CARDIOTHORACIC TRANSPLANTATION

ADENOVIRUS INFECTION IN THE LUNG RESULTS IN GRAFT FAILURE AFTER LUNG TRANSPLANTATION

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Objectives: **Our goal was to examine the relationship between viral pneumonia and outcome in pediatric patients undergoing lung or heart-lung transplantation.** ***Methods:*** **Prospective surveillance for common respiratory viruses of childhood was performed in all patients undergoing lung or heart-lung transplantation. Specimens were examined for the presence of replicating virus (by culture), viral genome (by polymerase chain reaction), and viral antigen (by immunofluorescence and immunohistochemical staining). The relationship between viral infection and outcome was examined.** ***Results:*** **Sixteen patients underwent 19 transplants during the study period, with follow-up of 1 to 26 months. Virus was identified in the transplanted lung in 29 instances; adenovirus was identified most commonly (8/16 patients) and had the greatest impact on outcome. In 2 patients with early, fulminant infection, adenovirus was also identified in the donor. Adenovirus was significantly associated with respiratory failure leading to death or graft loss and with the histologic diagnosis of obliterative bronchiolitis ($P \leq .002$ in each case).** ***Conclusions:*** **Adenovirus infection in the transplanted lung is significantly associated with graft failure, histologic obliterative bronchiolitis, and death. Health care personnel and families must be vigilant in preventing exposure of transplant recipients to this virus. Availability of a rapid and reliable test for adenovirus in donors and recipients would have an impact on management and could improve outcome for pediatric lung recipients. (J Thorac Cardiovasc Surg 1998;116:617-23)**

Acute and chronic graft failure are major causes of graft loss and death after lung transplantation. The etiology of these events is often poorly understood and may be variously attributed to reperfusion injury, acute cellular rejection, or "chronic rejection." Experience with very young lung transplant recipients has indicated that infection of the graft with the common viruses of childhood is an important determinant of outcome.[1] We report here the results of systematic surveillance for a viral pneumonitis in a predominantly pediatric lung transplant population. We examine the impact of viral infection of the transplanted lung on graft survival, patient survival, and the development of obliterative bronchiolitis (OB).

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Received for publication Feb 17, 1998; revisions requested May 26, 1998; revisions received June 26, 1998; accepted for publication June 29, 1998.

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0022-5223/98 $5.00 + 0 **12/1/92812**

Methods

The patient population consisted of all patients undergoing lung or heart-lung transplantation at the Children's Hospital of Philadelphia between December 1994 and December 1996, with follow-up through February 28, 1997. Surveillance for viral infection in donor tissue and recipients was performed at the time of transplantation and at all subsequent evaluations. Our routine schedule for surveillance transbronchial biopsy has changed over time. Initially, surveillance transbronchial biopsy was performed each month for the first 3 months and then at 6 months, 1 year, and yearly thereafter. After the first 12 months' experience in this program, we revised the sched-

ule to eliminate the biopsy specimens obtained 1 and 2 months after transplantation. Throughout, we have obtained biopsy specimens to investigate clinical findings consistent with infection or rejection when the diagnosis could not be made by other means or if a patient did not respond to pulsed steroid therapy. Materials tested for the presence of virus included lung biopsy tissue, bronchoalveolar lavage (BAL) fluid, tracheal aspirate fluid, and (at the time of transplantation) hilar lymph nodes. Tests included examination of biopsy tissue and BAL fluid for viral genome by polymerase chain reaction (PCR); culture of tissue and BAL for viral isolation; "rapid panel" testing of tracheal aspirates and BAL fluid for virus by immunofluorescence; and histopathologic examination of tissue for cytopathologic effect, with immunohistochemical staining for adenovirus and cytomegalovirus (CMV).

All laboratory studies other than PCR were performed in the clinical virology laboratory at the Children's Hospital of Philadelphia. Direct immunofluorescence testing was performed for respiratory syncytial virus (RSV), influenza virus types A and B, parainfluenza virus types 1, 2, and 3, and adenovirus. All PCR analyses were performed in the Phoebe Willingham Muzzy Pediatric Molecular Cardiology Laboratory at Baylor College of Medicine. The method used for PCR identification of viruses has been previously reported.[2] PCR primer pairs were designed to detect enteroviruses, CMV (all serotypes), adenovirus (all DNA-sequenced subgenera); herpes simplex viruses 1 and 2; and Epstein-Barr virus. In all cases these analyses were performed by investigators blinded to the clinical picture. Serotyping of viruses was not performed.

Definition of clinical disease and OB. Laboratory evidence of viral infection in the lung was correlated with the presence or absence of clinical disease. A significant lung infection was defined as the presence of at least 2 of the following: new densities on chest radiograph; decreased arterial oxygen saturation, compared with the patient's baseline level; or fever, cough, dyspnea, or new abnormal auscultatory findings. In the context of these clinical findings, the date of diagnosis of viral pneumonitis was defined as the date on which the specimen in which virus was ultimately identified was obtained. OB was diagnosed according to the criteria of the working formulation group of the International Society for Heart and Lung Transplantation[3]: that is, the presence of eosinophilic fibrous scarring in the walls of the small conducting airways, with partial or complete obliteration of the lumen. Because only 5 of the 16 patients in this study were mature enough to reliably perform pulmonary function testing, the clinical diagnosis of bronchiolitis obliterans syndrome was not used. However, for each of those 5 patients, the results of pulmonary function testing correlated with the presence or absence of histologically defined OB. Graft survival was defined as the interval between implantation and explantation in the case of patients receiving a second transplant, or from implantation to death in patients who died.

Statistical methods. Variables examined for a statistically significant association with graft survival, patient survival, and OB included adenovirus infection in the lung, other viral infection in the lung (CMV, RSV, influenza B virus, or rhinovirus), age at transplantation, sex, and number of episodes of acute rejection graded A3 or higher. Univariate analysis was performed with the use of the χ^2 test for discrete variables and regression for continuous variables. Among the variables examined, only adenovirus infection was significantly associated with graft loss, patient survival, or OB. These outcomes were examined by means of the Cox proportional hazards model, with adenovirus infection entered as a time-dependent variable. Statistical analysis was carried out with the use of Stata software (Stata Corporation, College Station, Tex).

Results

Patient characteristics are shown in Table I. The group comprised 16 patients (8 female) who had 19 thoracic organ transplants: 11 primary lung transplants, 4 primary heart-lung transplants, and 4 second lung transplants. Patients' ages ranged from 3 months to 41 years (median 4.6 years). Among the 15 patients undergoing primary transplantation, there was 1 early death (patient 16) caused by adenovirus pneumonia, for an operative survival of 93%. Among the 4 patients undergoing a second transplant operation, there was 1 early death (patient 6) caused by *Aspergillus* cerebritis, for an operative survival of 75%.

Results of viral surveillance. In all, 59 specimens (lung tissue, BAL, or tracheal aspirate) were examined by PCR; 84 specimens (lung tissue, BAL, or tracheal aspirate) were cultured for viral isolation; 61 specimens (BAL or tracheal aspirate) were studied by direct immunofluorescence, and 59 specimens (lung tissue) were subjected to histologic examination. Of the 59 biopsy specimens, 28 (47%) were obtained within the first 3 months of transplantation. Virus was identified in the transplanted lung on 29 occasions, for a frequency of 0.13 events per patient-month of follow-up. In 2 instances, 2 viruses were identified concurrently at the time of a clinical illness: in 1 case (patient 7), CMV and adenovirus were identified concurrently, and in the other (patient 14), parainfluenza and RSV were identified concurrently. Both of these cases are discussed later. Adenovirus was the virus most frequently identified and most commonly associated with severe illness in this group of patients and thus became the primary focus of our analysis.

Next in frequency of identification after adenovirus was RSV, which was found 9 times in 8 patients. One patient was identified as having RSV at the time of transplantation, with no clinical illness evident either before or after transplantation. In 7 instances, RSV was associated with a mild respiratory illness characterized by small decreases in arterial oxygen saturation, mild

Table I. *Patient characteristics*

Patient	*Indication for transplantation*	*Age at transplantation (y)*	*Transplant procedure*	*Outcome*
1	PHN with CHD	19.8	Primary bilateral lung with cardiac repair	Second transplant for OB
2	PHN with CHD	0.25	Primary bilateral lung with cardiac repair	Alive and well, histologic diagnosis of OB
3	Pulmonary vein stenosis	2.3	Primary bilateral lung with cardiac repair	Alive and well
4	PHN with CHD	12.8	Primary bilateral lung with cardiac repair	Alive and well, histologic diagnosis of OB
5	OB due to GVHD after bone marrow transplantation	5.8	Primary bilateral lung	Alive and well
6 (first graft)	Bronchopulmonary dysplasia	1.9	Bilateral lung	Second transplant for graft failure
6 (second graft)	OB after adenovirus pneumonia	2.6	Bilateral lung	Died 9 days after second transplant, from cerebral *Aspergillus* infection
7 (first graft)	Primary pulmonary hypertension	2.1	Bilateral lung with cardiac repair	Second transplant for graft failure
7 (second graft)	Fulminant graft failure after adenovirus pneumonia	2.2	Repeat bilateral lung	Died 15 mo after second transplant, from *Pseudomonas* sepsis
8	Cystic fibrosis	15	Primary bilateral lung	Died of OB after refusing a second transplant
9	OB after heart and lung transplantation	4.6	Repeat bilateral lung	Died 12 mo after second transplant, from respiratory failure after adenovirus pneumonia
10 (first graft)	PHN with CHD	7	Primary heart and lung	Second transplant for graft failure; see below
10 (second graft)	Acute graft failure after adenovirus pneumonia and aspiration	7.1	Bilateral lung	Died 11 mo after second transplant, after a second adenovirus infection
11	Congenital pulmonary vein stenosis	0.23	Primary bilateral lung with cardiac repair	Alive and well
12	PHN with CHD	41.5	Primary heart and lung	Alive and well
13	PHN with CHD	7.1	Primary heart and lung	Alive and well, with histologic diagnosis of OB
14	Congenital chylothorax	0.7	Primary bilateral lung	Alive and well
15	PHN with CHD	24.8	Primary heart and lung	Alive and well
16	PHN after repair of congenital cystic adenomatoid malformation	0.3	Single lung	Died of respiratory failure from adenovirus pneumonia, while waiting for a second transplant

PHN, Pulmonary hypertension; *CHD,* congenital heart disease; *OB,* obliterative bronchiolitis; *GVHD,* graft-versus-host disease.
*Patient 9 underwent her first transplant procedure (heart and lung transplantation for pulmonary hypertension in association with congenital heart disease) at another institution.

wheezing on auscultation, little or no change in roentgenographic appearance of the lungs, and in 2 instances, gastroenteritis. In 3 of these cases, patients were hospitalized for intravenous hydration, for supplemental oxygen via nasal cannula, or for both treatments. All of these patients recovered without sequelae. In 1 patient (patient 7), RSV was identified in a tracheal aspirate specimen obtained at the time of overwhelming, fatal *Pseudomonas* sepsis; the significance of this finding is unclear.

Both cases of CMV were associated with significant respiratory disease. In 1 case, CMV was identified concurrently with adenovirus, at a time when the patient was receiving ganciclovir; that patient had fulminant respiratory failure and underwent a second lung transplantation. In the other, the patient's pneumonitis was treated with intravenous ganciclovir, and she recovered. However, OB subsequently developed and she underwent a second lung transplantation.

Both cases of parainfluenza were also associated with significant respiratory disease, characterized by decreased arterial oxygen saturations, increased work of breathing, wheezing on auscultation, and diffuse interstitial densities on chest radiograph. In 1 of these 2 patients, RSV was identified concurrently with parainfluenza. Both patients were hospitalized and treated

Table II. *Detection of adenovirus in the transplanted lung*

Patient	*Interval from transplantation to detection of adenovirus (d)*	*Laboratory evidence*	*Histology*	*Clinical pneumonitis?*
4	458	PCR	Lymphocytic bronchitis	No
6	232	PCR, rapid, culture	Acute pneumonia, viral cytopathic effect	Yes
7	1	PCR, culture	Diffuse necrotizing bronchitis, positive tissue stain for adenovirus	Yes
9 (first infection)	16	PCR, rapid, culture	Nonspecific mild acute inflammatory infiltrate	Yes
9 (second infection)	298	PCR	Diffuse alveolar damage; normal airways	Yes
10 (first graft)	46	PCR	Organizing pneumonia and OB	Yes
10 (second graft)	290	PCR	Organizing pneumonia and OB	Yes
13	37	PCR, rapid, culture	Organizing pneumonia and OB	Yes
16	18	PCR, rapid, culture	Diffuse alveolar damage, acute bronchitis, OB	Yes

PCR, Polymerase chain reaction; *rapid,* rapid panel testing by immunofluorescence; *OB,* obliterative bronchiolitis.

with intravenous hydration and supplemental oxygen by nasal cannula; both recovered. OB later developed in 1 patient after an episode of adenovirus pneumonia.

Both cases of rhinovirus were associated with mild upper respiratory tract illnesses. Identification of Epstein-Barr virus, herpes simplex virus, and influenza B was not associated with clinical respiratory illness.

Identification of adenovirus in the transplanted lung. In 10 grafts, there was no evidence of adenovirus infection. Of these, 2 are in patients who had adenovirus identified in a prior graft. Thus 8 of 16 patients have been free of adenovirus in the transplanted lung. Among these 8 patients, 6 have no evidence of OB, 1 is free of symptoms but has a histologic diagnosis of OB, and 1 has undergone a second transplant operation because of OB in the first graft.

Adenovirus was identified in 9 grafts over a period of almost 18 months (Table II). In 2 instances, 2 patients were infected within a 1-week period. In the first instance, 1 patient acquired the infection from the donor, and the other acquired it in the community. In the second instance, 2 infections were identified within a 5-day period in patients in the intensive care unit. The other 5 infections were separated by time intervals of 1 to 6 months. The remaining 8 patients (9 grafts) all had evidence of adenovirus infection. One of the grafts was infected with adenovirus on 2 separate occasions, 11 months apart, for a total of 10 infectious episodes in 9 grafts in 8 patients. In patients identified as having adenovirus pneumonia, routine triple-drug immunosuppression was maintained, with tacrolimus or cyclosporine (INN: ciclosporin) levels maintained at the low end of the therapeutic range (6-10 ng/mL or 150-200 ng/μL, respectively).

In 2 patients, adenovirus was identified in the transplanted lung by PCR only, without clinical pneumonitis or confirmation by other laboratory studies. Both of these patients subsequently had both histologic and clinical evidence of OB; one died after refusing a second lung transplant operation, and the other has been listed for a second lung transplantation. For the purposes of statistical analysis, these patients were not considered to have had adenovirus infection in the lung.

In 2 patients (3 grafts), adenovirus was identified in the lung by PCR at the time of a clinical pneumonitis, without other laboratory confirmation. No other organisms were identified to account for the clinical findings. In 1 of these patients, fulminant graft failure developed, and the patient underwent a successful second transplant operation; she died 11 months later of respiratory failure, with adenovirus identified only by PCR in the second graft. The other patient had progressive graft failure starting at the time of the adenovirus infection; she died of respiratory failure.

Finally, in 5 patients (5 grafts), adenovirus was identified at the time of clinical pneumonitis by PCR as well as at least 1 other laboratory method. In 2 of these 5, both of whom had early, rapidly progressive infections leading to graft failure, adenovirus was also identified by PCR in the donor lung before implantation. One of these patients had successful retransplantation after a period of support with extracorporeal membrane oxygenation, and the other died while waiting for a second donor organ. Chronic graft failure with histologic evidence of OB and graft vasculopathy developed in a third patient, who had a second transplant operation. Acute severe respiratory failure developed in the fourth patient in this group; although he recovered and is clinically well, he has a histologic diagnosis of OB 1 year later. The last patient in this group had a less severe clinical illness at the time that adenovirus was identi-

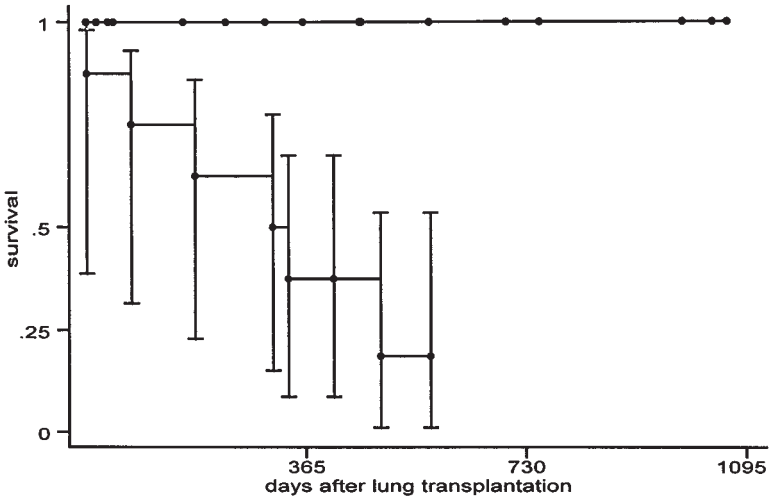

Fig 1. Actuarial survival after lung transplantation. Survival without adenovirus infection, shown in the *upper curve*, is taken as the interval from transplantation to last follow-up or to the date of identification of adenovirus infection, at which point patients were censored; survival after adenovirus infection is taken as the interval between identification of adenovirus infection and last follow-up or death. The difference in survival is significant (P = .001 by Wilcoxon-Gehan test).

fied in her lung; she recovered from that episode but died 12 months later of respiratory failure after a second adenovirus lung infection.

Impact of adenovirus on graft and patient survival. Among the 8 patients in whom adenovirus was identified in the transplanted lung, only 2 were still alive at the end of the follow-up period. Both have histologic evidence of OB. Death from respiratory failure occurred in 4 patients 3 weeks, 10 months, 12 months, and 15 months after transplantation, respectively. The other 2 patients died of unrelated extrapulmonary infections after a second lung transplantation (*Aspergillus* cerebritis in 1, *Pseudomonas* sepsis in the other), with good graft function.

Among the 19 grafts implanted during the study period, 3 failed abruptly in the immediate postoperative period. Adenovirus was identified in all. Two of these patients underwent a second lung transplantation; the third died before organs became available. In all, 3 patients underwent a second lung transplantation for respiratory failure after adenovirus infection (2 early and 1 late). In only 1 of these 3 patients was adenovirus identified in the second graft, and that patient died of chronic progressive respiratory failure. The other 2 died of unrelated infections, with good graft function.

In a Cox proportional hazards analysis in which adenovirus infection was entered as a time-dependent variable, adenovirus infection was significantly associated with graft loss (P = .002, coefficient 2.67, 95% CI 1.0-4.3), patient death (P < .001, coefficient 37.7, 95% CI 36.9-38.5) and with the histologic diagnosis of OB (P < .0001, coefficient 36.2-37.5, 95% CI 36.2-37.5). Survival with and without adenovirus is depicted in Fig 1; survival without adenovirus infection is taken as the interval from transplantation to last follow-up or to the date of identification of adenovirus infection, at which point patients are censored; survival after adenovirus infection is taken as the interval between identification of adenovirus infection and last follow-up or death. The difference in survival is significant (P = .001 by the Wilcoxon-Gehan test). None of the other variables examined (age, sex, number of episodes of acute rejection, and identification of other viruses in the transplanted lung) were significantly associated with graft loss, death, or OB in this group.

Discussion

Adenovirus is a ubiquitous virus of childhood, accounting for about 5% of acute upper respiratory tract illnesses and about 10% of pneumonias in children under age 5 years; asymptomatic carriage of the virus is common, and the transmission rate is high.[4,5] Adenovirus is also known to be an important pathogen in immunocompromised hosts, including newborn infants[6,7] and recipients of bone marrow, kidney, and liver transplants, infecting both the transplanted and other organs.[8-10] Ohori and associates[11] reported on 4 patients (3 of them children) with fulminant adenovirus pneumonia after lung transplantation, all of whom died. We[1] have previously reported the high incidence of adenovirus infection in a series of very young chil-

dren undergoing lung transplantation. In the current report, adenovirus is again shown to be an agent of acute fulminant graft failure. To our knowledge, this is the first report to demonstrate a significant association between adenovirus in the transplanted lung and histologically proven OB.

Although the cause of OB remains elusive, there is some consensus that it is a multifactorial, immunologically mediated process.[12,13] Several investigators have demonstrated a relationship between OB and acute cellular rejection, and this relationship appears to be potentiated by infection, most notably CMV.[14-18] Although neither rejection nor CMV emerged as an important predictor of early or late graft failure in the current analysis, both patients who had CMV pneumonitis eventually had OB and graft failure leading to a second lung transplantation. Thus the lack of statistical significance for these variables is likely due to the small number of patients in this study. It is also possible that these factors are overshadowed by other features (specifically, susceptibility to viral pneumonitis) related to our patients' young age; previous authors have noted that infection with respiratory viruses is a more serious problem in younger transplant recipients.[19]

Adenovirus, whether wild type or replication deficient, elicits a strong immune response in the lung.[20] Thus the relationship demonstrated in this study between adenovirus and OB in lung transplant recipients is plausible. Adenovirus pneumonia is a known (though rare) cause of OB in immunocompetent children[21] and has been demonstrated to cause OB in immunocompetent animal models.[22] Adenovirus can be associated with chronic or persistent infection and, in either case, is known to be associated with chronic airway obstruction and deterioration of lung function.[23,24] Finally, adenovirus is a mediator of apoptosis,[25,26] a process that may have a role in the pathogenesis of OB.[27]

The prevalence of adenovirus in young patients and the ease with which it is transmitted, particularly as a nosocomial infection,[28,29] make this a troubling finding. Two of the patients in this series who had early graft loss as a result of adenovirus pneumonia received the virus from their donors. Mild viral symptoms in an infant or toddler are so common that this history might be overlooked in the evaluation of a donor. Furthermore, viral respiratory infections of all sorts are common in healthy children, as well as in those who receive transplants. In the early stages of infection, those that are generally benign in transplant recipients, such as RSV and rhinovirus, are clinically indistinguishable from those with more serious consequences, such as adenovirus and parainfluenza. PCR methodology has been demonstrated to be a reliable and clinically useful tool in the specific diagnosis of viral infections in heart transplant recipients.[30] However, given the time constraints that exist at the time of cadaveric donor lung transplantation, reliable confirmation of the presence or absence of adenovirus in a potential donor before transplantation is usually not feasible.

Summary and conclusions

Systematic surveillance for viral infection in the lung in a predominantly pediatric group of lung transplant recipients reveals a significant association between adenovirus infection and graft loss, OB, and death. The prevalence of adenovirus in young children makes this an important finding. Personnel in inpatient units caring for lung transplant recipients must be vigilant in isolation precautions to prevent the nosocomial spread of this common virus, and families must be counseled to prevent contact between transplant recipients and individuals with even mild respiratory infections or conjunctivitis. Identification of adenovirus pneumonitis is an indication for relisting in our program, and this approach has been successful when organs can be obtained in time; early reinfection has not occurred. The ability to make a rapid and reliable assessment for the presence or absence of adenovirus in donors and recipients would improve our ability to care for these patients and could potentially have an important effect on their outcome.

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