Coccidioidal Meningitis

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Residents of the area now occupied by the southwestern United States and northwestern Mexico have had to deal with coccidioidomycosis and complicating meningitis for >1500 years. The hundredth anniversary of the reporting of disseminated coccidioidomycosis has just passed. This year has the dubious distinction of being the hundredth anniversary of the first description of coccidioidal meningitis. Although intrathecal amphotericin B began to be used for therapy 50 years ago, and although we have benefited from azole therapy for >10 years, the morbidity and mortality associated with this all-too-common disease remain unacceptably high. This review will endeavor to discuss the pathogenic, pathophysiologic, clinical, laboratory, radiologic, and therapeutic features of meningitis secondary to Coccidioides infection.

Cutaneous disseminated coccidioidomycosis was originally described in the last decade of the 19th century by Wernicke and Posadas [1] in Buenos Aires, Argentina, and was subsequently described by Rixford and Gilchrist [2] in California. In 1905, Ophuls [3] first described coccidioidal meningitis. Evans [4] provided further description in 1909. The first living patient with coccidioidal meningitis and associated hydrocephalus was described by Ryfkogel [5]. The definitive description of coccidioidal meningitis from the pretherapy era can be found in the Veterans Affairs Armed Forces studies from 1955–1958 [6].

EPIDEMIOLOGY

Coccidioidomycosis is only found in the Western Hemisphere, especially in the southwestern United States and northwestern Mexico. The annual incidence of disease in areas of endemicity, although not known exactly, appeared to be relatively stable through the middle decades of the 20th century. For reasons only partially explained by population growth and migration and by the existence of a greater number of immunocompromised hosts, the absolute and relative frequency of primary disease and consequent dissemination have multiplied [7]. This increase has involved both endemic and epidemic disease, as documented in the early 1990s and now in the early years of this millennium.

The majority of coccidioidal infections are asymptomatic. Primary infections are almost universally respiratory. Influenza-like, pneumonic, and pleural presentations are the most common. If one takes into account the large number of asymptomatic infections, the rate of dissemination is low. In high-risk, symptomatic populations, the dissemination rate can be >15% [8]. A smaller percentage of disseminated infections will present with the disseminated focus without an identified primary pulmonary antecedent.

PATHOGENESIS

The first identified Coccidioides species was Coccidioides immitis. Recently, Taylor et al. [9] identified a second species, Coccidioides posadasii. C. immitis is more common in California, and C. posadasii is more common in Texas, Central America, and South America. Both species are found in Arizona. No clinical distinctions have thus far been noted for the 2 species.

Lymphatic and lymphohematogenous dissemination to virtually any site may occur. Meningitis is the most feared form of dissemination and is found in nearly one-half of individuals with disseminated disease. Before the advent of therapy, death within a few months was nearly universal. There are rare reports of survival for >2 years [10]. Most cases of dissemination, including cases of meningitis, occur within weeks to months after primary infection. Rare instances of meningitis presenting years after the original diagnosis of primary or other disseminated disease have been reported.
CLINICAL PRESENTATION

The clinical presentation of meningitis is protean. The most common symptom is headache. Altered mental status, with or without fever, personality changes, nausea, vomiting, and focal neurological deficits may be additional findings. Physical examination will reveal some degree of meningismus in ~50% of the cases. Gait abnormalities and focal neurologic deficits may be seen in a minority of cases.

Hydrocephalus may be either a presenting manifestation or a late complication of coccidioidal meningitis. When initially present, the hydrocephalus may dominate the clinical findings. In persons at risk for coccidioidal infection, the primary diagnosis of acquired hydrocephalus should engender a search for the underlying cause, including an evaluation for coccidioidomycosis. Neuroimaging may be a substantial aid in the clinical evaluation and will be discussed in Diagnosis below.

Evaluation of CSF samples is requisite for the diagnosis and management of coccidioidal meningitis. The CSF findings are almost always those typical of other chronic meningitides.

COMPLICATIONS

The most common complication of coccidioidal meningitis is hydrocephalus, as noted above. Most—but not all—individuals with late-onset hydrocephalus continue to have CSF-based evidence of active disease, despite receipt of therapy.

Cerebral infarction may be a presenting manifestation of coccidioidal meningitis or may present later in the course of recognized illness [11–13]. As with hydrocephalus, it appears that an active inflammatory process in the CSF is a risk factor for this complication [14, 15]. Vasculitic infarctions have usually been ascribed to inflammation of small- to middle-sized blood vessels. On rare occasions, venous and dural thrombosis may occur [16].

Spinal arachnoiditis may occur as a complication, but unlike infarctions and hydrocephalus, arachnoiditis tends to occur after presentation (figure 1). Similar to these complications, arachnoiditis appears to have persistent inflammation as its antecedent. Arachnoiditis has been reported as a complication of intrathecal therapy, particularly intralumbar therapy with amphotericin B deoxycholate [14, 17]. Although amphotericin given intrathecally often causes transient paraparesis and urinary retention, the rate of chronic arachnoiditis appears to have increased since fluconazole became the mainstay of therapy. In this latter circumstance, arachnoiditis may respond to a switch to intrathecal therapy with amphotericin B.

Cerebral abscesses secondary to Coccidioides infection have been rarely reported [18–20]. There are also reports of mass lesions [16]. Both of these complications—especially the latter—appear to be rare.

Hyponatremia as a complication of both severe coccidioidal pneumonia and meningitis has been observed on many occasions. Apparently, the association between hyponatremia and the syndrome of inappropriate antidiuretic hormone secretions has only recently been reported [21].

Coccidioidal infection is an infrequent but potentially devastating complication of pregnancy. This is particularly true if meningitis develops in a pregnant female or if a patient with coccidioidal meningitis becomes pregnant. Most clinicians with significant experience with coccidioidal meningitis do not recommend any attempt to become pregnant, although successful treatment during pregnancy has been accomplished. None of the currently available azaoles have been demonstrated to be safe during pregnancy. Teratogenesis associated with ketoconazole and fluconazole therapy has been reported [22, 23]. The only available current therapy for pregnant patients is intrathecal amphotericin B deoxycholate.

DIAGNOSIS

Modest CSF pleocytosis usually occurs. The cell count seen ranges from the low double-digits to >10,000 cells/mm³. The majority of cells are typically lymphocytic, but a predominance of neutrophils is not uncommon. Eosinophils are not common, but when present, they are highly suggestive of the diagnosis [24]. (It is preferred that the CSF differential cell count be routinely performed on a stained cytospin preparation.) The CSF protein level is almost always elevated; it is usually ≥150 mg/dL, and occasionally it can be measured in grams. The CSF glucose level is usually depressed.

The definitive diagnosis of coccidioidomycosis rests on the careful histopathologic identification of endosporulating spherules, a positive culture result with confirmation of Coccidioides

Figure 1. T1-weighted image with gadopentetate dimeglumine contrast showing arachnoiditis-thickened compression of the dura matter and the spinal cord at approximately C4 secondary to coccidioidal meningitis.
species, and identification by serologic techniques. Thus far, there is no antigen detection method for 
_Coccidioides_ infection.

Histopathologic examination is not routinely applicable for coccidioidal meningitis, although if there is a pulmonary focus or other focus of disseminated infection, histopathologic examination of these lesions may be useful. Culture of CSF specimens on bacteriologic or fungal media is diagnostic. Unfortunately, culture results are positive for only a small percentage of cases of meningitis.

The foregoing notwithstanding, on occasion, _Coccidioides_ organisms can be observed on direct microscopic examination of the CSF specimen. This rare event suggests an unusually high meningeal fungal burden. Even more perverse is the visualization of the mycelial or arthrocondial forms of the fungus in CSF samples. The majority of these reports have involved individuals with ventriculoperitoneal or other shunt devices in place. Less often, individuals without such foreign material are reported to have hyphal elements visualized [16, 25–27].

Serologic examination is the mainstay of confirming the diagnosis. Although a negative result of a serologic test cannot exclude the diagnosis of _Coccidioides_ infection, a negative serologic test result for a patient with untreated disseminated disease, if found in an experienced laboratory, is quite rare. An exception to this may be the patient with HIV infection or another severe immunocompromising illness. The measurement of coccidioidal antibodies in the CSF is considerably less sensitive but of greater diagnostic specificity. If a patient has a high titer of IgG antibody in the serum, some low-titer “spill over” can occasionally be seen in the CSF [28]. In cases of meningitis, the finding of coccidioidal IgG antibody in CSF samples is virtually diagnostic [29].

A wide variety of serologic studies are available. The most reliable are the immunodiffusion tests for IgM and IgG and the complement fixation test for IgG, performed in a laboratory with considerable experience. ELISAs for IgM and IgG and latex agglutination tests are less reliable and should not be used to include or exclude the diagnosis of coccidioidal meningitis without subsequent confirmatory testing. It should be noted that monitoring of the serum coccidioidal IgG level should not be used as a guide for the course of the meningeval illness, as it is with primary and nonmeningeal disseminated disease.

Radiographic evaluation of the patient with coccidioidal meningitis is useful, as is suggested above. CT of the brain without contrast can be used to diagnose hydrocephalus, which may be present at diagnosis or present as a late complication. CT is not as sensitive as MRIs for the evaluation of the meningeal involvement or vasculitic complications. An MRI as a baseline test is desirable for evaluation of the extent of the disease and for comparison purposes later in the course of illness, especially if neurologic complications develop. There are a small number of reports on the use of CT and MRI in cases of coccidioidal meningitis [30, 31]. Neuroimaging studies will reveal hydrocephalus in 30%–50% of patients at some time in the course of disease. MRI with contrast enhancement is more sensitive at identifying the typical basilar cisternal enhancement. Fifteen percent to 20% of patients will have evidence of vasculitic infarction. MRI is also useful at identifying and evaluating spinal arachnoiditis. A CT or MRI will rarely reveal an abscess or other focal brain complication of _Coccidioides_ infection.

**THERAPY**

The treatment of coccidioidal meningitis is challenging even for experienced clinicians. Antifungal therapy has been and is of lesser efficacy than what our patients need. A treatment guideline for most coccidioidal syndromes has been published [32]. The treatment of coccidioidal meningitis began ~50 years ago when William Winn gave a patient intrathecal amphotericin B deoxycholate [14]. This was refined and expanded on by Einstein et al. [17] and became the “gold standard” of therapy for >50 years. There was some success with early azoles, including intrathecal miconazole and high-dose oral ketoconazole therapy [33–35]. These have been superseded by newer azoles. Itraconazole was reported to be potentially efficacious for coccidioidal meningitis [36]. The treatment of 2 patients with coccidioidal meningitis with fluconazole was reported in 1988 [37]. A pivotal change in the therapeutic paradigm came with the fluconazole study by Galgiani et al. [38]. Although it was not a comparative trial, this study suggested that therapy with fluconazole at a dosage of 400 mg daily compared favorably with historic results for intrathecal amphotericin B deoxycholate therapy. Subsequent experience has made fluconazole the new gold standard. Although there are still debates on the matter, most experts now prefer therapy with high-dose fluconazole (800–1200 mg once per day). Even higher doses are used by some on occasion. Other experts continue to administer 400 mg of fluconazole daily as a starting dose and increase the dose if clinical or CSF parameters fail to improve.

Voriconazole was used in 2 published cases of therapeutic failure for rescue therapy [39, 40]. From a pharmacologic standpoint and on the basis of in vitro analysis, voriconazole has significant appeal and may offer the potential for rescue therapy. Voriconazole therapy is associated with toxicities, including transient visual abnormalities. Also noteworthy and not emphasized is voriconazole’s propensity to cause photodermatitis (occasionally severe), which appears to be more common among white subjects.

Intravenous amphotericin B deoxycholate was traditionally given during the initiation of intrathecal amphotericin B therapy. Animal studies have shown increased benefit of lipid preparations of amphotericin B in experimental coccidioidal meningitis [41]. One significant report about rescue therapy for a patient for whom other therapy apparently failed has been presented
Whether this approach has merit that can be generalized remains to be seen. Therapy with a lipid amphotericin B preparation suffers from the need for intravenous access, substantial cost, nephrotoxicity, and tolerability problems that could be limiting for treatment that might be necessary for years.

The practice at one of our facilities, Kern Medical Center (Bakersfield, CA), is to describe therapeutic options to persons who are neurologically capable of understanding them and to families when the patients are not so capable. After discussion of the risks, benefits, and alternatives, most individuals opt for high-dose fluconazole treatment, which is initiated at 1000 mg once per day. Each patient is then evaluated sequentially, clinically, and by repeated CSF analyses. Those with no response by clinical and CSF parameters are offered alternative therapy. Currently, voriconazole (4 mg/kg every 12 h orally) or intrathecal amphotericin B (usually administered by direct cisternal injection, but occasionally administered by ventricular injection or cisternal injection via an Ommaya reservoir) is used. Other investigators have successfully administered amphotericin B deoxycholate in the lumbar region [43]. Drug-induced arachnoiditis has limited the use of lumbar therapy.

The technique of intrathecal administration of amphotericin B deoxycholate has been described elsewhere [43, 44]. This treatment has the virtue of potentially being less than life-long. Vigorous courses have eventuated in long-term remission after 2–8 years of therapy. The complications of cisternal puncture (especially bleeding) and puncture of the Ommaya reservoir (especially bacterial infection), as well as the neurotoxicity of amphotericin B deoxycholate, militate against the use of intrathecal amphotericin B deoxycholate as primary therapy in most circumstances.

There have been supply problems with amphotericin B deoxycholate. Currently, amphotericin B deoxycholate is available from Pfizer (Amphocin) and is generically available from X-Gen Pharmaceuticals and Spectrum Chemical.

In the initial stages of treatment for patients who start with regimens of fluconazole, clinical and CSF parameters should be monitored at least monthly. As the parameters improve, the interval between follow-up visits and CSF analyses can be lengthened. If the response is salutary with respect to both clinical and CSF parameters, follow-up evaluations and CSF assessments should be made every 3 months for life. Patient adherence to treatment over an extended period is a problem. Lapses in therapy and follow-up can have dire consequences [45]. It needs to be made clear to patients that therapy is life-long.

The complication of hydrocephalus is usually treated by ventriculoperitoneal shunting. In many patients, ventriculoperitoneal shunting is highly successful and provides long-lasting relief from this aspect of the disease. This may be particularly true in individuals who respond to effective medical treatment of the underlying meningitis [26]. Other patients develop the problems of repeated distal obstruction, intraventricular foraminral obstruction, and the development of clinical shunt failure. Any recurrent persistent headache, nausea and vomiting, gait disturbance, or change in mentation should be evaluated by CT or MRI.

Vasculitic infarction represent a difficult and controversial management issue. Some experienced clinicians note improvement in neurologic status concomitant with the use of high-dose, relatively short-term glucocorticosteroid therapy. At Kern Medical Center, the usual course of therapy is 20 mg of dexamethasone given orally once per day for 7 days, followed by a reduction in dose of 4 mg every other day, until the patient has been weaned off therapy. Other experienced clinicians have doubted the efficacy of this approach [11–13].

How to care for individuals with coccidioidal arachnoiditis manifested by back pain or, in more-severe forms, with paraplegia, quadriplegia, urinary retention, and sexual dysfunction, is far from clear. If arachnoiditis occurs in relation to intrathecal injection of amphotericin B, a temporary or occasionally permanent discontinuation of therapy is in order. If arachnoiditis is related to the primary disease process in a fluconazole-treated patient, an increase or, more often, a change in therapy is indicated. Intrathecal amphotericin B therapy may well ameliorate the symptoms in these latter patients. In at least 1 particularly severe and protracted case in which this approach was used, a transient increase in neurologic deficits occurred with the introduction of amphotericin B. This necessitated withdrawal of intrathecal therapy. Voriconazole has been used in this individual with what thus far appears to be success, as indicated by clinical and CSF parameters. This experience may or may not prove to be helpful for others. The possible role of glucocorticosteroids in this circumstance is not clear.

SUMMARY

Coccidioidal meningitis was first described 100 years ago. For >50 years, there have been effective therapeutic interventions. These have decreased the mortality rate from 100% to ~30%.

The advent of fluconazole therapy for meningitis in the last decade of the past millennium has allowed for less toxic and less costly therapy, but there has been no substantial change in disease-precipitated morbidity or mortality. We can only hope that new agents or approaches to the care of this devastating illness will produce a significant reduction in the suffering and death experienced by patients with coccidioidal meningitis.

Acknowledgments

We thank Kimberly Johnson, Diana Caldwell, and Frances Hardin for their assistance in data acquisition and preparation of this manuscript. Potential conflicts of interest. R.H.J. has received grant support from Pfizer pharmaceuticals; is a member of the speakers’ bureaus for Sanofi-Aventis, Enzon, and Merck; and has been on the speakers’ bureaus for Bristol-Myers Squibb and Bayer. H.E.E: no conflicts.
References


