HRCT Features of Acute Rejection in Patients With Bilateral Lung Transplantation: The Usefulness of Lesion Distribution

C.H. Park\(^a\), H.C. Paik\(^b\), S.J. Haam\(^b\), B.J. Lim\(^c\), M.K. Byun\(^d\), J.A. Shin\(^d\), H.J. Kim\(^d\), S.H. Hwang\(^a\), and T.H. Kim\(^a,^*\)

\(^a\)Department of Radiology and Research Institute of Radiological Science, Yonsei University Health System, Seoul, Republic of Korea; \(^b\)Department of Thoracic and Cardiovascular Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; \(^c\)Department of Pathology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; and \(^d\)Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

ABSTRACT

Purpose. This study sought to evaluate the high-resolution computed tomography (HRCT) features of acute rejection and to assess the diagnostic accuracy of HRCT for acute rejection considering distribution of lesions in patients with bilateral lung transplantation (BLT).

Materials and Methods. Between March 2010 and June 2012, 48 transbronchial lung biopsies (TBLBs) and HRCT were performed simultaneously in 26 patients who underwent BLT. We evaluated the presence of ground glass opacity (GGO), consolidation, nodule, bronchial wall thickening, interlobular septal thickening, pleural effusion, atelectasis, bronchiectasis, and cardiomegaly on the HRCT images. The distribution of lesions was analyzed according to bilaterality or upper/lower predominance. Acute rejection was determined on the basis of the pathologic results of TBLB. We evaluated potential correlations of HRCT features with acute rejection, then assessed overall diagnostic accuracy of various HRCT features in combination to diagnose acute rejection in the transplanted lung.

Results. Among the 48 TBLBs, 8 were diagnosed as acute rejection (A1, 4 cases; A2, 2 cases; and A3, 2 cases) pathologically. Two A1 rejections and one A2 rejection appeared normal on computed tomography images. Without considering the distribution of lesions, interlobular septal thickening was significantly associated with acute rejection \((P = .010)\) only. Regarding the distribution of lesions on HRCT images, not only interlobular septal thickening but also GGO was significantly associated with acute rejection \((P < .05)\). The sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy of the HRCT scan in the evaluation of acute rejection were 50\%, 97.5\%, 80\%, 90.1\%, and 89.6\%, when the bilateral GGO and interlobular septal thickening with lower predominance were considered as the positive finding.

Conclusions. HRCT findings considering lesion distribution could be a useful tool in diagnosing acute rejection in patients with BLT.

LUNG transplantation is performed worldwide as an established treatment for various end-stage lung diseases [1–3]. One of the most common complications encountered after lung transplantation is acute rejection, which is defined as circumferential perivascular mononuclear infiltrates mediated by cellular immune response. It can occur as early as 2 to 5 days after operation and frequently within the first year [3–5]. Acute rejection is not fatal, but repetition increases the risk of chronic rejection,
which is a major cause of mortality at the late period after lung transplantation [6,7]. Therefore, it is important to detect acute rejection at the very beginning because steroid pulse therapy can improve the progression of acute rejection and may reduce the risk of chronic rejection [1,8].

The diagnosis of acute rejection is challenging due to its nonspecific features. Clinical symptoms vary and include cough, dyspnea, fever, sputum, and hypoxia [9,10]. Furthermore, the differential diagnosis includes reperfusion edema after lung transplantation or various infectious conditions during the conservative management period. The diagnostic accuracy of high-resolution computed tomography (HRCT) for acute rejection was not robust [4] despite various radiologic features of acute rejection previously reported, including ground glass opacity (GGO), interlobar septal thickening, nodules, consolidation, volume loss, or pleural effusion [1,4,5]. We assumed that the distribution of lesions such as bilaterality or upper/lower predominance on HRCT may be useful to diagnose acute rejection because acute rejection is a systemic immune response [10]. Thus, the aims of this study were to evaluate the HRCT features of acute rejection considering the lesion characteristics and distribution after bilateral lung transplantation, as well as to determine the diagnostic accuracy of HRCT findings in evaluating acute rejection using transbronchial lung biopsy (TBLB) results for reference.

MATERIALS AND METHODS

This study was performed retrospectively, and informed consent was waived. The study received institutional review board approval. Between March 2010 and June 2012, 26 patients who underwent transbronchial lung biopsies and corresponding HRCT scans according to scheduled follow-up or diagnostic work-up after bilateral lung transplantation were enrolled in this study. Time intervals between the HRCT scans and TBLBs were within 6 days (mean interval, 2 days). Nine of the patients were male, and 17 were female. The mean age at the time of examination was 45.4 ± 13 years (range, 21 to 67 years).

Twenty-five patients underwent bilateral lung transplantation, and heart and lung transplantation was performed on 1 patient. Disease entities in 26 patients before lung transplantation were idiopathic pulmonary fibrosis in 10 patients, lymphangioleiomyomatosis in 5 patients, bronchiectasis in 3 patients, acute respiratory distress syndrome in 2 patients, Eisenmenger syndrome in 2 patients, diffuse panbronchiolitis in 2 patients, bronchiolitis obliterans in 1 patient, and systemic sclerosis lung involvement in 1 patient. The intervals between lung transplantation and TBLBs/HRCT of 26 patients are shown in Fig 1 (mean: 7.3 ± 8.2 months, median: 6 months, range: 1 to 51 months). The clinical and pathological data were obtained retrospectively from the medical records and pathology reports of each patient.

CT Scanning

CT scans were performed using 1 of 2 scanners: a 64-slice multidetector CT (MDCT) scanner (Somatom Sensation 64; Siemens Medical Solutions, Erlangen, Germany) or a 128-slice MDCT scanner (Somatom Definition AS+; Siemens Medical Solutions). Scanning was performed in the supine position from the lung apices to the level of the adrenal gland during inspiration. After acquiring the scout image to determine the field of view, conventional CT scanning was performed without contrast enhancement using a helical technique, with a 5-mm reconstruction interval in the mediastinal window setting. The exposure parameters for the CT scans were 100 kVp, 17.5 mA, 5-mm slice thickness, and 5-mm reconstruction increment. Image reconstruction for conventional CT scan was performed on the scanner’s workstation using commercially available software (Syngo, Somaris 5; Siemens Medical Solutions). Subsequent HRCT scans were performed using 1-mm slices at 10-mm intervals with a high-resolution algorithm (bone algorithm). The exposure parameters for the HRCT scans were 120 kVp and 130 mAs. All CT images were retrieved on a picture archiving and communication system (Centricity 1.0; GE Medical Systems, Mt. Prospect, Ill) and then analyzed in the mediastinal (level, 20 HU; width, 400 HU) and lung (level, −700 HU; width, 1500 HU) window settings.

CT Image Analysis

Two radiologists (T.H.K. and C.H.P.) with over 20 and 8 respective years of experience in chest radiology interpretation were blinded to the TBLB results and assessed the HRCT images in 1-image interpretation sections. Decisions regarding the CT features were determined in consensus. The presence or absence of GGO, consolidation, nodules, bronchial wall thickening, interlobar septal thickening, atelectasis, bronchiectasis, pleural effusion, and cardiomegaly were evaluated. Bronchial wall thickening was defined when the bronchial wall was thickened compared to the normal bronchus in the adjacent normal lung or the contralateral normal lung on the same CT image. Cardiomegaly was defined when the cardiothoracic ratio was >0.55 on the scout images. To reduce bias, only newly developed cardiomegaly was regarded as a positive finding in this study. When the lesion mentioned above was present on CT images, we evaluated the lesion as bilateral or unilateral. If the lesion was bilateral, we determined vertical predominance of lesion distribution as follows: upper or lower predominance, and no predominance.

Histopathologic Sampling and Analysis

Surveillance or diagnostic bronchoscopy was performed with a transbronchial lung biopsy under local anesthesia by an experienced pulmonologist (J.A.S., M.K.B., or H.J.K.) in all patients. The sites of lung biopsies were determined according to HRCT findings. In the case that the CT findings were normal, the biopsy was typically performed in the lower lobes. In contrast, if the CT findings showed abnormal features, the biopsy sites were targeted to the most severe lesion areas on CT images. A total of 48 TBLB examinations were performed in 26 patients after lung transplantation; once in 12 patients, twice in 9 patients, 3 times in 2 patients, and 4 times in 3 patients. At least 4 samplings were performed in each TBLB procedure in all except 1 patient, who had 3 samplings, for a total of 289 samplings. The presence or absence of acute rejection was reported by an experienced pathologist (B.J.L.) according to the standardized nomenclature for clinical staging of acute rejection (A0, none; A1, minimal; A2, mild; A3, moderate; or A4, severe) as outlined in the International Society of Heart-Lung Transplantation guidelines [11].

STATISTICAL ANALYSIS

Fisher’s exact test was used to evaluate potential correlations of various HRCT features with acute rejection, using TBLB results as a reference. A P value <.05 was considered to be statistically significant. The sensitivity, specificity, positive
predictive value, negative predictive value, and overall diagnostic accuracy were calculated for the various criteria using the significant HRCT features to diagnose acute rejection in the transplanted lung. All statistical analysis was performed with commercially available software (SPSS 20; Statistical Package for the Social Sciences, Chicago, Ill).

RESULTS

Eight patients were diagnosed with acute rejection by pathology. The mean interval between operations and TBLBs within those 8 patients was 6.6 ± 5.9 months (range, 1 to 18 months). Pathological diagnosis was graded as A1 in 4 patients, A2 in 2 patients, and A3 in 2 patients. Demographic data and the corresponding HRCT findings in the 8 patients who had acute rejection are summarized in Table 1. No abnormal CT findings were found in 2 patients with A1 acute rejection (Fig 2). One patient with A2 acute rejection had nondiagnostic findings only with minimal septal thickening on HRCT imaging. Five patients who had acute rejection had positive CT findings that were mostly bilateral. Four of 5 patients showed lower predominance (Fig 3). The 1 remaining patient with grade 1 acute rejection had bilateral GGO, interlobular septal thickening, and unilateral consolidation without vertical predominance. The relationships between HRCT findings and acute rejection are summarized in Table 2. Without considering the distribution of lesions, interlobular septal thickening was significantly associated with acute rejection \((P = .010)\) only. Because considering the distribution of lesions on HRCT images, not only interlobular septal thickening, but also GGO were significantly associated with acute rejection \((P < .05)\). Newly developed cardiomegaly did not result in a statistically significant relationship to acute rejection \((P > .05)\). However, none of the 8 patients with acute rejection had cardiomegaly. The sensitivity, specificity, positive predictive value, and negative predictive value of HRCT imaging in the evaluation of acute rejection were 50%, 97.5%, 80%, and 90.1%, respectively.
when bilateral GGO and interlobular septal thickening with lower predominance were considered positive CT findings for acute rejection. The overall accuracy of the HRCT scan was 89.6% in diagnosing acute rejection. According to the grade of acute rejection, the sensitivities of the HRCT scan were 25% in A1, 50% in A2, and 100% in A3.

**DISCUSSION**

Our study demonstrated that GGO and interlobular septal thickening on HRCT imaging are related to acute rejection. Additionally, lesions in acute rejection were mostly bilateral and more prominent in the lower lung. The CT features in patients with a lower grade of acute rejection could be normal or nonspecific. Overall accuracy of the HRCT scan was approximately 90% in diagnosing acute rejection.

Clinically, diagnosing acute rejection and excluding other processes in the lung such as infection or edema after lung transplantation are crucial due to different treatment strategies [4]. Although TBLB may be the gold standard method of diagnosing acute rejection, a lung biopsy is invasive, and sampling errors can occur due to the heterogeneous involvement of acute rejection [12]. Therefore, noninvasive diagnostic tools for acute rejection are mandatory in patients with lung transplantation.

Chest radiography results were not robust in evaluating acute rejection after lung transplantation [13-15]. Bergin et al. [16] retrospectively reviewed 83 TBLBs in 16 heart-lung transplantations and reported that chest radiographs resulted in a sensitivity, specificity, and overall accuracy for acute rejection of 68%, 90%, and 83%, respectively, when septal lines and newly developing or increasing pleural effusions were used as positive findings. However, Kundu et al. [15] reported that chest radiograph findings were abnormal in about 50% of biopsy-proven acute rejections. Millet et al. [13] also reported that chest radiographs were only abnormal in 23% of acute rejection episodes that occurred later than 1 month after heart or lung transplantation.

HRCT scans have been used in an attempt to evaluate acute rejection after lung transplantation using the findings of GGO, peribronchial cuffing, interlobular septal thickening, nodules, consolidations, pleural effusion, and lung volume loss [1,10,17]. However, it was difficult for these CT findings to be

<table>
<thead>
<tr>
<th>Grade of Acute Rejection</th>
<th>Number</th>
<th>Sex</th>
<th>Age (months)</th>
<th>Interval (months)</th>
<th>High-Resolution Computed Tomography Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>1</td>
<td>F</td>
<td>34</td>
<td>6</td>
<td>Negative</td>
</tr>
<tr>
<td>A1</td>
<td>2</td>
<td>F</td>
<td>46</td>
<td>18</td>
<td>Negative</td>
</tr>
<tr>
<td>A1</td>
<td>3</td>
<td>M</td>
<td>50</td>
<td>2</td>
<td>GGO*, consolidation*, nodules, bronchial wall thickening*, interlobular septal thickening*, pleural effusion* Lower predominance</td>
</tr>
<tr>
<td>A1</td>
<td>4</td>
<td>F</td>
<td>38</td>
<td>3</td>
<td>GGO*, consolidation, interlobular septal thickening*, atelectasis No vertical predominance</td>
</tr>
<tr>
<td>A2</td>
<td>5</td>
<td>F</td>
<td>45</td>
<td>1</td>
<td>Nondiagnostic minimal change</td>
</tr>
<tr>
<td>A2</td>
<td>6</td>
<td>F</td>
<td>36</td>
<td>4</td>
<td>GGO*, interlobular septal thickening*, pleural effusion*, atelectasis Lower predominance</td>
</tr>
<tr>
<td>A3</td>
<td>7</td>
<td>M</td>
<td>55</td>
<td>13</td>
<td>GGO*, interlobular septal thickening* Lower predominance</td>
</tr>
<tr>
<td>A3</td>
<td>8</td>
<td>F</td>
<td>43</td>
<td>6</td>
<td>GGO*, consolidation, nodules*, bronchial wall thickening*, interlobular septal thickening* Lower predominance</td>
</tr>
</tbody>
</table>

Abbreviations: Interval, interval between transplantation and acute rejection (months); F, female; M, male; GGO, ground glass opacity.

*Bilateral findings.

Fig 2. False-negative computed tomography study in a 46-year-old female patient with grade 1 acute rejection. High-resolution computed tomography images (A, B and C) in a 46-year-old female patient with bilateral lung transplantation for lymphangiomyomatosis show no abnormal findings. The histopathologic results in corresponding transbronchial lung biopsies specimens indicated grade A1 rejection.
differentiated from transient pulmonary edema, pneumonia, or posttransplantation lymphoproliferative disorder in patients with lung transplantation [17]. Although the finding of GGO on HRCT had a sensitivity of 65% and a specificity of 85% in diagnosing acute rejection after lung transplantation, no individual CT finding was significantly associated with acute rejection [4, 12]. In contrary, HRCT scans showed relatively good results in animal studies, with a sensitivity and specificity of 86.7% and 85.6%, respectively, for acute rejection in single-lung transplanted pigs, with the common positive findings of bronchial wall thickening, GGO, and volume loss of the transplanted lung [18].

Pathophysiologically, acute rejection may occur through a systemic immune response such as an allograft T-cell response [10]. Therefore, the distribution of lesions may be an important factor to differentiate acute rejection from other conditions, such as infectious diseases. Most of the previous human studies were performed in patients with single-lung transplantation or simultaneous bilateral lung transplantation [4, 12, 15]. We evaluated the usefulness of distribution factors in patients who underwent bilateral lung transplantation. In our study, out of 40 cases without TBLB results of acute rejection, 11 cases showed abnormal CT findings such as GGO, consolidation, nodules, bronchial

Table 2. Correlation of Various High-Resolution Computed Tomography Features With Acute Rejection

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Number With AR (%)</th>
<th>Number Without AR (%)</th>
<th>P Value</th>
<th>Number With AR (%)</th>
<th>Number Without AR (%)</th>
<th>P Value</th>
<th>Number With AR (%)</th>
<th>Number Without AR (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ground glass opacity</td>
<td>5 (62.5)</td>
<td>10 (25)</td>
<td>.088</td>
<td>5 (62.5)</td>
<td>8 (20)</td>
<td>.025</td>
<td>4 (50)</td>
<td>1 (2.5)</td>
<td>.002</td>
</tr>
<tr>
<td>Consolidation</td>
<td>3 (37.5)</td>
<td>11 (27.5)</td>
<td>.676</td>
<td>2 (25)</td>
<td>6 (15)</td>
<td>.605</td>
<td>1 (12.5)</td>
<td>3 (7.5)</td>
<td>.530</td>
</tr>
<tr>
<td>Nodule</td>
<td>2 (25)</td>
<td>5 (12.5)</td>
<td>.330</td>
<td>1 (12.5)</td>
<td>4 (10)</td>
<td>.616</td>
<td>1 (12.5)</td>
<td>1 (2.5)</td>
<td>.309</td>
</tr>
<tr>
<td>Bronchial wall thickening</td>
<td>2 (25)</td>
<td>7 (17.5)</td>
<td>.633</td>
<td>2 (25)</td>
<td>5 (12.5)</td>
<td>.330</td>
<td>2 (25)</td>
<td>3 (7.5)</td>
<td>.189</td>
</tr>
<tr>
<td>Interlobular septal thickening</td>
<td>5 (62.5)</td>
<td>6 (15)</td>
<td>.010</td>
<td>5 (62.5)</td>
<td>5 (12.5)</td>
<td>.006</td>
<td>4 (50)</td>
<td>2 (5)</td>
<td>.005</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>2 (25)</td>
<td>13 (32.5)</td>
<td>.671</td>
<td>2 (25)</td>
<td>6 (15)</td>
<td>.605</td>
<td>2 (25)</td>
<td>6 (15)</td>
<td>.605</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>2 (25)</td>
<td>20 (50)</td>
<td>.260</td>
<td>2 (25)</td>
<td>18 (45)</td>
<td>.440</td>
<td>2 (25)</td>
<td>2 (5)</td>
<td>.440</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>0 (0)</td>
<td>1 (2.5)</td>
<td>.833</td>
<td>0 (0)</td>
<td>1 (2.5)</td>
<td>.833</td>
<td>0 (0)</td>
<td>1 (2.5)</td>
<td>.833</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>0 (0)</td>
<td>6 (15)</td>
<td>.571</td>
<td>0 (0)</td>
<td>6 (15)</td>
<td>.571</td>
<td>0 (0)</td>
<td>6 (15)</td>
<td>.571</td>
</tr>
</tbody>
</table>

Abbreviation: AR, acute rejection.
wall thickening, or interlobular septal thickening with a unilateral distribution or bilateral patchy distribution. When taking into consideration the lesion distribution or predominance on the CT images, the GGO and interlobular septal thickening were significantly correlated with acute rejection. Additionally, heart size may be useful for diagnosing acute rejection in patients with lung transplantations because a concomitant increase in cardiac size is absent in patients with acute rejection [16]. In our study, 8 patients with acute rejection had a normal heart size, whereas 6 cases with cardiomegaly had negative TBLB results.

In our study, the sensitivity of HRCT for acute rejection was not high (50%) due to false negatives in low-grade acute rejections. Two cases of A1 acute rejection showed negative findings on HRCT, and 1 case of A2 showed only minimal interlobular septal thickening in both lungs, which was not diagnostic. Acute rejection is pathologically graded by intensity and extent of infiltrates [2]. Mild microscopic changes of the lung by acute rejection processes may not directly correlate with HRCT findings [19]. However, some studies have reported that the rejection grade on pathology might be correlated with the severity of the HRCT features [12,18]. In our study, the sensitivity of HRCT was variable and gradually increased according to the rejection grade on the pathology as follows: 25% for A1, 50% for A2, and 100% for A3.

Our study has several limitations that can be overcome with future studies. First, our sample size was rather small. There were 8 patients with biopsy-proven acute rejection, and there were only 2 patients in each of the A2 and A3 groups. There were no cases of A4 disease. For a more accurate evaluation, further study with a larger number of patients should be conducted. Second, we included both asymptomatic patients undergoing routine surveillance as well as those who were symptomatic. It is likely that the radiologic features in the symptomatic patients were more severe than those in the asymptomatic patients [4]. Third, we used TBLB results as a gold standard for diagnosing acute rejection. However, false negatives may have been possible due to a sampling error during the TBLB procedure. To minimize the sampling error, at least 4 samples were obtained during each TBLB, and biopsies were performed at the region of abnormality on HRCT. Fourth, CT scans were performed at various time points after transplantation. Transplanted lungs could have been incompletely inflated and under postoperative changes at an early time point. Different appearances including lower lung predominance in the CT might have been due to physiologic changes during the posttransplantation course. Finally, donor-recipient size mismatch, which has an important impact on atelectasis [1], was not considered when analyzing HRCT findings of acute rejection.

In conclusion, in 26 lung transplantation patients who had a TBLB, HRCT findings of GGO and interlobular septal thickening were significantly correlated with biopsy-proven acute rejection. The lesions were mostly distributed in the bilateral and lower lung zones. A low sensitivity of HRCT for acute rejection seems to be caused by false-negative cases with mild pathologic findings. HRCT findings considering distribution of lesions may be useful in diagnosing acute rejection in patients with bilateral lung transplantation.

REFERENCES