Upper lung fibrosis: An unusual manifestation of chronic lung transplant rejection

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Purpose

Lung transplantation has become an established technique for the treatment of end-stage pulmonary disease. Overall survival after lung transplantation has greatly improved because of advances in surgical techniques, careful harvesting and preserving of the donor organs, improvements in immunosuppressive therapy, and earlier detection of the complications [1-3]. However, transplant patients are prone to a variety of complications. These complications are classified in relation to the point that occurred along the postoperative time continuum in early and late onset complications [4]. Chronic complications also include constrictive bronchiolitis, organizing pneumonia, many types of pulmonary infection, posttransplantation lymphoproliferative disorder, primary disease recurrence, bronchogenic carcinoma, and rarely upper lobe fibrosis [4-11]. The unusual distribution of pulmonary fibrosis is rarely reported [12,13].

The purpose of this study was to evaluate the spectrum of imaging findings in patients with the unusual manifestation of chronic lung allograft transplant rejection; upper lung fibrosis.
Methods and Materials

Retrospective review of patient's data and images was approved by our institutional review board. No patient consent was required for our Health Insurance Portability and Accountability Act-compliant study.

Identification of cases

Since 2000, 489 patients had undergone lung transplantation at University of Washington Medical Center. We identified 13 consecutive patients between 2000-2011 with pulmonary fibrosis due to chronic lung transplant rejection by using keyword search of our radiology information system and clinical data from the hospital information system. A total 13 patients in the age range of 34 to 74 years were included, 8 men and 5 women.

Histopathology

Acute rejection can be reliably diagnosed on tranbronchial biopsy based on the presence of perivascular mononuclear infiltrates with eventual involvement of pulmonary interstitium [14]. Chronic rejection consists of chronic airway and chronic vascular rejections. Chronic airway rejection is diagnosed histologically based on the presence of obliterative bronchiolitis, resulting in partial or complete narrowing of the airway lumen. Chronic vascular rejection is diagnosed histologically by the presence of fibrointimal thickening of arteries and veins [14].

Clinical diagnosis of rejection

The clinical picture of chronic allograft rejection in the lung as described by bronchiolitis obliterans syndrome (BOS) and is graded to loss of function. The pulmonary function test abnormality in BOS is airflow obstruction manifest by a decrease in forced expiratory volume in one second (FEV₁) [15].

Computed tomography

Computed tomographic scans were obtained on GE scanners: LightSpeed Qx/I, LightSpeed Ultra, and HiSpeed scanners and discovery CT750HD (GE Medical Systems, Waukesha, Wis). Because our study was retrospective, there was some variation in the protocol scanning. Computed tomographic scans were obtained with collimations of 0.625 mm, 1 mm, 1.25 mm, 2.25 mm, and 5 mm. Images were reviewed in lungs, soft tissue, and bone windows. The CT scan findings were analyzed by two dedicated chest radiologists (W.S. and S.M.), with 7 and 18 years of experience in thoracic imaging, respectively. Disagreements were resolved by consensus. The CT
scans were assessed for the features and distribution of fibrosis: ground-glass opacities (GGO), reticular opacities, traction bronchiectasis/bronchiolectasis, honeycombing, and architectural distortion. In addition, we noted the presence or absence of: consolidation, cyst, pleural and pericardial effusions, and mediastinal lymphadenopathy (lymph node >1 cm in short-axis diameter). The predominant patterns, craniocaudal distribution (upper, middle, or lower lung zones) and axial distribution (peribronchovascular, peripheral, diffuse, or nonspecific) were also evaluated. For craniocaudal distribution, the upper lung zone was defined as the region above the tracheal carina; middle zone as the region between the tracheal carina and inferior pulmonary veins; and lower zone as the region below the inferior pulmonary veins. The axial distribution of each findings were recorded as subpleural or peripheral if abnormalities were mainly in contact with the visceral pleura; peribronchial or peribronchovascular if abnormalities occurred along the bronchovascular bundles; diffuse if abnormalities involved all these compartments; or nonspecific if no particular anatomic distribution was observed. Overall response of the disease and evolution of pulmonary opacities also assessed by evaluation of available every follow-up chest CT if no symptom or diagnostic chest CT if clinically indicated e.g. respiratory symptom or abnormal pulmonary function test etc.
Results

Of our 13 lung transplant patients, 4 (30%) patients had underlying IPF, 3 (23%) patients had COPD, 3 (23%) patients had CF and the remaining patients had alpha-1 antitrypsin deficiency, pulmonary hypertension, and polymyositis. There were 8 (62%) male and 5 (38%) female patients aged from 34-74 years, with mean age of 59.8 years. Nine (69%) patients received double lung transplant, 2 (15.5%) received right-sided single lung transplant and 2 (15.5%) received left-sided single lung transplant (see Table 1).

The patients developed symptoms between 1 year to 13 years 8 months after transplantation. Predominant symptoms were dyspnea in nine (69%) patients, cough in 2 (15%) patients, hoarseness in 1 (8%) patient and 1 (8%) had no symptom. The pulmonary function testing showed an obstructive pattern in 6 (46%) patients, restrictive pattern in 4 (31%), mixed obstructive and restrictive pattern in 2 (15%) and near normal in 1 (8%) (see Table 1&2).

Eleven (84%) patients had reticular opacities as the dominant pattern on CT, one (8%) patient also had consolidation and one (8%) patient had predominant GGO. Twelve (92%) patients had upper lung zone predominant in craniocaudal CT distribution and the remaining patient had diffuse distribution. Eleven (84%) patients had subpleural distribution on axial plain on CT, one (8%) patient had diffuse and one (8%) patient had peribronchovascular distribution (see Table 2&3 and Figure 1).

Disease progression: Eight patients had available follow-up imaging. The indication of chest CT were presence of respiratory symptom e.g. dyspnea, cough or abnormal pulmonary function test. The number of follow-up CT ranged from 2-10 chest CT. The frequency of chest CT scanning ranged from 11 days to 2 years 1 month. Six patients had progression of their pulmonary fibrosis while two patients had persistent pulmonary fibrosis (see Figure 2-4).

Three patients had progressive dyspnea which let to their death. Two of these patients had underlying IPF while one had COPD of the native lungs.
**Fig. 1:** A 58-year-old man with underlying IPF underwent double lung transplant. 1A, 1B Axial CT scan at the level of trachea and aortic arch 1C, 1D Coronal CT scan at the level of carina and descending thoracic aorta obtained on 87 months after transplant show subpleural/peripheral coarse reticular opacities, traction bronchiectasis and architectural distortion with upper lung zone predominance.

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Fig. 2: A 69-year-old man with underlying COPD underwent double lung transplant. 2A, 2D Axial and coronal CT scan obtained on 45 months after transplant at level aortic arch and descending thoracic aorta show peribronchovascular ground-glass opacities and mild subpleural/peripheral reticular opacities with upper lung zones predominance. Note minimal right pneumothorax. 2B, 2E Axial and coronal CT scan obtained on 8 months after 2A, 2D at same level show interval resolution of ground-glass opacities but progression of reticular opacities and new development of traction bronchiectasis and architectural distortion. 2C, 2F Axial and coronal CT scan obtained on 7 months after 2B, 2E at same level show substantial progression of coarse reticular opacities, traction bronchiectasis, architectural distortion, and cystic changes.

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Fig. 3: A 61-year-old man with underlying alpha-1 antitrypsin deficiency underwent left-sided single lung transplant. 3A, 3B Axial CT scan obtained on 160 months after transplant at the level of trachea and aortic arch show coarse reticular opacities, traction bronchiectasis, architectural distortion, and cystic changes at the left lung apex. 3C, 3D Axial CT scan at the level of trachea and aortic arch 3E, 3F Coronal CT scan at the level of carina and descending thoracic aorta obtained on 50 months after 3A, 3B show progression of advanced pulmonary fibrosis predominantly at the left upper lobe. Note persistent panlobular emphysema at the right lung.

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**Fig. 4:** A 73-year-old woman with underlying COPD underwent right-sided single lung transplant. 4A, 4B Axial CT scan obtained on 2 months after transplant at the level of trachea and aortic arch show mild pleural thickening at the left hemithorax and centrilobular emphysema at the left lung. Otherwise, no significant pulmonary abnormality is seen. 4C, 4D Axial CT scan at the level of trachea and aortic arch 4E, 4F Coronal CT scan at the level of carina obtained on 96 months after 4A, 4B show new development of peribronchovascular ground-glass opacities and subpleural/peripheral reticular opacities with predominant at the right upper lobe. Note persistent centrilobular emphysema at the left lung.

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Table 1: Demographic Characteristics, Type of Transplant, Pulmonary Function Test Pattern, Bronchiolitis Obliterans Syndrome, Biopsy Method, and Pathology of Lung Transplant Recipients

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Table 2: Symptom, Imaging Features and Evolution of Lung Transplant Recipients

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Table 3: Chest CT Findings and Distribution of Lung Transplant Recipients

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<table>
<thead>
<tr>
<th>Imaging Findings</th>
<th>Patient Number (%)</th>
<th>Imaging Findings</th>
<th>Patient Number (%)</th>
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<tbody>
<tr>
<td>Ground-glass opacities</td>
<td>11 (85%)</td>
<td>Air trapping</td>
<td>5 (38%)</td>
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<tr>
<td>Upper</td>
<td>8</td>
<td>Upper</td>
<td>1</td>
</tr>
<tr>
<td>Lower</td>
<td>1</td>
<td>Lower</td>
<td>3</td>
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<tr>
<td>Diffuse</td>
<td>2</td>
<td>Diffuse</td>
<td>1</td>
</tr>
<tr>
<td>Reticular opacities</td>
<td>13 (100%)</td>
<td>Consolidation</td>
<td>3 (23%)</td>
</tr>
<tr>
<td>Upper</td>
<td>12</td>
<td>Upper</td>
<td>3</td>
</tr>
<tr>
<td>Diffuse</td>
<td>1</td>
<td>Cyst</td>
<td>3 (23%)</td>
</tr>
<tr>
<td>Traction bronchiectasis</td>
<td>7 (54%)</td>
<td>Pneumothorax</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Upper</td>
<td>7</td>
<td>Pleural thickening</td>
<td>3 (23%)</td>
</tr>
<tr>
<td>Honeycombing</td>
<td>6 (46%)</td>
<td>Pleural effusion</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Upper</td>
<td>6</td>
<td>Pericardial effusion</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Architectural distortion</td>
<td>13 (100%)</td>
<td>Mediastinal lymphadenopathy</td>
<td>-4 (31%)</td>
</tr>
<tr>
<td>Upper</td>
<td>13</td>
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Conclusion

Lung transplantation has developed into an important role for a wide range of advanced chronic lung disease. Chronic rejection commonly manifests pathologically as constrictive bronchiolitis, a chronic progressive fibroinflammatory occlusion of the airway. However, there are a few prior case reports or small series representing rare manifestation of chronic rejection as upper lobe predominant pulmonary fibrosis [12,13].

In our series, the largest so far, we found that the CT features of all 13 lung transplant recipients representing gradual progression of pulmonary fibrosis. Although the reticular opacities were frequently seen and occur in dominant pattern on CT in most of our patients (84.6%), consolidation and ground-glass opacities were also seen in dominant pattern on CT in some of our patients (15.4%) and have not been described in previous reports [12,13]. One explanation for the difference dominant pattern between interstitial abnormality (reticular opacities) and air-space opacities (consolidation and ground-glass opacities) may be due to variable time range between the time of diagnosis and time of the CT scans.

We found that the reticular opacities were progressed in most of our patients (75%) while the air-space opacities (consolidation and ground-glass opacities) were partially resolved. Thus, reticular opacities may represent chronic process due to pulmonary fibrosis and subsequently change to more specific findings of pulmonary fibrosis including traction bronchiectasis/bronchiolectasis, honeycombing, and architectural distortion.

In our study, the craniocaudal distributions were predominantly upper lung zone in 12 patients (92.3%) and diffuse in one patient (7.7%). This is similar to the earlier report [12] in which the upper lung zone distribution was the most common craniocaudal distribution pattern. The axial distributions were predominantly subpleural in 11 patients (84.6%), peribronchovascular in one patient (7.7%) and diffuse in one patient (7.7%).

The air trapping was found in 5 patients (38%). The distributions of air trapping were predominantly lower lung zone in 3 patients (60%), upper lung zone in one patient (20%) and diffuse in one patient (20%). These findings may represent obliterative bronchiolitis which could be due to different pathological process of pulmonary fibrosis in the upper lung zones.

In our study, there are associated findings including small pneumothorax in one patient (8%), pleural thickening in 3 patients (23%), small pleural effusion in one patient (8%), small pericardial effusion in one patient (8%) and mediastinal lymphadenopathy in 4 patients (31%).
According to the pathologic and laboratory findings, there were not specific in determining the pathological process of pulmonary fibrosis in our patients. One explanation may be due to low sensitivity of the transbronchial biopsy to diagnosed rejection [16] and the pulmonary abnormalities seem to be located at peripheral location. However, we suggest most frequent location of the pulmonary fibrosis at the upper lung zone and subpleural/peripheral location for tissue diagnosis if clinically indicated.

Limitation of the study includes the small sample size and the retrospective nature. Another limitation was that the CT scans were obtained at variable times which might effects the detection of chronic abnormality. There was no standardization of frequency or length for follow-up study. In addition, there is no definite pathological proof in our patients.

CONCLUSION: In this unusual manifestation of chronic lung transplant rejection, upper lung fibrosis has a peripheral predominant distribution, is often progressive, and is associated with basilar predominant findings of air-trapping (bronchiolitis obliterans syndrome).
References


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