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Donor-derived organ transplant transmission of coccidioidomycosis

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Abstract

Coccidioidomycosis in solid organ transplant recipients most often occurs as a result of primary infection or reactivation of latent infection. Herein, we report a series of cases of transplant-related transmission of coccidioidomycosis from a single donor from a non-endemic region whose organs were transplanted to 5 different recipients. In all, 3 of the 5 recipients developed evidence of *Coccidioides* infection, 2 of whom had disseminated disease. The degree of T-cell immunosuppression and timing of antifungal therapy initiation likely contributed to development of disease and disease severity in these recipients. This case series highlights the importance of having a high index of suspicion for *Coccidioides* infection in solid organ transplant recipients, even if the donor does not have known exposure, given the difficulties of obtaining a detailed and accurate travel history from next-of-kin.

Keywords

coccidioidomycosis; fungal infection; solid organ transplantation; transmission

Coccidioides immitis is a dimorphic fungus, endemic to the southwestern United States, Mexico, and parts of Central and South America (1–4). Infection caused by *Cocciodioides* species occurs after inhalation of aerosolized arthroconidia, with the organism potentially becoming latent within resident and recruited pulmonary phagocytes and cells of the reticuloendothelial system. Primary infection is usually asymptomatic; however, patients

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with human immunodeficiency virus infection or other underlying immunosuppression are more likely to develop symptomatic disease and extrapulmonary manifestations (1, 3, 4).

Coccidioidomycosis in solid organ transplant recipients most often occurs as a result of primary infection or reactivation of latent infection in patients who reside in endemic areas (3, 4). Transmission from donor organs has only been rarely reported, with 3 cases reported from donor lungs and 1 case series of *Coccidioides* infection from a donor liver and kidney (5–8). We report a series of cases of transplant-related transmission of coccidioidomycosis from a single donor from a non-endemic region whose 2 kidneys, pancreas (as a kidney-pancreas), liver, lungs, and heart were transplanted into 5 different recipients (Table 1). In all, 3 of the 5 recipients developed evidence of *Coccidioides* infection, 2 of whom had disseminated disease.

Case reports

Donor

A 22-year-old male presented to a local hospital after a self-inflicted gunshot to the head and was pronounced brain dead 4 days later. The patient was originally from Jamaica and immigrated to the United States, to Maryland, in 2001. His only other known travel was to Canada. His past medical history was unremarkable and he was not known to have been ill prior to this incident.

Recipient 1

A 19-year-old African-American man received a compatible cross match kidney transplant. He was born in Baltimore, and had never traveled out of the state of Maryland. On post-transplant day (PTD) 29, he was admitted with fevers (Tmax: 41.5°C), nausea, diarrhea, severe headache, and left eye ptosis. On PTD 35, a computed tomography (CT) of his chest revealed bilateral multiple small pulmonary nodules. Empirical treatment with piperacillintazobactam, vancomycin, azithromycin, and voriconazole was initiated, but he continued to have persistent headaches and fevers. Cerebrospinal fluid analysis was unrevealing. Repeat chest CT on PTD 39 demonstrated interval increase in the size and number of the bilateral pulmonary nodules.

A blood culture from PTD 32 became positive for a filamentous organism 10 days later and the organism was identified as *C. immitis/posadasii*. A bronchoalveloar lavage (BAL) from PTD 37 and culture from transbronchial biopsy recovered *C. immitis/posadasii*. A total antibody titer for *Coccidioides* by enzyme immunoassay (EIA) was positive at 6.39 (reference range <0.90) on PTD 59. *Coccidioides* serology by complement fixation (CF) on PTD 67 was positive at a titer of 1:4 (reference <1:2).

Voriconazole was changed to liposomal amphotericin B (5 mg/kg daily) on PTD 50. On PTD 58, he was readmitted with elevated creatinine, so amphotericin B was changed to fluconazole; however, because of fever recurrence, liposomal amphotericin B was restarted (at 3 mg/kg daily) until PTD 80. Therapy was transitioned to fluconazole 400 mg daily, and on 6-month follow-up he had no recurrence of his symptoms.

Recipient 2

A 45-year-old Caucasian woman received a simultaneous deceased donor pancreas and renal transplant from the same donor. She lived in Baltimore, and her only travel history was to a camp site in Pennsylvania. She presented on PTD 26 with fever, diarrhea, nausea, vomiting, sinus congestion, rhinorrhea, non-productive cough, and decreased urine output. She received empiric vancomycin and piperacillin-tazobactam without resolution of her fever. A chest radiograph and CT of the abdomen and pelvis were without abnormalities. On PTD 33, she developed dyspnea and tachypnea, deteriorating renal function, and required intubation. Micafungin and ganciclovir were added to her antibiotic regimen, but she died on PTD 36. Blood cultures drawn 2 days after admission became positive for a mold on the day she died; 8 days later, this mold was identified as *C. immitis/posadasii*. BAL from the day before her death revealed the same organism. *Coccidioides* serologies were not performed.

Recipient 3

A 63-year-old Caucasian woman received an orthotopic liver transplant from the same donor. She lives in Baltimore, Maryland, and has never traveled to areas known to be endemic for *Coccidioides*. She presented on PTD 51 with fevers, nausea, and vomiting, and was started on empiric vancomycin and piperacillin/tazobactam. Fungal and bacterial blood cultures were negative. A CT of the chest demonstrated small bilateral pulmonary nodules. Her fevers resolved and she was discharged on fluconazole 200 mg daily. *C. immitis* antibodies were negative by immunodiffusion (ID) and CF. She continued to receive fluconazole and remained asymptomatic by PTD 91.

Recipient 4

A 62-year-old Caucasian woman underwent bilateral orthotopic lung transplant from the same donor. She lives in Maryland and had traveled to Colorado. The donor's bronchial cultures recovered *Stenotrophomonas maltophilia, Pseudomonas aeruginosa, Streptococcus anginosus, Enterococcus faecalis*, and *Aspergillus fumigatus*. Based on donor sputum cultures, treatment with levofloxacin and oral voriconazole was started on PTD 3. A surveillance BAL on PTD 30 was negative. The patient was evaluated at the Transplant Infectious Disease outpatient clinic on PTD 50, because of exposure to the donor with *Coccidioides* species. A chest CT on PTD 50 revealed bilateral pleural effusions. A thoracentesis was performed on PTD 63 that revealed a transudative effusion. *Coccidioides* serology (PTD 53) was positive at 1:2 by CF (reference <1:2), but negative by EIA and ID. Repeat serologies were positive with a low titer of 1:2 by CF (PTD 83 and 93). She was asymptomatic at 5-month follow-up, and a chest CT on PTD 203 demonstrated no evidence of consolidation or nodules.

Recipient 5

An 18-year-old African-American man underwent an orthotopic heart transplant from the same donor. He was born and raised in Maryland, with a reported history of travel to Georgia, Ohio, and Illinois. His post-transplant course was complicated by several syncopal episodes and atrial fibrillation. He was evaluated in the Transplant Infectious Disease clinic on PTD 56, because of his exposure to the donor with *Coccidioides*. His review of systems

and physical examination were unremarkable. Fluconazole 400 mg once a day was initiated on PTD 53 for primary antifungal prophylaxis because of his exposure; *Coccidioides* serology was negative by CF (PTD 56). The patient died on PTD 88 from sudden cardiac death. Postmortem exam revealed no evidence of *Coccidioides* infection.

Conclusion

We report 3 cases of donor-transmitted *Coccidioides* infection from a donor not known to have prior disease or endemic exposure. Of the 5 organ recipients, 3 developed evidence of infection and 2 of them had evidence of disseminated disease. The donor was not known to be sick before his death, and had no known history of *Coccidioides* exposure or active infection. However, donor blood obtained from the Organ Procurement Organization in retrospect tested positive for *Coccidioides* at 5.48 by EIA (reference range <0.90). Testing by CF was indeterminate because of interference with anti-complement activity, but ID testing was also positive (reference: negative). This organism is not known to be endemic in Jamaica, where the donor originated, but is found in some neighboring islands and in the northern region of Mexico (3). Hence, it is unlikely that the donor acquired his infection in Jamaica. We hypothesize that he was probably exposed to *Coccidioides* during unknown travel(s) to endemic regions, while living in the United States. Medical and travel history taken before organ donation was limited, as the history was taken from a family member with whom the donor had had limited contact for many years. Unfortunately, none of the isolates were available to assess species (*C. immitis* vs. *posadasii*), given the laboratory requirements to destroy the isolate. Identification to the species level may have been informative, given known geographic restrictions of the organism (2, 3).

The mechanism for transmitted *Coccidioides* infection from this donor is unclear. As 3 of the 5 organ recipients developed infection, it is quite possible that the donor was fungemic at the time of death, or had latent infection with reservoirs in the donated organs. The degree of immunosuppression and the timing of antifungal treatment initiation in the recipients may explain the presence or absence of *Coccidioides* infection in these recipients, as well as disease severity. Recipients who received significant T-cell-depleting immunosuppression may have been unable to contain donor-transmitted latent infection. Notably, both patients who developed disseminated infection received a kidney and were profoundly T-cell suppressed with an absolute lymphocyte count <500 cells/mm^3. Both recipients with disseminated disease became sick in the first month post transplant, which is consistent with previous reports, including a case report of liver and renal transplant recipients who developed disseminated coccidioidomycosis on PTD 13 and 17, respectively (6). Furthermore, neither of these 2 recipients was on prophylactic antifungal therapy at the time they became ill.

The lung recipient developed evidence of infection by serology but never had signs or symptoms of active infection. She was not lymphopenic and received prophylactic voriconazole, both of which factors likely contributed to her lack of active disease. The liver transplant recipient received fluconazole immediately post transplant per protocol, which in addition to the relatively higher absolute lymphocyte count may have prevented seroconversion. It is unclear why the heart recipient did not develop evidence of

Coccidioides infection, despite lack of empiric antifungal prophylaxis. It is possible he would have developed infection later in his post-transplant course; however, he was started on prophylactic fluconazole after discovery of the infection in the other organ recipients.

This case series also highlights several challenges to diagnosing *Coccidioides* infection in transplant recipients. Obtaining a detailed donor history, especially travel history, is difficult and sometimes not accurate when obtained from next-of-kin. Making a diagnosis of acute coccidioidomycosis can be challenging, particularly with lack of clinical suspicion, and associated with delays in identifying the fungus. For instance, blood cultures turned positive 8 and 10 days after the initial test was performed, and took an additional 7 and 8 days to identify, for Recipients 1 and 2, respectively. Other specimens (i.e., from BAL and transbronchial biopsy) took an additional 20 days to identify. Given these limitations, testing for fungal infections should be performed early in the evaluation of fevers of unclear etiology, even with no known exposures in the donor or recipient. The diagnosis of coccidiomycosis in both renal transplant recipients was promptly reported to the Organ Procurement and Transplantation Network from both institutions. Communication between transplant centers about post-transplant complications is essential, especially when several organs from the same donor are transplanted at multiple transplant centers. This notification is crucial for timely diagnosis and initiation of life-saving treatment in the other organ recipients.

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Table 1

Summary of baseline, transplant-related, and infection characteristics in 5 organ recipients from a *Coccidioides*-positive donor

	Recipient 1	Recipient 2	Recipient 3	Recipient 4	Recipient 5
Demographics					
Age (years)	19	45	63	62	18
Gender	Male	Female	Female	Female	Male
Ethnicity	African-American	Caucasian	Caucasian	Caucasian	African-American
Underlying disease	FSGS	DM, HTN	DM, HTN, ETOH/cirrhosis	COPD	NIFDC
Transplanted organs	Kidney	Kidney/pancreas	Liver	Bilateral lung	Heart
Transplant regimens					
Immunosuppression, induction	ATG, corticosteroids	Basiliximab, alemtuzumab	Basiliximab	Basiliximab, corticosteroids	Basiliximab, corticosteroids
Immunosuppression, maintenance	Tacrolimus, prednisone, MMF	Tacrolimus, prednisone, MMF	Sirolimus, prednisone, MMF	Tacrolimus, prednisone, MMF	Tacrolimus, prednisone, MMF
Antibiotic prophylaxis	TMP/SMX, VGCV, clotrimazole	TMP/SMX, VGCV, clotrimazole	TMP/SMX, VGCV, FLU	TMP/SMX, VGCV, VOR	TMP/SMX, VGCV
Coccidioides infection					
Symptoms and signs	Fever, headache, dry cough, ptosis, nausea, diarrhea	Fever, dry cough, nausea, vomiting, diarrhea	NA	Asymptomatic seroconversion	NA
Coccidioides diagnosis	Blood culture, BAL culture, transbronchial biopsy	Blood culture, BAL culture	NA	NA	NA
Coccidioides serology	+ (PTD 59)	ND	–	+ (PTD 53)	− (PTD 56)
Laboratory values					
WBC (cells/μL)	4770	5700	4100	6520	5630
ALC (cells/μL)	470	0	700	1740	2800
Creatinine (mg/dL)	3.1	0.85	1.0	1.1	0.9
Antifungal agent	VOR (PTD: 30–50), LAMB (PTD: 50–58, 65–80), FLU (PTD: 58–65, 80–ongoing)	Micafungin (PTD: 35-death)	FLU (PTD: 35–ongoing)	VOR (PTD: 3–ongoing)	FLU (PTD: 53–88)
Outcome[1]	Alive (PTD 210)	Death (PTD 36)	Alive (PTD 91)	Alive (PTD 203)	Death (PTD 88)

[1] PTD noted represents the last follow-up day available.

FSGS, focal segmental glomerulosclerosis; DM, diabetes mellitus; HTN, hypertension; ETOH, ethanol; COPD, chronic obstructive pulmonary disease; NIFDC, non-ischemic familial dilated cardiomyopathy; ATG, anti-thymocyte globulin (Thymoglobulin); MMF, mycophenolate mofetil; TMP/SMX, trimethoprim/sulfamethoxazole; VGCV, valganciclovir; FLU, fluconazole; VOR, voriconazole; NA, not applicable; BAL, bronchoalveolar lavage; PTD, post-transplant day; ND, not determined; WBC, white blood cell count; ALC, absolute lymphocyte count; LAMB, liposomal amphotericin B.