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Brief Communication

Coccidioidomycosis Transmission Through Organ Transplantation: A Report of the OPTN *Ad Hoc* Disease Transmission Advisory Committee

S. Kusne[1,*], S. Taranto[2], S. Covington[2], D. R. Kaul[3], E. A. Blumberg[4], C. Wolfe[5] and M. Green[6]

[1]*Division of Infectious Disease, Mayo Clinic in Arizona, Phoenix, AZ*
[2]*United Network for Organ Sharing, Richmond, VA*
[3]*Division of Infectious Disease, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI*
[4]*Division of Infectious Disease, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA*
[5]*Division of Transplant Infectious Disease, Duke University Medical Center, Durham, NC*
[6]*Division of Pediatric Infectious Diseases, Department of Pediatrics and Surgery, University of Pittsburgh Medical School, Pittsburgh, PA*
**Corresponding author: Shimon Kusne, kusne.shimon@mayo.edu*

Donor-derived coccidioidomycosis has caused unexpected morbidity and mortality in transplant recipients. All proven or probable reports of donor-derived coccidioidomycosis to the Disease Transmission Advisory Committee between 2005 and August 2012 were reviewed. Six reports of proven or probable coccidioidomycosis were discovered. In four of six, the infection was first detected at autopsy in the recipient. In two cases it was first identified in the donor. Twenty-one recipients received organs from these six donors. Transmission occurred in 43% at a median of 30 days posttransplant with a mortality rate of 28.5%. Eleven recipients received preemptive antifungals, seven did not receive treatment, and treatment information was not reported for three recipients. Five of seven who did not receive prophylaxis/treatment died and all 11 who received early therapy survived. Six deaths occurred 14 to 55 days after transplant, with a median of 21 days. For exposed recipients, donor-derived coccidioidomycosis is a significant cause of morbidity and mortality. Evidence of infection in one recipient should prompt immediate evaluation for treatment of all other recipients from the same donor as preemptive treatment was effective. Further studies are needed to decide whether all donors from endemic areas should have routine serologic screening.

Abbreviations: DTAC, Disease Transmission Advisory Committee; OPTN, Organ Procurement and Transplantation Network; PDDTE, potential donor-derived transmission events

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Introduction

When recognized in the donor and not treated in recipients, donor-derived coccidioidomycosis has been a significant cause of unexpected morbidity and mortality after organ transplantation, and fatal outcomes have been reported (1–7). In the United States, most cases involve donors from Organ Procurement and Transplantation (OPTN) region 5, an area that includes New Mexico, Arizona, Utah, Nevada, and California. The optimal management and the efficacy of preventative antifungal treatment for exposed recipients are not well defined. The purpose of this study was to review all the cases of potential transmission of coccidioidomycosis reported to the Disease Transmission Advisory Committee (DTAC) and examine possible strategies to prevent donor-derived coccidioidomycosis.

Materials and Methods

All reports of potential donor-derived transmission events (PDDTEs) to DTAC between January 2005 and August 2012 were searched for coccidioidomycosis. Coccidioidomycosis was diagnosed based on any positive serology test, positive pathology, or positive culture for *Coccidioides immitis/posadasii* in donors and/or recipients. The definition of donor-derived infection was based on the previously published DTAC categories related to donor derivation and include proven, probable, possible, unlikely, intervention without documented transmission, and excluded (8,9). Only PDDTEs classified as proven or probable as determined by review of DTAC were analyzed. DTAC collects information under confidential medical peer review, and thus demographic and clinical information was summarized to prevent recognition of a particular case or a particular institution.

A PubMed and Medline search of English language journals from 1950 to 2013 was performed to find case reports of donor-derived coccidioidomycosis. The search keywords included *Coccidioides immitis/posadasii*,

Coccidioides Species, Coccidioidomycosis, Valley fever, transmission, solid organ transplant. The demographic and clinical data of these cases were tabulated.

Results

Between January 2005 and August 2012, DTAC investigated 14 donors implicated in PDDTEs for transmission of coccidioidomycosis; 6 (43%) were classified as proven (n = 5) or probable (n = 1) transmissions from donors to at least one recipient. Of the six coccidioidomycosis donor transmissions, four were first diagnosed in a recipient at the time of autopsy and the remaining two cases were first detected in the donor after the transplant operation. Coccidioidomycosis transmission occurred in 9 (43%) of 21 exposed organ recipients (including the 4 fatal index recipient cases) at a median of 30 days (range 6–64) after the transplant operation, and 6 (67%) of 9 recipients developed fungal dissemination to multiple organs. The mortality at 4 months follow-up after transplantation was 6/21 (28.5%) exposed recipients; none of the 11 exposed recipients who received preventative or early treatment died (Figure 1). The six deaths occurred at a median of 21 days after transplantation (range 14–55). Five of the 6 donors with proven or probable transmission were from OPTN region 5 (endemic area) and 11 of 14 PDDTE donors reviewed were also from OPTN region 5.

Our review of the literature identified 7 donors of organs that were placed in 18 organ recipients, resulting in 11 (61%) recipients with donor-derived coccidioidomycosis (Table 1). Several of these cases occurred outside the United States and others in the United States before 2008 (our first DTAC case occurred in 2008); none of these would be duplicated by the DTAC series**.** Of the recipients with known information, 40% were female, and median age was 46 years (range 18–66). Donor-derived coccidioidomycosis was recognized at a median of 14 (range 6–60) days after transplantation. The overall mortality was 44.4% (8/18), with 88% (7/8) of these deaths directly attributable to coccidioidomycosis; all 7 deaths had evidence of disseminated coccidioidomycosis to multiple organs (n = 6) or the central nervous system (n = 1). In the seven deaths, transmission and dissemination occurred after kidney alone (n = 3), simultaneous kidney and pancreas (n = 1), kidney-liver (n = 1), heart (n = 1), and bilateral lung transplantation (n = 1). Five of the 7 (71%) donors had been living in or had visited areas endemic for coccidioidomycosis. One donor was from France, but visited Arizona 2 months before becoming a donor to a single lung transplant recipient (case 6 in Table 1). Three donors had evidence of active infection at procurement of organs, two with dissemination to central nervous system with meningitis (cases 1 and 2 in Table 1) and one with evidence of coccidioidomycosis in a hilar lymph node (case 4 in Table 1).

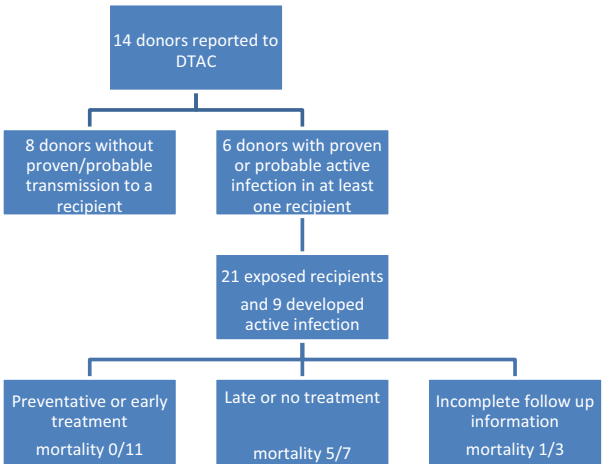

Figure 1: Outcome of recipients exposed to coccidioidomycosis. DTAC, Disease Transmission Advisory Committee.

Discussion

The use of organ donors from areas endemic for coccidioidomycosis may lead to transmission of this fungal pathogen to organ recipients as illustrated in the published literature and the DTAC experience presented here (1–7). Donors may have active infection not recognized at their evaluation for organ donation or may have prior infection with contained but viable organisms that reactivate in the setting of recipient immunosuppression. In one series, seropositivity of potential kidney and liver donors in an endemic area was 2.1% (10). Also, a living donor may be incubating coccidioidomycosis at the time of evaluation with no symptoms and negative serology but later develop symptoms and become seropositive (10). As our report illustrates, for exposed recipients the risk of significant morbidity and mortality is high, and poor outcomes typically occur soon after transplantation, allowing little time for diagnosis and treatment once symptoms occur. Our data suggest, however, that preventative treatment of exposed individuals with antifungal drugs is very effective in preventing disseminated disease and death compared to those exposed recipients who are not treated. Thus, we believe that evidence of coccidioidomycosis infection in one recipient should prompt initiation of treatment in all other recipients preemptively. Similarly, if serologic or other evidence of coccidioidomycosis in the donor becomes available after transplant, we also recommend evaluation of the need for treatment of all recipients of organs from this donor.

Our data do not address the appropriate duration, dose, or drug that should be used as part of preventative therapy. The American Society of Transplantation's Infectious Disease Community of Practice provides some expert opinion regarding these questions (11). The guidelines recommend that recipients of an organ from a donor

Table 1: Published cases of donor-derived coccidioidomycosis and outcome

Case	Donor demog	Donor history and risk	Recip	Recip organ	Recip age/sex	Recip race	Fungal prophylaxis or early treatment	Outcome	Cocci death/outcome	Comment
1 [1]	52F, AfAm	Had been living in Los Angeles, confusion, abnormal CSF, abnormal brain MRI with hydrocephalus, serum CF is 1:4, liver bx at procurement with granulomas	1	Heart	66M	His	No	III day 16, died	Yes, diss multiple organs	Donor at time procurement with cocci meningitis
			2	2nd kidney	40M	AfAm	No	III day 13, died	Yes, diss multiple organs, also kidney abscess	
			3	Kidney-liver, previous living liv	23M	His	No but treated D14 vori, then ampho B, then flu	III day 14, Survived, liver bx granulomas and spherules	Diss to liver, lung, blood, CF at 3 months is 1:64	
2 [2]	36M, AfAm	Presented with headaches, had cocci meningitis, CF was 1:32. Previous treated diss cocci in AZ	1	Liver	46M	W	No, treated D14 flu, then ampho B	III day 13, died	Yes, diss to multiple organs, including liver	Donor in AZ 1995-2000 and diagnosed with disseminated cocci in 1996 to skin and bone
			2	Kidney	28M	AfAm	No, treat D19 flu	III day 11, died	Yes, diss to multiple organs including kidney, pre-Tx CF was negative	
			3	Kidney	58F	AfAm	No but given itra 200 mg bid for 3 mos	Asymptomatic, survived		
3 [3]	22M, AfAm	Immigrated to the US from Jamaica in 2001 to nonendemic area	1	Kidney	19M	AfAm	No but treated D30 vori, then liposomal ampho B, then flu	III day 29, survived	Pos cocci in lung and blood, serology positive at day 59 with CF of 1:4	
			2	Kidney pancreas	45F	W	No, micafung D35	III day 26, died	Yes, diss lung and blood	
			3	Liver	63F	W	Yes flu, and D35 on fluc	Survived	III day 51, developed bil lung nodules, negative serology	
			4	Bil lung	62F	W	Yes, vori	Survived	Day 53 serology CF 1:2	
			5	Heart	18M	AfAm	No, D53 flu	Died	No, sudden cardiac death, CF day 56 negative	
4 [4]	F	Resided in AZ, hilar lymph node was positive for cocci, she liked to hike	1	Bil lung	21M	W	No but treated, D6 flu	III day 6, survived		1-cm firm level 4 hilar lymph node found at organ harvest positive for cocci

Table 1. *Continued*

Case	Donor demog	Donor history and risk	Recip	Recip organ	Recip age/sex	Recip race	Fungal prophylaxis or early treatment	Outcome	Cocci death/outcome	Comment
5 [5]	30	Resident of nonendemic area, visited Mexico 2 years earlier	1	Bil lung	61		No	Ill first week, died	Yes, diss multiple organs	
6 [6]		France resident, visited AZ few months before donation	1	Single lung	58M	France	Yes, itra	Survived	Yes, diss multiple organs, also kidney abscess	
7 [7]	38/F	Not known	1	Kidney	62M	Portugal	No	Died	Diss to liver, lung, blood, CF at 3 months is 1:64	No travel history was obtained on donor and no pretx serology was obtained
			2	2nd kidney		Portugal	No	Survived	Yes, diss to multiple organs, including liver	
			3	Liver		Portugal	No	Survived	Yes, diss to multiple organs including kidney, pre-Tx CF was negative	
			4	Heart		Portugal	No	Survived		

AfAm, African American; ampho B, amphotericin B; Bil, bilateral; bx, biopsy; CF, complement fixation; cocci, coccidioidomycosis; diss, disseminated; Demo, demographics; F, female; Flu, fluconazole; His, Hispanic; Itra, itraconazole; M, male; micafung, micafungin; MRI, magnetic resonance imaging; Pos, positive; Recip, recipient; Tx, transplantation; Vori, voriconazole; W, white.

with pulmonary coccidioidomycosis should receive fluconazole 400 mg daily for 3–12 months if non-lung organ recipient with an option of lifelong therapy at 200 mg daily after the first year. For lung recipients of organs from donors with pulmonary coccidioidomycosis, the recommendation is lifelong fluconazole, 400 mg daily. All recipients of donors with evidence of extrapulmonary coccidioidomycosis should receive lifelong fluconazole 400 mg daily, with careful laboratory, clinical, and radiological follow-up if prophylaxis is discontinued. If a donor is seropositive without a documented focus of infection, the lung recipient should receive 400 mg of fluconazole daily for life, and a non-lung organ recipient 400 mg daily for 12 months and 200 mg thereafter.

An important issue is the potential role of universal or targeted serological donor screening in endemic regions in order to identify donors at risk of transmitting coccidioidomycosis. Information regarding endemicity of coccidioidomycosis was obtained by skin test (12). In the United States, OPTN region 5 (California, Arizona, Nevada, Utah, New Mexico) and Southern Texas is the primary geographic region endemic for coccidioidomycosis. Within this region, parts of Arizona and California are at a particularly high risk (for example, Sonoran desert in Arizona, and San Joaquin valley in California) (13,14). Because of the risk of "imported" cases, clinicians should also be aware of the epidemiology outside the United States (12). Countries with endemic areas include Mexico, Guatemala, Honduras, and other countries in South and Central America (12). The predictably elevated risk for prior infection with coccidioidomycosis within an endemic region suggests that recipients of organs from donors who live in Region 5 might benefit from targeted serologic screening of donors. This recommendation might be extended to potential donors who visited or lived in the past in Region 5 but were not residing there at the time of donation. While clearly cases of donor-derived transmission of coccidioidomycosis have occurred from such donors, the lack of data to differentiate what might be a "high risk" exposure for donors with a history of travel to an endemic region would suggest that screening donors for any transient travel to a high-risk region would not likely be cost-effective nor could it be reliably implemented. Further studies are needed to determine whether all donors in endemic areas (e.g. OPTN region 5) should have routine coccidioidomycosis serology testing. In the absence of such data, it is worth noting that one of the authors of this report who works in an endemic area for coccidioidomycosis uses routine prophylaxis for coccidioidomycosis in all organ recipients for 12 months together with serological screening of all donors and recipients. Seronegative organ recipients are usually rechecked yearly, or if there is a clinical indication. This center is currently using universal prophylaxis because of failure of targeted prophylaxis with diagnosis of new cases of coccidioidomycosis within 1 year after transplantation (15).

The OPTN/DTAC has published guidance regarding testing of potential living donors for seasonal and endemic infections (16). A consideration for coccidioidomycosis screening includes those who reside or stayed in endemic areas, those with symptoms or signs of active infection, and those with a history of coccidioidomycosis (16). Implementation of epidemiologic risk-based screening will not likely eliminate all cases of donor-derived coccidioidomycosis in the United States. It is unrealistic to believe that Organ Procurement Organizations would be able to get a reliable travel history on all potential donors. Additionally, in some reported cases there is no clear residence or travel to endemic areas in or outside the United States. Recently three nontransplant cases of coccidioidomycosis reported from Washington State had no history of residence or travel to an endemic area (17). Soil was sampled and investigated by the Centers for Disease Control and Prevention's Mycotic Disease Laboratory by polymerase chain reaction. *C. immitis/posadasii* was found in 6 of 22 soil samples, and viable fungus was isolated in 4 samples (18). This shows that coccidioidomycosis may be found outside the known endemic areas, although currently the major risk area remains the Southwestern United States.

This study has a number of important limitations. In some cases the information was incomplete; furthermore, the diagnostic methods and treatments varied between treating medical centers. The DTAC reporting system is required but passive, and all cases of donor-derived coccidioidomycosis or donor infection with coccidioidomycosis may not have been reported. Thus, we are not able to reliably assess the risk faced by a recipient of an infected donor, especially one with latent infection. As DTAC reports are collected under confidential peer review, information is reported in aggregate. Thus, no attempt was made to compare our information and the information obtained from review of the literature. We cannot confirm or exclude the possibility of duplication between DTAC records and cases reported in the literature during the same time period. Nevertheless, viewing these confirmed donor-derived cases in the aggregate provides a useful alert for transplant professionals who may not be fully aware of this risk.

In summary, data from the review of the DTAC experience and the literature demonstrate that donor-derived coccidioidomycosis can be life threatening and typically occurs soon after transplantation. Preventative antifungal treatment, however, may be lifesaving if administered to exposed recipients. Efficient communication between OPOs and transplant centers is critical to this process. While our data do not specifically address the value of universal or targeted donor testing in endemic areas (or those with previous residence in endemic areas), the lethality of donor-derived coccidioidomycosis combined with the availability of effective preventative therapy emphasizes the need for a careful evaluation of the potential benefit of such a practice. Clinically appropriate screening and prophylaxis are crucial to prevent coccidioidomycosis in endemic areas where there is potential constant exposure.

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Disclosure

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