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Invasive aspergillosis among heart transplant recipients is rare but causes rapid death due to septic shock and multiple organ dysfunction syndrome

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Abstract

Between 2000 and 2011, proven or probable invasive aspergillosis (IA) was diagnosed in 1.7% (8/455) of heart transplant (HTx) recipients at our center, in the absence of antifungal prophylaxis. All patients had invasive pulmonary infections and 75% (6/8) were diagnosed during 2 separate 3-month periods. Cases were notable for their association with septic shock and multiple organ dysfunction syndrome (MODS) (75%, 6/8 each), non-specific clinical and radiographic findings, and rapid mortality despite mould-active antifungal therapy (88%, 7/8; occurring at a median 11 days after diagnosis). All patients had predisposing conditions known to be risk factors for IA. For patients with early IA (within 90 days of HTx), conditions included hemodialysis, thoracic re-operation, and the presence of another case in the institution within the preceding 3 months. For late-onset IA, conditions included hemodialysis and receipt of augmented immunosuppression. Clinicians should suspect IA in HTx recipients with risk factors who present with non-specific and unexplained respiratory syndromes, including those in septic shock and MODS, and institute prompt antifungal therapy without waiting for the results of cultures or other diagnostic tests.

Keywords

Aspergillosis; septic shock; heart transplant

Introduction

Invasive aspergillosis (IA) affects up to 14% of heart transplant (HTx) recipients [1]. Nevertheless, IA is less well described following HTx than other solid-organ transplants (SOT) and risk factors are poorly defined [2]. With mould-active azoles as alternatives to amphotericin B and improved diagnostic tests [3–5], mortality rates for patients with IA in general have decreased [6]. Antifungal prophylaxis in many SOT populations has delayed

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

the onset of IA [6,7], which has also contributed to improved survival [6]. Reported mortality rates among HTx recipients range from 0% to 67% [1,2,7–9] and it is unclear if outcomes have improved. Moreover, the role of antifungal prophylaxis remains controversial [1,2,7,10]. The objective of this study was to describe the epidemiology, clinical manifestations, and outcomes of IA among HTx recipients during the era of an expanded antifungal armamentarium at a center that did not employ antifungal prophylaxis.

Methods

We reviewed all HTx recipients from January 2000 to February 2011 at the University of Pittsburgh Medical Center (UPMC) who survived ≥ 7 days post-transplant. Selective induction therapy with anti-thymocyte globulin or an interleukin 2-receptor antagonist (basiliximab or daclizumab) was given at clinician discretion from 2000 to 2006. Standard maintenance immunosuppression consisted of tacrolimus, mycophenolate mofetil (MMF), and corticosteroids [11]. Beginning in October 2006, all patients received induction therapy with alemtuzumab and steroid-free maintenance with tacrolimus and MMF.

Only cases of proven or probable IA were included, as defined by modified EORTC/MSG criteria [12]. IA was defined as occurring in temporally-related groupings if diagnosed within 3 months of another case at our center. Early-onset IA was diagnosed at ≤ 90 days from HTx, and late-onset IA at > 90 days from HTx. Patients with septic shock and multiple organ dysfunction syndrome (MODS) were classified according to consensus recommendations [13]. The study protocol was reviewed and approved by the Institutional Review Board at the University of Pittsburgh.

Results

Four hundred and fifty-five consecutive HTx patients were evaluated. *Aspergillus* species were isolated from respiratory cultures in 9 patients, including 8 with proven or probable IA and 1 with colonization. Overall, IA was diagnosed in 1.7% (8/455) of HTx recipients (incidence 0.4 cases per 100 patient-y). All patients with IA were diagnosed with invasive pulmonary aspergillosis (IPA). One patient each had concomitant IPA and sinus aspergillosis and disseminated aspergillosis. Only 1 patient was colonized with *Aspergillus fumigatus* prior to developing IPA. Seventy-five percent (6/8) of IPA was caused by *A. fumigatus*; *Aspergillus terreus* and *Aspergillus versicolor* caused disease in 1 patient each (Table I). Two distinct groupings of 3 cases each were identified (Figure 1).

Patient demographics were representative of our HTx population. The median age was 56 y (range 44–67 y) and 50% (4/8) were men. Seventy-five percent (6/8) of patients were smokers pre-transplant and 38% (3/8) had diabetes mellitus. Underlying heart diseases included dilated myopathy ($n = 6$), congenital heart disease ($n = 1$), and hypertrophic cardiomyopathy ($n = 1$). Sixty-two percent (5/8) of patients developed early-onset IPA (median time to diagnosis 15 days post-HTx (range 9–33)). The median time to late-onset IPA was 1145 days (range 129–2803). All 5 patients with early-onset IPA were diagnosed during their HTx hospitalizations. One patient with late-onset IPA was diagnosed 1 month into hospital re-admission; the other 2 cases of late-onset IPA occurred in outpatients who had hospital visits within the preceding 3 months. All patients who developed IPA required hemodialysis following HTx; 87% (7/8) remained on hemodialysis at the time of diagnosis. Other clinical factors varied by time of onset. All patients with early-onset IPA required post-transplant intubation for > 7 days and a second thoracic operation prior to diagnosis; 80% (4/5) received induction immunosuppression. All patients with late-onset disease received high-dose steroids within the previous 30 days; however, none received leukolytic immunosuppression (Table I).

All patients presented with evidence of respiratory tract infections, such as fever, shortness of breath, increased sputum production, and cough. Furthermore, 80% (4/5) of patients with early-onset IPA and 67% (2/3) of patients with late-onset IPA had septic shock and MODS requiring vasopressor support at the time of diagnosis (Table I). One patient had sepsis due to *Pseudomonas aeruginosa* bacteremia 5 days prior to IA diagnosis (patient 5, Table I). *Aspergillus* was the sole organism recovered from the bronchoalveolar lavage (BAL) or sputum of all patients with MODS, except 1 patient in whom *Mycobacterium avium* intracellulare (MAI) was also identified. This patient had a serum galactomannan index of 19.8 and *A. fumigatus* in her peritoneal fluid; as such, her clinical syndrome was attributed to IA, and MAI was believed to be a colonizer. Three patients with MODS also had primary graft dysfunction requiring extracorporeal membrane oxygenation. The etiology of MODS in the remaining 2 patients was attributed to IA.

All patients had leukocytosis, with white blood cell counts as high as $69.8 \times 10^9/l$ (median $34.6 \times 10^9/l$). Computed tomography (CT) imaging revealed consolidation or dense infiltrates (87%, 7/8), nodules (25%, 2/8), patchy or tree-in-bud infiltrates (25%, 2/8), and/or cavitation (12%, 1/8). Antifungal therapy was not initiated prior to the diagnosis, which was made a median 2.5 days (range 2–6) after the respiratory cultures growing *Aspergillus* sp were obtained (Table I). Serum galactomannan was markedly elevated in the 3 cases in which it was assessed.

Therapy consisted of 2- or 3-drug combinations of voriconazole, amphotericin B lipid complex, and caspofungin (62%, 5/8), or monotherapy with a mould-active azole (voriconazole or itraconazole; 37%, 3/8). Eighty-eight percent (7/8) of patients with IPA died within 90 days, including everyone with early-onset IPA and everyone with septic shock and MODS. In each case, death was attributable to IPA (median time to death 11 days (range 4–90)). The lone survivor received 180 days of itraconazole for late-onset IPA.

Discussion

This study is notable for 3 important findings. First, IA was rare in our HTx program, even in the absence of antifungal prophylaxis. Second, disease manifested exclusively as IPA, which was remarkable for its severity. Regardless of the time of onset post-transplant, a high percentage of patients were in septic shock and had MODS, and died rapidly due to IPA despite receiving appropriate antifungal therapy. Third, conditions previously shown to be risk factors for IA were identified, which may be useful for improving disease recognition and devising targeted prophylaxis strategies.

Our 1.7% rate of IA was at the low end of the 1–14% range reported for HTx recipients [1,2,7–10,14], and it was less than that of several programs that have employed universal antifungal prophylaxis [2,7]. Moreover, only 1 of our HTx recipients was colonized with an *Aspergillus* species in the absence of IA, which was less common than at other centers reporting such data [7,15]. The reasons for infrequent colonization or disease among our patients are unclear, but the data are particularly striking since induction immunosuppression was widely used. Rates of IA are reported to have decreased following HTx with the evolution of immunosuppressive regimens and improvements in preventing and treating events like rejection and cytomegalovirus infections that are associated with increased risk [7,16,17]. Most of our patients were transplanted after the completion of previous large studies of IA among HTx recipients [2,7–9], and our lower rates may reflect ongoing advances in post-transplant management in general.

Our mortality rate of 88%, despite appropriate antifungal treatment, exceeded earlier reports of HTx recipients. Our poor outcomes are likely multifactorial [18]. First, most cases of IA

developed within 3 months of HTx [10], which corresponds to the peak time of immunosuppression. Second, 75% of our patients had MODS and septic shock. It is difficult to conclusively determine the relationships between IA and septic shock or MODS [19]. We ascribed MODS to primary graft dysfunction ($n = 3$), IA ($n = 2$), or *P. aeruginosa* sepsis ($n = 1$). On the one hand, MODS is believed to predispose patients to IA and other opportunistic infections by inducing an initial inflammatory stage that results in a state of relative immunoparalysis [19]. At the same time, IA has been reported to cause sepsis and MODS in rare instances [14]. Lastly, IA was not suspected and antifungal therapy not initiated until culture results became positive after 2–6 days. Prompt antifungal therapy is the most important determinant of successful treatment of IA [1], so even short delays can have deleterious consequences. Respiratory cultures for *Aspergillus* have high positive predictive value for IPA following HTx [15], but they are limited by both turn-around time and poor sensitivity [4,19]. Emerging data suggest that non-culture-based diagnostics like galactomannan detection or DNA amplification by polymerase chain reaction may facilitate diagnosis, particularly when performed on BAL fluid [20]. These modalities have not been extensively studied in HTx recipients, but it is notable that serum galactomannan was strongly positive in the 3 cases in which it was tested.

Empiric antifungal therapy was not initiated in our patients prior to the diagnosis of IA, which speaks to the rarity of the disease and its non-specific clinical presentations and CT findings. Although earlier studies of IPA among HTx recipients have described classic CT findings such as nodules or cavities [7], more recent experience in other immunosuppressed populations has found these lesions to be less common [21]. Early disease recognition depends upon identifying patients who are most at risk. Previous studies have identified post-transplant hemodialysis, re-operation, CMV disease, and the presence of another case of IA in the program within 3 months as major risk factors for early-onset IA [2]. As a result, antifungal prophylaxis has been recommended in these settings [1]. Due to the low incidence of IA in our program, targeted antifungal prophylaxis was not routinely recommended prior to May 2011. However, as a result of the high mortality identified in this review we now advocate targeted antifungal prophylaxis among our high-risk patients. Furthermore, in the setting of appropriate risk factors and the absence of alternative diagnoses, clinicians should consider IA in patients with non-specific respiratory symptoms and CT findings, including those in septic shock and MODS. Empiric antifungal therapy should be started without waiting for results of cultures or non-culture diagnostics.

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Figure 1.

The timing of newly diagnosed cases of invasive aspergillosis among heart transplant recipients at our center. The gray bars are cases that occurred within 90 days from the day of heart transplantation (early-onset) and the black bars are cases that occurred after 90 days post-transplant (late-onset).

Table 1

Patient demographics and characteristics of invasive aspergillosis.

Subject	Age/ sex	HTx	Known risk factors for IA					Onset (days from HTx to IA)	Disease type/ classification	Aspergillus species/site of isolation	Clinical presentation	Contributory factors for shock	Radiographic changes	Antifungal therapy	Outcome (days from diagnosis)
			Thoracic re- operation	Dialysis	CMV	Another case within 3 months	Induction agent ^a								
1	47/M	2011	No	No	Yes	Yes	Alemtuzumab	Early (9)	IPA and sinus disease/probable	A. fumigatus/BAL ^b	Septic shock	Primary graft dysfunction and MODS	Bibasilar consolidation and left lower lobe collapse	Caspofungin + ABLC	Death (11)
2	54/M	2010	Yes	No	Yes	No	Alemtuzumab	Early (11)	IPA/proven	A. fumigatus/BAL	Septic shock	Primary graft dysfunction and MODS	Extensive bilateral consolidations	Caspofungin + voriconazole + inhaled amphotericin B	Death (10)
3	56/M	2000	No	Yes	Yes	No	None	Early (15)	IPA/probable	A. terreus/sputum	Dyspnea, leukocytosis	NA	Moderate bibasilar consolidations	Itraconazole ^c	Death (90)
4	44/M	2006	No	No	No	Yes	Thymoglobulin	Early (16)	IPA/probable	A. fumigatus/BAL	Septic shock	Primary graft dysfunction and MODS	Bilateral consolidations	Caspofungin + voriconazole ^c	Death (9)
5	67/F	2006	No	Yes	Yes	Yes	Thymoglobulin	Early (33)	IPA/probable	A. fumigatus/BAL	Septic shock	Pseudomonas sepsis and MODS	Patchy airspace opacities and panlobar consolidations including areas of nodularity	Caspofungin + voriconazole ^c	Death (20)
6	59/F	2004	Yes	Yes	No	No	None	Late (129)	IPA/proven	A. fumigatus/BAL ^d	Increased sputum, cough, fever	NA	5.8 × 3.8 cm airspace consolidation, multiple nodules and tree-in-bud opacities	Itraconazole ^a	Survival
7	62/F	2003	No	No	No	No	Thymoglobulin	Late (1145)	IPA/probable	A. versicolor/ sputum	Septic shock	MODS due to IA	Septic emboli with cavitary lesions, bilateral parapneumonic effusions	Voriconazole	Death (21)
8	55/F	2003	Yes	No	No	Yes	None	Late (2803)	IPA, meningitis, septic emboli in spleen/proven	A. fumigatus/BAL ^e	Septic shock	MODS due to IA	Dense bilateral lower lobe infiltrates	Caspofungin + voriconazole + ABLC	Death (4)

ABLC, amphotericin B lipid complex; BAL, bronchoalveolar lavage; CMV, cytomegalovirus; F, female; HTx, heart transplant; IA, invasive aspergillosis; IPA, invasive pulmonary aspergillosis; M, male; MODS, multiple organ dysfunction syndrome; NA, not applicable.

^aWithin the 6 months preceding IA diagnosis. All patients received intravenous methylprednisone at the time of transplant.

^bSerum galactomannan index of 20.9.

^cABLC added prior to death.

^dBAL from this patient grew both A. fumigatus and Dactylaria gallopava. She also had a serum galactomannan index of 29.

^eBAL from this patient grew both A. fumigatus and Mycobacterium avium intracellulare, although her peritoneal fluid only grew A. fumigatus. She had a serum galactomannan of 19.8 and was previously colonized with A. fumigatus (disease triggered by high-dose steroids).