

SHORT COMMUNICATION

Outbreak of invasive aspergillosis in heart transplant recipients: The role of screening computed tomography scans in asymptomatic patients and universal antifungal prophylaxis

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Abstract

Background: Delays in diagnosing pulmonary invasive aspergillosis (IA), a significant cause of morbidity and mortality among heart transplant recipients (HTRs), may impact on successful treatment. The appropriate screening strategy for IA in these patients remains undefined, particularly in the setting of nosocomial outbreaks. We describe our experience employing chest computed tomography (CT) scans as a screening method for IA. In addition, we comment on antimicrobial prophylaxis in HTRs in the setting of an outbreak.

Methods: Screening CT scans of the chest and serum galactomannan (GM) were performed in HTRs during an outbreak that followed the index case of IA. Abnormal CT findings prompted a diagnostic workup. Antimicrobial prophylaxis for new transplant recipients included intravenous micafungin while hospitalized, followed by outpatient inhaled amphotericin B for up to 3 months.

Results: During a 10-month period, five cases of IA were identified among HTRs. Two additional asymptomatic patients were diagnosed with IA among 15 asymptomatic HTRs who underwent screening chest CT scans. Among the five cases of IA in HTRs, two of five (40%) had a partial response and the other three failed voriconazole therapy. Complete response to voriconazole therapy assessed at 12 weeks was achieved in these two asymptomatic HTRs diagnosed via screening CTs. Serum GM was positive only in one of the symptomatic cases. The negative predictive value of CT scans was 100% (95% confidence interval, 71.5%-100%).

Conclusions: In an outbreak setting, screening CT scans of the chest may aid in early detection of asymptomatic HTRs with IA and improve outcome.

KEYWORDS

heart transplant, imaging, invasive aspergillosis, outbreak, screening

1 | INTRODUCTION

Pulmonary invasive aspergillosis (IA) remains a significant cause of morbidity and mortality in solid organ transplantation (SOT). IA has been reported in 1.6%-14% of heart transplant recipients (HTRs), with

most the cases occurring within the first 3 months post transplant.¹ Nosocomially acquired IA has been noted in setting of outbreaks, and has been linked to construction work within the hospital settings or surroundings. Delay in establishing an early diagnosis remains a major impediment to the successful treatment of IA. Data in hematological

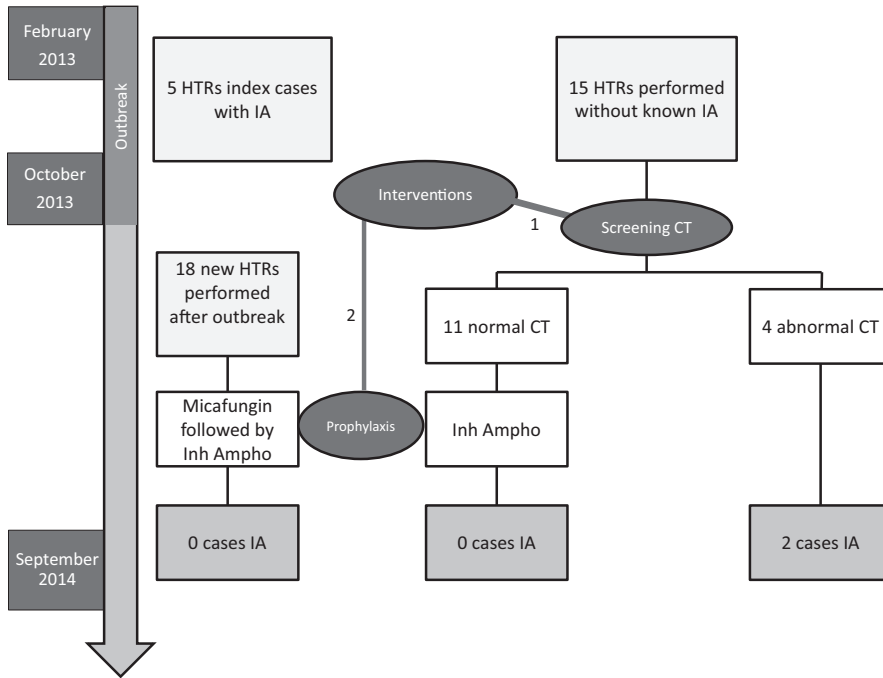


FIGURE 1 From February to October 2013, five heart transplant recipients (HTRs) were diagnosed with invasive aspergillosis (IA). An outbreak was declared and two interventions were undertaken simultaneously. In HTRs transplanted between February and October of 2013, serum galactomannan (GM) and screening chest computed tomography (CT) scans were performed, and if the CT scan of the chest was normal, they were started on inhaled amphotericin (Inh Ampho) for 3 months. From October 2013 onward, all new HTRs were started on micafungin 50 mg intravenously daily while the patients were hospitalized, followed by inhaled amphotericin 20 mg twice a day for 3 months. 1: Screening CT, 2: Antifungal prophylaxis

malignancies suggest that computed tomography (CT) scans of the chest may detect the diseases earlier than serum galactomannan (GM).² However, the appropriate screening strategy for IA in the setting of an outbreak in HTRs remains undefined.

From February to October 2013, an unusually high number of IA cases were noted in HTRs at our institution. The present retrospective report describes our experience utilizing CT scans of the chest, as an early detection screening method for IA in asymptomatic HTRs in the setting of an institutional outbreak. In addition, we describe the

antimicrobial prophylaxis undertaken and the outcomes at the end of prophylactic period.

2 | METHODS

This retrospective cohort study evaluated all consecutive HTRs between January 2013 and September 2014. Institutional ethics approval was obtained. As a part of the outbreak investigation,

TABLE 1 Clinical characteristics and outcomes of invasive aspergillosis cases among the outbreak in heart transplant recipients

Age, years/ gender	Days from transplant	HF etiology	Bridge-to-transplant LVAD	Status at transplant	Diagnostic vs screening CT	Symptoms
43M	7	Congenital	No	Home	Diagnostic	Respiratory failure requiring intubation
51M	79	Idiopathic	No	ICU on inotropes	Diagnostic	Cough, dyspnea and chest pain
58M	88	Idiopathic	No	Home	Diagnostic	Cough, dyspnea and chest pain
53F	70	Myocarditis	No	Home	Diagnostic	Cough, dyspnea, chest pain and fever
60M	87	Ischemic	Yes	Home	Diagnostic	Cough and fever
57M	67	Ischemic	No	Home	Screening	No
63M	100	Idiopathic	Yes	Home	Screening	No

^aDeath caused by intracranial hemorrhage related to treatment-induced thrombocytopenia.

M, male; HF, heart failure; LVAD, left ventricular assist device; CT, computerized tomography; BAL, bronchoalveolar lavage; GM, galactomannan; FNA, fine-needle aspiration; ICU, intensive care unit; IA, invasive aspergillosis; F, female; PCR, polymerase chain reaction.

environmental sampling of air in several locations and equipment was conducted by the Infection Prevention and Control Team at our institution. The antimicrobial prophylaxis implemented during the outbreak following heart transplantation for all new HTRs from October 2013 onward was micafungin 50 mg intravenously daily while the patients were hospitalized, followed by inhaled amphotericin (AmB) 20 mg twice a day for 3 months. For recipients transplanted between February and October of 2013, serum GM and screening chest CT scans were performed; and if the CT scan of the chest was normal, they were started on inhaled AmB for 3 months. Abnormal CT findings prompted a diagnostic workup including bronchoscopy with cultures and GM, and/or biopsy. In addition, a follow-up chest CT scan was performed on patients who did not tolerate prophylaxis.

IA was defined according to clinical and radiological criteria established by the European Organization for Research and Treatment of Cancer (EORTC)/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG) and the International Society for Heart and Lung Transplantation (ISHLT) Infectious Diseases Council Working Group Definitions criteria for invasive fungal pneumonia.^{3,4} Response to treatment was characterized by the MSG and the EORTC Consensus Criteria.⁵ The proportions of IA cases identified by chest CT among screened individuals were accounted.

3 | RESULTS

Thirty-eight heart transplantations were performed during the study period (Figure 1). Mean age at transplant was 54 ± 13 years and

79.5% were male. Approximately half of them were bridged to transplant with mechanical circulatory support devices. All cases received low-dose induction therapy with anti-thymocyte globulin (<3 mg/kg/total dose) and subsequent triple therapy immunosuppression with prednisone, tacrolimus, and mycophenolate mofetil. For the 10-month period (February–October 2013), five cases of proven/probable IA were identified among HRTs (median time from transplant to diagnosis was 79 days). Of those, three of five HTRs with IA died (Table 1).

A total of 15 recipients underwent screening chest CT scans (Figure 1). During the screening period, a median of two scans per patient were performed. The median time from transplantation to initial chest CT was 164 days (IQR 115–216), 292 days (IQR 248–335) for second CT, and 366 days (IQR 348–388) for third CT. Four (27%) HTRs had abnormal initial CT scans, two of which were diagnosed with IA (Figure 2A and B). Both IA cases had the diagnosis of IA established after imaging screening although they were asymptomatic. The other two HTRs with abnormal CT chest were diagnosed with post-transplant lymphoproliferative disease and coronavirus lower respiratory tract infection respectively. The two asymptomatic cases of IA that were identified by screening had complete response to therapy at 12 weeks of treatment with voriconazole compared to partial or failure of therapy in the five index cases (Table 1). Serum GM was performed on 30 HTRs; it was positive only in one of five symptomatic cases. Bronchoalveolar lavage GM was performed in five of the symptomatic HTRs with IA and was positive in four patients. Of a total of 28 who received inhaled AmB, 53% had to discontinue treatment before the end of 3 months because of side effects. None of the HTRs who had normal CTs and subsequently received prophylaxis developed IA. No additional cases of IA were

CT findings	Method of diagnosis	<i>Aspergillus</i> culture	BAL GM	Treatment	Outcome at 12 weeks
Dense bilateral consolidation	BAL GM	Negative	Positive 1.98	Voriconazole	Treatment failure and non-IA-related death ^a
Left lower lobe consolidation and middle lobe nodule with pleural effusion	BAL GM + sputum culture	<i>Aspergillus terreus</i>	Positive 3.85	Voriconazole and micafungin	Treatment failure and IA-related death
Bilateral nodules, masses and consolidations	BAL GM + BAL culture	<i>Aspergillus fumigatus</i>	Positive 1	Voriconazole followed by posaconazole	Partial response
Mass-like opacity in lower lobe with surrounding ground glass and numerous scattered parenchymal small nodules	BAL GM + CT-guided biopsy (mucormycosis identified by PCR from lung biopsy)	Negative	Positive 1.6	Voriconazole and amphoterecin	Treatment failure and IA and mucormycosis related death
Mass-like opacity in the superior segment of the right lower lobe	FNA and BAL culture	<i>Aspergillus fumigatus</i>	Negative	Voriconazole	Partial response
Multiple bilateral hazy nodules	CT-guided biopsy	<i>Aspergillus nidulans</i>	Not done	Voriconazole	Complete response
Left upper lobe nodule	CT-guided biopsy	<i>Aspergillus fumigatus</i>	Not done	Voriconazole	Complete response

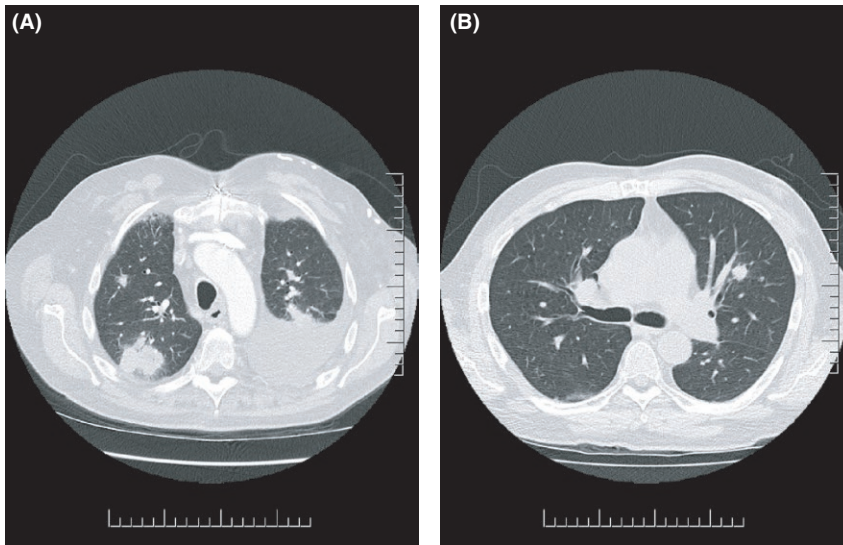


FIGURE 2 (A and B) Computed tomography scan findings in two heart transplant recipients diagnosed with invasive aspergillosis: (A) Multiple bilateral hazy nodules and left-sided pleural effusion, and (B) left upper lobe nodule

identified since the screening and prophylactic measures were instituted (Figure 1).

Air and environmental sampling investigations of potential common pre- and post-admission exposure links during this outbreak failed to reveal a common environmental source of infection, although it was thought that the construction around the hospital might have played a role.

4 | DISCUSSION

Our study underscores the high mortality rate (43%, 3/7) associated with IA in HTRs in an outbreak setting. Munoz et al¹ described a similarly adverse outcome, with two deaths of three patients affected during an outbreak of IA in a major heart surgery unit. In addition, similar to other SOT studies,¹ the sensitivity of serum GM in detecting cases of IA was poor; only one HTR with IA had a positive serum GM. Hence, we could not rely on the latter as a screening tool, and performed low radiation dose CT scans of the chest on asymptomatic HTRs. This helped to identify two asymptomatic HTRs with IA, who achieved complete response to therapy at 12 weeks, as compared to partial response or failure to therapy in the rest of cohort, including three deaths. Although this screening strategy might be costly and expose patient to increased radiation, it helped identify asymptomatic HTRs early in the course of disease. The concept of early diagnosis and improved outcomes has been shown in patients with hematological malignancy and invasive fungal infection.^{2,6} This strategy also helped in following patients who did not tolerate prophylaxis because of side effects, and ensuring that these HTRs did not develop IA.

Our study possesses several limitations. Despite our limited single-center, retrospective, small cohort, and the absence of a control group, we have shown that, in an outbreak setting, early diagnosis of IA by CT scanning of the chest may be an effective screening strategy in HTRs and improve outcomes. The negative predictive

value of CT scans in diagnosis IA was 100%; 95% confidence interval (71.5%-100%). Based on our experience during an outbreak of aspergillosis, we propose a combination of screening thoracic CT scans on patients transplanted during the same period as the index cases, in addition to universal prophylaxis on all new HTRs. However, since this study represents the experience of a single center in the context of an outbreak, larger studies will be needed before our strategy can be recommended for generalization.

5 | CONCLUSIONS

The best screening and prophylaxis strategies in the setting of an outbreak of IA in HTRs remain unclear. CT scans of the chest as a screening procedure prior to the institution of antifungal prophylaxis may aid in the early detection of IA, which is associated with better outcomes.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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