Case Report

Early-onset *de novo* invasive pulmonary aspergillosis in an orthotopic heart transplant recipient

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ABSTRACT

Invasive aspergillosis generally occurs during the first 1–6 months after heart transplantation. It has been rarely seen in the first 2 weeks postcardiac transplant. We herein describe a unique case of invasive pulmonary aspergillosis (IPA) diagnosed on day 9 postorthotopic heart transplantation. The known risk factors for IPA in cardiac transplant recipients were not identified in our case. The organ recipients from the same donor did not report *Aspergillus* infection. Hospital environmental samplings failed to demonstrate *Aspergillus* spores in the patient's room and his adjacent rooms. A diagnosis of early-onset *de novo* IPA was made. The patient initially received combined antifungal therapy (voriconazole plus micafungin), followed by voriconazole maintenance monotherapy with favorable clinical outcome.

KEY WORDS: *Aspergillus* infection, early-onset invasive pulmonary aspergillosis, *de novo* invasive aspergillosis, heart transplantation, solid organ transplantation

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INTRODUCTION

Invasive aspergillosis (IA) is the second most common invasive fungal infection in solid organ transplant recipients with the exception of lung transplantation where IA is the most common invasive mold infection.[1,2] IA has been reported in up to 15% of all solid organ transplant recipients.[3] In cardiac transplantation, IA occurs in 1%–14% of patients with the overall 12-month cumulative incidence of 3.4%.[1,4,5] The reported mortality rate of IA in cardiac transplant recipients has ranged from 36% to 88%.[4-6] Invasive pulmonary aspergillosis (IPA) commonly occurs after a month posttransplantation, with *Aspergillus fumigatus* being the most commonly implicated species.[3,5,7] Herein, we report a unique and a rare case of early-onset (day 9 postcardiac transplant) *de novo* IPA in an orthotopic heart transplant recipient. There was absence of previously reported risk factors of IA and there was no evidence of donor-derived *Aspergillus* infection in the other organ recipients. Environmental contamination as the source of IA was also excluded. Heightened clinical vigilance and immediate initiation of combination therapy with voriconazole and micafungin were paramount in the management of life-threatening IA. This resulted in a favorable clinical recovery in our patient.

CASE REPORT

An 18-year-old male underwent orthotopic heart transplant for familial hypertrophic cardiomyopathy. He was closely monitored in the cardiothoracic Intensive Care Unit

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postoperatively. His immunosuppressant regimen included prednisone, mycophenolate mofetil, and tacrolimus. He was extubated successfully on day 2 postcardiac transplantation. On the next day (posttransplant day 3), he developed sudden onset of shortness of breath with hypoxic respiratory failure, necessitating endotracheal intubation and mechanical ventilation. He was hemodynamically unstable, requiring vasopressor support. Significant laboratory blood tests showed total white blood cell count of 48,000 cells/mm^3 (normal 4400–11,300 cells/mm^3), 80% neutrophils, 14% bands, 3% lymphocytes, and 3% monocytes. Renal and liver function tests were within normal range. Blood cultures were obtained, and broad-spectrum antibiotics (intravenous vancomycin, cefepime, and azithromycin) were initiated. Computed tomography (CT) of the chest revealed bilateral pulmonary consolidations with air bronchograms and bilateral pneumothoraces [Figure 1]. Bronchoscopy and bronchial washings were performed on day 4 posttransplantation. Bronchoalveolar lavage (BAL) cultures revealed normal respiratory flora and *Candida albicans*. Blood cultures showed no microbial growth after 5 days of incubation.

Despite appropriate antimicrobial therapy, marked leukocytosis persisted. Blood cultures were repeated and they were unrevealing. A repeat CT chest demonstrated worsening diffuse pulmonary consolidations. Bronchoscopy was again performed on postoperative day 9. BAL cultures of mycobacteria, *Mycoplasma pneumoniae*, and *Legionella* showed no growth. BAL viral cultures (using primary monkey kidney, MRC-5, and A549 cell lines) of adenovirus, *Cytomegalovirus* (CMV), influenza, parainfluenza, and respiratory syncytial virus were negative. Blood CMV viral load by polymerase chain reaction (PCR) was undetectable. HIV serology was nonreactive. Serum cryptococcal antigen, serum *Aspergillus* galactomannan assay, serum (1→3)-β-D-glucan assay, and urine for *Histoplasma* antigen were sent. BAL cytology demonstrated acute inflammatory cells without viral cytopathic changes or malignant cells. Gomori's methenamine silver stain of BAL cytology was negative of cystic forms of *Pneumocystis jirovecii*, but identified numerous acute angle septated hyphae, highly suggestive of *Aspergillus* species [Figure 2]. Multiple BAL cultures isolated *Aspergillus flavus* after 3 days of incubation. The minimal inhibitory concentration of voriconazole to *A. flavus* was reported susceptible at 0.5 μg/mL. Given poor clinical response to broad-spectrum antibacterial therapy with positive *Aspergillus* BAL cultures, empiric therapy with intravenous voriconazole and micafungin was promptly initiated due to high clinical suspicion of early-onset IPA. Among fungal assays, serum *Aspergillus* galactomannan was significantly elevated at 4.8 optical density (OD) (normal <0.5 OD), and serum (1→3)-β-D-glucan was high at 263 pg/mL (negative <60 pg/mL). Serum cryptococcal antigen and urine *Histoplasma* antigen were reported negative. The results supported a diagnosis of IPA. After 48 h of combined antifungal therapy, the patient responded dramatically, and vasopressor support was discontinued. Once the patient's clinical status improved and therapeutic voriconazole trough levels (normal: 1.5–5 μg/mL) were attained, micafungin was discontinued, and intravenous voriconazole was transitioned to oral route as the maintenance therapy.

We did request our microbiology laboratory to have the review of day 4 posttransplant BAL fungal cultures to see whether *Aspergillus* species were mistaken as *C. albicans*. The microbiologist confirmed that there were only *Candida* colonies seen on the culture.

We asked the patient's family if the patient did gardening or spreading mulch prior to hospital admission; none of those activities were reported. Then, concern for the donor-derived infection or nosocomial environmental source of *Aspergillus* contamination was raised. Other organ recipients from the same donor were contacted; none of them were diagnosed with IA. There was no hospital construction or renovation which could increase mold exposure to our patient. The Infection Prevention team

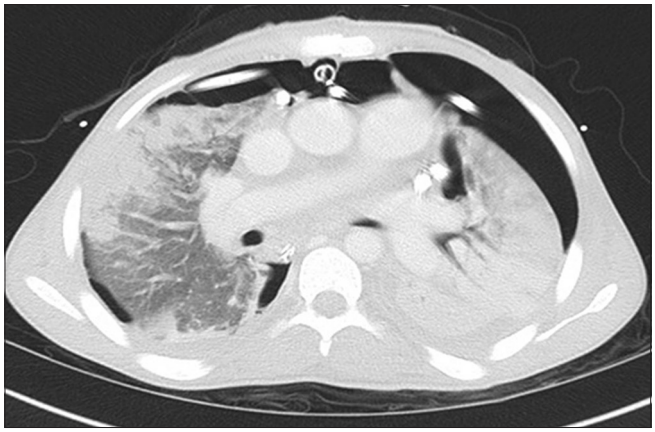

Figure 1: Chest computed tomography illustrated extensive bilateral diffuse pulmonary consolidations with air bronchograms with bilateral pneumothoraces

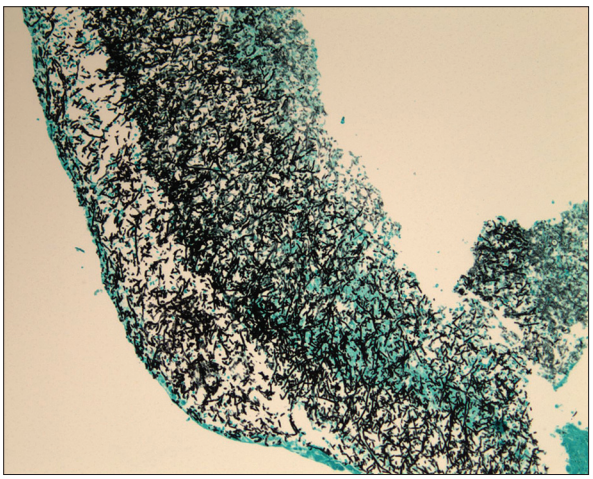

Figure 2: Bronchoalveolar lavage demonstrated numerous acute angle septated hyphae (suggestive of *Aspergillus*) on Gomori's methenamine silver stain

from our institution conducted air sampling cultures in the patient's room and his adjacent rooms. The analysis of the samples found a total mold spore concentrations of 78 S/m^3 and 26 S/m^3 in the patient's room and his adjacent rooms, respectively. All the detected spores were of the basidiospore variety and no *Aspergillus* spore was identified.

Immunosuppression was decreased judiciously. Bilateral chest tubes were placed for a prolonged period of time for persistent air leak. The patient responded appropriately to antifungal therapy and was discharged on the 43rd posttransplant day with voriconazole maintenance monotherapy. A repeat serum *Aspergillus* galactomannan assay was 0.61 OD (normal <0.5 OD) after 6 weeks of antifungal therapy. The patient received voriconazole therapy for 6 months, and a complete pulmonary recovery was achieved clinically and radiologically. At the time of writing the case, the patient has been off antifungal therapy for 1½ years, and there are no clinical signs of relapse of *Aspergillus* infection.

DISCUSSION

Aspergillus species are ubiquitous in the environment. The primary portal of entry is inhalation of fungal spores and thus the *Aspergillus* sinopulmonary disease is the most common clinical manifestation. The cumulative incidence of IA in heart transplant recipients was reported to be 3.4%.[3] IA poses a major determinant of high mortality and morbidity in patients with cardiac transplantation.[5,8] Mortality from IA at 1 year can be as high as 66.7% in heart transplant recipients.[4] In one case series, all cardiac transplant patients with early-onset IPA (<1 month posttransplantation) had succumbed to the infection.[6] *A. fumigatus* is most commonly isolated, followed by *A. niger* and *A. flavus*.[3,8]

Depending on the risk factors and types of solid organ transplantation, indications for antifungal prophylaxis are varied. In patients with liver transplantation, prophylaxis for IA is indicated for re-transplantation, renal failure (particularly in those requiring renal replacement therapy), or reoperation involving thoracic or abdominal cavity. In lung transplant recipients, the risk factors for IA are pretransplant *Aspergillus* colonization, posttransplant *Aspergillus* colonization within a year of transplant, induction with alemtuzumab or thymoglobulin, single lung transplant, *Aspergillus* colonization following CMV infection, rejection and augmented immunosuppression, particularly with the use of monoclonal antibody, or acquired hypo-gammaglobulinemia (IgG <400 mg/dL). Antifungal prophylaxis is currently not recommended in patients with kidney transplantation.[3]

The antifungal prophylaxis is recommended in cardiac transplant recipients with the following risk factors: isolation of *A. fumigatus* in respiratory tract cultures prior to transplant, reoperation, CMV disease, posttransplant hemodialysis, and cases of IA in the institution 2 months before the transplant.[3] Antifungal prophylaxis, preferably with voriconazole or posaconazole, is recommended in cardiac transplant patients with one or more aforementioned predisposing factors.[3,9] There were no pretransplant respiratory tract fungal cultures in our patient as they are not routinely performed in the orthotopic heart transplant recipients. In contrast, in lung transplant patients, pretransplant surveillance respiratory tract fungal cultures are recommended because the incidence of IPA is the highest (up to 23.3%) in these solid organ recipients.[3] Our patient did not have any of the above reported risk factors, and thus the patient did not receive antifungal prophylaxis.

IA is typically seen 1–6 months after solid organ transplantation because the patient's immune system is most profoundly suppressed in that period and this is the period patients are most at the risk of opportunistic infections.[7] Early-onset (<1 month) IA in the cardiac transplantation warrants a thorough investigation to exclude donor-derived infection or secondary to hospital environmental source.[3,7,9] The onset of IA in our patient was 9 days after the orthotopic heart transplantation, and it is likely one of the earliest cases described in literature.[6] We contacted the United Network for Organ Sharing which supervises Organ Procurement and Transplantation Network in the United States. There was no reported incident of IA in other recipients from the same organ donor and that effectively ruled out donor-derived *Aspergillus* infection.

No history of gardening or handling mulch prior to the hospitalization makes community-acquired IA less likely. There was no construction or renovation in the hospital to suggest environmental mold exposure as the cause of IA. Our institution's Infection Prevention team conducted the environmental samplings and there was no *Aspergillus* spores detected in the patient's rooms that negates there was a risk of hospital outbreak of invasive mold infection. We did not have pretransplant fungal cultures from the respiratory tract samples since they are not indicated in the heart transplantation. However, there was BAL fungal culture on day 4 posttransplant and it had only positive growth of *C. albicans*, which was confirmed on the second thorough review by the microbiologist. This may indicate low possibility of pretransplant *Aspergillus* colonization in our patient. Hence, in the absence of concrete evidence of an identified source and risk factor of IA, the patient was seemed to have *de novo* IPA.

A diagnosis of early-onset IA in cardiac transplant recipients is a challenge given the nonspecific symptoms, variable imaging findings, and rarity of the disease. Those patients usually present with septic shock and multi-organ dysfunction, leading to 100% mortality.[6] The gold standard of diagnosis of proven IA is a combination of positive culture of *Aspergillus* spp. and angioinvasion of fungal hyphae seen on the histopathologic specimens.[9] However, bronchial tissue biopsy is usually a high-risk

procedure in those patients due to severe hypoxemia, thrombocytopenia, or bleeding complication. Thus, noninvasive methods are favorable to diagnose IA and they include serum surrogate biomarkers (*Aspergillus* galactomannan and (1→3)-β-D-glucan) in conjunction with positive respiratory cultures (sputum or BAL) of *Aspergillus* spp.[3,9] Notably, both fungal biomarkers are not exclusively positive in aspergillosis and they could be positive in other invasive fungal infections (such as *Fusarium* and *Histoplasma*).[9] Thus, interpretation of the test results should be made after consideration of the clinical context, culture, and histopathologic data.[3,9] Testing of *Aspergillus* galactomannan in the BAL specimen is now recommended in patients with suspected IPA since it is more sensitive and specific than that of serum in patients with IPA. The PCR-based test to identify *Aspergillus* is a potential tool for a rapid diagnostic test, but has not been intensively validated and is not widely available.[3,9]

Early initiation of antifungal therapy in patients with suspected IPA is warranted while diagnostic tests are conducted.[3,9] Voriconazole is recommended as the drug of choice for primary therapy for IA. Other alternative treatment modalities include isavuconazole or liposomal amphotericin B. There has been reported mortality benefit of utilizing combined voriconazole plus an echinocandin (caspofungin, micafungin, or anidulafungin) in serious life-threatening patients with IPA because of the synergistic effects with improved efficacy.[3,9,10] Duration of antifungal therapy of IPA is a minimum of 6–12 weeks; however, the definite duration of therapy largely depends on the clinical improvement and response as well as intensity and duration of immunosuppressants.[3,9]

In conclusion, it is a truly diagnostic challenge for early-onset IPA in cardiac transplant patients, especially <14 days posttransplantation. Our current case is possibly the earliest onset of IPA in orthotopic heart transplant recipients reported in literature. In addition, it is regarded as *de novo* infection without an identifiable etiology after the extensive and exhaustive search. Hence, a high clinical index of suspicion is warranted for early recognition of infection since delayed diagnosis usually results in fatality. Immediate administration of antifungal therapy in patients with strongly suspected IA is highly recommended while waiting for the results of diagnostic tests.

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Conflicts of interest

There are no conflicts of interest.

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