Cytomegalovirus Pneumonitis Is a Risk for Bronchiolitis Obliterans Syndrome in Lung Transplantation

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Rationale: Cytomegalovirus pneumonitis is one of the most prevalent opportunistic infections after lung transplantation. Early studies reported that cytomegalovirus pneumonitis was a risk factor for chronic allograft dysfunction. More recently, in the era of routine prophylaxis and ganciclovir treatment, the adverse impact of treated cytomegalovirus pneumonitis on bronchiolitis obliterans syndrome has been challenged.

Objectives: We hypothesized that cytomegalovirus pneumonitis contributes to adverse outcomes in the current antiviral era. We sought to define the impact of treated cytomegalovirus pneumonitis on bronchiolitis obliterans syndrome and survival in a large single-center cohort (n = 231) of consecutive patients undergoing lung transplantation from 2000 to 2004, all receiving short-course ganciclovir prophylaxis.

Methods: Transbronchial biopsies were performed at defined intervals with prospective cytomegalovirus immunostaining on every biopsy (n = 1,887). Cox proportional hazards models were used to assess the relationship between treated cytomegalovirus pneumonitis and clinical outcomes.

Measurements and Main Results: Forty-nine (21%) recipients developed cytomegalovirus pneumonitis a median of 106 days after transplantation. Treated cytomegalovirus pneumonitis within the first 6 months after transplantation significantly increased the risk for bronchiolitis obliterans syndrome (P = 0.001; hazard ratio, 2.19; 95% confidence interval, 1.36–3.51) and post-transplantation death (P = 0.02; hazard ratio, 1.89; 95% confidence interval, 1.11–3.23). This risk persisted when cytomegalovirus pneumonitis was considered as a time-dependent predictor as well as in multivariable models controlling for other risk factors.

Conclusions: Cytomegalovirus pneumonitis affects more than 20% of lung transplant recipients. Despite treatment, it increases the risk for bronchiolitis obliterans syndrome and death. More effective preventive strategies for cytomegalovirus pneumonitis are needed to improve long-term outcomes after lung transplantation.

Keywords: lung transplantation; cytomegalovirus; bronchiolitis obliterans

Long-term survival after lung transplantation is limited by a condition of progressive allograft dysfunction known as bronchiolitis obliterans syndrome (BOS). Approximately 50% of lung transplant recipients develop BOS within 5 years of transplantation (1). Median survival after the onset of BOS is less than 3 years (2). While various risk factors for BOS have

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The correlation between cytomegalovirus pneumonitis and bronchiolitis obliterans syndrome after lung transplantation is controversial in the current era of ganciclovir prophylaxis and treatment.

What This Study Adds to the Field

Despite effective treatments, late-onset cytomegalovirus pneumonitis is a risk factor for chronic allograft dysfunction and shorter survival after lung transplantation.

been proposed and validated, the importance of cytomegalovirus (CMV) infection or disease has proven one of the most difficult to clarify. This challenge stems from the various definitions of CMV (infection, syndrome, and disease), varying diagnostic modalities, and changing prophylaxis and treatment regimens.

Although early reports linked allograft invasive CMV pneumonitis (CMV-P) to an increased risk for BOS, the strongest evidence of this association comes from the preprophylaxis era (3, 4). Small retrospective studies indicated that routine use of ganciclovir for CMV prophylaxis perioperatively decreased CMV disease and delayed the onset of BOS as compared with no prophylaxis (5, 6). Consequently, most lung transplantation centers routinely employ a fixed duration of intravenous ganciclovir and/or oral valganciclovir prophylaxis immediately after transplantation. Although this practice is effective in preventing disease during the prophylactic period, CMV disease occurring after prophylaxis ends is increasingly recognized as an emerging problem among all solid organ transplant recipients (7). This “late-onset CMV disease,” often defined as disease after the prophylactic period ends, has been associated with increased risk for graft failure after kidney transplantation and increased mortality in liver transplant recipients despite adequate treatment for CMV disease once detected (8, 9). Several retrospective reports have also suggested that late-onset disease occurs frequently in lung recipients despite courses of prophylaxis as long as 3–6 months (10, 11).

We sought to clarify the clinical significance of treated CMV-P occurring as late-onset disease in the era of routine ganciclovir prophylaxis and treatment. Given the controversy and discrepancies between CMV infection, syndrome, and disease, we focused exclusively on CMV-P defined through prospective immunohistochemical staining of transbronchial biopsies. We hypothesized that, despite appropriate treatment, CMV-P will lead to a significantly increased risk for BOS and post-transplantation mortality. To test this idea, we evaluated the significance of CMV-P occurring in a large cohort of consecutive lung transplant recipients (n = 231) transplanted from 2000 to 2004 receiving short-course ganciclovir prophylaxis and

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standard CMV treatment. Recipients were monitored for a mean exceeding 6 years, allowing adequate follow-up for assessment of BOS or death.

We demonstrate that 21% of lung transplant recipients develop CMV-P, despite short-course prophylaxis. Furthermore, we demonstrate that treated CMV-P is associated with a significantly increased risk for BOS and worse post-transplantation survival in univariate and multivariate proportional hazards models. Some of the results of this study have been previously reported in the form of an abstract (12).

METHODS

Recipient Cohort

The institutional review board–approved study cohort consisted of all adult, first, cadaveric lung transplant recipients transplanted at Duke University Medical Center (Durham, NC) between January 1, 2000 and December 31, 2004. Of the 284 consecutive lung transplantations performed, 231 recipients met inclusion criteria and were monitored through October 2008. Excluded from the cohort were 8 retransplant recipients, 6 pediatric patients (age, <18 yr), 6 heart–lung recipients, 17 patients who died in the early post-transplantation period (<90 d), 13 patients with no pulmonary function test data available, and 3 patients who died more than 90 days but less than 180 days after transplantation with an insufficient number of pulmonary function tests available to adequately assess BOS. All recipients received similar immunosuppression and serial transbronchial biopsies (see the online supplement). CMV antibody serology was performed on all donor (D) and recipient (R) peripheral blood. Recipients at medium risk for CMV (D^+/R^+ or D^-/R^+) received 4 weeks of intravenous ganciclovir starting on the day of transplantation. Recipients at high risk for CMV (D^+/R^-) received 14 weeks of intravenous ganciclovir. Recipients at low risk for CMV (D^-/R^-) received 3 months of acyclovir. CMV immunoglobulin preparations were not used for prophylaxis.

Definition and Treatment of CMV-P

Prospective immunohistological staining for CMV was consistently performed on all transbronchial tissue biopsies (additional details may be found in the online supplement) throughout the study period. Once detected, CMV-P was treated with 3 weeks of intravenous ganciclovir at 5 mg/kg every 12 hours, with the dose adjusted for renal dysfunction.

Definition of Acute Rejection and BOS

Acute rejection was defined as per International Society for Heart & Lung Transplantation (ISHLT, Addison, TX) criteria (13). The acute rejection ratio was calculated by dividing the cumulative acute rejection score (e.g., $A1 + A2$ = acute rejection score of 3) by the number of evaluable transbronchial biopsies (Tbbx) per patient. Only acute rejection events and Tbbx occurring before BOS or the censor date were included in the acute rejection ratio. BOS (defined as grade 1 or higher) reflects a sustained drop in the current FEV₁ from the post-transplantation highest baseline average as defined by the ISHLT criteria (14). A diagnosis of BOS was made only after other causes of allograft dysfunction were excluded.

Statistical Analysis

Descriptive statistics were used for recipient demographics and include median and interquartile range when appropriate. Continuous variables were analyzed using nonparametric *t* tests and dichotomous variables were analyzed using chi-square tests. Cox proportional hazards models and Kaplan-Meier analyses were used to assess the relationship between CMV-P and BOS or death. CMV-P was considered both as a time-independent binary variable (present or absent in the first 6 mo) and as a time-dependent variable modeling the change in status once a CMV-P event occurred at any point after transplantation. Only CMV-P events before BOS were considered in the BOS analysis. Additional clinical predictors were considered in univariate analysis; significant predictors were then included in multivariate Cox models for BOS or death. Proportional hazard assumptions

were assessed and satisfied. All statistical analysis was performed using SAS software, version 9.1 (SAS, Cary, NC).

RESULTS

Recipient Characteristics

Recipient demographics are presented in Table 1. The cohort was predominantly white with a median age at transplantation of 54 years (interquartile range [IQR], 39–62). Obstructive lung disease was the most common indication for transplantation and the type of lung transplantation operation was almost entirely bilateral, reflecting our operation preference. There were 26 (11%) CMV low-risk recipients, 154 (67%) medium-risk recipients, and 51 (22%) high-risk recipients. Patients with pretransplantation gastroesophageal reflux disease underwent Nissen fundoplication within 6 months of transplantation, consistent with our center-specific evaluations and practice. Mean follow-up time for the study cohort was 6.7 years (maximum, 8.8 yr) with 1,887 transbronchial biopsies (mean, 9 biopsies per recipient) and 6,946 pulmonary function tests performed (mean, 30 tests per recipient). During the follow-up period, 103 (45%) subjects met criteria for BOS. At the conclusion of the follow-up period, 149 patients were alive and 82 patients (35.5%) were deceased.

Incidence and Time to CMV-P

Of the 231 recipients in the cohort, 49 (21%) had at least one episode of CMV-P with 33 (67%) experiencing CMV-P within the first 6 months after transplantation. Only two recipients (4%) received lympholytic therapy before the onset of CMV-P. The median time to onset for CMV-P was 106 days (IQR, 83–198). When CMV-P incidence was considered by CMV mismatch status, it occurred in 2 (7.7%) of the 26 low-risk recipients, 36 (23.4%) of the 154 medium-risk recipients, and 11 (21.6%) of the 51 high-risk mismatch recipients. The two low-risk recipients developed CMV-P at 44 days and 107 days after transplantation. The median time to CMV-P among

TABLE 1. LUNG TRANSPLANT RECIPIENT COHORT CHARACTERISTICS

Characteristic	Value
Sex	
Male	55% (n = 128)
Female	45% (n = 103)
Race	
White	91% (n = 210)
Other	9% (n = 21)
Median age at transplant, yr (IQR)	54 (39–62)
Native disease	
Obstructive	45% (n = 105)
Vascular	2% (n = 5)
Cystic fibrosis	23% (n = 54)
Restrictive	29% (n = 67)
Type of transplant	
Single lung transplant	4% (n = 9)
Bilateral lung transplant	96% (n = 222)
Early Nissen fundoplication	22% (n = 51)
CMV donor/recipient serology	
D^-/R^- (low risk)	11% (n = 26)
D^- or D^+/R^+ (medium risk)	67% (n = 154)
D^+/R^- (high risk)	22% (n = 51)
Patients with BOS	45% (n = 103)
Mean time to onset of BOS (SE)	5.0 yr (61 d)
Mean post-transplantation survival, yr (max)	6.7 (8.8)

Definition of abbreviations: BOS = bronchiolitis obliterans syndrome; CMV = cytomegalovirus; IQR = interquartile range.

medium-risk recipients was 96 days (IQR, 81–186) or 68 days after discontinuation of prophylaxis. The high-risk recipients that developed CMV-P had their first episode a median of 198 days after transplantation (IQR, 89–417) or 94 days after discontinuation of prophylaxis.

CMV-P as a Predictor of BOS

To fully characterize the relationship between treated CMV-P and BOS, we considered the impact of CMV-P in two separate models. First, as shown in Figure 1, when considered as a time-independent variable, CMV-P, occurring within the first 6 months after transplantation, was associated with a significantly increased risk for BOS ($P = 0.001$; unadjusted hazard ratio [HR], 2.19; 95% confidence interval [CI], 1.36–3.51). Second, when considered as a time-dependent variable, the development of CMV-P at any time post-transplantation, before the onset of BOS, also was associated with a significantly increased risk for BOS ($P = 0.003$; unadjusted HR, 1.92; 95% CI, 1.24–2.96).

Next, we sought to determine whether the effect of CMV-P varied by CMV risk group. In subset analysis comparing CMV high-risk versus medium-risk groups, a similar increased hazard for BOS was observed. Furthermore, a formal test for an interaction between CMV-P and CMV risk groups was not significant, suggesting the effect of CMV-P did not vary among CMV risk groups.

We then considered whether the increased risk for BOS with treated CMV-P was related to a difference in the incidence of acute rejection. Within the first 6 months, the incidence of acute rejection was 61% in those with CMV-P and 57% in those without CMV-P ($P = 0.70$). In addition, before the onset of BOS, the mean acute rejection ratio did not differ between patients with CMV-P and those without CMV-P (0.39 vs. 0.35, respectively; $P = 0.96$).

Finally, we examined whether the increased risk for BOS among patients with CMV-P was due to sampling bias. The mean number of biopsy samples obtained before the onset of BOS and immunostained for CMV was similar among those

Figure 1. Cytomegalovirus pneumonitis (CMV-P) within 6 months of transplantation increases the risk for bronchiolitis obliterans syndrome (BOS) ($P = 0.0009$; unadjusted hazard ratio, 2.19; 95% confidence interval, 1.36–3.51). Numbers under the graph indicate the recipients at risk for BOS and those who had developed BOS (failed) at each time point for CMV-P.

with or without CMV-P (9.84 vs. 9.08, respectively; $P = 0.40$). In addition, the mean number of pulmonary function tests over the course of transplantation did not vary between those with and without CMV-P (30.33 vs. 30.00, respectively; $P = 0.54$).

Multivariate Analysis of CMV-P as a Predictor of BOS

We sought to confirm that the impact of treated CMV-P on BOS was independent of other factors that might affect the risk of BOS. In univariate analysis that individually considered sex, age, race, type of transplantation, Nissen fundoplication (for gastroesophageal reflux, within 6 mo of transplantation), acute rejection ratio, era (before or after May 2002), and CMV risk group, only the type of transplantation and acute rejection ratio were identified as significant predictors of BOS (single lung transplantation: $P = 0.006$; HR, 2.77; 95% CI, 1.34–5.71; acute rejection ratio: $P = 0.01$; HR, 2.42; 95% CI, 1.23–4.75). Therefore, in multivariable analysis, the impact of treated CMV-P either as a time-independent or time-dependent predictor was considered in conjunction with these other terms. As shown in Table 2, treated CMV-P remained a significant predictor of BOS and hazards were relatively constant when adjusting for type of transplantation and acute rejection ratio.

CMV-P and Conditional Survival

When considered as a time-independent variable, CMV-P within the first 6 months predicted significantly worse conditional survival ($P = 0.02$; unadjusted HR, 1.89; 95% CI, 1.11–3.23). Five-year conditional survival by Kaplan-Meier estimates was 71% in those patients without CMV-P over the first 6 months as compared with 53% in those patients with CMV-P, $P = 0.018$ (Figure 2). When considered as a time-dependent predictor, a similar trend was observed ($P = 0.05$; unadjusted HR, 1.63; 95% CI, 0.99–2.69). In a multivariate model, CMV-P within the first 6 months remained significantly associated with increased mortality, independent of acute rejection ratio and bilateral transplantation ($P = 0.03$; adjusted HR, 1.82; 95% CI, 1.06–3.11).

DISCUSSION

CMV is one of the most prevalent and important opportunistic infections affecting lung transplant recipients. Direct manifestations include tissue-invasive CMV-P, symptomatic viral syndrome, and asymptomatic viremia (15). Retrospective studies suggest that antiviral prophylaxis has reduced the incidence of CMV infection and invasive disease as compared with no prophylaxis (16). More recently, the concern about CMV in solid organ transplantation has shifted to late-onset CMV disease and its implications for long-term outcomes.

In the current analysis, we demonstrate that 21% of lung transplant recipients develop tissue-invasive CMV-P despite short-course prophylaxis. CMV-P episodes were treated with appropriate antiviral therapy, yet CMV-P led to an increased risk for BOS and worse survival in both univariate and multivariate models. Strengths of our study include a well-characterized cohort that received standardized management and surveillance bronchoscopy protocols consistently applied in all patients as well as extended follow-up that provides adequate time for BOS to develop. In addition, our report is the only analysis of CMV-P in lung transplantation to use prospective immunostaining to precisely define the occurrence of CMV-P, rather than relying on subjective identification of virally infected cells on the basis of conventional histology or bronchoalveolar lavage shell vial culture. Immunohistochemical staining for early CMV nuclear antigens has been shown to detect CMV pneumonitis before culture or cytopathic changes, particularly in asymptomatic lung

TABLE 2. ASSOCIATION OF CYTOMEGALOVIRUS PNEUMONITIS WITH INCREASED RISK OF BRONCHIOLITIS OBLITERANS SYNDROME: UNIVARIATE AND MULTIVARIATE MODELS

CMV Variable Type	Univariate Model		Multivariate Model*	
	HR (95% CI)	P Value	HR (95% CI)	P Value
CMV-P time-independent variable (in the first 6 mo)	2.19 (1.36–3.51)	0.001	2.11 (1.31–3.39)	0.002
CMV-P time-dependent variable	1.92 (1.24–2.96)	0.003	1.88 (1.21–2.90)	0.005

Definition of abbreviations: CMV = cytomegalovirus; CMV-P = cytomegalovirus pneumonitis; CI = confidence interval; HR = hazard ratio.

* Adjusted for type of transplantation and acute rejection ratio.

transplant recipients (17). In this analysis of 78 transbronchial lung transplantation biopsies, cytopathic changes consistent with CMV pneumonitis correlated with positive immunostains for early and early-immediate CMV nuclear antigens in biopsies from symptomatic recipients (93 and 87%, respectively). However, immunohistochemistry was positive for CMV antigens without cytopathic changes in 50% of the asymptomatic recipients. All of these recipients subsequently developed symptoms that prompted an additional biopsy, which then produced evidence of CMV cytopathic changes. Bronchoalveolar lavage shell vial culture was positive in 60% of symptomatic recipients and 3% of asymptomatic recipients, thus far inferior to histology or immunohistochemistry. Thus, we believe immunostaining for early and immediate-early CMV antigen, as was done in this study, provides the most specific and sensitive assessment for CMV-P. Finally, our statistical analysis recognizes and adjusts for the time-dependent nature of CMV-P as a risk factor for the time-dependent outcomes of BOS or death. We first considered CMV-P as a dichotomous time-independent variable occurring within the first 6 months of transplantation. This approach captured most CMV events and simplified the model by avoiding inclusion of CMV as a time-dependent predictor variable. In addition we considered CMV-P development at any point in time as a time-dependent predictor on the risk for BOS. Collectively, these approaches yielded similar results and provide compelling evidence that CMV-P significantly increases the risk for BOS. In addition, the multivariable model that accounts for other BOS risk factors demonstrates that the effect of CMV-P is independent of other factors.

In contrast to our findings, another single-center report failed to identify treated CMV-P as a predictor of BOS or worse survival (18). Several factors, however, limit the strength of that study's conclusions and likely explain the differences observed between our cohorts. First, the cohort in that study included lung and heart–lung patients transplanted over a 14-year period. Although of historical interest, the cohort demographics and clinical management are not comparable to current practices. Furthermore, CMV-P was diagnosed by cytopathic effect rather than prospective immunohistochemistry, creating potential misclassification bias. Most importantly, the analysis treated CMV disease as a fixed variable at the start of transplantation regardless of the time post-transplantation at which it occurred; failure to recognize the time-dependent nature of CMV-P could have easily biased results and obscured the effect of CMV-P on BOS and survival.

Despite the unique strengths of our study, several potential limitations also exist. First, although our sample generally is representative of a large cohort of lung transplant recipients, certain aspects of the cohort limit generalization to all lung transplant recipients. Our center has a strong preference for a bilateral lung transplantation operation and Nissen fundopli-

CMV-P, # At Risk:	33	27	20	8	1
# Failed:	0	6	13	16	17
No CMV-P, # at Risk:	198	180	147	66	18
# Failed:	0	18	39	62	65

Figure 2. Cytomegalovirus pneumonitis (CMV-P) within 6 months of transplantation increases the risk for death ($P = 0.018$; unadjusted hazard ratio, 1.89; 95% confidence interval, 1.11–3.23). Numbers under the graph indicate the recipients at risk for death and those who had died (failed) at each time point for CMV-P.

cation in appropriate patients, and while these practices are increasingly being adopted by other centers, it is not a universal approach. Second, although all patients in our study received intravenous ganciclovir prophylaxis, CMV prophylaxis has continued to evolve and now often includes longer prophylactic periods. Although there is no standard of care regarding CMV prophylaxis among lung transplantation centers, reports of longer CMV prophylactic periods (up to 6 mo) have resulted in rates of CMV-P similar to those in this report (11, 19). These data would indicate that longer course ganciclovir prophylaxis delays, but does not ultimately prevent, CMV disease. An important question concerns whether a delay in CMV disease changes the risk of BOS. As longer CMV prophylactic strategies are a relatively recent concept, the impact of delayed onset of CMV-P on BOS will not be apparent for several years, but clearly warrants further study. Third, our analysis did not consider all the factors that could potentially influence the development of BOS (20). For

example, evidence suggests humoral immunity or autoimmunity might contribute to BOS, factors not measured in this analysis. Pulmonary infections other than CMV have also been implicated as possible risks for BOS. We reviewed the positive respiratory cultures for bacterial, viral (other than CMV), or fungal pathogens of all recipients in our cohort and did not find a significant difference in pulmonary infections between recipients with or without CMV-P before the onset of BOS. Given the strength of our findings, it seems unlikely that the inclusion of additional predictor variables would significantly alter our results. Finally, we limited our analysis to CMV-P, rather than CMV infection or syndrome. With changing diagnostic modalities (antigenemia vs. PCR) and inconsistent sampling for the diagnosis of CMV in peripheral blood, we chose to focus on the definite diagnosis of CMV-P by prospective immunohistochemical staining. Thus, our results cannot address the impact of other CMV infections on BOS.

In summary, our results demonstrate that treated CMV-P is a risk factor for BOS and worse survival after lung transplantation. The mechanisms underlying this association are unclear but may involve local pulmonary up-regulation of chemokines and cytokines that occurs despite treatment and promotes subsequent adaptive alloimmune injury (21). Further understanding of the mechanisms contributing to post-transplantation CMV disease is needed. Ultimately, a strategy in which the duration of antiviral prophylaxis is linked to measures of recipient CMV-specific immunity might provide the best means to ensure sustained prevention of CMV in this high-risk patient population.

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