

# Donor-Derived *Coccidioides immitis* Endocarditis and Disseminated Infection in the Setting of Solid Organ Transplantation

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**Background.** Endocarditis is a rare manifestation of infection with *Coccidioides*. This is the first reported case of donor-derived *Coccidioides* endocarditis obtained from a heart transplant.

**Methods.** We present a unique case of donor-derived *Coccidioides immitis* endocarditis and disseminated infection in a heart transplant patient. We also conducted a review of the literature to identify other cases of donor-derived coccidioidomycosis in solid organ transplant recipients and reviewed their clinical characteristics.

**Results.** Fifteen prior cases of donor-derived coccidioidomycosis were identified. A majority of these cases were diagnosed by positive culture (83%). Mortality was high at 58%.

**Conclusions.** Clinicians should maintain a high index of suspicion for disseminated coccidioidomycosis in patients who received transplants with organs from donors with a history of residing in endemic regions.

**Keywords.** coccidioidomycosis; donor-derive; endocarditis; solid organ transplant.

The patient was a 52-year-old white female with idiopathic non-ischemic cardiomyopathy for which she underwent orthotopic heart transplant (recipient cytomegalovirus [CMV] immunoglobulin [Ig]G negative, donor CMV IgG positive). Pretransplant workup was notable for computerized tomography (CT) of the chest a few months before transplant that showed scattered ground-glass opacities, up to 4 mm in diameter. She had no perioperative complications, and she received antithy-mocyte globulin as induction immunosuppression. She recovered as expected in the immediate postoperative period. Six weeks after her transplant, she had a routine transthoracic echocardiogram that was notable for a new mobile mass in the left atrium. She complained only of fatigue at the time, and she denied fever or chills; blood cultures were negative for any microbial growth. She was started on anticoagulation for a presumed left atrial thrombus.

The patient's immunosuppressive regimen consisted of tacrolimus 3 mg twice daily (level ranged from 7.5 to 15.7 ng/mL), mycophenolic acid 720 mg twice daily, and prednisone at a

total daily dose of 20 mg. She was taking trimethoprim/sulfa-methoxazole 80 mg/400 mg daily, itraconazole 200 mg in the morning and 100 mg at night (serum level <0.1 mcg/mL), and valganciclovir 900 mg daily for antimicrobial prophylaxis. She was living in the coastal city of Morro Bay, California, but had previously resided in New Mexico for several years.

Ten weeks posttransplant, the patient represented with 2 weeks of progressive left ankle pain and swelling and was admitted to the hospital for further evaluation. She denied any associated fevers, chills, or rash, but complained of few days of severe headache located in occipital area radiating down her neck. The headache was worse with movement without associated photophobia, changes in vision, or focal neurologic complaints.

On admission, the patient was afebrile, hemodynamically stable, and in no acute distress. Her physical examination was notable for stiff neck with mild paraspinal tenderness to palpation. Cardiac exam revealed regular rhythm and no murmurs. The left ankle had an effusion but no erythema or warmth; tenderness to palpation was present, greatest over the lateral malleolus. The ankle joint had good range of motion. Neurological exam was nonfocal, and the remainder of physical exam was within normal limits.

Admission laboratory values were notable for white blood cell count 9.7 kg/ $\mu$ L with a normal differential, hemoglobin 10.0 g/dL, and platelets 297 kg/ $\mu$ L. The patient was hyponatremic with Na 127 mmol/L. Creatinine (Cr) was 1.4 mg/dL, and liver function tests were within normal limits. International normalized ratio (INR) was 8.3. Inflammatory markers were elevated with erythrocyte sedimentation rate 82 mm/hour and C-reactive protein 13.6 mg/dL. The patient underwent aspiration

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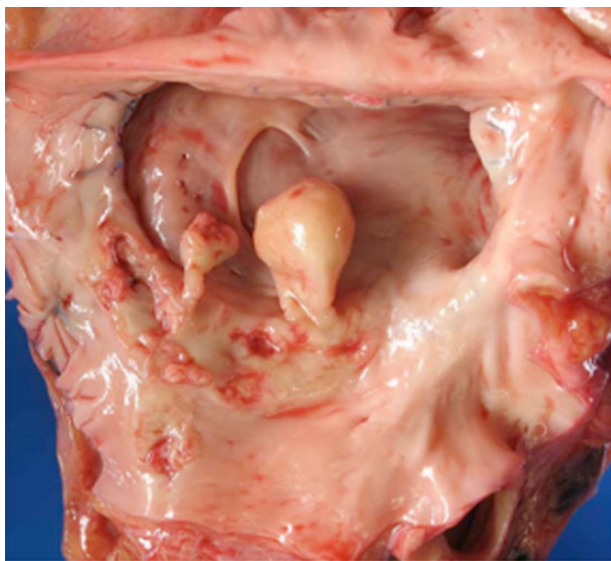
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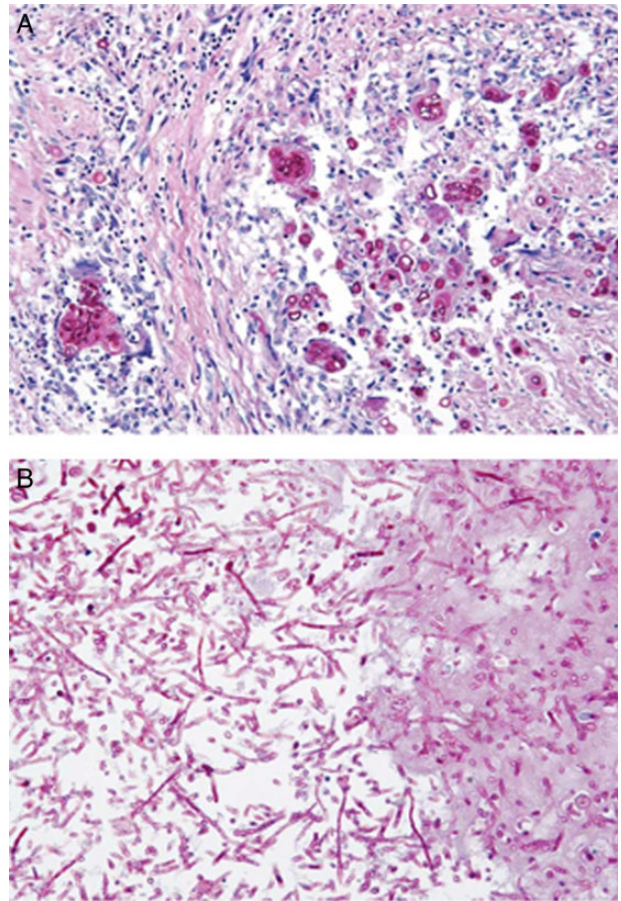
of left ankle, which revealed 256 nucleated cells and 46 000 red blood cells per  $\mu\text{L}$ , and no crystals were seen. Gram stain of synovial fluid was negative; bacterial and fungal cultures showed no growth. Lumbar puncture was not initially performed due to supratherapeutic INR.

Magnetic resonance imaging (MRI) of the brain showed the presence of few nonspecific white matter lesions, which were thought to be secondary to chronic ischemic small vessel disease. Cardiac MRI was done to further evaluate her mobile left atrial mass and showed 2 highly mobile pedunculated masses in the left atrium, measuring 1 cm and 8 mm in diameter. There was also a lobulated pseudoaneurysm in the ascending aorta at the site of anastomosis. She had repeat blood cultures as well as *Bartonella* spp, *Coxiella burnetii*, and *Brucella* spp serologies to evaluate for culture-negative endocarditis, which were all negative. On hospital day 3, a positron emission tomography-CT was also ordered to better assess for underlying infection; however, before the test was performed, the patient had an acute change in mental status and was found unresponsive. A CT angiography of the head and neck revealed a large hemorrhage in the posterior fossa. Despite aggressive treatment, including reversal of anticoagulation and external ventricular drain placement, her condition did not improve and the patient died on hospital day 7.

Post mortem examination revealed a mycotic aortic aneurysm at the anastomotic site with infection extending to the pericardium, right ventricular myocardium, pulmonary artery trunk, and left atrial anastomosis with a 2 cm pedunculated left atrial mycotic thrombus (Figure 1). Histopathology revealed spherules and hyphal elements (arthroconidia) consistent with *Coccidioides* (Figure 2). Autopsy also showed



**Figure 1.** Gross pathologic specimen showing pedunculated mycotic thrombus at the left atrial anastomosis.

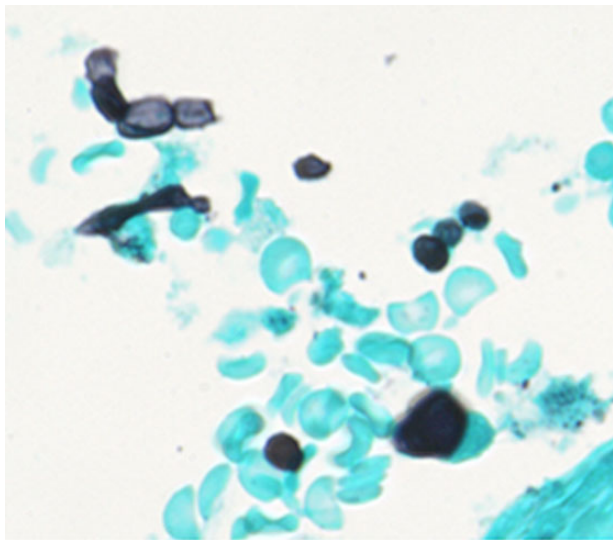


**Figure 2.** (A) Periodic acid-Schiff stain of epicardial tissue showing spherules consistent with *Coccidioides* infection. (B) Periodic acid-Schiff stain of left atrial mycotic thrombus showing fungal hyphal elements.

evidence of disseminated fungal infection involving lungs and brain.

The patient's donor was a 58-year-old female, from Las Vegas, Nevada, with a past medical history of substance use and renal artery aneurysm, and she died of an unexplained subarachnoid hemorrhage. On CT of the chest, she was found to have a  $2.3 \times 3.8 \times 2.8$  cm cavitory lesion in her right upper lung that was biopsied during organ procurement, and pathological examination showed inflammation and fibrosis but no evidence of malignancy and no granulomas. Although the tissue was not cultured and no stains for microorganisms were performed, a bronchoalveolar lavage specimen was negative for bacterial, fungal, or mycobacterial growth. The only other organ procured from this donor was the liver, and the recipient had immediate graft failure and required retransplant.

Post mortem, the patient's pretransplant serum was obtained and testing for *Coccidioides* by immunodiffusion and complement fixation was negative. Further investigation on the donor after our patient's death revealed that the donor serum was positive for *Coccidioides* by immunodiffusion but had a negative complement fixation titer, most consistent with



**Figure 3.** Grocott's methenamine silver stain of donor lung tissue showing arthroconidia.

localized disease. The donor's lung pathology was reviewed and showed arthroconidia in deep tissue block samples consistent with fungal disease, likely coccidioidomycosis in this clinical context (Figure 3). The original pathology review was not performed at our institution so it is difficult to speculate why the diagnosis was not made initially. In retrospect, it is possible that knowing the diagnosis allowed pathologists to locate arthroconidia that were seen deep in the tissue block.

Our patient had expressed desire to be an organ donor herself before her death, and she was taken for organ procurement after she passed away. At the time of surgery, she was noted to have a small amount of purulence deep to the sternum. This was sent for culture and ultimately grew *Coccidioides immitis*. Her kidneys were removed, and initial review of histopathology on frozen section did not reveal evidence of infection. Her 2 kidneys were subsequently transplanted into a single recipient before availability of the results of the culture of the retrosternal specimen. A subsequent review of sections from the donated kidney revealed evidence of spherules consistent with *Coccidioides* infection. With these findings, the recipient transplant center was contacted immediately; the recipient was started on fluconazole 400 mg daily and continues to do well with Cr near baseline 6 months posttransplant.

## DISCUSSION

Coccidioidomycosis is an endemic fungal disease found in the desert regions of southwestern United States, northern Mexico, and parts of Central and South America. In immunocompetent adults, it can be asymptomatic in up to 60% of cases; if symptomatic, it usually manifests with influenza-like symptoms or pneumonia. Less often, it can disseminate to extrapulmonary

sites in approximately 1%–5% of infections, most commonly to the meninges, bone, joints, and skin. Dissemination is more common in those of African or Filipino ancestry, pregnant women, or those who are immunosuppressed [1].

Endocarditis is a rare manifestation of coccidioidomycosis, and to date there have been only 7 other reported cases [2, 3]. To our knowledge, this is the first reported case of *Coccidioides* endocarditis acquired through the cardiac allograft. The involvement of the anastomotic site in particular suggests either fungemia, which allowed the fungus to seed injured endothelium at the anastomosis, or infection derived from the donor organ, which then disseminated widely. On subsequent pathology review of the donor's lung tissue, infectious arthroconidia were seen. Therefore, it is also conceivable that at the time of organ procurement, resection of the lungs might have led to a small amount of organisms contaminating the donated heart and then subsequently infecting the recipient. In either of these scenarios, the donor was the source of the *C immitis* in this recipient.

The incidence of coccidioidomycosis after solid organ transplantation in endemic areas has been reported to be from 3.8% to 8.7% [4, 5]. The highest risk of coccidioidomycosis after solid organ transplant occurs in the first year posttransplant, accounting for as many as 70% of cases in one series [4, 6]. In areas of high endemicity, the risk of symptomatic posttransplant coccidioidomycosis is increased with history of prior infection, positive serology just before transplant, or antirejection therapy [4]. An intact and effective cellular immune response is paramount in controlling *Coccidioides* infection, and thus immunosuppressive agents used to prevent rejection impair the immune response to coccidioidomycosis [5]. As such, dissemination is much more common in transplant patients compared to immunocompetent patients, occurring in up to 75% of cases [7]. Mortality is reported to be from 30% to 63% [5, 7, 8].

Coccidioidomycosis infection after transplant is a result of either de novo acquisition of the infection posttransplant, reactivation of previously acquired infection in the recipient, or infection transmitted through the donor organ. The most common mechanism is reactivation of previously acquired infection [5]. Our patient had lived in New Mexico and had pulmonary nodules on pretransplant chest imaging, making reactivation of previous infection plausible. However, after her death, saved pretransplant serum was tested for *Coccidioides* serology and results were negative. Based on (1) the donor's positive *Coccidioides* serology and residence in an endemic area and (2) arthroconidia found in her cavitory lung lesion, we concluded that this was most likely a donor-derived infection.

Visualization of arthroconidia in the atrial thrombus in this patient as well as in the cavitory lesion of the donor is unusual because *C immitis* has the characteristic thermal dimorphism of endemic fungi, growing as yeast form at body temperature (37°C) and as mold at lower temperatures (25–30°C). Exception to this behavior has been observed in patients with chronic

**Table 1. Previous Reported Cases of Donor-Derived *Coccidioidomycosis***

Author	Donor	Transplanted Organ	Recipient	Manifestation	Timing of Symptom Onset <sup>a</sup>	Diagnosis	Outcome
Wright et al [16]	Incarcerated in AZ, history of extrapulmonary disease	Liver	46-yr-old white male with cryptogenic cirrhosis	Bone marrow, lungs, kidneys, heart, thyroid, pancreas, brain, liver, spleen	13	Blood culture, bronchial wash culture	Deceased
		Kidney	26-yr-old African American male with ESRD	Bone marrow, lungs, kidneys, heart, thyroid, pancreas, brain, testes, liver, spleen	17	Blood culture, bronchial wash culture	Deceased
Miller et al [14]	30-yr-old female who had visited Mexico	Bilateral Lung	61-yr-old male with COPD	Lung	14	Bronchial wash culture	Deceased
Tripathy et al [15]	Female from Arizona	Lung	21-yr-old French male with pulmonary hypertension	Lung	6	Bronchial wash culture	Survived
Blodgett et al [18]	52-yr-old African American woman from Southern California	Heart	66-yr-old Hispanic with ischemic cardiomyopathy	Pericardium, liver, lungs, spleen, pancreas, adrenals	16	Blood cultures, cytology of pericardial fluid	Deceased
		Kidney	40-yr-old African American male with postobstructive glomerulonephritis	Liver, spleen, bone marrow, thyroid, pancreas	13	Blood cultures, sputum cytology	Deceased
		Kidney/Liver	23-yr-old Hispanic male with cryptogenic cirrhosis	Lung, liver, bone marrow, blood	14	Blood cultures, bronchial wash culture, transbronchial biopsy culture, pleural fluid culture	Survived
Dierberg et al [19]	22-yr-old male from Jamaica, living in Maryland, no known travel to endemic area	Kidney	19-yr-old African American Male with FSGS	Lung, blood	29	Blood cultures, bronchial wash culture, transbronchial biopsy culture	Survived
		Kidney/Pancreas	45-yr-old white female with DM and HTN	Lung, blood	26	Blood cultures, bronchial wash culture	Deceased
		Bilateral Lung	62-yr-old white female with COPD	asymptomatic seroconversion	n/a	serology	Survived
Brugiere et al [17]	Male who had visited Arizona months before organ donation	Lung	58-yr-old French male with IPF	Lung	1050	Bronchial wash culture	Survived
Carvahlo et al [20]	38-yr-old female with unknown travel history	Kidney <sup>b</sup>	62-yr-old white male with ESRD	CNS	210	Brain biopsy with spherules on path and PCR	Deceased

Abbreviations: AZ, Arizona; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis; HTN, hypertension; IPF, idiopathic pulmonary fibrosis; PCR, polymerase chain reaction.

<sup>a</sup> Days posttransplant.

<sup>b</sup> Presumed donor derived, not confirmed.

cavitary pulmonary lesions [9, 10], ventricular peritoneal shunt specimens [11, 12], and a previously reported case of *coccidioidomycosis* also presenting as left atrial thrombus endocarditis [13]. It is possible that endothelialization that takes place during formation of vegetations creates the environment of a biofilm that facilitates transition from yeast to mold morphology.

Donor-derived *Coccidioides* infections are rare with only 15 previous reported cases (Table 1) [14–21]. Only 12 cases have clinical data available for review: 4 lung transplants, 1 heart transplant, 1 liver transplant, 1 liver/kidney transplant, 1 kidney/pancreas transplant, and 4 kidney transplants. Three of 9 cases for which race was reported were of the higher risk African

or Filipino ethnicity, possibly contributing to their susceptibility to disseminated infection. Also of note, 5 of 7 donors came from or visited an endemic area. Symptom onset in most cases (9 of 11 of cases with symptoms) was within 1 month after transplant. The 2 cases that presented later than 1 month had recent increase in immunosuppression due to concern for graft rejection. Of these 12 cases, 7 patients (58%) who received organs from infected donors died of *Coccidioides* infection [14–20]. Of the 5 patients who survived, 4 had active disease and 1 had asymptomatic seroconversion. In these reports, another 3 recipients of organs from infected donors never developed signs or symptoms of infection, were started on appropriate

antifungal prophylaxis, and survived [16, 19]. Ten of 12 (83%) cases were diagnosed by positive culture, and 7 of 12 (58%) patients had positive blood cultures. *Coccidioides* fungemia is a rare entity but has been found more commonly in the setting of fulminant, disseminated coccidioidomycosis [22]. The high proportion of transplant recipients with positive culture results suggests that cultures can significantly aid in diagnosing *Coccidioides* infection in this patient population.

Recently published guidelines suggest that live donors from endemic areas be tested for coccidioidomycosis before donating organs and that deceased donors have serology performed if pathology from suspicious lung lesions shows *Coccidioides* on fungal stain [23]. Furthermore, any recipients of organs from deceased donors who are found to have evidence of coccidioidomycosis should (1) have baseline *Coccidioides* serological testing before transplantation if possible and with development of any suspicious clinical symptoms and (2) receive prolonged prophylaxis [23]. However, it is important to realize that serologies can also be falsely negative in this population given their immunosuppression. One study showed that in 27 cases of newly acquired coccidioidomycosis posttransplant in an endemic area, single serologic test was positive in only 21%–56% of patients, depending on the test. Sensitivity improved if multiple assays were performed (77%) and if repeated 1 month later (92%) [24]. The *Coccidioides* skin hypersensitivity test is now available again as an adjunctive diagnostic test; however, given limitations similar to tuberculin skin testing, it is unclear how reliable this test will be in the immunocompromised patient population [25].

Despite the recommendations listed above, a review at a center where *Coccidioides* is endemic showed a relatively low rate of seropositive live organ donor candidates (2.1%). Of these, 4 donors did go onto donate organs (kidney or liver). Recipients received prophylactic fluconazole for range of 1 to 8 months, and none developed coccidioidomycosis [26]. Blair and Mulligan [26] concluded that it is not clear, based on the relatively low rate of seropositivity, whether it can be recommended to perform serology on all donors from endemic areas. However, as is illustrated in our patient, coccidioidomycosis posttransplant can be difficult to diagnose and is associated with high rates of dissemination and mortality. Furthermore, in prior cases of suspected donor transmitted infection as well as in the case of the recipient of our deceased patient's kidneys, when infection is caught early and when antifungal prophylaxis is initiated, outcomes improved.

To be maximally effective, antifungal prophylaxis for recipients from suspected donor cases should be started before clinical symptoms are present. Our patient was on prophylactic itraconazole per our institutional protocol, but her itraconazole serum level when checked was <0.1 mcg/mL and unlikely to be therapeutic. Earlier awareness of a positive donor serology could have appropriately intensified prophylactic antifungal therapy

and monitoring. In general, fluconazole is the recommended agent for prophylaxis, but other azoles also have activity against *Coccidioides* [23]. Based on this case, if concern for donor-derived *Coccidioides* is raised, it is now our policy to monitor itraconazole levels; if therapeutic level is unobtainable, we switch to an alternate agent such as fluconazole. Voriconazole or posaconazole would be substituted if prophylaxis against molds is also needed.

## CONCLUSIONS

This case is especially unique in that it highlights a chain of donor-derived coccidioidomycosis from one donor to organ recipient and then to her subsequent recipient. As is illustrated by this case, organ transplant recipients who die of unexplained causes should not be considered as donors. In addition, it is important to maintain a high index of suspicion for coccidioidomycosis in patients with solid organ transplants who come from, or have donors from, endemic areas. Consideration should be given to perform routine serologic testing on donors from endemic areas, especially for donors with suspicious lung lesions found on imaging. This could direct appropriate prophylaxis in organ recipients, raise awareness of the possibility of disseminated infection, and hopefully prevent further morbidity and mortality from donor-derived coccidioidomycosis. The initiation of effective prophylaxis with good outcome in the recipient of our patient's kidneys later known to be infected with *Coccidioides* highlights the effectiveness of appropriate antifungal prophylaxis in this setting. Further study is needed to assess the usefulness of testing for all donors from endemic areas as well as improve diagnostics in transplant recipients.

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