Pulmonary arterial lesions in Takayasu arteritis: Relationship of inflammatory activity to scintigraphic findings and sequential changes

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In order to investigate the relationship between inflammatory activity and pulmonary arterial changes in Takayasu arteritis and the progression of the disease, we retrospectively reviewed 110 perfusion lung scans obtained by using 99mTc-macroaggregated albumin in a total of 57 patients. The scintigraphic findings were compared with the inflammatory activity and clinical course. Inflammatory activity was determined on the basis of the physical findings and laboratory data, i.e., the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) value. Scintigraphic abnormality was seen in 32 (56%) of the patients. The incidence of scintigraphic abnormality in the patients with active inflammation (7 of 21 patients, 33%) was lower than that in the patients in the chronic stage (22 of 32, 69%) (p < 0.02). Six of 22 patients who had undergone more than one scintigraphic examination showed progression in the scintigraphic findings. Four of the 6 patients showed relapse clinically, and corticosteroid medication could not be withdrawn from them. The lower incidence of scintigraphic abnormality in the patients with active inflammation suggests that in the acute phase no stenotic or occlusive changes in the pulmonary artery have yet been produced. Pulmonary arterial lesions can progress. The incidence of progression may be slightly higher in the patients who have had a relapse after corticosteroid therapy than in those who remained in remission after therapy or who were in the chronic stage, although neither difference was significant.

Key words: Takayasu arteritis, pulmonary artery, pulmonary perfusion scintigraphy, pulmonary angiography

INTRODUCTION

Takayasu arteritis involves the pulmonary arteries as well as the aorta and its branches, but there are few reports as to the relationship between the pulmonary arterial change and inflammatory activity of the arteritis, nor has the progression of the disease yet been thoroughly investigated.1,2 Pulmonary perfusion scintigraphy is a useful and non-invasive method for detecting pulmonary artery involvement.1,3 The purpose of this study was to investigate the relationship between inflammatory activity and pulmonary scintigraphic findings in Takayasu arteritis, together with the sequential changes in pulmonary arterial lesions.

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MATERIALS AND METHODS

One hundred and ten perfusion lung scans of 57 patients with Takayasu arteritis were retrospectively reviewed. The disease had been diagnosed on the basis of the angiographic and clinical features. Forty-eight of the patients were women and 9 were men, and their ages ranged from 14 to 68 years (mean, 40 years).

Each patient underwent pulmonary perfusion scintigraphy after an injection of 111 MBq of 99mTc-macroaggregated albumin in the supine position. Six views (anterior, posterior, right and left lateral, and right and left posterior oblique) with a total of 600,000 counts were obtained in each patient with a gamma camera with a low-energy, high-resolution parallel hole collimator. Pulmonary ventilation scintigraphy with 133Xe was also performed in all patients. Scintigraphic abnormality was defined as a perfusion defect or decreased perfusion with normal ventilation.
The pulmonary scintigraphic findings were compared with the inflammatory activity and clinical course. Inflammatory activity was assessed according to the physical findings including fever and chest pain, and laboratory data, viz., the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level. The patients were classified into two groups as follows: 21 patients with (acute stage; Group A) and 32 patients without (chronic stage; Group B) inflammatory activity at the initial examination. Group A consisted of 2 male and 19 female patients ranging from 14 to 42 years of age (mean, 26 years), and Group B consisted of 5 men and 27 women ranging from 31 to 68 years of age (mean, 50 years). Vasculitic activity in the remaining four patients was unknown, but they had other inflammatory diseases, such as pyoderma gangrenosum and lymphadenitis. According to the clinical course, Group A was subdivided into Group A-1, 10 patients who showed resolution of inflammation upon corticosteroid therapy, and Group A-2, 11 patients with relapse in whom corticosteroid could not be withdrawn. These two subgroups and Group B were compared as to the incidence of scintigraphic abnormality.

Twenty-two of the 57 patients had undergone more than one scintigraphic examination, and the interval between these examinations ranged from one to 14 years (average, 6 years).

Aortography was performed in all patients. Of 65 pulmonary angiographic examinations performed in 40 patients, six were conducted by conventional film-screen angiography and 59 by digital subtraction angiography (DSA).

Laboratory data are expressed as the mean ± standard deviation. The relationship between inflammatory activity and the incidence of scintigraphic abnormality was analyzed statistically by the chi-square method and Fisher's exact probability test.

RESULTS

Inflammatory activity

The mean ESR and CRP level in Group A was 108 ± 38 mm/hour and 18.7 ± 16.6 mg/dl, respectively, in quantitative measurement, and the qualitative measurement for CRP ranged from 1+ to 6+. After corticosteroid therapy in Group A-1, the ESR and CRP decreased to 18 ± 11 mm/hour and 0.32 ± 0.24 mg/dl, respectively, and the CRP measured qualitatively in 5 patients decreased to –.

In Group B, the mean ESR and CRP level was 24 ± 19 mm/hour and 0.31 ± 0.25 mg/dl, respectively, and the qualitatively measured CRP was – in 14 patients and 1+ in 2 patients. Six of the 32 patients in Group B had increased ESR exceeding 30 mm/hour or 1+ CRP, but they were considered to be in the "chronic stage" on the basis of the physical findings and clinical course.

All of 21 patients with active inflammation were treated with corticosteroid. The initial daily dose of corticosteroid (prednisolone) ranged from 20 mg to 60 mg (mean, 34 mg). Three patients in Group B had a prior history of corticosteroid therapy for active vasculitis, and three patients with unknown activity had been given corticosteroid as a treatment for other inflammatory diseases.

<table>
<thead>
<tr>
<th>Group</th>
<th>Scintigraphic abnormality (+)</th>
<th>Scintigraphic abnormality (−)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-1</td>
<td>7 (33%)</td>
<td>14 (67%)</td>
<td>21 (100%)</td>
</tr>
<tr>
<td>A-2</td>
<td>6 (30%)</td>
<td>5 (70%)</td>
<td>11</td>
</tr>
<tr>
<td>B</td>
<td>22 (69%)</td>
<td>10 (31%)</td>
<td>32 (100%)</td>
</tr>
</tbody>
</table>

Total 29 24 53

Relationship between scintigraphic findings and inflammatory activity

Scintigraphic abnormality was seen in 32 (56%) of the 57 patients. Abnormality was seen in both lungs in 14 patients, in the right lung in 14, and in the left lung in 4. In 3 patients, the pulmonary scintigram disclosed a complete defect in the right lung.

The incidence of scintigraphic abnormality in each group is shown in Table 1. The incidence of scintigraphic abnormality in the patients with active inflammation (7 of 21 patients, 33%) was lower than that in the patients in the chronic stage (22 of 32, 69%) (chi-square test, p < 0.02).

Pulmonary angiography revealed abnormal findings in 24 (60%) of 40 patients. The angiographic findings in 37 of the 40 patients corresponded with the scintigraphic findings. Angiography in two patients in Group B with scintigraphic abnormality disclosed normal findings. In one patient with active vasculitis (Group A-1), stenosis of the pulmonary artery was noted, but the scintigraphic findings were normal (Fig. 1).

Sequential change in the pulmonary arterial lesions

The number of patients in each group who had undergone more than one scintigraphic examination is shown in Table 2. Progression of the disease was seen in 6 patients, 4 of whom needed long-term steroid therapy (Group A-2) (Fig. 2), and 1 patient was also given immunosuppressant (azathioprine, 100 mg/day). In the patients who showed signs of complete or almost complete clinical remission with corticosteroid therapy (Group A-1), follow-up scintigram disclosed no change during the interval. The difference in frequency of progression was not statistically significant either between Group A-2 and B or between Group A-2 and A-1 (Fisher's exact probability test).

Fourteen patients had undergone more than one angiographic examination. Three (21%) of them showed progression of stenotic lesions during the follow-up intervals ranging from 4 to 6 years. These 3 patients were among...
Fig. 1 In a 23-year-old man with active vasculitis (the same patient as described in reference 19), the angiogram (a) reveals smooth narrowing of the left pulmonary artery (arrows). The CT scan (b) demonstrates the thickening of the aortic and pulmonary arterial wall (arrowheads) that are the acute-phase findings in Takayasu arteritis. No perfusion defect is seen on the lung scintigram (c).

Table 2 Numbers of patients who showed scintigraphic progression

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of patients who showed progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A-1 (n = 2)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Group A-2 (n = 7)</td>
<td>4 (57%)</td>
</tr>
<tr>
<td>Group B (n = 9)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Unknown activity (n = 4)</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>Total (n = 22)</td>
<td>6 (27%)</td>
</tr>
</tbody>
</table>

n: Number of patients who underwent follow-up scintigraphy

the 6 patients who showed progression on scintigraphic studies.

**DISCUSSION**

**Evaluation of inflammatory activity**

To evaluate inflammatory activity, we used ESR, which is commonly used as a marker of disease activity, and CRP, which also represents inflammatory condition, but it has been reported that ESR is not a consistently reliable marker of disease activity. The relationship between ESR/CRP and progression of the disease is uncertain.

Kerr et al. reported that active vasculitis was present in the surgical bypass specimens in 4 (44%) of 9 patients with clinically inactive disease. In autopsy cases, active lesions are often observed near old cicatricial lesions even in cases of fibrotic type. Difficulty in evaluating inflammatory activity may arise due to the coexistence of lesions in various stages of the disease. In this study, we evaluated inflammatory activity comprehensively by means of clinical findings as well as laboratory findings.

**Pathological and clinical features in the acute stage**

The histopathologic findings for the involved pulmonary arteries are reported to be the same as those for the involved systemic arteries. There are few descriptions of the pathological findings in the initial stage of the disease. Saito described how inflammatory cells infiltr-
trate into the media-adventitial boundary of the elastic arteries, forming small regions of necrosis and micro-abscesses, with destruction of the elastic fibers in the media in the acute stage.

Accurate diagnosis of Takayasu arteritis in the acute stage may be difficult due to the vague character of the systemic manifestations. Early diagnosis is nevertheless important since corticosteroid therapy is effective against acute inflammatory changes. In some recent reports, CT and MR imaging are described as useful for demonstrating the vascular wall changes in the acute stage, i.e., wall thickening and contrast enhancement of the aorta and pulmonary arteries.

Although we could not document the duration of the disease in the present series because of the insidious onset, we believe that Group A and Group B corresponds to the patients in the acute and in the chronic stage, respectively. The lower average age in Group A than in Group B supports this presumption.

Fig. 2 Initial and follow-up lung scintigram in a 42-year-old woman. The initial scintigram discloses perfusion defects of both lower lungs (a). The follow-up scintigram discloses new perfusion defect in the right apex one year after the initial examination (b). Five years after the initial examination, her right radial pulse was absent. Angiography demonstrated stenosis of the right subclavian and common carotid artery, and the diagnosis of Takayasu arteritis was made. She received corticosteroid therapy, but reactivation occurred two years after therapy was started. The follow-up lung scintigram demonstrates new perfusion defect in the right lung (c).

**Scintigraphic findings in acute stage**

Perfusion defects or decreased perfusion in lung scintigraphy suggest occlusion or stenosis of pulmonary arteries. Pathological study of the stenotic arteries has disclosed marked fibrosis of the adventitia, thinning of the media, and fibrous thickening of the intima. The reduced external diameter suggests that the main cause of arterial stenosis is cicatricial contracture. These changes occur in the late stage. Stenosis and occlusion of the arteries are thought to occur less frequently in the acute stage.

We demonstrated that the frequency of scintigraphic abnormality in the patients who had active inflammation was lower than that in the patients at the chronic stage. This result indicates that the stenotic or occlusive changes in the pulmonary artery have not been produced in the acute stage. Acute inflammatory change causes arterial wall thickening, but the arteries are still patent in the acute stage.

The frequency of scintigraphic abnormality in Group A-2 (6/11, 55%) is higher than that Group A-1 (1/10, 10%). The reason for the difference is unknown. It may be related to the severity of the disease, because the response to corticosteroid was different in these two subgroups.

As shown in Figure 1, the absence of scintigraphic abnormality does not exclude the possibility of acute
pulmonary arterial lesions. Pulmonary arterial lesions were pathologically observed in all cases of Takayasu arteritis, but arterial obstruction was seen in only about a third of the cases. It is important to recognize that perfusion scintigraphy may underestimate the extent of pulmonary arterial lesions in the acute stage.

**Progression of pulmonary arterial lesions**

There have been few reports describing the sequential changes in Takayasu arteritis. Yamada et al. reported that stenotic lesions in the aorta and its branches progressed in 5 (45%) of 11 patients, and pulmonary artery lesions were seen to progress in 1 of 3 patients. Umehara et al. reported that in 6 (20%) of 30 patients deterioration was demonstrated in the pulmonary scintigraphic studies. Our study revealed progression of scintigraphically observed abnormality in 6 (27%) of the 22 patients. Of these, 4 patients showed signs of relapse and continued to require corticosteroid.

Sharma emphasized inflammatory activity as the cause of progression of stenotic lesions, and acute inflammation is considered to be one of the exclusion criteria for percutaneous transluminal angioplasty because of the associated high restenosis rate. Our results also demonstrate that reactivation or persistence of the inflammatory activity may be important in the progression of the disease.

A recent angiographic follow-up study revealed frequent development of new lesions of the aorta and its branches, even in patients who were in apparent remission. Hall and Hunder pointed out the possibility that stenosis may progress due to noninflammatory fibrosis as a sequela to previous inflammatory changes that have been resolved. One of our patients in the chronic stage showed progression of scintigraphic findings, and the progressive change was mild compared with those described in the cases reported previously. It is possible that the mild change is due to noninflammatory fibrosis. In our study, the number of patients who underwent follow-up scintigraphy was small in Groups A-1 and B, and further investigation in a larger number of patients is necessary.

Since arterial lesion can progress in Takayasu arteritis, follow-up examination is needed for proper management of the disease. MR imaging is a noninvasive technique that may be useful for evaluating the sequential change in the arterial wall after corticosteroid therapy. Perfusion lung scintigraphy is also noninvasive and suitable for diagnosis and follow-up examination of pulmonary arterial lesions. It should be kept in mind, however, that scintigraphy can demonstrate decreased pulmonary blood flow, but not arterial wall changes.

**REFERENCES**