Coccidioidomycosis in Persons Infected with HIV Type 1

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Coccidioidomycosis is a fungal disease endemic to large parts of the southwestern United States and northern Mexico [1]. In the vast majority of cases, infection occurs by inhalation of soil or dust containing the fungus. Among immunocompetent individuals, nearly two-thirds of those infected are asymptomatic. The vast majority of the remainder have a self-limited pulmonary syndrome that resembles community-acquired pneumonia. A small number of individuals develop either chronic, progressive pulmonary coccidioidomycosis or disseminated disease beyond the thoracic cavity. Control of coccidioidal infection depends on a specific cellular immune response. Persons deficient in such a response are at increased risk for symptomatic disease.

Over the past decade, the number of cases of coccidioidomycosis reported to health agencies has risen dramatically [2, 3]. At least a part of this increase has been caused by the increase in the number of cases of symptomatic disease seen among persons infected with HIV-1. Fortunately, with the introduction of potent combination antiretroviral therapy, the impact of concomitant HIV infection on the incidence of symptomatic coccidioidomycosis has been ameliorated.

This article will review the history, epidemiology, clinical manifestations, diagnosis, and treatment of coccidioidomycosis occurring in patients infected with HIV infection. It will also explore questions regarding therapy, including therapy in the face of immune reconstitution, whether immune-response inflammatory syndrome occurs in patients with coccidioidomycosis, and prevention of coccidioidomycosis.

INITIAL DESCRIPTIONS AND EPIDEMIOLOGY

The first reports of coccidioidomycosis associated with AIDS occurred just a few years after the initial reports of AIDS. In these reports, the disease was invariably fatal and frequently manifested by diffuse pulmonary infiltrates [4]. Subsequently, several case-studies were published that more fully described the clinical manifestations of coccidioidomycosis in persons with HIV infection. These studies all emanated from the coccidioidal-endemic zone, and each demonstrated a high proportion of patients presenting with bilateral pulmonary processes and a mortality rate of 40%–85% [5–7], establishing coccidioidomycosis as an opportunistic infection in persons with HIV infection.

The results of a prospective study [8] performed during the late 1980s revealed that nearly 25% of a cohort living in the coccidioidal-endemic region developed symptomatic coccidioidomycosis within 3.5 years of follow-up. Two related factors were associated with the development of symptomatic coccidioidomycosis in this cohort: a peripheral blood CD4 lymphocyte count of <250 cells/µL and a diagnosis of AIDS. In a follow-up study, specific in vitro cellular responsiveness to coccidioidal
antigen was found to be lost among a group of HIV-infected persons when the CD4 cell count was <250 cells/μL. [9]. Approximately one-half of all cases of coccidioidomycosis occurring in persons with AIDS were found to be from the coccidioidal-endemic area, and >90% of these were either from California or Arizona [10]. The other half were from all other parts of the United States. Thus, the diagnosis of coccidioidomycosis should be considered, regardless of the geographic locale of any immunosuppressed HIV-infected patient presenting with a compatible syndrome.

It is unclear what proportion of cases reported from the region of endemicity represent acute infection or are due to reactivation of latent infection. Data from the prospective study cited above [8] demonstrate that neither a history of prior coccidioidal infection nor a length of time spent in the coccidioidal-endemic region are risk factors for the development of symptomatic coccidioidomycosis in HIV-infected persons living in the zone of endemicity. This would suggest that most such cases are due to acute infection. On the other hand, reactivation of latent infection should be suspected in patients diagnosed with coccidioidomycosis who have not recently been in the area of endemicity. Because coccidioidomycosis may initially manifest several months after primary infection, this period should be at least 6 months. A travel history should be routinely obtained from patients with suspected cases of coccidioidomycosis that are identified outside the area of endemicity. Clinically, outcome does not appear to vary on the basis of whether infection was recently acquired or is due to reactivation.

Although there are no prospective studies, the impact of potent antiretroviral therapy on the incidence of coccidioidomycosis was demonstrated by Woods and et al. [11] in a retrospective cohort study in Arizona. They noted 77 cases of symptomatic coccidioidomycosis associated with HIV infection in 1995. This number had decreased to just 15 by 1997 [11]. Observations of cases in my HIV-clinic located within the coccidioidal-endemic region are that the incidence of severe, symptomatic coccidioidomycosis has declined dramatically since the advent of potent antiretroviral therapy. When such cases occur, they are typically in patients with previously undiagnosed HIV infection and profoundly low peripheral blood CD4 cell counts.

**CLINICAL MANIFESTATIONS**

As mentioned above, one of the most striking presentations of coccidioidomycosis during HIV infection is a patient with diffuse pulmonary infiltrates. These infiltrates have been called “reticulonodular” because of their mixture of interstitial abnormalities and nodules. At times, this pattern can resemble *Pneumocystis* pneumonia. As noted above, mortality in patients with diffuse pulmonary coccidioidomycosis is extremely high. Clinical symptoms include dyspnea, fever, and night sweats, which are not clearly distinct from those of pneumocystosis [12]. Such cases invariably occur in persons with profoundly depressed peripheral blood CD4 lymphocyte counts.

In less-immunocompromised patients, coccidioidomycosis presents in a manner similar to that in patients without HIV infection. The most common presentation resembles that of community-acquired pneumonia, with cough, fever, and a focal pulmonary infiltrate. Primary focal pulmonary coccidioidomycosis can sometimes be distinguished from other causes by the presence of hilar or mediastinal adenopathy, failure to improve while receiving standard antibiotic therapy, and peripheral blood eosinophilia.

As noted, disseminated coccidioidomycosis, defined as disease that has spread beyond the thoracic cavity, is frequent among patients with HIV infection. Common forms of disseminated coccidioidomycosis in these patients are meningitis and lymph-node and skin involvement [6]. For reasons that are unclear, bone and joint disease is rare in patients with HIV infection. In addition, there is a distinctly unusual form of coccidioidomycosis among persons with HIV infection presenting with fever, weight loss, and a positive coccidioidal serologic test result without any clear organ involvement. In addition, patients may initially present with a positive coccidioidal serologic test result without any symptoms. There is a high risk of subsequent development of clinically active coccidioidomycosis in these patients [13].

**DIAGNOSIS**

The mainstays of diagnosis of coccidioidomycosis are serologic testing, histopathological identification, and culture. Currently, there are no genomic or proteomic assays to directly identify *Coccidioides* species in clinical specimens. Serologic tests for coccidioidomycosis were first developed by Smith [14] >50 years ago, and they have reasonable sensitivity and specificity for the immunocompetent patient. However, serologic testing is clearly less reliable for patients with HIV infection than for immunocompetent patients. For example, in 2 case-studies, serologic test results were positive for 68% and 74% of cases, respectively [6, 7]. Thus, serologic testing should always be performed for cases of suspected coccidioidomycosis, but results may not always be positive.

*Coccidioides* species can be detected in tissue or in clinical samples using a variety of standard histochemical staining techniques, including the hematoxylin-eosin stain. Cytological staining methods, particularly the Papanicolaou and Gomori methenamine stains, are very useful for rapid detection of *Coccidioides* species in respiratory secretions [15]. However, results of such stains are only positive in ~40% of cases that are confirmed by culture [16]. Of note, the potassium hydroxide stain, used traditionally to detect fungi in clinical specimens, is far less sensitive than the Papanicolaou and Gomori methenamine...
stains [15, 16] and should probably be abandoned as a clinical test.

Culture is a very useful diagnostic tool, and clinical samples obtained from suspected coccidioidal infection should always be cultured. Unlike other pathogenic, endemic fungi, *Coccidioides* is frequently isolated from infected samples within ≤5 days, even when plated onto routine bacteriologic culture medium and incubated at 37°C. A caveat regarding the culture of CSF is that *Coccidioides* is isolated in less than one-half of cases [17, 18]. The diagnosis is usually established by a positive result of an IgG antibody test of a CSF sample. On the other hand, results of culture of respiratory specimens are frequently positive in cases of pulmonary coccidioidomycosis, including instances of diffuse pulmonary disease, often when findings of a cytological examination are negative [15, 16]. Although diffuse pulmonary infiltrates associated with coccidioidomycosis have been associated with growth of *Coccidioides* species in blood cultures [4], results of commercial blood culture systems are variable, and prolonged incubation is required [19, 20]. Given this, I do not recommend performing blood cultures as part of the evaluation of an HIV-infected patient with suspected coccidioidomycosis.

The lack of sensitivity of cytological staining for diagnosis of pulmonary coccidioidomycosis contrasts with its sensitivity for diagnosis of *Pneumocystis* pneumonia, for which staining has a very high sensitivity. This is of clinical importance because pulmonary coccidioidomycosis and pneumocystosis may coexist [12]. A negative cytological stain result for a clinical respiratory specimen should not lead one to rule out active pulmonary coccidioidomycosis. The use of corticosteroids in HIV-infected patients with pneumocystosis and undiagnosed pulmonary coccidioidomycosis may lead to subsequent clinical deterioration [12] and should be used cautiously.

**TREATMENT**

Given the profound variability in outcome and the paucity of controlled trials, it is difficult to propose firm treatment recommendations for each clinical manifestation of coccidioidomycosis in patients with HIV infection. However, some guidelines can be offered [21, 22]. Specific recommendations revolve around the following 3 questions: Who should be treated? What antifungal agents should be used? and What should be the length of therapy?

All patients with HIV infection who receive a diagnosis of clinically active coccidioidomycosis should be offered antifungal therapy. Patients with focal pulmonary coccidioidomycosis presenting as community-acquired pneumonia who are immunocompetent (defined as a peripheral blood CD4 lymphocyte count of ≥250 cells/μL) represent a special case, because they frequently do well without therapy. Because some experts on coccidioidomycosis would treat all patients with focal pulmonary coccidioidomycosis, including those without HIV infection, it is reasonable to treat all HIV-infected persons with focal pulmonary coccidioidomycosis, regardless of the peripheral blood CD4 lymphocyte count.

There has been only 1 controlled, comparative trial of antifungal therapy of coccidioidomycosis [23]. Because of this, recommendations regarding a specific treatment for an HIV-infected patient are based principally on clinical experience. Clinical observations suggest that patients with severe forms of coccidioidomycosis, particularly forms involving diffuse pulmonary infiltrates, have a very high mortality rate, regardless of therapy, but that survival is more likely for persons who receive therapy with a formulation of amphotericin B. My own experience is that therapy with a combination of an amphotericin B formulation and a triazole antifungal leads to more rapid clinical response than does use of a single antifungal agent alone. Although there is theoretical concern that combined use of an azole antifungal with amphotericin B could be antagonistic to antifungal activity [24], I have never observed such antagonism clinically. My approach in severe cases of coccidioidomycosis, including cases with diffuse pulmonary disease and those with extrathoracic dissemination, is to start with a combination of amphotericin B and a triazole antifungal.

There have been no studies of the use of newer lipid formulations of amphotericin B for treating coccidioidomycosis. Although these formulations offer reduced renal toxicity, there are no data regarding efficacy. I still prefer to use the original deoxycholate formulation of amphotericin B, unless renal dysfunction is already present or likely to occur during therapy. I administer a dose of 50 mg in 500 mL of water with 5% dextrose and infuse this over a 2-h period. The patient also receives vigorous saline hydration with an intravenous infusion of normal saline at the rate of 125–150 mL/h and receives replacement of potassium and magnesium as necessary. As the patient’s condition improves, the frequency of amphotericin B administration can be reduced from daily to several times per week. The amphotericin B therapy can usually be stopped after 500–1000 mg has been administered, and triazole therapy can be continued alone. Although there are studies of continuous infusion of amphotericin B that suggest reduced renal toxicity [25, 26], I do not advocate this approach in cases of coccidioidomycosis, given the lack of data regarding efficacy.

As for triazoles, I prefer either fluconazole or itraconazole. A placebo-controlled study that included HIV-infected patients compared fluconazole to itraconazole and found that itraconazole was slightly superior, particularly regarding bone and joint disease [23]. However, with itraconazole therapy, there are more drug interactions, increased potential for hypokalemia and congestive heart failure, and decreased absorption, particularly in patients with achlorhydria. Given this, in the absence of bone and joint disease, I administer fluconazole at a daily dose of
400–800 mg per day. If itraconazole is prescribed, I begin at 200 mg either 2 or 3 times per day. Reports have been published that demonstrate improvement after therapy with voriconazole when other therapies have failed [27]. However, no ongoing controlled studies have been published, and none are planned. Given this, I reserve the use of voriconazole for cases in which current therapy is failing. A dose of 400 mg administered twice per day typically has been used. Posaconazole is a new triazole antifungal that will soon be approved for use in the United States. Unpublished studies suggest that it is effective in treating coccidioidomycosis [28]. Finally, a single report describes a renal transplantation recipient with diffuse pulmonary coccidioidomycosis improving after treatment with caspofungin [29]. My own experience has been less promising.

Although there are several potential interactions between antifungal agents and antiretroviral therapy, no dosage adjustment is usually required. For example, neither fluconazole nor voriconazole appear to affect or be affected by concomitant HIV protease inhibitor therapy [30, 31]. However, levels of itraconazole (but not its metabolite hydroxyitraconazole) are increased when administered with the combination HIV protease inhibitor lopinavir/ritonavir [32], and a reduced dosage may be used. Posaconazole may act similarly. Although the older formulation of didanosine required buffering and reduced absorption of itraconazole, the newer enteric-coated formulation does not interfere with either fluconazole or itraconazole pharmacokinetics [33]. Finally, because tenofovir has been associated with reduced renal function [34], it should be used cautiously in patients also receiving amphotericin B.

Adjunctive IFN-γ therapy has been reported to have been successful in 1 case of disseminated coccidioidomycosis at a subcutaneous dosage of 50 μg/m² 3 times per week [35]. However, there are no other published results, and I have heard many anecdotal reports in which no improvement has occurred. I have not administered IFN-γ for the treatment of coccidioidomycosis. Controlled clinical studies would be useful to eventually define its use.

Besides monitoring the patient for clinical improvement, serial assays of the titer of complement-fixing (IgG) antibody are very useful in determining a patient’s response to antifungal therapy. Such titers should be obtained every 6–12 weeks and will demonstrate a progressive decrease if therapy is effective. Patients with serologic test results that are initially negative may have a delayed improvement in their serologic test results that does not correlate with clinical illness. This lag in response, occurring during the first 1 or 2 months of therapy, should not be construed as treatment failure.

Because the critical factor in the control of coccidioidomycosis is cellular immune function, institution of effective antiretroviral therapy should be done contemporaneously with the initiation of antifungal therapy, if possible. Immune response inflammatory syndrome has been observed in HIV-infected patients with a variety of underlying infections as they respond to potent antiretroviral therapy [36]. However, I have not observed immune response inflammatory syndrome in patients with coccidioidomycosis, nor have there been any published reports describing it.

Duration of therapy in the age of immune reconstitution is undefined. However, patients should be treated for at least 1 year. In HIV-infected patients whose initial presentation of coccidioidomycosis was a focal pneumonia that responded quickly to oral antifungal therapy and whose peripheral blood CD4 lymphocyte counts were well above 250 cells/μL at the time of diagnosis, it may be reasonable to consider either stopping or decreasing the dosage of antifungal therapy after this time. For those with disseminated disease, prolonged and even life-long antifungal therapy is the rule.

The presentation, management, and outcome of coccidioidal meningitis in persons with HIV infection are not different than those for persons without HIV infection [37]. However, meningitis is distinct from other forms of coccidioidal infection. First, it does not respond to intravenous amphotericin B. Because of this, therapy must include a triazole antifungal. Failure of triazole therapy, which occasionally occurs, will require the initiation of intrathecal amphotericin B therapy. A clinician experienced in this technique should be consulted. Second, in the face of appropriate antifungal therapy patients may develop hydrocephalus that requires CSF shunting. Lastly, therapy for coccidioidal meningitis with a triazole antifungal should be lifelong, given the high rate of relapse when such therapy is discontinued [38]. Because of these problems, it is always wise to seek consultation from an experienced clinician when treating a patient with coccidioidal meningitis.

PREVENTION

If a patient resides or visits the coccidioidal-endemic region, there are no absolute ways to avoid the risk of infection. Because outbreaks of coccidioidomycosis are known to occur with heavy exposure to local soil or dust [39], individuals should attempt to avoid activities associated with this. However, restriction of such activities may be difficult, and most coccidioidal infections occur without any definable exposure.

No prospective studies that examine the role of preventive antifungal therapy have been published. Data from a retrospective, case-control study suggested that HIV-infected individuals with oropharyngeal candidiasis living in the coccidioidal-endemic zone had a slightly reduced risk of developing coccidioidomycosis if they were receiving treatment with fluconazole [11]. However, the benefit of such prophylaxis is small, and the costs—monetary costs and an increasing risk of resistance to other fungi—are substantial. I do not prescribe prophylactic antifungals for patients with HIV infection living in the coccidioidal-endemic zone.
the coccidioidal-endemic region. There is active interest in developing a vaccine for coccidioidomycosis [40], but whether this will prove useful for patients with immunodeficiency, such as patients with HIV infection, awaits further study.

References