Cytomegalovirus Infection Is a Risk Factor for Invasive Aspergillosis in Lung Transplant Recipients

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Invasive aspergillosis (IA) remains a major cause of morbidity and mortality following solid organ transplantation. To assess the incidence of IA following lung transplantation and to identify risk factors for its occurrence, we performed a case-control study involving 101 patients undergoing lung transplantation at our institution from 1990 to 1995 and reviewed the findings. Fourteen patients (14%) developed IA. The mean time from transplantation to diagnosis was 15 months. Nine patients died; the mean time to death from diagnosis was 13 days. Risk factors associated with developing IA included concomitant cytomegalovirus (CMV) pneumonia or viremia and culture isolation of *Aspergillus* species from a respiratory tract specimen after lung transplantation. Optimal strategies to prevent IA in lung transplant recipients remain to be determined, but prevention of aspergillus airway colonization and CMV viremia and disease after transplantation may be important targets for prophylactic interventions.

Since the first successful lung transplantation in 1983, >6,000 lung transplantations have been performed, including 953 in the United States in 1996 [1, 2]. Infectious complications remain a major cause of morbidity and mortality, responsible for ~31% of deaths occurring 60 days after transplantation [1]. Aspergillosis is a major problem, occurring in up to 15% of patients following lung transplantation [3–6]. We report our experience with invasive aspergillosis (IA) in lung transplant recipients at The Cleveland Clinic Foundation and examine risk factors associated with this complication.

Materials and Methods

The Cleveland Clinic Foundation lung transplantation program was begin in 1990, and details regarding the program have been reported previously [7]. Prophylaxis for cytomegalovirus (CMV) infection was used for all lung transplant recipients except those CMV-seronegative patients who had received an organ from a CMV-seronegative donor. All patients received primary chemoprophylaxis for *Pneumocystis carinii* infection. Following transplantation, patients were not housed in areas with laminar air flow or high-efficiency particulate filters.

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Case Definitions

Definitive IA was defined as culture isolation of *Aspergillus* species together with histopathologic evidence of tissue invasion during either biopsy or postmortem examination. The presence of septate hyphae with dichotomous branching at 45° angles within tissue was considered histological evidence of aspergillosis. Probable pulmonary IA was defined as a characteristic clinical and radiographic picture (nodular or cavitary lesions on a chest radiograph) with either histopathologic evidence of tissue invasion or culture of a respiratory tract specimen that yielded *Aspergillus.* Disseminated aspergillosis was defined as the presence of extrapulmonary disease.

The diagnosis of CMV pneumonia was established by the recognition of cytomegalic inclusion bodies in tissue. CMV infection was defined as isolation of CMV from blood (viremia), respiratory secretions (bronchoalveolar lavage fluid), or urine in the absence of recognition of inclusion bodies in tissue. CMV infection was considered concomitant if it occurred within 30 days of the diagnosis of IA.

The clinical diagnosis of acute lung rejection was based on the clinical presentation, characteristic radiographic changes, absence of infection, and results of lung biopsy.

Case-Control Study

To identify risk factors associated with IA in the lung transplant recipients, a case-control study was conducted. A case was defined as a lung transplant recipient with definite or probable IA at The Cleveland Clinic Foundation between January 1990 and December 1995. Controls were defined as all lung transplant recipients without IA who survived at least 1 year after transplantation (if the transplantation was performed before 1995). The medical records of study patients were re-

viewed retrospectively, and cases and controls were compared regarding a variety of possible risk factors for aspergillosis.

Data Analysis

All statistical analysis was performed by using Epi-Info Version 6.02 [8]. Differences between cases and controls were analyzed with the χ^2 test and Fisher's exact test (two-tailed). A P value of $\leq .05$ was considered statistically significant.

Results

Incidence of IA

We identified 14 lung transplant recipients with definitive or probable IA during the 5-year study period (93 cases per 1,000 patient-transplant–years) (figure 1). Eight patients had definite IA, and six had probable IA. Two patients had ulcerative tracheobronchitis at their bronchial anastomotic sites, and disseminated disease (brain abscesses and skin infection) occurred in three.

The mean interval from transplantation to diagnosis of IA was 15 months (range, 29 days to 5 years). All lung transplant recipients with IA had *Aspergillus* recovered from at least one clinical specimen after transplantation. The mortality rate associated with IA was 64%, with a mean interval from diagnosis to death of 13 days (range, 0–30 days). For the nine patients with pulmonary IA who died, the mean survival after the first positive culture was 13 days (range, 1–187 days).

Concomitant CMV infections (positive cultures of buffy coat specimens) occurred in eight lung transplant recipients with IA (57%), three of whom also had CMV pneumonia. One additional patient with IA had CMV retinitis without CMV pneumonia or a buffy coat specimen positive for CMV.

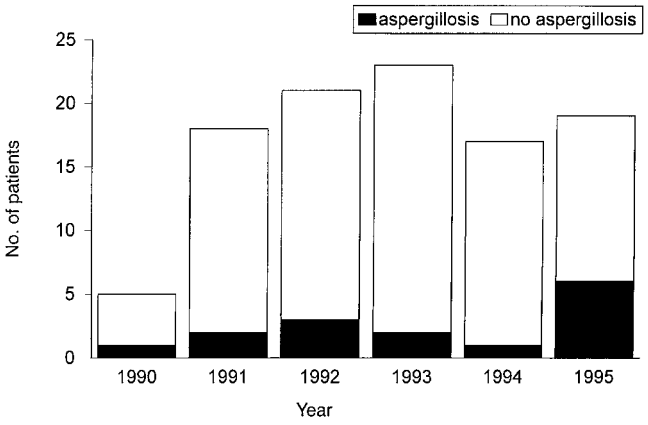

Figure 1. Invasive aspergillosis in 101 lung transplant recipients by date of transplantation at The Cleveland Clinic Foundation during 1990–1995.

Case-Control Study

Cases were significantly more likely to have CMV disease and/or CMV infection than controls (eight of 14 cases vs. 17 of 57 controls; $P = .02$; OR, 4.2 [95% CI, 1.1–17]). Culture isolation of *Aspergillus* from a respiratory tract specimen before clinical or radiographic findings of IA was also significantly associated with an increased risk for IA (four of 14 cases vs. one of 57 controls; $P = .004$; OR, 22.4 [95% CI, 1.9–588]). No other significant differences between cases and controls were identified regarding any other potential risk factors studied, including underlying disease, concomitant organ rejection, CMV serological status of donor and recipient, or double vs. single lung transplantation.

Discussion

Previous studies have documented high rates of pulmonary IA following lung transplantation. Our attack rate of 14% among 101 lung transplant recipients is within the range of 3.4% to 16% that was reported by five different institutions studying 446 patients [5, 9–12]. We identified concomitant CMV pneumonia or infection and culture isolation of *Aspergillus* from a respiratory tract specimen after lung transplantation as significantly associated with an increased risk of IA. An association between aspergillosis and CMV infection in lung transplant recipients has been reported previously [5].

A major consequence of CMV infection in solid organ transplant patients is a higher risk of opportunistic superinfection because CMV itself is an immunomodulator [13]. CMV infection is an independent risk factor for the development of other systemic infections in liver transplant recipients [14], heart transplant recipients [15], and renal allograft recipients [16]. The precise mechanisms for the immunosuppression associated with CMV infection are unknown but involve lymphocyte suppression with reversal of the helper-suppressor cell ratio and suppressed function of natural killer cells [17].

In conclusion, IA remains a devastating disease in organ transplant recipients, especially lung transplant recipients. Concomitant CMV infection is a risk factor for IA in lung transplant recipients. Optimal strategies to prevent IA in lung transplant recipients remain to be determined, but prevention of *Aspergillus* airway colonization and CMV viremia and disease after transplantation may be important targets for prophylactic interventions.

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