms recurred. Repeat MR imaging showed enlargement and morphologic change in the prepontine lesion (Fig 2B), and subtle enhancement was seen along the course of the left middle cerebral artery.

Within 2 weeks of the final MR examination, the patient died suddenly. At autopsy, subarachnoid hemorrhage was seen at the base of the brain and along the brain stem. The blood appeared to arise from the basilar artery immediately distal to the confluence of the vertebral arteries. Microscopically, a focus of numerous necrotic spherules of *Coccidioides immitis* was present in the perivascular space. The basilar artery showed full-thickness granulomatous inflammatory change with necrosis of the vascular wall (Fig 2C–E).

Discussion

Coccidioides immitis is a dimorphic fungus that resides in the topsoil of endemic areas of the South-

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From the Departments of Radiology (W.K.E., R.F.C., J.F.S.) and Pathology (D.M.L.), The University of Arizona, Tucson, AZ; the Veterans Affairs Medical Center (E.L.), Tucson, AZ; and the Visalia Medical Clinic (P.L.W.), Visalia, CA.

Address reprint requests to William K. Erly, MD, Department of Radiology, The University of Arizona, 1501 N. Campbell Avenue, Tucson, AZ 85724–5067.

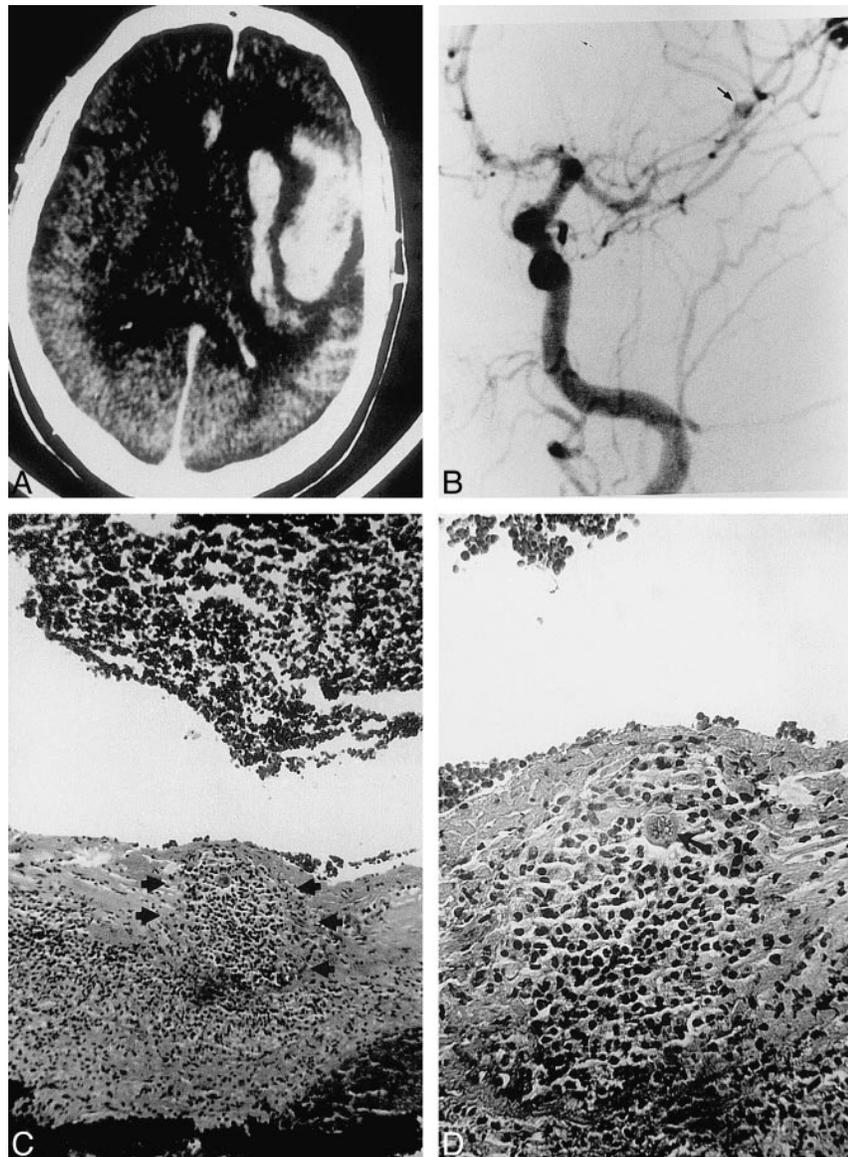
FIG 1. Case 1.

A, CT scan, obtained on the first day of final hospital admission, shows a large left lentiform nucleus and left sylvian fissure hematomas.

B, Left common carotid injection with long area of vasospasm in the left middle cerebral artery with focal aneurysm (arrow).

C, Pathologic specimen from left middle cerebral artery with local inflammation within the vessel wall (arrows).

D, Higher magnification shows the coccoioid spherule (arrow) more readily.



western United States and Northern Mexico. Within the soil, a spore-like structure called an “arthroconidium” may bud from a mature mycelium. This can become airborne and can be inhaled, at which time a primary pulmonary infection is established. In the host, the cell enlarges while undergoing mitosis and internal septation. The mature structure is known as a spherule, which may contain hundreds of endospores. When the spherule ruptures, the endospores are released and continue the cycle of infection (5). In some patients, the primary infection is not contained, resulting in hematogenous spread of the organism and disseminated disease. Individuals of Mexican, Filipino, and African ancestry are at increased risk of dissemination, as are pregnant women, the very young or old, and the immunosuppressed.

Within the CNS, the meninges comprise the most common site at which the hematogenous seeding occurs (6). Vasculitis has been observed in

up to 40% of cases of meningitis; however, this typically involves the small penetrating branches of the major cerebral vessels, resulting in deep ischemic infarction (6). Subarachnoid hemorrhage is a rare complication and, to our knowledge, has been reported as having occurred only once previously (4).

These two cases are unusual in that both patients experienced a common fatal event with the same organism via different routes of dissemination. In Case 1, direct seeding of the intracranial vasculature developed and arterial necrosis and rupture subsequently occurred. In Case 2, necrosis also developed, either from external invasion arising from the CSF or from hematogenous seeding to the basilar artery. We favor the former explanation, because the rupture was at the site of a focal meningeal collection of *Coccidioides immitis*.

In Case 2, the microscopic evaluation of the lesion in the pontine cistern revealed a dense col-

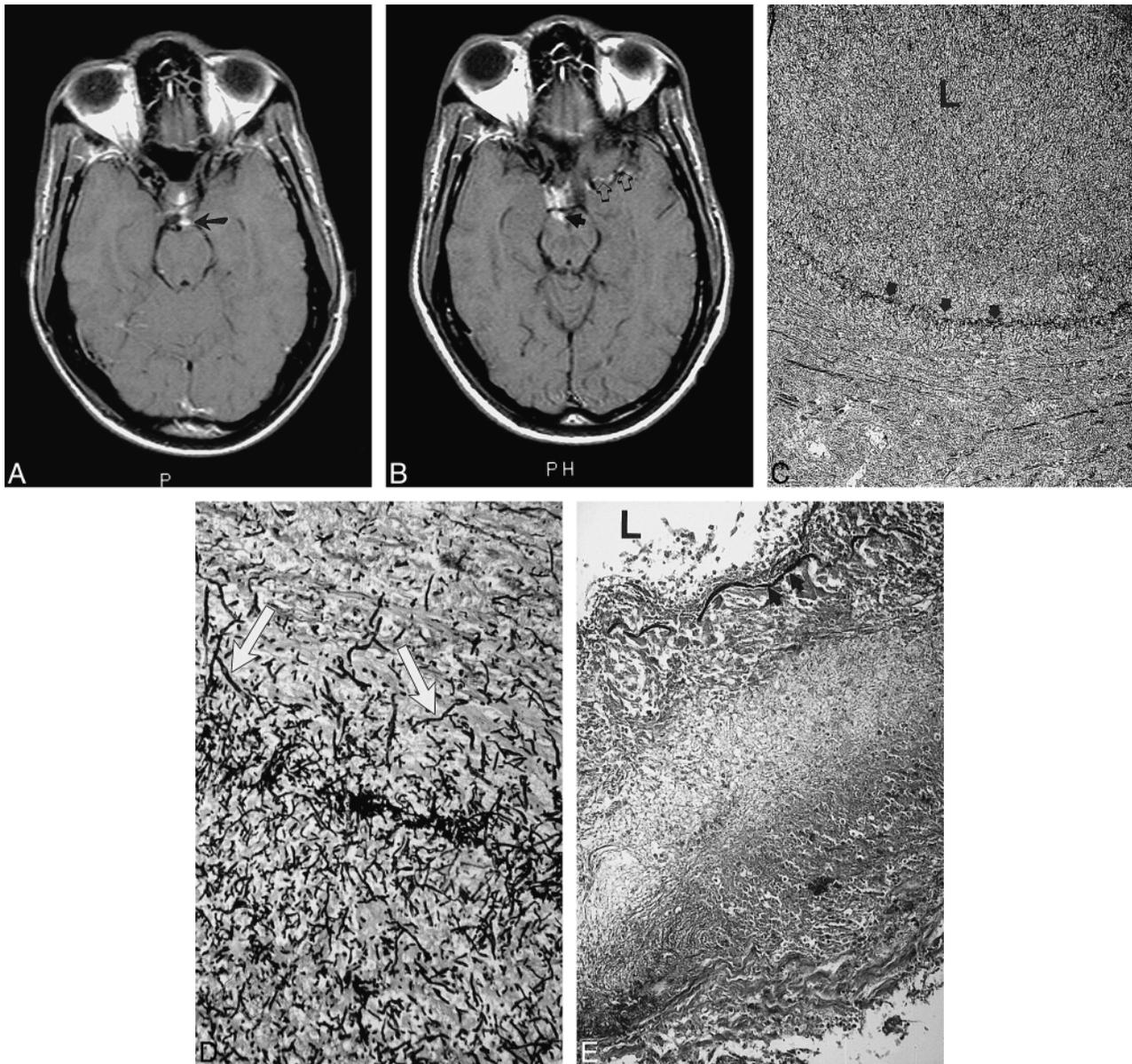


FIG 2. Case 2.

A, Nineteen months after presentation, axial contrast-enhanced T1-weighted MR image shows abnormal enhancement within the preoptine cistern, to the left of the basilar artery (*arrow*).

B, Two weeks before death, a follow-up examination shows enlargement and change in morphology of the preoptine granuloma (*arrow*) despite improving CSF parameters. Enhancement is present along the left middle cerebral artery (*open arrows*).

C, Photomicrograph of basilar artery cross section shows fungal stain of the same lesion shown in B, with innumerable hyphae invading the basilar artery. The lumen (L) and intimal surface (*arrows*) are shown.

D, Photomicrograph of basilar artery cross section shows the same section at higher magnification, depicting the hyphae (*arrows*) more clearly.

E, Photomicrograph of basilar artery cross section shows the basilar artery slightly more proximal than shown in C. Elastin stain shows medial necrosis and interruption of the internal elastic laminae. The remaining intact lamina (*arrows*) can be seen. The luminal surface (L) is at the top of the image.

lection of *Coccidioides immitis* in the mycelial phase. This is the life cycle phase that is generally found in the soil at ambient temperatures. This phase, however, has been described rarely as occurring in patients with *Coccidioides immitis* meningitis and may represent a true finding. Alternatively, the time delay between death and autopsy may have allowed the endospore to transform into the mycelium (7, 8).

The paradox of the worsening MR findings coupled with improved CSF parameters in Case 2 raises the question of whether the MR image depicted true worsening of disease despite the improved CSF profile. Vasculitic complications of *Coccidioides immitis* may occur despite stable CSF parameters (3). It is likely that meningitis was improving in this patient whereas changes in the granuloma observed on the MR images reflected an inflam-

matory process not detectable by lumbar puncture. MR imaging and lumbar puncture seem to be complementary examinations for the evaluation of patients with coccidioidal meningitis in that the worsening inflammatory changes seen on the MR images were not reflected in the CSF.

The incidence of abnormalities detectable by imaging studies has been reported to be as high as 93% for patients with coccidioidal meningitis (9, 10). For this reason, we suggest routine screening with contrast-enhanced MR imaging for these patients. At our institution, we suggest imaging at the time of diagnosis at 3 months, 6 months, and 1 year, and every 6 months thereafter until clinical and imaging stability is achieved. MR angiography can be included with this screening study to assess for vasculitis or aneurysm formation.

Intracranial hemorrhage may occur as a rare complication of disseminated coccidioidomycosis. In patients with meningitis, MR imaging and lumbar puncture may be complementary examinations when assessing for disease progression.

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