Coccidioidomycosis in Liver Transplant Patients


Eight (0.59%) of 1,347 patients who underwent liver transplantation at the UCLA Medical Center (Los Angeles) developed coccidioidomycosis. Whereas only one case occurred during the first 8 years and 10 months of the UCLA Liver Transplant Program (February 1984 to December 1992), seven cases occurred within the following 23-month period (December 1992 to November 1994). The median time of onset for infection after transplantation was 8 weeks (range, 4–312 weeks). Clinical presentations of patients with coccidioidomycosis included pneumonia (six cases), pneumonia with meningitis (one case), hepatitis (one case), and monarticular arthritis (one case). Despite therapy with amphotericin B alone (six cases) or amphotericin B plus fluconazole (two cases), infection was fatal in four of eight cases. As of this writing, the four surviving patients are receiving chronic maintenance therapy with either fluconazole (three patients) or itraconazole (one patient). These experiences show that coccidioidomycosis can be a serious and frequently fatal infection after liver transplantation and that the incidence of this disease appears to be increasing.

Coccidioidomycosis is an illness commonly seen in residents of the southwestern United States and other warm, dry environments in the Western Hemisphere [1–7]. The estimated incidence of coccidioidomycosis in the United States ranges from 50,000 to 100,000 cases each year [1, 3, 5, 6, 8]. Recently, the incidence of coccidioidomycosis has been increasing in California, especially in Kern County, as the result of extremely dry environmental conditions [6, 9]. Furthermore, the number of cases of coccidoidal infection in the Southern California county of Ventura increased following the 1994 Northridge earthquake [9, 10].

Most immunocompetent individuals who develop coccidioidomycosis remain asymptomatic or experience a relatively mild, self-limiting respiratory tract infection [2–6, 9]. Disseminated coccidioidomycosis extending beyond the pulmonary parenchyma or hilar lymph nodes occurs in <1% of the general population [2–6, 9]. Although respiratory tract disease can affect any individual, disseminated coccidioidomycosis is more frequent in men, Filipinos, blacks, pregnant patients, Mexican-Americans, and immunosuppressed patients [2–6, 8, 9].

Limited data on coccidioidomycosis in individuals who have undergone transplantation are available. Most experiences with coccidoidal infection have been described in renal [5, 11–13], heart [5, 14, 15], and bone marrow transplant recipients [5, 16]. Only one case report of coccidioidal disease in a liver transplant patient has been previously published [17]. Thus, we describe eight liver transplant patients with coccidioidomycosis at the University of California at Los Angeles (UCLA) Medical Center.

Similar to the recent increase in the incidence of coccidioidomycosis in the general population of the southwestern United States, there appears to be an increasing number of cases of coccidioidomycosis in our liver transplant patients. In view of the morbidity and mortality due to coccidioidal infection in immunosuppressed liver allograft recipients and other transplant recipients, an awareness of this rising incidence, the common clinical manifestations of infection, and the options for therapy and prophylaxis is critical for improving the outcome of transplantation.

Patients and Methods

From February 1984 through October 1994, 1,347 adults and children underwent primary liver transplantation at UCLA Medical Center. All patients were observed prospectively by members of the UCLA Liver Transplant Team for infections and other transplant-related complications. The methods for patient selection for liver transplantation as well as the transplantation procedure, immunosuppressive therapy, and post-transplantation care have been previously reported [18].

Patients received prophylaxis with ampicillin/sulbactam (or ceftizoxime and vancomycin if they were allergic to penicillin) intraoperatively and postoperatively. Patients also received antiviral prophylaxis with ganciclovir or acyclovir. Postoperative antifungal prophylaxis with nystatin or clotrimazole was administered to 1,135 patients for 100 days but was not administered to 212 patients enrolled in a randomized, double-blind,
controlled trial comparing fluconazole with placebo for postoperative fungal prophylaxis.

The diagnosis of coccidioidomycosis was made if one or more of the following conditions were met for patients who had a clinical syndrome consistent with the disease: (1) biopsy material of tissue demonstrated coccidioides spherules; (2) the latex precipitin test for IgM was positive, with confirmation by the immunodiffusion tube precipitin test, and the immunodiffusion and CF tests for IgG were positive; and (3) fungal cultures of pulmonary secretions, blood, CSF, joint fluid, or biopsy material were positive for *Coccidioides immitis*.

**Results**

Coccidioidomycosis developed in eight (0.59%) of 1,347 liver transplant recipients, including one patient whose case was previously reported [17]. Seven (1.61%) of the cases occurred only within the 23-month period between December 1992 and November 1994, when 435 liver transplants were performed. Only one case (0.11%) occurred during the previous 8 years and 10 months of the UCLA Liver Transplant Program (February 1984 to December 1992) (table 1), when 912 liver transplants were done. All patients were adults (mean age, 58 years; range, 44–69 years); five patients were Hispanic and three were Caucasian.

Seven of eight patients received induction immunosuppressive therapy with cyclosporine, azathioprine, and corticosteroids. The remaining patient (no. 1) developed severe oliguria while receiving cyclosporine and was given OKT3 (Orthoclone, Ortho Biotech, Raritan, NJ) during the episode of renal failure. Patient 5 also received OKT3 after a third transplant. After patient 1 received 14 days of OKT3 therapy and patient 5 received 10 days of this drug, therapy for both patients was changed to cyclosporine, azathioprine, and corticosteroids.

Five of eight patients also required additional immunosuppression with boluses of methylprednisolone to treat rejection. None of the patients received tacrolimus (FK506) before the onset of coccidioidomycosis; therapy for one patient (no. 4), was changed to tacrolimus for refractory rejection after successful treatment of his coccidioidal disease.

The median time to onset of coccidioidomycosis was 8 weeks following transplantation (range, 4–312 weeks) (table 1). All patients resided in areas that were endemic for coccidioidomycosis, including the Central Valley of California (two patients), Southern California (three patients), Arizona (two patients), and northern Mexico (one patient).

The most common presentation of coccidioidomycosis was pneumonia, which was present in six of eight patients. The pulmonary presentation of coccidioidomycosis was both acute and subacute. Patients 1, 2, 3, and 5 were acutely ill with fever, productive cough, shortness of breath, and altered sensorium. One patient (no. 3) also had meningitis. In contrast, patients 6 and 7 had a more subacute presentation that was characterized by anorexia, weight loss, and fatigue in the absence of fever or any pulmonary symptoms. In these two cases, the diagnosis was made only after an asymptomatic cavitary pulmonary infiltrate was found on a chest roentgenogram and led to a fine-needle aspiration; culture of the aspirate subsequently yielded *C. immitis*.

Similarly, the diagnosis of coccidioidomycosis was made for patient 4 only when culture of a specimen from a liver biopsy, which was performed for evaluation of possible rejection, yielded *C. immitis*. Blood cultures from this patient also yielded *C. immitis*, and a pulmonary nodule was subsequently found. Patient 8 presented with disabling arthritis of his right knee of several weeks’ duration and was afebrile; culture of the synovial fluid and a synovial biopsy specimen yielded *C. immitis*. Patient 1 also had concomitant pneumonia due to cytomegalovirus and *Pneumocystis carinii*.

*C. immitis* was most commonly isolated in culture from bronchoalveolar lavage specimens (five cases), blood specimens (four cases), liver biopsy specimens (three cases), lung aspirates obtained by fine-needle aspiration (two cases), a sputum specimen (one case), CSF (one case), and synovial fluid or tissue (one case). The results of pretransplantation coccidioidal skin testing were not available for these patients. Pretransplantation coccidioidal serologies were not routinely performed, but one patient (no. 2) had a positive immunodiffusion test for IgG and a CF antibody titer of >1:16 before transplantation.

Posttransplantation tube precipitin serologies were positive for one of two patients tested, and CF antibody serologies were positive for five of seven patients tested. CF antibody titers were >1:64 in four cases (table 1). Only one patient with both clinical and cultural evidence of coccidioidal meningitis had a positive CSF CF antibody titer. Six (75%) of eight patients had cultural or serological evidence of dissemination.

All patients initially received therapy with amphotericin B (1 mg/[kg·d]). The cumulative amphotericin B dose exceeded 900 mg (range, 940 mg to 4,000 mg) in all four survivors but in only one of four fatal cases (table 1). Patient 3, who had coccidioidal meningitis, died despite the fact that she received high doses of iv fluconazole (800 mg/d) and intrathecal amphotericin B in addition to therapy with iv amphotericin B. Patient 5 also received high doses of iv fluconazole (800 mg/d) in addition to amphotericin B therapy when her condition failed to improve after she received 1,750 mg of amphotericin B. This patient also died despite combination therapy.

The overall mortality among the liver transplant patients with coccidioidomycosis was 50% (four of eight patients). All four patients who died had evidence of disseminated coccidioidomycosis. Among the four surviving patients, two had disseminated disease, and two had disease limited to the lungs. Patient 8, who had coccidioidal arthritis, underwent open drainage, debridement, and synovectomy of the right knee in addition to receiving amphotericin B therapy. Of note, patient 6 experienced recurrent pulmonary coccidioidomycosis after he discontinued maintenance therapy with fluconazole 1 month after
Table 1. Clinical characteristics of eight liver transplant patients with coccidioidomycosis.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Date of OLT</th>
<th>Age (y)/sex</th>
<th>Race</th>
<th>Underlying liver disease</th>
<th>Date of onset of coccidioidomycosis; no. of weeks or years posttransplantation</th>
<th>Clinical findings on presentation</th>
<th>Chest roentgenogram findings</th>
<th>Results of pretransplantation serologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8/88</td>
<td>55/M</td>
<td>Hispanic</td>
<td>Cryptogenic cirrhosis</td>
<td>10/88; 8 w</td>
<td>Pneumonia</td>
<td>Bilateral interstitial infiltrates</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>12/92</td>
<td>55/M</td>
<td>Hispanic</td>
<td>Alcoholic liver disease</td>
<td>12/92; 4 w</td>
<td>Pneumonia</td>
<td>Left pleural effusion; bilateral patchy infiltrates</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>9/91</td>
<td>61/F</td>
<td>Hispanic</td>
<td>Cryptogenic cirrhosis</td>
<td>12/92; 60 w</td>
<td>Pneumonia, meningitis</td>
<td>Left-lower-lobe infiltrates</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>12/92</td>
<td>66/M</td>
<td>Caucasian</td>
<td>Cryptogenic cirrhosis</td>
<td>1/93; 6 w</td>
<td>Hepatitis</td>
<td>Bilateral pleural effusion; pulmonary nodule</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>10/93</td>
<td>69/F</td>
<td>Caucasian</td>
<td>Hepatitis C</td>
<td>11/93; 6 w</td>
<td>Pneumonia</td>
<td>Right-middle-lobe granulomatous lesion with consolidation</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>5/88</td>
<td>45/M</td>
<td>Caucasian</td>
<td>Primary biliary cirrhosis</td>
<td>5/94; 6 y</td>
<td>Pneumonia</td>
<td>Right-upper-lobe cavitary lesion with peripheral nodules</td>
<td>NA</td>
</tr>
<tr>
<td>7</td>
<td>5/94</td>
<td>65/F</td>
<td>Hispanic</td>
<td>Hepatitis C</td>
<td>7/94; 8 w</td>
<td>Pneumonia</td>
<td>Left-lower-lobe cavitary mass</td>
<td>NA</td>
</tr>
<tr>
<td>8</td>
<td>9/94</td>
<td>44/M</td>
<td>Hispanic</td>
<td>Hepatitis C</td>
<td>10/94; 4 w</td>
<td>Monoarticular arthritis</td>
<td>Right pleural effusion and left-upper-lobe granulomatous lesion</td>
<td>NA</td>
</tr>
</tbody>
</table>

NOTE. BAL = bronchoalveolar lavage; FNA = fine-needle aspiration; ID = immunodiffusion; NA = not available; OLT = orthotopic liver transplant; PPTN = tube precipitin.

completion of amphotericin B therapy. The upper lobe of his right lung was then surgically removed. As of this writing, he is doing well and is receiving maintenance therapy with itraconazole (400 mg/d). Thus, of the four surviving patients, three are receiving maintenance therapy with fluconazole (400 mg/d), and one is receiving maintenance therapy with itraconazole (400 mg/d) (table 1).

Discussion

Fungal infections occur in 6%–42% of all liver transplant patients and may be associated with a high mortality (50%–80%) [19, 20]. Fungal pathogens that commonly occur in liver allograft recipients include Candida species (up to 75% of cases) and Aspergillus species (10%–20% of cases). Infrequently encountered fungal pathogens include Coccidioides species, Histoplasma species, and Blastomyces species) have been in renal, heart, and bone marrow transplant recipients [21–25]. Except for one previous case report of coccidioidomycosis [17], infections due to the endemic fungi have not been described in liver allograft recipients.
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Results of posttransplantation serologies</th>
<th>Positive cultures</th>
<th>Therapy</th>
<th>Cumulative intravenous amphotericin B dose</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPTN Serum ID</td>
<td>Serum CF</td>
<td>CSF ID</td>
<td>CSF CF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>+</td>
<td>1:16</td>
<td>–</td>
<td>&lt;1:2</td>
<td>BAL, blood, liver biopsy specimen</td>
</tr>
<tr>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>–</td>
<td>&lt;1:1</td>
<td>BAL, blood</td>
</tr>
<tr>
<td>NA</td>
<td>+</td>
<td>&gt;1:256</td>
<td>+</td>
<td>1:8</td>
<td>BAL, blood, CSF</td>
</tr>
<tr>
<td>NA</td>
<td>–</td>
<td>&gt;1:64</td>
<td>–</td>
<td>&lt;1:1</td>
<td>Blood, liver biopsy specimens</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>&gt;1:64</td>
<td>–</td>
<td>&lt;1:1</td>
<td>BAL, liver biopsy specimen</td>
</tr>
<tr>
<td>NA</td>
<td>+</td>
<td>&lt;1:2</td>
<td>–</td>
<td>&lt;1:1</td>
<td>BAL, lung aspirate (obtained by FNA)</td>
</tr>
<tr>
<td>–</td>
<td>NA</td>
<td>&lt;1:2</td>
<td>–</td>
<td>&lt;1:1</td>
<td>Sputum, lung aspirate (obtained by FNA)</td>
</tr>
<tr>
<td>NA</td>
<td>+</td>
<td>&gt;1:256</td>
<td>–</td>
<td>&lt;1:1</td>
<td>Synovial fluid and biopsy specimen</td>
</tr>
</tbody>
</table>

Our experience with coccidioidomycosis in liver transplant patients resembles that reported for renal, heart, and bone marrow transplant patients [5, 12–16]. Most patients live in areas that are endemic for coccidioidomycosis and receive an organ allograft at a transplant center located in a similar area of endemicity. However, some patients may have reactivation of previous coccidioidal infection after transplantation at centers outside regions of endemicity [5].

Among renal and heart transplant recipients who live in areas of endemicity, the incidence of coccidioidomycosis is 6% during the first year after transplantation but declines over subsequent years [5, 13–15]. Disseminated infection occurs in about two-thirds of renal allograft recipients and is usually fatal. Disseminated infection and death occur less often in heart allograft recipients [13–15]. Two of three cases of coccidioidomycosis reported in bone marrow transplant patients were disseminated and fatal [16]. These reports did not document whether fungal prophylaxis with amphotericin B, fluconazole, or itraconazole was administered.

The incidence of coccidioidomycosis in our liver transplant patients was 0.59%, which is lower than the incidences reported in renal and heart transplant patients. However, seven of our eight patients developed infection only within the 23-month period between December 1992 and November 1994, which corresponds with the recent increase in coccidioidomycosis in the general population of California. Moreover, six (75%) of our eight patients had disseminated infection, and four died (50%). Thus, similar to renal, heart, and bone marrow trans-
plant patients, liver transplant patients who develop coccidioidomycosis are at high risk for disseminated disease, which is frequently fatal.

Active coccidioidomycosis can be either a primary infection or reactivation of a previously acquired quiescent infection. The results of pretransplantation immunodiffusion and CF serological tests for serum IgG antibody that may be indicative of latent infection were obtained for only two of our patients and were positive for one patient. The results of coccidioidin skin tests, which can be used to assess both prior exposure as well as cellular immunity, were not available for our patients. However, negative skin and serological tests may not necessarily exclude latent infections in immunosuppressed patients who may be anergic [1, 5].

Although pneumonia was the most common clinical presentation of coccidioidomycosis in our liver transplant patients, there were no clinical features or radiographic findings in these cases that could determine whether pneumonia was caused by C. immitis or by other organisms. Furthermore, a pulmonary infiltrate or nodule was found in several patients without pulmonary symptoms (patients 4, 6, 7, and 8; table 1) only when an incidental chest roentgenogram was obtained during evaluation for extrapulmonary symptoms.

The diagnosis of coccidioidomycosis for patient 4 (table 1) was made on the basis of examination of a specimen from a liver biopsy performed for evaluation of rejection, while coccidioidomycosis was diagnosed for patient 8 (table 1) on the basis of examination of a specimen from a synovial biopsy of the right knee joint after previous knee joint aspirations had been nondiagnostic. Thus, similar to the diagnosis of other infections in immunosuppressed patients, the diagnosis of coccidioidomycosis requires a high index of clinical suspicion followed by appropriate and sometimes invasive diagnostic procedures.

Because of the potential severity of coccidioidomycosis in transplant patients and other immunosuppressed patients, therapy is always indicated [2, 3, 5, 6, 8, 9, 26, 27]. Amphotericin B is still the agent most frequently used as initial therapy for coccidioidomycosis in immunosuppressed patients who have disseminated infection or are clinically unstable [2, 3, 5, 6, 8, 9, 18–20, 27]. The intensity and duration of therapy are determined by the severity of the disease and the subsequent clinical and serological responses [5, 6, 9, 10].

We administered amphotericin B at a dosage of 1 mg/(kg·d) to our liver transplant patients; this dosage was tapered to 1 mg/kg every other day once clinical improvement occurred. Survivors had received a total dose of 1 g to 4 g, and this dose was followed by chronic maintenance therapy with oral fluconazole (400 mg/d). Despite the fact that administering amphotericin B with cyclosporine could result in nephrotoxicity [28], our surviving patients were able to complete therapy. Nonetheless, it may be reasonable to treat selected clinically stable transplant patients who have only pulmonary coccidioidomycosis or who cannot tolerate amphotericin B therapy with high doses of fluconazole (800–1,200 mg/d) to avoid the toxicity of amphotericin B [9, 29, 30]. Similarly, perhaps patients who have coccidioidal meningitis (patient 3; table 1) or who fail to respond to therapy with amphotericin B alone (patient 5; table 1) should receive high doses of fluconazole (800 mg/d) in addition to iv amphotericin B. However, additional data are required to further define the role of fluconazole in the treatment of coccidioidomycosis in critically ill transplant patients.

Oral itraconazole has also been successfully used to treat nonmeningeal coccidioidomycosis [9, 29, 31, 32]. However, its use in transplant patients and other critically ill patients may be limited by the fact that in these cases there is relatively poor absorption from the gastrointestinal tract [29–31]. New lipid complexing formulations of amphotericin B may prove to be less toxic than amphotericin B, but more clinical studies are needed to determine whether these preparations have any therapeutic advantages [33, 34]. Finally, surgical removal of isolated cavitary disease may be indicated for transplant patients who fail to respond despite drug therapy or for patients with disease complicated by hemoptysis or cavitary enlargement. Open surgical drainage and synovectomy may also be useful adjunctive therapy for transplant patients with coccidioidal arthritis.

No well-controlled trials of antifungal prophylaxis in a large number of solid-organ transplant patients have been published. We just completed a large double-blind, placebo-controlled study of prophylactic fluconazole (400 mg/d) in more than 200 liver transplant patients at UCLA Medical Center [35]. Proven fungal infections occurred in 43% of the patients who received placebo but in only 9% of patients who received prophylactic fluconazole. Two of the patients (patients 2 and 4; table 1) who had coccidioidomycosis and who are described in this report participated in this study. Both received placebo, and patient 2 died of his infection. There were no cases of coccidioidomycosis among patients who were receiving prophylactic fluconazole.

Thus, it would appear reasonable to consider administering prophylactic fluconazole (400 mg/d) to liver transplant patients who have a history of coccidioidomycosis and radiographic evidence of prior or recent disease or who are found to have high titers of coccidioidal CF antibody during pretransplantation evaluation. Itraconazole may also be considered for prophylaxis, although the specific dose, the duration of treatment, the safety profile, and the efficacy of this drug vs. fluconazole have yet to be determined.

In summary, coccidioidomycosis can be a serious and frequently fatal infectious complication in liver transplant patients who have lived in an area of endemicity. The incidence of coccidioidomycosis may be increasing in transplant patients as a result of local environmental conditions that are conducive to the acquisition of infection. A high index of clinical suspicion followed by aggressive diagnostic procedures is necessary for the diagnosis of coccidioidomycosis in liver transplant recipients. Since antifungal therapy is effective in only some patients,
antifungal prophylaxis should be considered for patients with historical, radiographic, or serological evidence of recent coccidioidomycosis before transplantation.

References


