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Original Article

CT findings of native lung after single lung transplantation in patients with idiopathic pulmonary fibrosis: long-term outcomes

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Abstract: To evaluate the progression of native lung fibrosis on thin-section computed tomography (CT) scans from patients with IPF after SLT, we retrospectively studied thin-section CT findings of the patients who survived more than 3 years. Three radiologists independently reviewed serial CT images from 12 patients who underwent SLT for IPF. Initial CT scans were performed up to 7 months before SLT or ≤12 months after SLT, and follow-up CT scan were performed >36 months after SLT. CT measurements of the total lung volume were performed on native lungs. CT scores were evaluated for native lung findings for each thin-section CT, including the fibrosis score (FS), ground-glass opacity score (GGS), and traction bronchiectasis score (TBS). Twelve patients survived 43-110 months after SLT. In the native lung, the FS and TBS values were positively correlated with time. Rates of increase in the FS and TBS values were 0.300/year and 0.147/year, respectively. The GGS showed a slight negative correlation with the lung volume from the CT reconstruction. Rates of decrease of the GGS and lung volume measurements were 0.307/year and 5.47%/year, respectively. The results show that despite more powerful immunosuppression, fibrosis of native lung continues to progress in patients who receive SLT for IPF.

Keywords: Lung transplant, idiopathic interstitial pneumonia, usual interstitial pneumonia, computed tomography, progression

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic relentlessly progressive and fatal lung disease that leads to reduction in lung volumes and impaired gas exchange [1]. Patients with IPF have a poor prognosis; the mean life expectancy from the time of diagnosis ranges 2.4-4.2 years [2]. Clinical trials have been initiated recently to determine the effectiveness of alternative therapeutic agents for IPF; however, to date, no pharmacological therapy has been demonstrated to be effective for IPF [3]. Currently, the only long-term effective treatment for IPF is lung transplantation. Patients who undergo lung transplantation have survival rates of only 50% at 5 years and 26% at 10 years after transplantation [4].

Single lung transplantation (SLT) for patients with IPF provides a unique opportunity to study fibrosis in the native lung over time in a setting of pronounced immunosuppression. At our institution, lung transplant recipients are typically treated with a lifelong regimen of steroids, an antiproliferative agent (e.g., mycophenolate mofetil), and a calcineurin inhibitor (e.g., tacrolimus). Quantitative scoring methods are an acceptable modality for evaluating lung fibrosis progression on CT scans [5, 6]. However, few published reports describe the analysis of long-term lung fibrosis from CT scans of the native

lung after SLT in patients with IPF [7-9]. Therefore, we performed a quantitative analysis of lung volumes and fibrosis severity in sequential thin-section chest CT scans of patients who underwent SLT for IPF. The goal of this retrospective analysis was to determine whether the above combination of immunosuppressive agents could arrest the progression of fibrosis. Our study is the first to perform a direct quantitative analysis of CT scans for fibrosis progression and to examine the longitudinal outcomes of IPF patients after SLT.

Materials and methods

Patients

Among the 76 patients who underwent SLT for IPF at our center between Sep 1994 and Mar 2008, sequential serial CT scans were available for 12 patients who, consequently, were included in this study. The CT scans of the 12 patients were performed at our institution between Jan 2000 and Jan 2011. Clinical diagnosis of IPF at our institution is made on the basis of the following criteria: exclusion of other known causes of interstitial lung disease, characteristic abnormalities on thin-section CT scans (i.e., bibasilar subpleural honeycombing, thick interlobular septa, traction bronchiectasis, and minimal ground-glass opacity [GGO]), and abnormal pulmonary function studies showing restriction and impaired gas exchange, according to the American Thoracic Society/European Respiratory Society (ATS/ERS) consensus classification criteria [10]. Pathological diagnosis of usual interstitial pneumonia was confirmed in the resected lung from all patients. Pulmonary function testing was performed in all patients within 3 months before lung transplantation.

All included patients had undergone at least two serial CT examinations; an initial CT scan was performed up to 7 months before or within 12 months after SLT, and follow-up CT scans were performed >36 months after SLT. Patients without a suitable preliminary CT scan or follow-up CT scan within 3 years after SLT were excluded.

The post-SLT immunosuppression regimen was a standard three-drug regimen consisting of tacrolimus, mycophenolate mofetil, and prednisone in all patients. Azathioprine, N-acetylcysteine, and gamma-interferon were added in some patients.

CT technique

Over the time course of this retrospective series, CT scans were performed on various hardware, including Lightspeed CT scanners (Lightspeed QX/i, Ultra, and VCT models; GE Healthcare, Milwaukee, WI, USA). CT images were obtained with a section thickness of 1.25-2.5 mm, interval of 10 mm during full inspiration, reconstruction matrix of 512*512, high-spatial-frequency reconstruction algorithm, tube voltage of 120-140 kV, and tube current-time product of 150-210 mAs, with or without injection of contrast material. CT images were evaluated by using a lung window, with a window level of -500 HU and window width of 1,500 HU. The soft-tissue window was not evaluated.

Image interpretation and thin-section CT scoring

All thin-section CT images were reviewed by three radiologists. The reviewers were aware of the diagnosis of IPF. Pre- and post-transplantation scans were reviewed without blinding to laterality of the native lung. For the analysis of all scans, readers were blinded to the names of patients and the length of time since transplantation.

To evaluate the native lung, we choose four sections from each patient's scan at the levels of the arterial arch, tracheal carina, inferior pulmonary vein, and 1 cm inferior to the diaphragm. On each section, the native lung was scored separately on a scale from 0 to 5 for the presence of fibrosis and GGO. A previously described fibrosis scoring system that integrates the severity of honeycombing and reticular opacities was used to evaluate the thin-section CT images [11]. The fibrosis score (FS) was determined as follows: 0, no interstitial disease; 1, interlobular septal thickening, no discrete honeycombing; 2, honeycombing (with or without septal thickening) involving ≤25% of the lobe; 3, honeycombing (with or without septal thickening) involving 25-49% of the lobe; 4, honeycombing (with or without septal thickening) involving 50-75% of the lobe; and 5, honeycombing (with or without septal thickening)

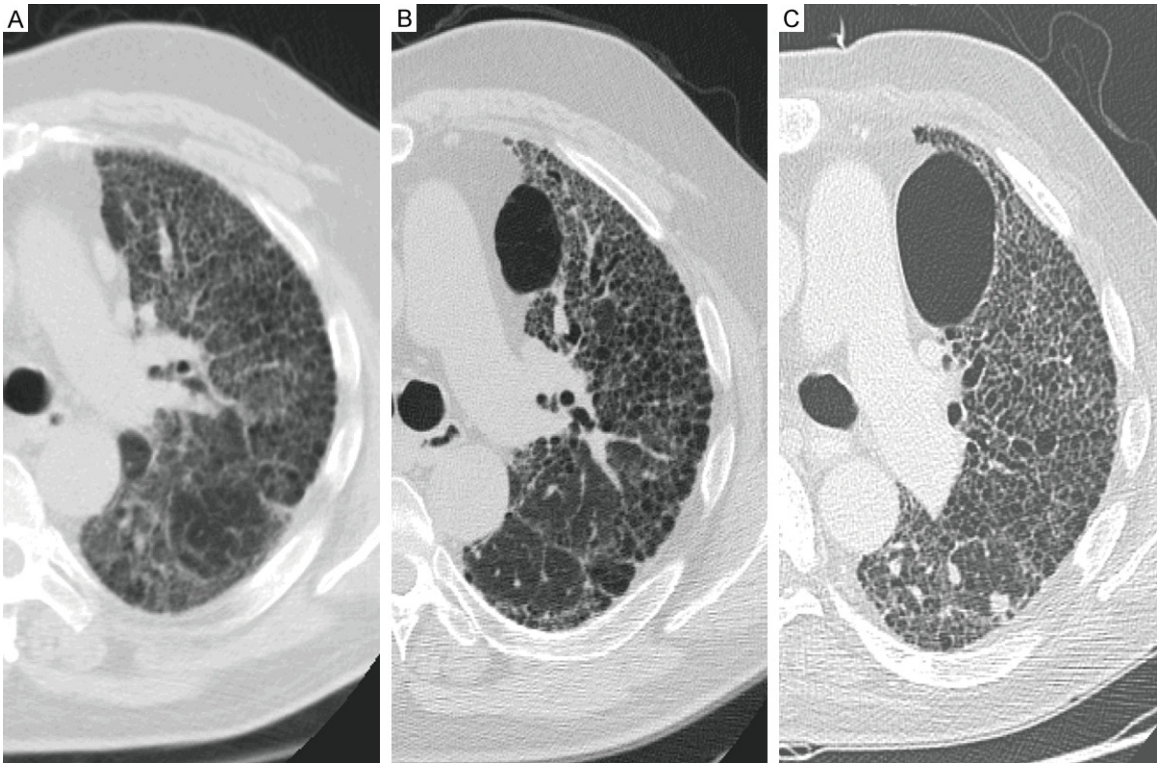

Figure 1. Progression of fibrosis on CT scans of the native lung of a 57-year-old male patient with IPF at (A) 11 months, (B) 36 months, and (C) 75 months post-SLT.

involving >75% of the lobe. The GGO score (GGS) was determined as follows: 0, no GGO; 1, GGO involving <5% of the lobe (minimal, but not normal); 2, GGO involving 5-25% of the lobe; 3, GGO involving 25-49% of the lobe; 4, GGO involving 50-75% of the lobe; and 5, GGO involving >75% of the lobe.

The degree of traction bronchiectasis or bronchiolectasis was quantified by assessing the level of the most proximal involved bronchial branches. The traction bronchiectasis score (TBS) was determined as follows [12]: 0, none; 1, bronchial dilatation involving bronchi distal to the fifth generation; 2, bronchial dilatation involving fourth-generation bronchi; and 3, bronchial dilatation involving bronchi proximal to the third-generation bronchi.

After each section was scored individually, an average score of all sections of a single scan was obtained and used for statistical analysis. We also recorded other manifestations of the native lung, transplanted lung, and pleural space, such as consolidation, nodules, emphysema, and pleural effusion.

CT lung volume measurement

We reconstructed the three-dimensional native lung and measured the volume of the native lung of each patient in the workstation (AW2, GE Healthcare), using the "Lung Volume" tool. We removed the volume of the threshold outside the scope of -2000 to 80 Hu, to obtain a three-dimensional representation of the native lungs and to assess their volume.

Statistical analysis

SPSS statistical software was used for the statistical analysis (SPSS v.13, SPSS Inc., Chicago, IL, USA). Pearson's linear regression analysis was used to test the correlation between years since transplantation and fibrosis in the prediction of IPF progression. A *P*-value <0.05 was considered statistically significant.

Results

Twelve patients (3 female, 9 male; age range: 49-66 years, mean age: 58.6 years) met our selection criteria between Jan 2000 and Feb 2012 and were entered into the study. Eight

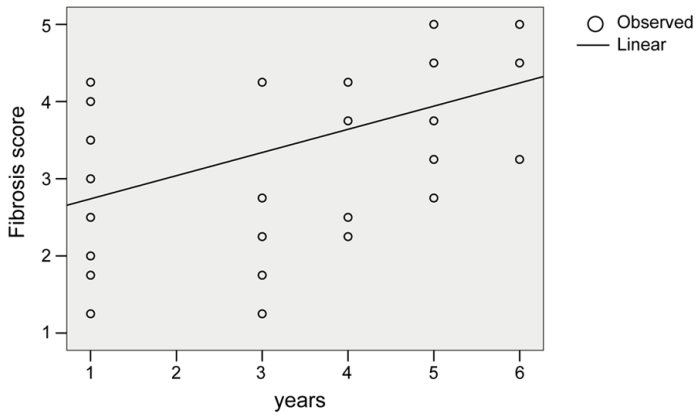

Figure 2. Changes in the fibrosis score over time.

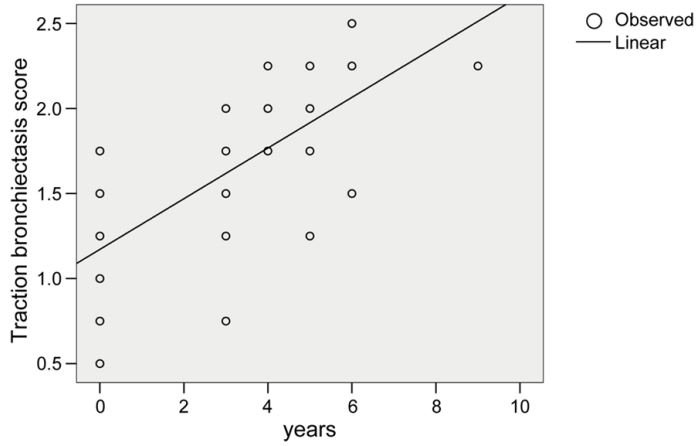

Figure 3. Changes in the traction bronchiectasis score over time.

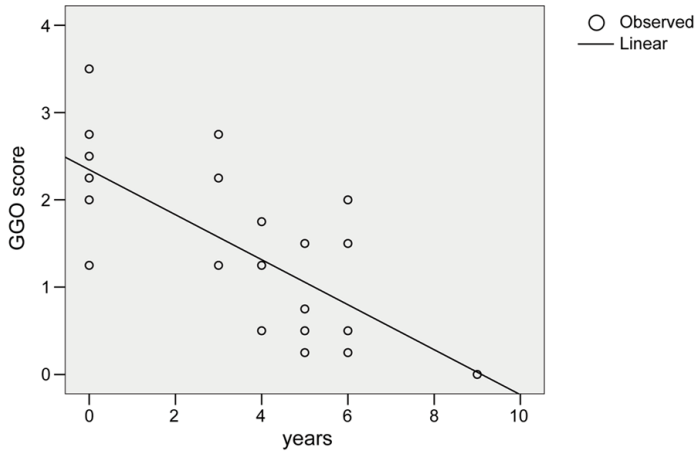

Figure 4. Changes in the GGO score over time.

patients died during the study period. SLT was performed on the right side in six patients and on the left side in six patients. Thirty one CT scans were evaluated. Initial CT examinations were obtained a mean of 3.7 ± 1.9 months after SLT (range: 7 months before to 11 months after SLT). The follow-up period after SLT ranged 43-110 months (mean: 74.7 ± 19.5 months). Two to five CT examinations were performed in each patient.

Eleven patients showed an increase in the extent of fibrotic changes in the native lung after SLT (**Figure 1**). One patient remained stable at 36 months post-SLT. The average FS increased with time since SLT (r= 0.515, P<0.001). Average rate of FS progression on the CT scans was 0.300/year (**Figure 2**). All patients showed progression in the TBS on later CT scans compared to the first scan, with a rate of progression of approximately 0.147/year (r= 0.696, P<0.001; **Figure 3**). GGS decreased in seven patients, was stable in one patient, and worsened in four patients (**Figure 4**).

The native lung volume decreased in nine and increased in three patients in later CT scans compared to the initial CT images. The three patients with increased lung volume had moderate to large pleural effusions, which affected the native lung volume measurements from their inferior CT scans. Therefore, the volume data for these three patients were excluded from the analysis. In nine patients, the native lung volume in lung CT reconstruction measurements decreased over time (rate of decrease: 5.4%/year, r=0.653, P= 0.001; **Figure 5**), Mean native lung volumes among all 12 patients at 1, 3, 4, 5, 6, and 9 years after SLT were 1243.70, 1168.69, 1227.84, 1084.52, 1275.12, and 860.59 ml, respectively.

Three patients had an increase in lung volume; two of these patients had medial pleural effusions on their initial CT scans, and one had atelectasis in the grafted lung on their follow-up CT scan. Three patients

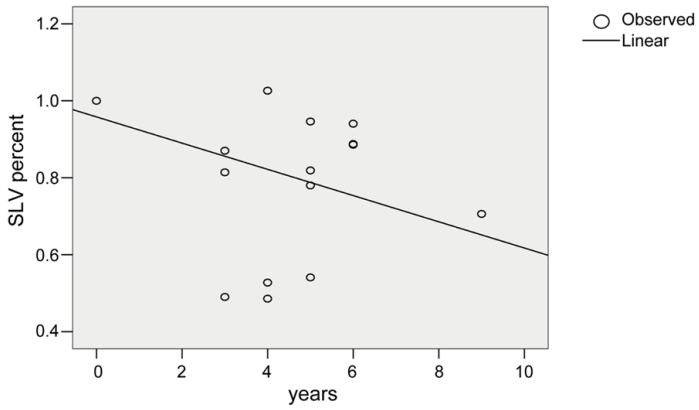

Figure 5. A negative linear correlation between the volume of the native lung and years since transplantation. SLV: single lung volume (native lung volume).

had consolidations in the native lung on follow-up CT scans. These consolidations were primary lung cancer (*n*=2) or bacterial infection (*n*=1). One patient had multiple small nodules that were diagnosed as an aspergillus infection. Three patients had pleural effusions and one patient had a pneumothorax. Two patients were diagnosed with emphysema on their first CT scan, and the affected area increased on follow-up CT images.

Discussion

IPF is a progressive disease with a very poor prognosis. To date, no large-scale randomized controlled trial has proven that pharmacological treatments are effective for reducing progression of fibrosis. Lung transplantation is the only recognized treatment for IPF, and the improved three-component immunosuppressant drug regimen has become generally accepted and widely used after transplantation. However, to our knowledge, no studies have evaluated IPF progression in the native lung under this regimen. CT scanning is a commonly used noninvasive imaging tool for evaluating lung fibrosis [12-16]. CT scoring is usually semi-quantitative, with low levels of inter observer variability when conducted by expert radiologists [5, 11, 17-20]. Several studies have proven the effectiveness of CT imaging analysis for scoring the degree of fibrosis in IPF [5, 21].

Our results showed that the use of the commonly accepted immunosuppressive treatment regimen could not prevent further development of IPF in the native lung of patients after SLT. Evaluation of the CT images showed similar results to those of prior studies [7-9].

With our scoring system, the FS increased at a rate of 0.300/year. This result differs from that of Elicker et al. [9], who found an increase of 11%/year. However, the Elicker et al. study included cases with follow-up times ranging from 6 months to 8 years after SLT, whereas the follow-up scans in the present study were obtained between 3 and 9 years after SLT. In the present study, the volume of the native lung decreased by 6%/year in patients without other complicating factors that could affect the lung's volume (e.g., pleural effusion). Similar to the findings of Elicker et al. [9], we observed a decrease in the GGO severity over time after SLT (*n*=10).

Certain limitations of our study need to be acknowledged. This was a retrospective review of patients evaluated at a single center, with all of the issues of selection and observational bias that this design carries. Secondly, although the sample size of our study was equivalent to or larger than that of prior studies, it still represents a small number of patients. Thirdly, the pulmonary functional test results from some patients were unavailable. Therefore, we could not test whether the CT lung volume correlated with these results. Additionally, we did not obtain our scans with reproducible respiratory gating. Lastly, the CT parameters used in this study were not uniform because of the long time period. Although we used the thinnest slices possible to reconstruct some of the early data, the FS and GGS may reflect some uncontrolled variations.

In conclusion, our study found that in the native lung of patients treated with SLT for IPF, fibrosis worsened and lung volume decreased at a rate of approximately 6%/year from the time of transplantation.

Disclosure of conflict of interest

None.

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