Allograft-Transmitted *Histoplasma capsulatum* Infection in a Solid Organ Transplant Recipient

Hayden T. Schwenk,1 Phuong Vo,2 Kristin Moffitt,1 Elizabeth Kehoe,3 Elizabeth Blume,3 Tanvi Sharma,1 and Umakanth Khatwa2

Divisions of 1Infectious Diseases 2Respiratory Diseases, and 3Department of Cardiology, Boston Children’s Hospital, Massachusetts

Corresponding Author: Hayden T. Schwenk, MD, Division of Infectious Diseases, Children’s Hospital Boston, 300 Longwood Ave, Boston, MA, 02115. E-mail: Hayden.Schwenk@childrens.harvard.edu.

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*Histoplasma capsulatum* is a dimorphic fungus known to be endemic to the Mississippi and Ohio River valleys of North America. Infection is the result of exposure to the microconidia of the mold phase of the organism, and the degree of exposure and immunocompetency of the host are thought to be important determinants in the severity of consequent illness [1]. In most patients, histoplasmosis manifests as a self-limited respiratory illness with protean complaints that include fever, dry cough, and fatigue. The more severe form of the disease, progressive disseminated histoplasmosis, is far less common and is usually seen in very young, elderly, and immunosuppressed patients. Unfortunately, the diagnosis requires a high level of suspicion and is often delayed. We describe a case of progressive disseminated histoplasmosis in a pediatric orthotopic heart transplant recipient from a nonendemic area whose disease was acquired from the donor allograft and whose diagnosis was delayed because of an incomplete donor history.

CASE REPORT

A 13-year-old girl underwent orthotopic heart transplant in 2010 for left ventricular noncompaction-type cardiomyopathy with progressive left ventricular dilatation, systolic dysfunction, and symptomatic congestive heart failure. Induction immunosuppression included a 5-day course of methylprednisolone and thymoglobulin, followed by maintenance immunosuppression with tacrolimus and mycophenolate mofetil. Peritransplant serologies demonstrated that both the donor and recipient were negative for cytomegalovirus (CMV) IgG and positive for Epstein-Barr virus (EBV) IgG. The patient had lived in New England for most of her life and had a travel history that was notable only for brief trips to California and the United Kingdom. Postoperative infection prophylaxis included sulfamethoxazole-trimethoprim. There were no peritransplant complications, and the patient was discharged to home on postoperative day 15.

The patient did well until approximately 5 weeks posttransplantation, when she presented with nausea, lethargy, tachypnea, and low-grade fever. She was subsequently hospitalized, and a preliminary infectious work-up including complete blood cell count, blood culture, urine culture, and CMV/EBV polymerase chain reactions (PCRs) was remarkable only for low-level EBV viremia (7392 copies/mL). The patient was discharged to home after experiencing an improvement in clinical symptoms and without changes to her immunosuppression. Three days later she developed fevers and worsening dry cough, prompting a second inpatient admission. At that time, the patient’s CBC was notable for mild anemia (hemoglobin 10 g/dL). Additional infectious disease studies sent during the hospitalization, including a respiratory viral direct fluorescent antibody, *Mycoplasma pneumoniae* PCR, *Chlamydia pneumoniae* PCR, pertussis PCR, and adenovirus PCR were negative. Over the next several weeks, the patient’s symptoms waxed and waned, prompting ongoing evaluations in both inpatient and outpatient settings. A course of azithromycin was prescribed for possible atypical pulmonary infection and she was closely monitored by the heart transplant team.

The patient’s symptoms progressively worsened and included recurrent fevers, decreased appetite, significant weight loss, malaise, and new-onset respiratory distress. A
computed tomography scan of the neck, chest, and abdomen was performed, and was notable for small nodules throughout both lungs, most striking in the right lower lung region, with a tree-in-bud appearance, and small mediastinal and perihilar lymph nodes (Figure 1A). In the setting of these radiographic findings and continued symptoms, the patient was readmitted and empirically started on vancomycin, piperacillin-tazobactam, and fluconazole. Her admission chest radiograph was notable for coarse interstitial markings (Figure 1B). The patient’s complete blood count on admission revealed mild anemia (hemoglobin 9.4 g/dL), but was otherwise normal. A broad infectious work-up was initiated and was notable for an elevated serum Aspergillus galactomannan of 1.677 IU (positive ≥0.5), raising the concern for invasive aspergillosis. A flexible bronchoscopy with bronchoalveolar lavage and transbronchial biopsy was performed, and both tissue and lavage specimens revealed abundant yeast-like organisms seen within macrophages and with a morphologic appearance consistent with Histoplasma capsulatum (Figure 1C). Both serum and urine histoplasma antigens sent on admission were found to be highly positive (>39 ng/mL) and a fungal blood culture from admission demonstrated growth of mold, ultimately identified by DNA probe testing as *H capsulatum*.

Intravenous liposomal amphotericin B (3 mg/kg once daily) was initiated, but due to evolving renal insufficiency was changed to oral itraconazole (200 mg three times daily for 3 days, followed by 200 mg twice daily) after approximately 72 hours. The patient’s tacrolimus dose was reduced with initiation of azole therapy, although goal tacrolimus levels were maintained between 5 and 7 ng/mL and no changes were made to her mycophenylate mofetil dosing. The patient exhibited dramatic clinical improvement, and by 3-month follow-up had complete resolution of fever, tachypnea, cough, and had improved weight gain and pulmonary function tests. Serial *H capsulatum* antigen testing over a 1-year period has demonstrated a gradual decline in serum antigen to 0.7 ng/mL with a persistently elevated (>25 ng/mL) urine antigen, despite consistently therapeutic serum itraconazole levels (combined itraconazole and hydroxy-itraconazole levels 2.7–9.9 µg/mL, therapeutic >1 µg/mL). As the patient’s serum antigen has become nearly undetectable and she remains clinically very well, she has been continued on itraconazole with no changes to her maintenance immunosuppression to date.

A thorough exposure history revealed that the patient had never traveled to the Mississippi or Ohio River valleys or any other histoplasma-endemic regions. Pretransplant serum was sent for histoplasma serologies and was negative. Upon review of the donor information, it was discovered that the allograft donor was a teenager who lived in an area known to be highly endemic for histoplasma. The donor had a history of asthma, and the cause of death was diffuse hypoxic brain injury following cardiac arrest thought to be secondary to status asthmaticus versus anaphylaxis. Of note, an admission chest radiograph did not demonstrate pulmonary disease or adenopathy. Donor serum was sent for serologic evidence of prior infection and was found to be positive for the yeast phase of *H capsulatum* with a titer of 1:16 by complement-fixation testing and a positive M-band by immunodiffusion testing. Histopathologic review of the donor lymph node tissue revealed narrow-based, budding, yeast forms morphologically consistent with *H capsulatum* (Figure 1D). Several cardiac tissue biopsies had been obtained in our patient for evaluation of allograft rejection. These biopsy specimens were later reexamined and no evidence of fungal infection was noted. Concern for a potential allograft-associated infection prompted an investigation by our organ procurement organization that revealed no other reported cases of histoplasmosis in the other organ recipients.

**DISCUSSION**

Despite being the most common endemic fungal infection among transplant recipients, histoplasmosis in this
population remains relatively rare, with reported incidence rates of approximately 0.5% [2]. A recent review of histoplasmosis cases in solid organ transplant recipients in an endemic area found the incidence of post-transplant disease to be 1 case per 1000 person-years [3]. An earlier report that looked at the incidence among both allogeneic bone marrow and solid organ transplant recipients in a hyperendemic area documented no cases of histoplasmosis among 596 patients transplanted during a 3-year period [4]. Rates of disease are variable, however, with a recent clustering of cases at another transplant center during a 2.5-year period resulting in an incidence of 1.9% [5].

The diagnosis of histoplasmosis is challenging and can be delayed in solid organ transplant recipients due to misleading laboratory data. Specifically, clinicians should be aware of the association between histoplasmosis and false-positive Aspergillus galactomannan results, as has been described in several reports [6, 7]. As in our case, patients with histoplasmosis, particularly those with high Histoplasma antigen levels (>39 ng/mL), may have false-positive reactions for Aspergillus galactomannan, leading to confusion regarding the actual underlying diagnosis. Particularly in immunocompromised patients from an endemic area, histoplasmosis should be excluded in those with a positive Aspergillus galactomannan.

The potential routes of H capsulatum acquisition in solid organ transplant recipients include new infection, reactivation of prior infection, and allograft-derived transmission. Recent literature suggests that among those solid organ transplant recipients living in endemic areas, the most likely mode of infection is through new exposure rather than reactivation [4]. Even less commonly reported is H capsulatum transmission via an infected allograft from a patient with unrecognized histoplasmosis. A review of the literature reveals only 5 such reported cases, all in adult renal or liver transplant recipients [8–10]. Given the organism’s usual route of spread through the reticuloendothelial system, it is not surprising that while posttransplant histoplasmosis has been described in liver and renal transplant recipients, there are far fewer reports of disease following heart transplantation, and allograft-derived infection has not been implicated in any of these cases [11–13]. To our knowledge, this is the first case of allograft-derived histoplasmosis infection in a pediatric patient or heart transplant recipient.

The first report of transplant-associated histoplasmosis was published in 1965 and described a renal transplant recipient whose donor who was subsequently diagnosed with disseminated histoplasmosis at postmortem examination. Two case reports from Asia also documented probable transmission of histoplasmosis via cadaveric renal transplantation, largely based on the lack of epidemiologic risk factors in the organ recipient, and in one case the finding of yeast cells on histopathologic examination of the nontransplanted donor kidney. More recently, a case of disseminated histoplasmosis was described in a liver transplant recipient from France who had no known exposures to endemic areas [8, 9]. The most well-substantiated case of allograft-related infection involved two geographically separate renal transplant recipients whose donor was known to be from a highly endemic area of the United States [10]. Molecular typing by random amplified polymorphic DNA-polymerase chain reaction confirmed that the H capsulatum recovered from each transplant recipient was genetically identical. Additionally, pretransplant serologies revealed no prior evidence of histoplasmosis infection in either recipient, while the donor had a low positive titer (1:16) to the yeast phase of H capsulatum by complement-fixation testing.

This case highlights the importance of a complete donor history when evaluating the febrile solid organ transplant recipient. Assessment of recipient exposures alone may be insufficient, and demographic characteristics of the donor along with donor serology and tissue testing for potential infectious causes can aid in establishing a diagnosis. While donor confidentiality must be respected, as organs come from increasingly disparate regions of the country, it will become important for clinicians to be aware of the unique demographic and environmental circumstances of individual donors. Although there are no uniform guidelines for the screening of endemic mycoses, a recent guidance document from the American Society of Transplantation suggests that H capsulatum screening should be considered in donors from endemic areas [14]. This recommendation is mirrored in a recently published comprehensive review of donor-derived infections that suggested donors and recipients from endemic areas have serologic testing if there is a history of pulmonary disease within the past 2 years or radiographic evidence of possible active or prior histoplasma infection [13]. Had the geographic details or serologic status of the organ donor been known at the time of transplant, consideration of diagnostic evaluation and/or possible antifungal prophylaxis may have occurred sooner and obviated the need for repeated hospitalizations and unnecessary diagnostic evaluations. This case illustrates the need for consideration of routine H capsulatum serologic testing as part of the donor screening process for individuals from an endemic area.

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