Role of Contrast-Enhanced Dynamic CT in the Diagnosis of Active Tuberculoma*

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Study objectives: To assess the role of contrast-enhanced dynamic CT in the diagnosis of active tuberculoma.

Setting: Hospitals with an isolated ward for tuberculosis.

Methods: Fifty-five subjects with newly diagnosed active tuberculoma and 24 subjects with inactive tuberculoma were examined and evaluated retrospectively. Six subjects with active tuberculomas and seven subjects with inactive tuberculomas were confirmed by histologic and microbiologic evaluation of resected specimens, whereas the remainder of the subjects with tuberculoma were confirmed clinically. The subjects were receiving iopamidol, 370 mg/mL IV, at a rate of 3.0 mL/s on contrast-enhanced dynamic CT. The time-attenuation curve was obtained and adapted to a $\gamma$ function. The peak height (PH), maximum attenuation subtracted by the background attenuation, relative flow (RF), and mean regional flow were used for comparison.

Measurements and results: In the surgically confirmed group, the PH and RF values of six subjects with active tuberculomas were significantly higher than those of the seven subjects with inactive tuberculoma ($p < 0.05$). Similarly, in the subjects with noninvasive diagnoses, the PH and RF values of 49 subjects with active tuberculoma were significantly higher than those of the subjects with inactive tuberculoma (mean $\pm$ SD PH, 43.4 $\pm$ 4.1 Hounsfield units [HU] vs 11.6 $\pm$ 2.7 HU, $p < 0.0001$; RF, 0.012 $\pm$ 0.001/s vs 0.006 $\pm$ 0.001/s, $p < 0.05$). When the cutoff value was defined as mean $\pm$ 2 SD, the sensitivity and specificity of the diagnosis for active tuberculoma were 77.1% and 96.4% in PH, and 68.5% and 88.8% in RF, respectively.

Conclusion: Contrast-enhanced dynamic CT is a potentially valuable tool for the diagnosis of active tuberculoma.

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Key words: dynamic CT; mycobacterium tuberculosis; tuberculoma

Abbreviations: HU = Hounsfield units; PCR = polymerase chain reaction; PH = peak height; RF = relative flow; ROI = region of interest

A tuberculosis typically appears as a fairly discrete nodule or mass in which repeated extensions of infection have created a core of caseous necrosis surrounded by a mantle of epithelioid cells and collagen with peripheral round cell infiltration.1 Most tuberculomas are < 3 cm in diameter, although lesions up to 5 cm have been reported.2 Patients with these tuberculomas are generally asymptomatic, and the lesions are excised because of the radiographic suspicion of malignancy. The presence of benign-looking calcification within the nodule, adjacent tree-in-bud lesions, or satellite nodules may help in discriminating tuberculomas from other conditions. However, tuberculomas without these findings are often experienced.3–7

Contrast-enhanced dynamic CT analyses of pulmonary tumors have been performed mainly to discriminate malignant nodules from benign ones.8–10 Although the peak height (PH) value of time-attenuation curves has been shown to reflect tumoral vascularity and to be correlated with the number of intratumoral microvessels in lung cancer, active inflammatory nodules including tuberculomas often show higher PH values than malignant tumors.10–13 Inflammatory processes other than tuberculoma often show enhancement on dynamic CT scans.12 However, tuberculomas are considered to

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be different from other inflammatory diseases, because active tuberculomas have the potential to shed bacilli into the sputum and the patient must be kept in isolation if in such a condition. Furthermore, active tuberculomas must be differentiated from neoplastic nodules. It is thus very important to discriminate active and inactive tuberculomas. In the present study, we attempted to elucidate the role of contrast-enhanced dynamic CT in the differential diagnosis of active and inactive tuberculomas.

Materials and Methods

Subjects

A total of 79 consecutive subjects with tuberculoma (49 men and 30 women; age range, 25 to 88 years; mean age, 62.8 years) were enrolled and evaluated retrospectively in the present study (Table 1). This study was set in hospitals with an isolation ward for tuberculosis. Institutional review board approval and informed consent were obtained. The diagnosis was based on the diagnostic standards and classification of tuberculosis in adults and children published by the American Thoracic Society.14 We evaluated tuberculoma to be active when the diagnosis was confirmed on the basis of positive culture results for Mycobacterium tuberculosis in the sputum, BAL fluid, and/or by the polymerase chain reaction (PCR) method. We diagnosed inactive tuberculoma when there was a history of a previous episode of tuberculosis and/or when the nodule on conventional CT scans was clinically stable over an interval of at least 3 months, associated with a positive reaction to tuberculin skin test, negative bacteriologic study findings, and no evidence of other granulomatous nodules. We excluded subjects from this study if they definitely had calcification in nodules on conventional CT scans. Thirteen subjects in whom lung cancer could not be ruled out clinically underwent video-assisted thoracoscopic surgery and were eventually and pathologically evaluated as having tuberculosis. The disease activity was then determined by the pathologic inflammatory findings and also by the existence of M tuberculosis microscopically or by the PCR method.

Contrast-Enhanced Dynamic CT Scan

Contrast-enhanced dynamic CT scans were obtained at the best demonstrated level of each tuberculoma with a helical CT scanner. Iodinated nonionic contrast material (iopamidol, 370 mg/mL; Iopamiron; Nihon Schering; Osaka, Japan) was administered IV at a rate of 3 mL/s for a total of 100 mL with an autoinjector. Scanning parameters were 2.0-mm thickness, rapid sequence scan, 1.0 s/rotation, 120 kilovolt peak, 50 mA. PH, which means the maximum value of the time intensity curve, was defined as the increase in the attenuation from the baseline precontrast attenuation. With an injection rate of 3.0 mL/s, the average transit time in the thoracic vasculature was within 30 s and the average time needed for the arrival of maximum attenuation was within 120 s, and changes in the first 120 s are the most clinically important.2, 3 To obtain an accurate time-attenuation curve, images were obtained at a single level through the nodule during three separate 20-s acquisitions that began 0 s, 35 s, and 120 s after administration of IV contrast, and resulted in a total of 60 images. A normal reconstruction algorithm without edge enhancement was used for dynamic scanning (slice thickness, 2 mm; window width, 350 Hounsfield units [HU]; window level, 40 HU). Time-attenuation curves were created with a circular region of interest (ROI) drawn over the lesion, aorta, or left subclavian artery if the aorta was not included in the section. The ROI was as large as possible to minimize noise but determined with care to avert any partial volume effects. The ROI encompassed the entire cross-sectional area of the lesion. In this setting, the intraobserver variability and interobserver variability determined by two radiologists (U.T. and M.K.) were within 3 HU and 6 HU, respectively, which would not affect contrast-enhanced dynamic CT analysis. To evaluate intratumoral regional blood flow, we established relative flow (RF) as an equation adapted by γ function: RF = [ʃC(t)dt]/[ʃC(t)dt − AT]−1, where t was time, d was delta, C(t) was the time-attenuation curve, and AT was the appearance time (the time at which contrast materials attach to the ROI after IV injection). The RF reflects the mean regional flow after the contrast agent appears within the lesion.

Statistical Analysis

The PH and RF served for the statistical computations. The values were represented as means ± SD and were analyzed with Student t test and Mann-Whitney U test, where a p value of < 0.05 was considered statistically significant.

Results

Among the total of 79 subjects, 66 subjects could be evaluated as having tuberculoma without surgical confirmation. They were classified into groups of active tuberculoma (n = 49, 62.0%) or inactive tuberculoma (n = 17, 21.5%). The presence of M tuberculosis was confirmed in the sputum or BAL fluid of 31 subjects (63.3%) with active tuberculoma microscopically and/or PCR confirmed (n = 34 subjects, 69.4%). Time-attenuation curves could be obtained and the peak time of PH was within 55 s after the injection of contrast material in the subjects. Time-attenuation curves could be fitted to the γ function in all subjects. Of 79 subjects, 68 subjects (86.1%) with tuberculomas showed ring-like enhancement on the last phase of dynamic CT scans. In 13 patients who underwent video-assisted thoracoscopic surgery, 6 subjects (46.2%) had active tuberculoma and the remainder had inactive tuberculoma. The PH and RF values in the six subjects with

Table 1—Clinical Characteristics of Subjects*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Active Tuberculoma</th>
<th>Inactive Tuberculoma</th>
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</thead>
<tbody>
<tr>
<td>Subjects, No.</td>
<td>55</td>
<td>24</td>
</tr>
<tr>
<td>Age, yr</td>
<td>64.7 ± 2.5</td>
<td>60.2 ± 2.7</td>
</tr>
<tr>
<td>Size, cm</td>
<td>2.2 ± 0.2</td>
<td>1.8 ± 0.3</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>54.8 ± 5.2</td>
<td>29.6 ± 6.4</td>
</tr>
<tr>
<td>CRP, mg/dL</td>
<td>0.66 ± 0.18</td>
<td>0.41 ± 0.16</td>
</tr>
<tr>
<td>WBC, μL</td>
<td>5,734 ± 212</td>
<td>5,610 ± 364</td>
</tr>
<tr>
<td>ZTT</td>
<td>13.2 ± 1.1</td>
<td>11.2 ± 2.0</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD unless otherwise indicated.

ESR = erythrocyte sedimentation rate; CRP = C-reactive protein;
ZTT = zinc sulfate turbidity test.
active tuberculoma were significantly higher than those in the subjects with inactive tuberculoma (PH, 42.9 ± 6.4 HU and 12.2 ± 9.0 HU; RF, 0.014 ± 0.002/s and 0.003 ± 0.001/s; p < 0.05). In the pathologically confirmed cases, six subjects with active tuberculoma also had a central necrotic lesion surrounded by granulomatous tissue without fibrous scar or capsulation, but with numerous polyclonal lymphocytes present in the periphery of the lesion. Seven inactive tuberculomas were encapsulated by dense layers of fibrous tissue regardless of the extent of necrosis. These pathologic findings may correspond to both the degree and the inflammatory phase of the disease. The PH value in the subjects with active tuberculoma was significantly higher compared with that in subjects with inactive tuberculoma (43.4 ± 4.1 HU vs 11.6 ± 2.7 HU, p < 0.0001; Fig 1). The RF value in the subjects with active tuberculoma was significantly higher than that of inactive tuberculoma (0.012 ± 0.001/s vs 0.006 ± 0.001/s, p < 0.05; Figs 2–4). When the cutoff value of the PH was defined as the mean ± 2 SD, the sensitivity and specificity of the diagnosis for active tuberculoma were 77.1% and 96.1%, respectively. The same values of the RF were 68.5% and 88.8%, respectively.

**Discussion**

In this study, we demonstrated that by using the PH and RF values, contrast-enhanced dynamic CT examinations could differentiate active from inactive tuberculoma with high sensitivity and specificity. It is, therefore, suggested that contrast-enhanced dynamic CT should be considered as a potential additional tool in the “activity” diagnosis of tuberculoma.

The characteristic CT findings of active tuberculosis are well documented. The centrilobular lesions (nodules or branching linear opacities) and poorly margined nodules are reported as the most characteristic CT feature of early active tuberculosis. Other findings consist of patchy or confluent consolidation, ill-defined nodules, and cavities that commonly involve the apical and posterior segments of the upper lobes. These findings may not be helpful for evaluating the disease activity of tuberculoma, because tuberculoma is defined as a tumor-like granuloma showing no presence of surrounding inflammation or spread. The present results show that the evaluation of the PH and RF values in tuberculoma on contrast-enhanced dynamic CT may be helpful in determining the activity of the disease.

It was reported that the characteristics of tuberculoma in contrast-enhanced CT are variable; they include peripheral rim enhancement, peripheral rim or central curvilinear enhancement, partial enhancement, and homogeneous enhancement. In the present study, most cases of tuberculoma presented peripheral enhancement patterns. However, the degree of contrast enhancement was lower and the enhancement had reached a plateau before the end of the dynamic sequential measurements. These results of contrast-enhanced CT images may reflect the histologic background.

The histologic findings of tuberculoma can change according to the inflammatory phase of the disease. At first, tuberculoma is probably patchy, corresponding to multiple microscopic foci of granuloma formation. The disease results in relatively large areas of necrotic debris surrounded by a layer of epithelioid histiocytes and multinucleated giant cells. These proliferative types of lesions containing tuberculous granulomatous tissue will heal when a good host defense is present. Fibroblasts at the periphery of the necrotic foci proliferate and form collagen. Al-
though this sometimes results in conversion of the entire area into a dense fibrous scar, more often the central necrotic material persists and becomes separated from the surrounding lung parenchyma by a well-developed fibrous capsule. The encapsulated nodules tend to keep such lesions in an arrested, nonprogressive, and inactive state.

Both the determination of disease activity and the patient population may have affected the present results. The proof of disease activity is considered to be relatively broad in the clinical setting. According to these criteria, subjects with inactive tuberculomas who have been reinfected with tuberculosis would be regarded as having active disease. Similarly, the subjects with previous tuberculosis who had active tuberculomas would be classified as inactive. We calculated the sensitivity and specificity for the same population from the cutoff value. Statistically, a high percentage of the population with active tuberculomas should have PH or RF values within 2 SD of the mean. The results might be quite different if the same cutoff values were applied to a different population because 69.6% of the subjects enrolled in the present study had active disease, which was considered to be a relatively high frequency.

There is some limitation associated with the contrast-enhanced dynamic CT scans. Because all of the tuberculomas had peripheral enhancement, the technique demands meticulous placement of the ROI such that it encompasses all of the lesions but does not include the surrounding lung, which might also enhance. The size of the lesion may also affect sequential scanning by dynamic CT. First, in smaller lesions, often < 8 mm in diameter, a time-attenuation curve cannot be obtained because of misregistration of the lesion. Second, calcification is often seen in tuberculomas, and its presence may have an effect on the measurements of CT attenuation. None of our subjects showed calcification within the lesion on conventional CT scans. Third, the contrast-enhanced dynamic CT imaging technique itself has limitations.

**Figure 3.** Sequential dynamic CT images of a 63-year-old male patient with active tuberculoma in the left lower lobe. Top: precontrast CT scan; bottom: 140 s after an injection of contrast material. Contrast-enhanced dynamic CT scans demonstrate ring-like enhancement. The enhanced area is enlarged on the delayed phase of the dynamic CT scan (arrow).

**Figure 4.** Sequential dynamic CT images of a 49-year-old male patient with inactive tuberculoma in the right upper lobe. Top: precontrast CT scan, 140 s after an injection of contrast material; bottom: subtle peripheral enhancement is seen on the delayed phase of the dynamic CT scan (arrow).
in both temporal and spatial resolution. Contrast-enhanced dynamic CT may be useful as a complementary examination, and further studies are warranted with improved imaging techniques.

To obtain a definite time-attenuation curve, we evaluated images at a single level through the nodule during three separate 20-s acquisitions that began 0 s, 35 s, and 120 s after administration of IV contrast, which is not recommended for routine use. Most dynamic CT protocols described in previous studies used a limited number of images. A more reduced image acquisition after confirmation of reproducibility will be proposed. In all subjects in the present study, the peak time of PH was within 55 s after the injection of contrast material. This evidence may suggest that scan delay can be set at < 55 s.

The contrast-enhanced dynamic CT examinations performed in the current study yielded overall activity values of tuberculomas as determined using the PH and RF values. It is, therefore, crucial to evaluate the PH and RF that would best help us distinguish between active and inactive tuberculoma. The use of contrast-enhanced dynamic CT should thus contribute to a more reliable discrimination of the disease activity. We emphasize the importance and usefulness of determining enhancing tuberculomas on dynamic CT examination that can be followed up by an appropriate period of observation.

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