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Revisiting the pathologic finding of diffuse alveolar damage after lung transplantation

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BACKGROUND: Diffuse alveolar damage (DAD) is a non-specific pathologic diagnosis frequently encountered after lung transplantation. We examined the relationship between DAD and different forms of chronic lung allograft dysfunction (CLAD).

METHODS: We reviewed the results of 4,085 transbronchial biopsies obtained from 720 lung transplant recipients. DAD detected in biopsies within 3 months and newly detected DAD after 3 months were defined as early DAD and late new-onset DAD, respectively. Among patients with CLAD (FEV_1 <80% baseline), restrictive allograft syndrome (RAS) was defined by a decline in total lung capacity to <90% baseline and bronchiolitis obliterans syndrome (BOS) as CLAD without restrictive allograft syndrome (RAS). Kaplan–Meier analyses and multivariate proportional hazard models were used.

RESULTS: DAD was observed in 320 of 720 (44.4%) patients at least once; early and late new-onset DAD were observed in 264 of 707 (37.3%) and 87 of 655 (13.3%) patients, respectively. Early DAD was associated with significantly higher 90-day mortality (20 of 264 [7.6%] vs 11 of 443 [2.5%]; $p = 0.001$). Moreover, among 502 bilateral lung transplant recipients who had sufficient pulmonary function tests to distinguish BOS and RAS, early DAD was associated with earlier BOS onset (hazard ratio [HR] 1.24; confidence interval [CI] 1.04 to 1.47; $p = 0.017$; median time of BOS onset: 2,902 vs 4,005 days). Conversely, treated as a time-varying covariate, late new-onset DAD was a significant risk factor for RAS in a Cox model (HR 36.8; CI 18.3 to 74.1; $p < 0.0001$).

CONCLUSIONS: Early DAD is associated with early mortality and BOS, and late new-onset DAD increases the risk of RAS.

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Diffuse alveolar damage (DAD) is a histologic pattern seen on lung biopsies and can be caused by infections, drug reactions, inhalational injuries and other forms of insult.[1] In lung transplantation, DAD is frequently encountered in biopsies, particularly in the early post-transplant period. The prevalence of DAD decreases from 30% at Week 2 to <10% thereafter; in one retrospective analysis, during the first 3 months post-transplantation, 36% of patients were diagnosed with at least 1 episode of DAD.[2] Approximately 80% of DAD cases were observed within 4 months after lung transplantation.[3] This early DAD is likely to be associated with peri-operative insults to the transplanted lungs, such as primary graft dysfunction (PGD) related to ischemia–reperfusion injury with or without concurrent infection.[2,3] Fisher et al reported significant association between early post-transplant DAD and post-transplant 30-day mortality,[4] apparently reflecting the mortality risk of PGD after lung transplantation.

Despite those findings, the relationship between DAD and chronic lung allograft dysfunction (CLAD) remains to

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be explored in detail. Fisher and colleagues reported that, among patients who survived >30 days, early post-transplant DAD was not associated with survival or development of bronchiolitis obliterans syndrome (BOS).[4] Nevertheless, this result seems inconclusive, partly because of the relatively small cohort of patients. Because accumulating evidence suggests that BOS is not the only form of chronic lung allograft dysfunction (CLAD), it is also possible that the study was confounded by inaccurate diagnosis of BOS. We have recently identified a novel form of CLAD and named it restrictive allograft syndrome (RAS) because of the restrictive physiology and radiologic and pathologic characteristics of fibrosis in peripheral lung tissue, including alveoli, pleura and interlobular septa.[5] Identification of RAS separates it from the BOS population with true obstructive physiology and may affect the interpretation of previous reports.[5] Given that the pathologic process underlying RAS appears to affect peripheral lung tissue, it is possible that RAS is associated with DAD. Indeed, examination of the explanted lungs of some patients with RAS undergoing re-transplantation indicated evidence of DAD at various stages, and extensive fibrosis in the alveolar interstitium, visceral pleura and interlobular septa.[5]

In addition, the role of late new-onset DAD is unclear. Approximately 20% of DAD cases have been observed in the time period well after the lung transplant procedure.[2] The cause of DAD in such cases could include infection and severe acute rejection, but is frequently unknown.[2,3] The clinical outcome of such late new-onset DAD has not been well explored in the light of the new diagnosis of RAS as well as pure BOS.

The purpose of our study was to revisit the diagnosis of DAD and examine the role of DAD in the development of BOS and RAS as well as early mortality. We detected an association between early DAD and BOS, and a strong association between late new-onset DAD and RAS.

Methods

Patients and transbronchial biopsies

We systematically reviewed the clinical records and pathology reports of 824 patients who received lung transplantation, including single lung, bilateral lung, and heart–lung transplantation, from 1996 to March 2010, in the Toronto Lung Transplant Program. Scheduled transbronchial biopsies were recommended at 2 and 6 weeks and 3, 6, 9, 12, 18 and 24 months after lung transplantation in the program's protocol. Those who received at least one transbronchial biopsy (either scheduled or clinically indicated) were used for survival analyses. Among these patients, we analyzed the impact of DAD on CLAD (BOS and RAS) in those who received bilateral lung or heart–lung transplantation and survived >3 months with sufficient pulmonary function test (PFT) data, as described in what follows. This study was approved by the research ethics board of the University Health Network.

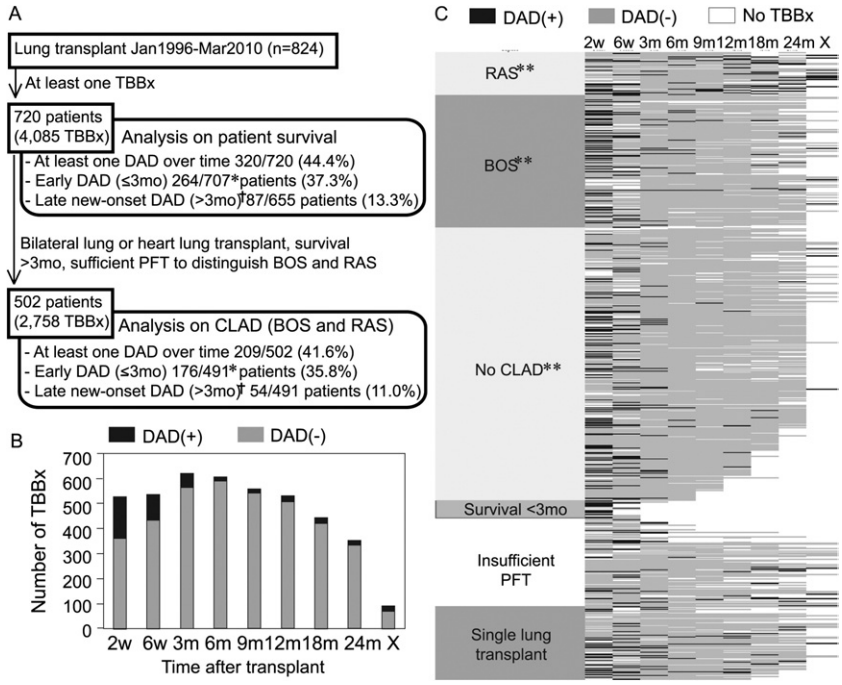

Figure 1 Overview of the separation of patients and frequency of DAD. (A) Overview of the separation of patients. (B) Frequency of DAD in transbronchial biopsies over time. (C) Distribution of DAD in transbronchial biopsies over time among different categories of patients. TBBx, transbronchial biopsies; PFT, pulmonary function test; CLAD, chronic lung allograft dysfunction; BOS, bronchiolitis obliterans syndrome; RAS, restrictive allograft syndrome. *Only patients who received at least one biopsy within 3 months included. †Only patients who received at least one biopsy after 3 months included. **Patients in the three groups, RAS, BOS and no CLAD, represent the 502 patients who were analyzed in the second step, as shown in (A).