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Progression pattern of restrictive allograft syndrome after lung transplantation

Masaaki Sato, MD, PhD,[a,b] David M. Hwang, MD, PhD,[a] Thomas K. Waddell, MD, MSc,[a] Lianne G. Singer, MD,[a] and Shaf Keshavjee, MD, MSc[a]

From the [a]Toronto Lung Transplant Program, University Health Network, University of Toronto, Ontario, Canada; and the [b]Department of Thoracic Surgery, Kyoto University, Kyoto, Japan.

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BACKGROUND: Restrictive allograft syndrome (RAS) is a novel form of chronic lung allograft dysfunction after lung transplantation. RAS is characterized by restrictive physiology and peripheral lung fibrosis. The purpose of the study is to analyze progression patterns of RAS.

METHODS: Clinical information, pulmonary function test results and radiographic findings were reviewed for 25 RAS patients who received bilateral lung or heart–lung transplantation between January 2004 and December 2009.

RESULTS: Average time from transplantation to RAS onset was 647 ± 544 (mean ± SD) days; RAS onset to end of observation (death or re-transplantation) was 490 ± 417 days. RAS patients had 1 to 4 episodes of acute exacerbation (2.48 ± 0.82 episodes/patient) that accompanied acute respiratory deterioration or distress, a sudden drop in pulmonary function, evidence of diffuse alveolar damage (DAD) on biopsies, and patchy or diffuse ground-glass opacities (GGO) with occasional consolidation on computed tomography scan. Patients were most frequently managed by high-dose steroid in combination with empirical antibiotics, with uncertain efficacy. Acute exacerbation was followed by an interval during which resolution of GGO and progression of consolidation, interstitial reticular shadows and traction bronchiectasis were frequently observed. The interval between episodes of acute exacerbation was 238 ± 165 days. In 21 patients, the last episode of acute exacerbation led to death or urgent retransplantation.

CONCLUSIONS: RAS shows a "stair-step" pattern of progression. Acute lung injury represented by DAD and GGO is followed by an interval period during which graft fibrosis often progresses.

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Restrictive allograft syndrome (RAS) is a novel form of chronic lung allograft dysfunction (CLAD) after lung transplantation.[1] In contrast to bronchiolitis obliterans syndrome (BOS), which is characterized by small airway fibrosis and obstructive physiology, RAS is characterized by peripheral lung fibrosis and restrictive physiology.[1] In our recent study, RAS accounted for 25% to 35% of CLAD,[1] and the survival of RAS patients after CLAD onset was significantly shorter than that of BOS (median survival 541 days vs 1,421 days).[1] Such wide prevalence and negative clinical impact of RAS have recently been confirmed by the Leuven investigators.[2]

A practical problem in the management of RAS patients is uncertainty in making the clinical diagnosis. We defined RAS as a form of CLAD that accompanies irreversible restrictive physiologic changes based on pulmonary function tests (PFTs).[1,3] Although the diagnostic criteria were useful in a retrospective study, they do not seem very helpful in prospective patient management. A patient

Reprint requests: Shaf Keshavjee, MD, MSc, Toronto Lung Transplant Program, Toronto General Hospital, 200 Elizabeth Street, 9N947, Toronto, ON M5G 2C4, Canada. Telephone: 416-340-4010. Fax: 416-340-4556.
E-mail address: dr.shaf.keshavjee@uhn.on.ca

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developing RAS is often too sick to undergo PFT[3] and, even if such testing can be performed, it is nearly impossible to determine whether the PFT decline can be reversed in a timely manner. Moreover, given the novelty of RAS as a diagnostic category, a detailed clinical course of RAS has not been well described. Thus, even if the diagnosis of RAS were to be made, it would be difficult for lung transplant physicians to predict what would happen next for the patient.

Given such difficulties in diagnosis and management of RAS, more detailed descriptions of RAS are needed. In particular, radiologic characterization of RAS may be a valuable aid for lung transplant physicians. RAS is characterized by multiple radiographic abnormalities, including ground-glass opacities (GGO), interstitial reticular shadows and interlobular septal thickening.[1] However, our previous study was limited in that only the latest computed tomography (CT) scan was evaluated; hence, the CT scans evaluated were mostly those of terminal-stage RAS patients. Understanding the progression patterns of radiographic abnormalities in RAS and their association with clinical information would be helpful for lung transplant physicians.

The purpose of the present study is to characterize progression pattern of RAS. We have demonstrated here that RAS shows a "stair-step" pattern of progression. Acute lung injury represented by diffuse alveolar damage (DAD) and GGO is followed by an interval period during which graft fibrosis often progresses.

Methods

Definition of CLAD and RAS

CLAD and RAS were defined as described previously.[1] In brief, baseline forced expiratory volume in 1 second (FEV_1) was defined according to criteria recommended by the International Society for Heart and Lung Transplantation,[4] and then the baseline values of other PFT parameters were taken as the average of the parameters measured at the time of the best FEV_1 measurements. CLAD was defined as an irreversible drop of FEV_1 to $<80\%$ of baseline. RAS was defined as a condition in which restrictive physiology, defined by an irreversible decline in total lung capacity (TLC) to $<90\%$ of the baseline, coexists with CLAD.

Patients

Among the 302 patients who received bilateral lung or heart–lung transplantation in the Toronto Lung Transplant Program from January 1, 2004 to June 30, 2009 and survived >3 months with sufficient follow-up data, including measurements of TLC, 89 developed CLAD by April 30, 2011. Of these, 27 patients (30.3%) showed a RAS phenotype. Monthly spirometry was recommended for at least the first 2 years after transplant, with testing every 1 to 3 months thereafter. TLC was measured using plethysmography at least every 3 months in the first year, every 6 months in the second year, and annually thereafter. Detailed clinical information, including symptoms at the time of acute exacerbation, treatment conducted, and pathologic, radiologic and microbiologic results were available from 25 patients and studied further.

Acute exacerbation

Acute exacerbation was defined as a sudden-onset or aggravation of respiratory distress that necessitated increased oxygen supplementation, hospital admission or mechanical ventilation. The first date when the symptomatic deterioration was recorded was defined as onset date of the episode of acute exacerbation. Symptoms (dry or productive cough and fever), results of sputum culture and bronchoalveolar lavage, biopsies (transbronchial or open lung biopsies) and treatment (changes or augmentation of immunosuppression, anti-microbial medication) at the time of acute exacerbation were reviewed in patient charts. Findings in chest CT reports were reviewed in patient charts; at the same time, chest CT scans were reviewed at 3 levels (aortic arch, tracheal bifurcation and inferior pulmonary vein). Appearance or aggravation of GGO, consolidation, interstitial reticular shadow and traction bronchiectasis were recorded. GGO was further classified into patchy (seen in fewer than 2 lobes) or diffuse.

Intervals between episodes of acute exacerbation

The first change in the slope of FEV_1 after the initiation of acute exacerbation was taken as the end of the acute exacerbation episode (Figure 1). Clinical courses after an episode of acute exacerbation were classified based on post-exacerbation FEV_1 changes (Figure 1). These included: *complete recovery*—recovery of pulmonary function (FEV_1) close to the level of pre-exacerbation over time ($>80\%$ from the end of acute exacerbation); *partial recovery*—recovery of pulmonary function (FEV_1) after acute exacerbation $>20\%$, but not to the level before acute exacerbation ($<80\%$); *stable disease*—stable FEV_1 after acute exacerbation (improvement or decline $<20\%$ to the end of acute exacerbation); and *progressive disease*—a progressive decline in FEV_1 after acute exacerbation (decline $>20\%$ after the episode of acute exacerbation).

Results

Patient demographics of the 25 RAS cases examined are shown in Table 1. Among them, 3 patients initially showed BOS phenotype and then developed RAS. Although the number of patients with cystic fibrosis was relatively large

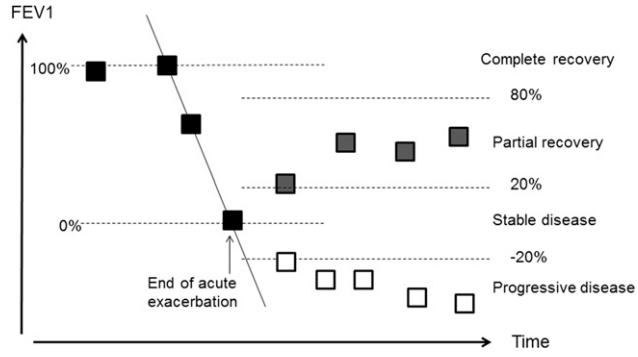

Figure 1 Acute exacerbation and definition of clinical course during the period of study. The first change in the slope of FEV_1 after the initiation of acute exacerbation was taken as the end of the acute exacerbation episode. Clinical courses after an episode of acute exacerbation were classified based on post-exacerbation FEV_1 changes.