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Coccidioidomycosis among persons undergoing lung transplantation in the coccidioidal endemic region

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Abstract

Background: Coccidioidomycosis, an endemic fungal infection, is more likely to be symptomatic and severe among those receiving allogeneic transplants. While several case series have been published for various transplanted organs, none has described the incidence and outcomes in those receiving lung transplants within the coccidioidal endemic region.

Methods: Patients receiving a heart-lung, single-lung, or bilateral-lung transplantation at the University of Arizona between 1985 and 2009 were retrospectively reviewed.

Results: Coccidioidomycosis occurred post transplantation in 11 (5.8%) of 189 patients. All but one patient was diagnosed with pulmonary coccidioidomycosis and only one had a history of prior coccidioidomycosis. Two patients received transplants from donors found to have coccidioidomycosis at the time of transplantation and one death was directly attributed to coccidioidomycosis. The risk of developing active coccidioidomycosis was significantly higher if the patient did not receive some type of antifungal therapy post transplantation (P<.001).

Conclusion: Within the coccidioidal endemic region, post-transplantation coccidioidomycosis was a definable risk among lung transplant recipients. Use of antifungals appeared to reduce this incidence of disease. Almost all cases resulted in pulmonary disease, suggesting that the lung is the primary site of infection.

Keywords:

coccidioidomycosis, fungal infections, lung, transplantation

1 INTRODUCTION

Coccidioidomycosis is an infection due to the dimorphic, soil-dwelling fungus *Coccidioides.* In the United States, the disease is endemic to the San Joaquin Valley of California and to the desert southwest, particularly the central portion of Arizona. Infection is most commonly acquired by inhalation of coccidioidal arthroconidia, and pneumonia is the most common presentation.[1] However, severe disease, including extrathoracic dissemination, may occur among individuals with suppressed cellular immunity.[2]

The incidence of symptomatic coccidioidomycosis has been found to be increased among patients who receive allogeneic solid organ transplants, including heart,[3] kidney,[4] and liver.[5] However, despite a recent review,[6] no series have been reported in those who have undergone lung transplantation (LT). This report describes an analysis of cases of coccidioidomycosis among heart-lung, as well as single- and bilateral-lung transplant recipients at a single transplantation center located in the coccidioidal endemic region over a period of 24 years.

2 MATERIALS AND METHODS

We performed a retrospective chart review on all LT cases performed at the University of Arizona Medical Center from November 1985 through December 2009. Information collected on each case included age, gender, and time residing in Arizona, signs and symptoms of

coccidioidomycosis, type of immunosuppression received, antifungal prophylaxis, and outcome. In addition, the data were examined for evidence of donor-derived coccidioidomycosis.

Patients were grouped as having evidence of coccidioidomycosis prior to the transplantation procedure. Evidence of pre-transplant coccidioidomycosis included a history of coccidioidomycosis documented in the medical record, a documented positive coccidioidal skin test, a positive coccidioidal serology, performed by enzyme immunoassay (EIA) or immunodiffusion, a positive culture for *Coccidioides*, or the finding of spherules on cytological examination. The diagnosis of post-transplantation coccidioidomycosis was based on the development of a new positive coccidioidal serologic test, a positive culture from a clinical site, or the finding of coccidioidal spherules on tissue examination after transplantation.

Statistical analysis consisted of the Fisher exact test or the Pearson χ^2 analysis to ascertain categorical relationships. Analyses were performed using Stata 14 (Stata Corp, College Station, TX USA).

3 RESULTS

Transplantations were performed in 189 patients for the time period studied. Thirteen individuals required a second transplantation. Procedures included 51 heart-lung transplants, performed between 1985 and 2008; 49 single-lung transplants, between 1990 and 2007; and 102 bilateral-lung transplants, between 1995 and 2009. Table 1 details the characteristics of the patients. More than two-thirds of the patients resided in the coccidioidal endemic region at the time of transplantation.

Screening for evidence of coccidioidomycosis prior to transplantation varied. In general, patients were asked if they had a previous diagnosis of coccidioidomycosis and a plain chest radiograph was obtained. In some cases prior to 2000, spherule-based skin testing was performed. If patients had evidence of coccidioidomycosis based on any of the above studies, coccidioidal serological tests were obtained, but were otherwise not done on a routine basis.

Fourteen (7.4%) patients had evidence of coccidioidomycosis before LT, including 2 with a positive skin test, 5 with positive coccidioidal serology results, 1 with a positive culture, and 2 with positive tissue cytology results. A total of 5 had a prior history of coccidioidomycosis without any positive laboratory tests. In these subjects, 3 had evidence of old granulomatous disease on plain chest radiograph (Table 1). In 11 of these cases, patients received antifungal therapy during the post-transplantation period.

Among the 189 subjects, coccidioidomycosis occurred after transplantation in 11 instances (Table 2). Of these 11, 5 were male and 6 were female. The mean age was 46 years. No cases of post-transplantation coccidioidomycosis occurred among the 51 heart-lung transplant recipients, while 3 (6.5%) of the 46 single-lung transplant and 8 (8.7%) of the 92 bilateral-lung recipients developed coccidioidomycosis (P = .237). Ten patients had disease confined to the lungs, while one patient had extrathoracic disease manifesting as a biopsy-proven coccidioidal cutaneous nodule associated with mediastinal adenopathy. In 10 cases, no coccidioidomycosis was documented prior to transplantation.

Overall, the median time from transplantation to development of coccidioidomycosis was 3 months with a range of 1-56 months (Table 2). No subject developed coccidioidomycosis after a second transplantation. In 9 instances, coccidioidomycosis was diagnosed within 1 year after transplantation. In one instance (Case 11, Table 2), a 42-year-old woman who received a single-lung transplant for interstitial pulmonary fibrosis developed active pulmonary coccidioidomycosis >4 years after transplantation. She had no history of coccidioidomycosis prior to transplantation.

In another instance (Case 1, Table 2), active coccidioidomycosis developed during chronic rejection >5 years after transplantation. This case requires further amplification. In January 2003, 22 months prior to LT, the patient was seen at an outside facility. A chest radiograph demonstrated multiple alveolar and interstitial pulmonary infiltrates and a coccidioidal serology was reported as positive. The patient was placed on fluconazole, but this was discontinued after 2 months. Because of progressive dyspnea, he was evaluated at the University of Arizona in March 2003. Surgical biopsy demonstrated findings consistent with interstitial pulmonary fibrosis without evidence of coccidioidomycosis. He received corticosteroids and interferon-γ without improvement. He underwent single-LT in October 2004; coccidioidal serological tests prior to transplantation were negative. Itraconazole 200 mg twice daily was started immediately postoperatively, because *Aspergillus* species was isolated from the donor lung. The patient remained on itraconazole. In early January 2010, he was admitted to the hospital for progressive lung failure and empirically treated for acute rejection with high-dose corticosteroids. A sputum culture subsequently grew one colony of

Coccidioides. A later wedge biopsy of the lung revealed chronic transplant rejection and bronchiolitis obliterans with organizing pneumonia, without evidence of coccidioidomycosis. He was placed on comfort care and died at the end of the month.

The diagnosis of post-transplantation coccidioidomycosis was made using several methods. Three (38%) of 8 who were tested had a new positive serologic test. Six (55%) of 11 patients had positive cultures for *Coccidioides*, including 4 obtained either by bronchoalveolar lavage, transbronchial biopsy, or fine-needle aspiration of the lung. One patient had a positive sputum culture and one patient had a positive culture from a skin biopsy. Three (27%) of 11 had a cytological examination demonstrating coccidioidal spherules by bronchoalveolar lavage, transbronchial biopsy, and fine-needle lung aspirate, respectively.

Two patients received lungs from donors who had evidence of coccidioidomycosis at the time of transplantation. One recipient died during the transplant procedure. No autopsy was performed. No evidence of active coccidioidomycosis was found in the donor except for a positive immunoglobulin-M (IgM) serology performed by EIA. The other recipient received a transplanted lung that was found to have coccidioidal spherules. Coccidioidal serology on that donor was negative. The recipient was given antifungal prophylaxis and did not develop active coccidioidomycosis. He died 2.5 years after transplantation from other causes.

Two deaths were associated with coccidioidomycosis. One death was directly attributable with the finding of diffuse pulmonary coccidioidomycosis on autopsy. In the other, coccidioidomycosis was a contributing cause of death based on autopsy. The direct cause of death was necrotizing pneumonia from *Pseudomonas aeruginosa*, but coccidioidal spherules were also identified in the lungs. Both patients died within 2 months after LT.

As shown in Table 3, the number of transplantations performed increased over time, from 13 performed in 1985-1989 to 63 done from 2005-2009. However, the number of cases of post-transplantation coccidioidomycosis did not increase significantly over these same years (*P* = .387). In addition, the use of antifungal prophylaxis increased significantly from none in 1985-1989 to 86% by 2005-2009 (*P* <.001), with voriconazole being most common by the end of the study.

In addition, a marked change in immunosuppressive regimens occurred over the course of the study, with significant decreases in the use of cyclosporine and azathioprine (*P* <.01) and commensurate increases in the use of tacrolimus and mycophenolate (*P* <.001), so that most patients received prednisone, cyclosporine, and azathioprine at the beginning of the study, while the most common regimen was prednisone, tacrolimus, and mycophenolate at the end.

We had no fixed protocols for immunosuppressive therapy. In general, induction corticosteroids consisted of intravenous methylprednisolone at 125 mg every 12 hours followed by a tapering dose of oral prednisone beginning at 50 mg daily. After 1 year, a maintenance dose of 7.5 mg daily of prednisone was given. Doses of tacrolimus began at 1500 mg twice daily and then were adjusted to maintain a peripheral blood white cell count > 4000/μL. Oral cyclosporine was given as 1.5 mg/kg twice daily for the first month, and then reduced to maintain serum levels of between 200 and 250 ng/mL. Azathioprine was used in those not on tacrolimus and was begun at 200 mg daily and was subsequently titrated to maintain a peripheral blood white cell count >4000/μL. Doses of mycophenolate mofetil ranged between 500 and 1500 mg twice daily and sirolimus dosages were between 1 and 4 mg daily, both with

adjustments made based on trough serum levels. For episodes of rejection, intravenous methylprednisolone at an initial dose of 125 mg every 12 hours was given.

Among the 178 patients in whom coccidioidomycosis did not develop post transplantation, 90 received some form of antifungal therapy during their follow-up. Unfortunately, it was impossible to precisely determine the start and stop dates of these treatments. In contrast, of the 11 transplantations after which post-transplant coccidioidomycosis occurred, only one patient was receiving antifungals at the time of diagnosis. Antifungal therapy was significantly more likely to be given in those transplantations where coccidioidomycosis did not develop, compared to those where it did occur (P <.001). The doses of azoles used for antifungal therapy was generally 400 mg daily for all four agents employed.

4 DISCUSSION

We present the first reported case series, to our knowledge, of coccidioidomycosis occurring after LT within the coccidioidal endemic region. It is interesting to note that only 1 of 11 instances had any evidence of prior coccidioidomycosis, and in that case the reportedly positive serological test was not confirmed. These data suggest that most cases of post-transplantation coccidioidomycosis may be the result of new infection rather than reactivation. The results do emphasize that the first year after transplantation is associated with the highest risk of developing infection.

The rate of coccidioidomycosis in this group is higher than that seen for other transplants[4,7,8] performed in Arizona. It is unclear if this is a true difference, but lung transplant

recipients may represent a unique group, because the lung is the most common portal of entry for the fungus. In addition, a remarkable finding is that the type of post-transplantation coccidioidomycosis observed was pulmonary in all but one case. This finding is similar to what Mendoza et al.[7] observed for allogeneic hematopoietic stem cell transplants but higher than among liver [8] and renal transplants.[4]

We identified two cases of possible donor-derived coccidioidomycosis. In one instance, it was based on the finding of an isolated positive coccidioidal IgM EIA serology, which may have been falsely positive.[9] One patient died rapidly without a diagnosis and the other, who received antifungal therapy, survived and died of other causes. Given this experience and that of other transplantation centers,[10-14] donors should be screened for evidence of active coccidioidomycosis prior to transplantation and recipients should receive antifungal therapy. Recent guidelines recommend screening prior to the recovery of organs of potential donors who have resided in the coccidioidal endemic area. Tests should include coccidioidal serology, chest imaging, and, if appropriate, fungal cultures of respiratory secretions or tissue specimens.[15] Recently, Kusne et al.[16] discussed 6 reports of possible donor-derived coccidioidomycosis involving 21 recipients. All 11 recipients who received antifungals survived, compared to only 2 of 7 who did not. [16]

Patients on antifungal therapy for any reason had a significantly decreased risk for developing post-transplantation coccidioidomycosis. This observation is in accordance with a recent study on orthotopic liver transplantation performed in the coccidioidal endemic region. That report[17] found that universal antifungal prophylaxis with 200 mg of daily fluconazole for the first year after transplantation resulted in no cases of post-transplantation

coccidioidomycosis compared to an incidence of 2.6% among those receiving targeted prophylaxis based on a pre-transplant history of coccidioidomycosis or asymptomatic coccidioidal seropositivity. Our study gives support to the concept that antifungal prophylaxis, at least for the first year after transplantation, could reduce the incidence of post-transplantation coccidioidomycosis within the endemic area.

The immunosuppression regimen changed dramatically over the course of the study. While it is possible that this had an effect on the number of cases of post-transplantation coccidioidomycosis, this cannot be definitively concluded by our results. It is interesting that no cases of post-transplantation coccidioidomycosis occurred in heart-lung recipients and none received antifungal prophylaxis. The reasons for this difference are unclear. One explanation is that these transplants were performed between 1985 and 1989, a time when the incidence of coccidioidomycosis in Arizona was far lower than it was in later decades. [18,19]

Weaknesses of this study include its retrospective nature, the fact that data collection ended in 2009, and that information is missing, particularly with regard to the timing of antifungal prophylaxis. In addition, the relatively prolonged period of the study and the lack of formal protocols resulted in different approaches to screening for prior coccidioidomycosis, as well as different types of transplants, varying types of immunosuppression, and different approaches to antifungal prophylaxis. Despite these issues, these data indicate that the risk of post-transplantation coccidioidomycosis among those undergoing LT in the coccidioidal endemic area may be higher than seen with other transplants. Most cases occur relatively soon after transplantation, most result in pulmonary disease only, and the overall prognosis is good.

Finally, antifungal prophylaxis appeared to reduce the incidence of symptomatic coccidioidomycosis in this group of patients.

Author contributions:

S.C. and L.M.: Conceived and developed the project and contributed equally to it; S.C., L.M., and Y.R.: Contributed to the data collection; H.A. and N.M.A.: Contributed to data analysis and interpretation; K.S.K. and N.M.A.: Contributed to drafting and revision of the article.

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TABLE 1 Characteristics of the patients who received transplants

	Type of transplant		
	Heart-lung	**Bilateral-lung**	**Single-lung**
Time period	1985–2008	1995–2009	1990–2007
Number	51	102	49
Median follow-up (months)	44	27	31
Mean age ± SD, years	35.6±11.6	46.1±14.4	50.7±9.2
Male gender (%)	17 (33%)	55 (54%)	23 (47%)
Residence			
AZ	35 (68%)	86 (84%)	33 (67%)
CA	3	1	1
NM, UT, NV	3	3	1
Other or unknown	10	12	14
Coccidioidomycosis prior to transplantation	3	6	5
History	0	2	
Positive skin test	1	1	
Positive serology	1	2	
Microbiology	0	1	
Cytology	2	1	

SD, standard deviation; AZ, Arizona; CA, California; NM, New Mexico; UT, Utah; NV, Nevada.

TABLE 2 Characteristics and outcomes of the 11 lung transplant recipients who developed coccidioidomycosis in the post-transplantation period.

Case No.	1	2	3	4	5	6	7	8	9	10	11
Age, years	57	49	21	13	55	54	53	52	55	52	42
Gender	M	M	M	M	F	F	F	M	F	M	F
Residence	AZ	AZ	AZ	AZ	AZ	AZ	AZ	AZ	Unkn	AZ	Unkn
Transplant year	2004	2006	2005	2003	2004	2002	1996	1995	2003	1991	2000
Underlying disease	IPF	ILD	PPH	LIP	ILD	COPD	COPD	IPF	IPF	COPD	IPF
Transplant type	SL	SL	BL	BL	BL	BL	BL	BL	SL	SL	SL
Pre-transplant coccy	P	N	N	N	N	N	N	N	N	N	N
Coccy type	Lung	Lung	Lung	Lung	Lung	Skin	Lung	Lung	Lung	Lung	Lung
Diagnosis	Sero, culture, cyto	Cyto	Sero, culture	Culture	Culture	Culture, cyto	Cyto	Culture, cyto	Sero, cyto	Sero, culture, cyto	Cyto
Time from transplant	64 mos	1 mos	3 mos	1 mos	1 mos	10 mos	1 mos	2 mos	6 mos	8 mos	56 mos
Antifungal prophylaxis	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y
Outcome	Died	Died	Died	Alive	Died	Alive	Died	Died	Alive	Died	Alive
Organ rejection at time of coccy	Yes	No	No	No	No	No	No	No	No	No	Yes
Death attributed to coccy	No	Yes	No	–	No	–	No	Yes	–	No	–

M, male; F, female; AZ, Arizona; Unkn, unknown; IPF, interstitial pulmonary fibrosis; ILD, interstitial lung disease; PPH, primary pulmonary hypertension; LIP, lipoid interstitial pneumonia; COPD, chronic obstructive pulmonary disease; SL, single-lung; BL, bilateral-lung; P, possibly; N, no; Y, yes; Sero, serology, cyto, cytology; mos, months; Coccy, coccidioidomycosis.

TABLE 3 Transplantation cases, number of cases of post-transplantation coccidioidomycosis, and antifungal prophylaxis by year-groups

Years	**1985-1989**	**1990-1994**	**1995-1999**	**2000-2004**	**2005-2009**
Transplantations	13	36	36	44	73
Post-transplant coccidioido-mycosis	0 (0%)	1 (3%)	2 (6%)	5 (11%)	3 (4%)
Antifungal therapy					
Prophylaxis	0 (0%)	6 (17%)	6 (17%)	16 (36%)	64 (88%)*
Ketoconazole	0	2	0	0	0
Fluconazole	0	4	3	10	1
Itraconazole	0	0	0	2	1
Voriconazole	0	0	0	4	52
Immunosuppressives					
Prednisone	9 (69%)	28 (78%)	31 (86%)	41 (93%)	70 (96%)
Cyclosporine	12 (92%)	31 (86%)	30 (83%)	8 (18%)	7 (10%)*
Tacrolimus	1 (8%)	1 (3%)	7 (19%)	39 (91%)	69 (95%)*
Sirolimus	2 (15%)	1 (3%)	1 (3%)	8 (18%)	7 (10%)
Azathioprine	11 (85%)	32 (89%)	16 (44%)	12 (27%)	20 (27%)**
Mycophenolate mofetil	1 (8%)	3 (8%)	22 (61%)	35 (80%)	65 (89%)*

*P <.001 over time.
**P<.01 over time.