Hyphal Forms in the Central Nervous System of Patients with Coccidioidomycosis


_Coccidioides immitis_ is a dimorphic fungus that grows as a filamentous mold in soil and as a spherule at human body temperature. The hyphal or soil form is found rarely in human tissue. We report 5 cases of coccidioidomycosis in which hyphae were found in brain tissue or spinal fluid. The presence of central nervous system plastic devices appears to be associated with morphological reversion to the saprophytic form. This reversion has implications for diagnosis and therapy and may increase the risk of obstruction of the device(s).

**Case Reports**

**Case 1.** A 46-year-old white woman who had had insulin-dependent diabetes mellitus for 32 years received a renal homograft in 1982. She frequently visited the southwestern United States and northern Mexico. In January 1987, she developed photophobia, headache, fever, nausea, and vomiting and was found to have an elevated CSF pressure and CSF pleocytosis. A chest radiograph revealed a lung nodule, which on biopsy was found to have an elevated CSF pressure and CSF pleocytosis. A chest radiograph revealed a lung nodule, which on biopsy was found to have an elevated CSF pressure and CSF pleocytosis. A chest radiograph revealed a lung nodule, which on biopsy was found to have an elevated CSF pressure and CSF pleocytosis. A chest radiograph revealed a lung nodule, which on biopsy was found to have an elevated CSF pressure and CSF pleocytosis. A chest radiograph revealed a lung nodule, which on biopsy was found to have an elevated CSF pressure and CSF pleocytosis.

She had a ventricular Ommaya reservoir placed in March 1987 and was treated for 4 years with intrathecal and (initially) iv amphotericin B, with oral fluconazole (1987–1989), and with itraconazole, beginning in 1989. She had multiple problems with intolerance to intrathecal amphotericin B, which required repeated, temporary cessation or reduction in dosage. She also had recurrent problems with cerebrovascular disease. She had a transient cerebral ischemic attack and a left-hemispheric stroke in 1988, a right-lacunar infarction and transient ischemic attack in 1990, and another cerebrovascular accident in October 1990.

Her infection had appeared to be controlled with a regimen of 0.16 mg of amphotericin B intrathecally every 3–6 weeks, in conjunction with 100 mg of oral itraconazole twice daily, but she was readmitted in January 1991 because of headache, nausea, and vomiting. The patient had a long and complex series of complications and procedures thereafter. A VP shunt was placed for management of hydrocephalus, and a lumbar Ommaya reservoir was also placed. Multiple shunt revisions were required because of repeated episodes of bacterial meningitis. She later had seizures and developed left-sided weakness and disturbance of balance.

In mid-1991 numerous cerebral ischemic events occurred, rendering her bedridden. Fever seemed to correlate with amphotericin B therapy. The patient was clinically stable on a regimen of 0.35 mg of intrathecal amphotericin B every 3 weeks and oral itraconazole, until the latter was stopped because of tube feedings. She was discharged to a nursing facility in June but returned within 72 h because of fever (temperatures to 40°C) and loss of consciousness. Respiratory failure occurred and was attributed to a brain-stem infarction. Late in her hospitalization she developed candidemia, which responded to amphotericin B, but she became comatose. Thereafter, therapy was restricted to comfort measures, and she died in July 1991.

_Autopsy:_ At postmortem examination, the lungs had bi-
lateral miliary fibrogranulomatous foci, and hematoxylin-eosin and Gomori methenamine-silver nitrate stains showed coccidiodal spherules. Cultures yielded *C. immitis*. There was chronic basilar granulomatous meningitis overlying the distal basilar artery, and a single 1-cm gray soft mass and multiple small 4–5 mm granulomas in the brain stem contained *C. immitis*, evident by smear and culture. Lesions adjacent to the vertebral artery contained *C. immitis* but did not involve the arterial lumen.

Sections of the brain stem and leptomeninges showed granulomas that consisted of hyphae, surrounded by multinucleated giant cells that contained hyphal elements and spherules (figure 1). Hyphae seen in the periodic acid–Schiff-stained smears had terminal expansions that resembled sporangia. This apparently represented mycelial germination from the spherule endospore phase. Numerous infarcts in the brain stem, leptomeningeal endarteritis obliterans, and chronic ependymitis in the fourth ventricle were noted.

Susceptibility test of isolates recovered at autopsy. The isolates were tested according to a modification (for testing filamentous fungi) of the recommendations by the National Committee for Clinical Laboratory Standards (document M27-T, 1996) [12]. The MIC and minimum lethal concentration (MLC) of amphotericin B at 48 h and 72 h was ≤0.3 μg/mL. Although the MIC of fluconazole at both times was 2.5 μg/mL, the MLC increased from 20 μg/mL to >80 μg/mL at 72 h. Likewise, the itraconazole MIC remained at ≤0.018 μg/mL, but the MLC increased from that value to 2.5 μg/mL at 72 h.

**Case 2.** A 56-year-old Korean man was found to have coccidiodial meningitis in 1984. After 4 years of therapy with intrathecal amphotericin B and miconazole and oral ketoconazole, fluconazole, or itraconazole, his neurological symptoms worsened, and hydrocephalus was diagnosed. In 1988 lumbar and ventricular reservoirs and a VP shunt were placed.

After 5 months of therapy with itraconazole taken irregularly, the clinical picture worsened, and CSF pleocytosis in both lumbar and ventricular fluid was noted, as well as an elevated CSF protein level and hydrocephalus. His CSF coccidiodial CF titer had also increased. Several shunt revisions were required, because fibrinous debris occluded the ventricular catheter and shunt valves.

In 1989 he had worsening meningitis, and cultures of CSF from both reservoirs yielded *C. immitis*. Gram stains of the ventricular fluid revealed mycelial forms suggestive of arthroconidia (figure 2). The patient was treated with itraconazole and intrathecal miconazole, but CSF cultures remained positive; he died soon thereafter.

**Case 3.** Pulmonary coccidioidomycosis in a 48-year-old white man was diagnosed in 1992. He was treated for 3 months with oral fluconazole at a dosage of 100 mg/d. After discontinuation of the fluconazole therapy, the patient developed meningial signs, and there was evidence of coccidoidal meningitis in the CF titer in CSF. He did well for 1 year with a regimen of fluconazole (400 mg/d), until 1994, when he developed hemiparesis.

The patient was treated with high-dose (1200 mg/d) flucon-
azole for 3 months, until cerebral ischemic events occurred and the CSF coccidioidal titers increased. He then started therapy with intrathecal amphotericin B, but the cerebral ischemic events continued. Intrathecal therapy was discontinued after 3 months because of neurotoxic side effects.

He subsequently did well symptomatically with fluconazole at a dosage of 600 mg/d for 1 year, but the CSF CF titers increased and he developed hydrocephalus, for which a VP shunt was placed. His fluconazole therapy was changed to administration of oral itraconazole (200 mg b.i.d.) because of anorexia and weight loss, believed to be related to fluconazole. The itraconazole dosage was increased to 200 mg t.i.d. in May 1996 because of increasing CSF coccidioidal titers.

In December 1996 the patient again developed hydrocephalus and underwent a VP shunt revision. Gram stain of the CSF revealed mycelia, possibly with arthroconidial forms; the mycelia were believed to be the cause of the shunt obstruction. Cultures subsequently yielded \textit{C. immitis}. The patient was discharged to a rehabilitation unit, and a regimen of oral fluconazole (400 mg/d) was initiated.

Case 4. A 45-year-old Latino man developed severe pulmonary coccidioidomycosis in 1990, which was complicated by coccidioidal meningitis. He was treated with oral fluconazole, usually in doses of 400 mg daily, but developed hydrocephalus and required a VP shunt in 1996. In November 1997 vomiting, abdominal pain, diplopia, ataxia, and anorexia developed. In January 1998 a CT scan of the head revealed hydrocephalus consistent with shunt failure.

On physical examination he was emaciated and partly disoriented, and had fine hand tremors and slurred speech. Muscle-wasting was also evident. A reservoir that had been inserted into the shunt line was pumped by external pressure, and the shunt line was aspirated; neither maneuver suggested shunt blockage. However, at surgery, the shunt was found to be nonfunctional.

Shunt fluid and ventricular fluid aspirated through the shunt were obtained. This CSF contained gross trabeculated proteinaceous debris and 10 leukocytes/mm$^3$, and the protein and glucose concentrations were 10 mg/dL and 60 mg/dL, respectively. CSF had a coccidioidal CF titer of 1:2 (a simultaneous serum titer was 1:256). Microscopic examination of this CSF revealed mycelia, apparently germinating from spherules (figure 3). Cultures were subsequently positive for \textit{C. immitis}.

Fungal peritonitis was discovered at the distal peritoneal end of the shunt; a CSF pool, thickened peritoneum, and peritoneal seeding were noted. The shunt tubing itself was coated with fibrous, granulomatous-appearing tissue. The shunt was irrigated, cleaned, and rerouted in the peritoneum. A central line was inserted for hyperalimentation, and during the next month a gastrostomy tube was placed surgically because of dysphagia and aspiration. Subsequent intracisternal and iv amphotericin therapy were complicated by nausea and vomiting.

Case 5. A Mexican immigrant had lived in California since 1987, employed as a farm worker and gardener, frequently in the Central Valley. He traveled to Morelia, Michoacan, Mexico twice yearly, often by car. On one such visit, at age 27 years, in November 1997, he experienced progressively worsening headache and fever. In January 1998, a CT scan of the head
suggested vasculitis, and he received a course of corticosteroids, which at first led to some improvement.

By February 1998 he had severe headache, nausea, and visual changes. CT was performed again and indicated the development of hydrocephalus. Lumbar puncture yielded CSF with a protein concentration of 82 mg/dL, a glucose concentration of 9 mg/dL, and 700 leukocytes/mm³, but all cultures and stains were negative; the opening pressure was reportedly normal. A VP shunt was placed, and he was treated with dexamethasone and antibacterials, resulting in minimal improvement. He elected to return to the United States for further treatment.

His admission work-up included chest radiography, which revealed a 2.5-cm, thin-walled cavity in the right upper lobe. Follow-up CT demonstrated resolution of the hydrocephalus. An HIV test, coccidioidal skin test, and PPD test were negative. Both the serum and CSF contained antibody to \textit{C. immitis}, evident by immunodiffusion. The patient was treated with fluconazole (800 mg daily) and was discharged.

Over the next 2 months he continued to have headache, nausea, and emesis, as well as anorexia, weight loss, and increasing lower-back pain. Because of his gastrointestinal symptoms, his fluconazole dosage was decreased to 400 mg daily. Repeated lumbar puncture in April 1998 revealed a protein concentration of 7800 mg/dL and coccidioidal antibody titer $>1:2048$, evident by immunodiffusion. The patient was readmitted to the hospital in May.

The patient had mild weakness of the distal upper extremities, particularly the intrinsic muscles of the hands, and hyperreflexia of the lower extremities. MRI of the spine revealed diffuse enhancement of the subarachnoid space from the cervical to the sacral spine, consistent with diffuse leptomenigitis, and an ill-defined, intramedullary, high-signal-intensity lesion was noted from levels C5–T2. MRI of the head showed basilar meningitis and involvement of the ependyma of the lateral and third ventricles. Fluconazole was withdrawn and therapy with itraconazole was started, at a dosage of 200 mg twice daily.

A lumbar CSF reservoir was placed in June 1998. Attempts to deliver amphotericin B by the intrathecal route were aborted after a total of $<2$ mg had been delivered, owing to the development of increased leg weakness and painful paresthesia of the legs. Injection of indium isotope into the lumbar CSF suggested blockage of CSF flow at the level of the midthoracic spine. CSF obtained from the VP shunt had a protein concentration of 91 mg/dL, glucose concentration of 73 mg/dL, and 27 leukocytes/mm³. Culture of this fluid was negative.

A ventricular dye-flow study demonstrated that the VP shunt was patent to the peritoneum, and there was no flow below the foramen magnum. He was discharged, and his dosage of itraconazole was increased to 1000 mg/d, which was well tolerated and gave peak serum levels (as indicated by bioassay) in the range of 15–20 \textmu g/mL.

The patient’s condition improved with this regimen over the following 6 months, with resolution of his headaches, decreased back pain, and increased strength. He was able to return to work and was bothered only by decreased grip strength and an inability to lift heavy objects. His serum coccidioidal antibody titer remained in the range of 1 : 64 to 1 : 128. Repeated attempts to obtain CSF for analysis via the lumbar reservoir or a lumbar puncture and cisternal tap failed.

In March 1999 the patient began to note increasing lower-
back pain radiating to the legs, increased weakness of the legs, and ataxia. Findings of a neurological examination in April were remarkable for decreased strength of wrist flexors, forearm extensors, and hip flexors, with a new incomplete left-foot drop. He had a positive Romberg sign and was unable to tandem-walk. MRI of the head showed new dilatation of the lateral and third ventricles, increased signal intensity in the periventricular regions surrounding the frontal and occipital horns, consistent with mild hydrocephalus, and a new 0.5-cm-diameter enhancing lesion of the right cerebellar peduncle.

In May an Ommaya reservoir was placed in the left lateral ventricle, and pressures of 12–18 cm of water were noted intraoperatively, suggesting adequate function of the contralateral VP shunt. Ventricular CSF had a protein concentration of 6 mg/dL, a glucose concentration of 61 mg/dL, and a leukocyte count of 0/mm³. No coccidioidal antibody was detected, and a culture was negative. The patient’s lumbar reservoir was removed. A fibrinous plug noted at the reservoir tip was sterile.

The patient’s leg strength continued to deteriorate, and he was readmitted for intrathecal amphotericin B therapy in June. Ventricular CSF obtained from the VP shunt was turbid, and direct–wet-mount CSF findings were notable for mats of hyphae that branched at acute angles (figure 4). The protein concentration was 5 mg/dL, the glucose concentration was 76 mg/dL, and the leukocyte count was 1/mm³; C. immitis was isolated in culture.

An interesting finding was that CSF withdrawn the following day from the Ommaya reservoir revealed no fungal elements on wet mount or gram stain. This CSF otherwise was essentially identical to that from the VP shunt. The patient’s therapy was switched to administration of fluconazole (800 mg twice daily orally), and at the time of this writing he was stable with a regimen of iv amphotericin B and intraventricular amphotericin (0.3 mg daily).

**Discussion**

*C. immitis* is a dimorphic fungus. Sixty percent of infections are asymptomatic. Ninety percent of symptomatic infections resolve without specific treatment. Less than 1% of patients develop disseminated disease, which involves the CNS in ~33%–50% of these patients [1]. Basilar meningitis is the usual CNS site of infection. Hydrocephalus and elevated intracranial pressure are potentially treatable CNS complications. CNS disease is universally fatal if left untreated, and prolonged survival occurs in only 50% of treated cases [2, 3]. Cerebral vasculitis is a recently recognized complication of coccidioidal meningitis [14]; our patients clearly demonstrated the serious consequences of that complication.

Of patients with *C. immitis* meningitis, 70% or more have negative CSF cultures and require ancillary diagnostic approaches such as determination of CSF CF titers [2]. Pathological findings include granulomatous meningitis with extensive involvement of the basilar meninges, and late findings of a thick inflammatory exudate consisting of plasma cells, lymphocytes, multinucleated giant cells, and coccidioidal spherules.

![Figure 4](image-url)  
**Figure 4.** Case 5. Gram stain of centrifuged CSF. Photograph shows most clearly the probability that hyphae in CNS can mature fully to form (in the usual manner, as noted in agar cultures) arthroconidia, which are infectious propagules of this fungus. Heavily staining barrel-shaped structures (presumed arthroconidia) are seen with adjacent hypoplastic (and presumed degenerating) weakly staining fungal cells (arrows) (original magnification, ×400).
The presence of hyphae, with or without formation of mature arthroconidia, in a leptomeningeal granuloma of coccidioidomycosis is distinctly unusual [4]. Likewise, the presence of coccidioidal mycelia in CSF is unusual. We found only 2 previously reported relevant cases [4, 5]. Encountering C. immitis as mycelia in tissues and body fluids, suggesting mold infection, could confound the clinician.

Extrathoracic dissemination occurs >70% of the time in immunocompromised patients and is often life-threatening. Patients who are immunosuppressed by malignancy, HIV disease, or organ transplantation are known to be at increased risk for dissemination, to have more severe primary infections, and to have reactivated latent disease at a higher incidence rate than normal hosts [6–8]. Patients who have undergone organ transplantation in areas of endemicity have a greater risk for coccidioidal infection in the first year after the transplantation. C. immitis is the single most common cause of infection in a transplantation population in Arizona [8, 9].

C. immitis proliferates in tissue, mainly as the parasitic spore form. The saprobiic mycelia, the soil form of C. immitis, are rarely identified in human tissue. Arthroconidia are the mature infectious propagules that develop from alternate cells on hyphal stalks; in light microscopy, vacuolization of segmented hyphae may incorrectly suggest true arthroconidia.

A review by Meyer et al. in 1982 found 750 cases of C. immitis infection [4]. In only 12% (95) was mycelial formation noted (the authors believed that arthroconidia could commonly be identified), and 92 of these cases were pulmonary. Twenty-three of 26 patients were white. Only 4% of the cases in which mycelial forms were noted involved women, and these infections were all localized to the lung.

Table 1 summarizes the 5 reported cases in which C. immitis mycelial forms were found at extrapulmonic sites. Our renal transplant recipient (case 1) had an especially unusual manifestation of CNS coccidioidomycosis. Less than 40 cases of CNS coccidioidomycosis have been reported to have parenchymal brain involvement [18]. Case 1 may represent the second reported case of parenchymal brain disease with C. immitis mycelia.

We report 5 more instances of mycelia in extrapulmonary sites and include the first report of such an instance in a woman. Furthermore, 2 of the cases in table 1 may represent only draining lesions with formation of mycelia at external tissue surfaces. This may be analogous to formation of mycelia with arthroconidia on the inner surfaces of orthopedic casts that contain sinus-tract drainage from C. immitis osteomyelitis.

In cases 2 and 4, the mycelia in CSF was associated with subcutaneous reservoirs, and in cases 1 and 5 reservoirs also were in place; all 5 case patients had CSF shunts, and the mycelia were associated with these shunts in cases 3, 4, and 5. Wages et al. described hyphal forms of C. immitis in the CSF of a patient with a CSF shunt [5]. This indicates that plastic surfaces, or perhaps low partial pressure of CO₂ in reservoirs or shunts, may provide an environment facilitating mycelial growth in human tissue or fluid [19, 20].

As our report suggests, transformation of C. immitis to the saprophytic form is being more frequently recognized, but it is unclear whether this may be related to more frequent use of these devices in such patients or to changes in the plastic materials themselves, because of developments in polymer chemistry. Mycelial growth on or in the presence of plastic could result in plugging of catheter lumens or development of nodules resistant to therapy (e.g., because of an associated biofilm). Whereas the CSF in all our cases yielded C. immitis, the differential diagnosis of mycelia seen in CSF or on implanted plastic could include opportunistic fungi colonizing an implanted device.

C. immitis meningitis is associated with a 30%–50% mortality, even with the best currently available regimens. Conventional therapy includes both systemic and intrathecal administration of amphotericin B. Previously, treatment with intrathecal amphotericin B often involved a slow, incremental increase to a dosage of 0.5 mg and continuation until remission [10]. Treatment with intrathecal amphotericin B is associated with substantial neurotoxic effects such as arachnoiditis that may limit treatment and mimic active infection. Unfortunately, amphotericin B cures coccidioidal meningitis in <25% of cases [1, 8].

Triazoles have been tested for efficacy in the treatment of C. immitis meningitis [8]. Levels of itraconazole in CSF are negligible, but it is reported to effectively suppress C. immitis meningitis [3]. Neither the optimal dosage nor the optimal duration of triazole therapy for C. immitis meningitis is known. Relapse is very common. Even immunocompetent patients probably need lifelong treatment, because their frequency of relapse after discontinuation of treatment is very high [11].

Fluconazole therapy for cryptococcal meningitis at a dosage

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<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Patient</th>
<th>Symptoms/signs</th>
<th>Pathology</th>
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<tbody>
<tr>
<td>[16]</td>
<td>1963</td>
<td>61-year-old Filipino male agricultural worker in San Joaquin Valley</td>
<td>Ulcerated scalp lesion after grapevine scratch, with headache and fever</td>
<td>Scalp biopsy with hyphae of C. immitis</td>
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<tr>
<td>[4]</td>
<td>1978</td>
<td>44-year-old male tree surgeon from Los Angeles</td>
<td>Seizure disorder, lip ulceration</td>
<td>Lip biopsy contained arthroconidia, and fluid in CSF reservoir had mycelia of C. immitis</td>
</tr>
<tr>
<td>[17]</td>
<td>1988</td>
<td>26-year-old HIV+ man from southern California</td>
<td>Headache, fever, weight loss</td>
<td>Brain abscess with arthroconidia of C. immitis</td>
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<tr>
<td>[5]</td>
<td>1995</td>
<td>31-year-old Laotian man with ventricular peritoneal shunt placed 6 w earlier for hydrocephalus</td>
<td>Headache, fever, lethargy, unsteady gait</td>
<td>CSF contained hyphal forms but no spherules; CSF yielded C. immitis</td>
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</table>
of ≤200 mg/d has been associated with progression to other disseminated disease [21]. The experience with case 1 provides some insight into the effect of fluconazole and itraconazole therapy for coccidioidal meningitis. The dosages of 100–200 mg/d were low by current standards [8], and the organism persisted in tissue. However, it remained susceptible to both drugs when postmortem isolates were tested. The meaning of the increase in MLC of triazoles with further incubation is unclear, but future clinical studies should examine correlations with persistence during therapy.

Although fluconazole is a dependably absorbed agent for suppressing coccidioidal meningitis, disease progressed in all 5 of our patients while they were receiving this therapy. The liquid formulation of itraconazole may provide an alternative because its bioavailability is reportedly more reliable than that of the capsule form, and this would overcome the problem of administration in the presence of a feeding tube (see case 1) [22]. As demonstrated by case 1, infection persisted and appeared to become exacerbated after cessation of therapy. The infections in cases 3 and 5 persisted despite high-dose itraconazole therapy. In cases of meningeal infection associated with a foreign body, replacement of hardware may be a necessary adjunctive therapy.

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References


Addendum. An article published while our manuscript was in preparation has come to our attention: Zapada MR, Kobayashi GK, Appleman MD, Navarro A. Coccidioides immitis presenting as a hyphal form in cerebrospinal fluid. J Nat Med Assoc 1998;90:435–6. The hyphae illustrated appear to be arthroconidia. No hardware was present in the CNS of this patient. Thus, taken together with the 5 patients presented and the 3 cases cited in our study, hardware was present in 7 of 9 instances where hyphae have been described in the CNS, and was present in 6 of 7 cases where the hyphae were in the CSF.