Prevalence of Pulmonary Arteriovenous Malformations as Estimated by Low-Dose Thoracic CT Screening

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Abstract

Background  Pulmonary arteriovenous malformations (PA VMs) are rarely encountered in clinical practice. The prevalence of PA VMs associated with hereditary hemorrhagic telangiectasia (HHT) has been estimated based on the rate in the family members of HHT patients, but the prevalence of PA VMs in the general population remains unknown.

Methods  We retrospectively examined the prevalence and clinical characteristics of PA VMs as detected by a low-dose thoracic CT screening program for lung cancer at the Hitachi Medical Center and the Hitachi General Health Care Center in the northern part of Ibaraki Prefecture, Japan.

Results  From 2001 to 2007, we identified eight patients (seven females and one male) with PA VMs among 21,235 initial screening participants (the mean age of the patients with PA VMs and that of the screening participants was 60.6 years). The prevalence of PA VMs was estimated at 38 per 100,000 individuals [95% confidence interval (CI)=18-76]. The diameter of the PA VMs was a mean of 6.6 mm, and none of the lesions could be detected by chest X-ray. Females older than 60 years tended to have larger PA VMs than younger women did (p=0.06). Two patients (25%) were diagnosed with HHT. One patient had previously undergone surgery for a brain abscess.

Conclusion  PA VMs are more prevalent than previously reported, especially among females.

Key words: pulmonary arteriovenous malformations (PA VMs), prevalence, low-dose CT screening, hereditary hemorrhagic telangiectasia (HHT)

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Introduction

Pulmonary arteriovenous malformations (PA VMs) are abnormal communications between pulmonary arteries and veins. Frequently reported complications associated with PA VMs are stroke, transient ischemic attack, brain abscess, massive hemothorax, and spontaneous hemothorax. PA VMs have been reported to be sporadic or to occur in association with hereditary hemorrhagic telangiectasia (HHT) (1). The prevalence of PA VMs associated with HHT has been estimated based on the rate in the family members of HHT patients (1-3), but the prevalence of PA VMs in the general population remains unknown.

Since 2001, we have been providing annual lung cancer screening using low-dose spiral thoracic CT to residents of the northern part of Ibaraki Prefecture, Japan (4, 5). Through this program, we have found that PA VMs can be
suspected by low-dose CT. Therefore, we planned the present study as a sub-analysis of this program, and estimated the prevalence of PAVMs in Japan.

## Materials and Methods

### Participants

In the northern part of Ibaraki Prefecture, Japan, the Hitachi Medical Center (HMC) has, since 2001, been providing low-dose spiral thoracic CT screening to local inhabitants aged 50 years or above. In addition, the Hitachi General Health Care Center (HGHCC) has, since 2001, provided similar screening to company employees and their spouses aged 50 years or above. The Hitachi General Health Care Center (HGHCC) has, since 2001, provided similar screening to company employees and their spouses aged 50 years or above as part of a general health examination similar screening to company employees and their spouses at HGHCC, applicants aged 50 years or above. In addition, the Hitachi General Health Care Center (HGHCC) has, since 2001, provided similar screening to company employees and their spouses aged 50 years or above. The Hitachi General Health Care Center (HGHCC) has, since 2001, provided similar screening to company employees and their spouses aged 50 years or above as part of a general health examination similar screening to company employees and their spouses aged 50 years or above as part of a general health examination.

### CT scanners and scan prescriptions

In the HMC group, a mobile multi-slice spiral CT scanner (Asteion; Toshiba Medical Systems, Tokyo, Japan) was used; the scanning parameters were 120 kV peak, 50 mA tube current, 8-mm collimation, and 5.5:1 pitch. In the HGHCC group, a single-slice spiral CT scanner (Pronto; Hitachi Medical, Tokyo, Japan) was used; the scanning parameters were 120 kV peak, 25 mA tube current, 10-mm collimation, and 2:1 pitch.

### Outline of lung cancer screening at HMC and HGHCC

From 2001 to 2007, 33,489 CT screens were performed across both institutions, including 21,235 initial and 12,254 repeat screenings (Table 1). The number of initial screening participants remained approximately constant each year, with 6,612 males and 9,684 females at HMC, and 3,399 males and 1,540 females at HGHCC, for a total of 10,011 male and 11,224 female participants. The mean age of the initial screening participants was 64.8 years (range 50 to 85 years) at HMC, and 57.4 years (range 35 to 80 years) at HGHCC; the overall mean was 60.6 years. The detection rate of primary lung cancer during this period was 0.90%, and 85.4% was stage IA.

### Diagnosis of PAVMs

Using low-dose CT, we suspected that the well-defined, homogeneous, round or lobular, nodule-like lesions, with vessels running towards them, were PAVMs. We further evaluated the lesions by high-resolution CT and confirmed the diagnosis of PAVMs by contrast-enhanced CT angiography and/or pulmonary angiography.

### Diagnosis of HHT

We consulted patients with PAVMs at Akita University Hospital, which is the specialist HHT center in Japan. Patients were examined on the basis of the Curaçao Criteria (6).

### Staging of lung cancer

Postoperative staging of lung cancer was conducted according to the TNM classification from the Union for International Cancer Control (UICC), 5th edition (7).

### Statistical analysis

We retrospectively examined the prevalence and clinical characteristics of PAVMs detected by low-dose CT as a sub-analysis of our lung cancer screening program. Quantitative data with a normal distribution were described using mean ± SD. The 95% confidence interval (CI) of PAVM prevalence was estimated with the Adjusted Wald Formula. Differences in PAVM prevalence between males and females were assessed with Fisher’s exact test. The relationship between PAVM diameter and age in females was analyzed using the Student’s t-test.

### Results

Of the 21,235 initial screening participants between 2001 and 2007, after low-dose CT we suspected eight participants to have PAVMs. After further evaluation, we confirmed the diagnosis of PAVMs in all eight patients, with a female predominance (87.5%). All patients had PAVMs confirmed for the first time in this screening. The detection rate of PAVMs (the number of patients with PAVMs / the number of initial screening participants, for seven years) was 0.038% overall, with 0.037% at HMC and 0.040% at HGHCC. We assumed the detection rate of PAVMs in CT screening participants to be close to the frequency in the general population. The prevalence of PAVMs was therefore estimated at 38 per 100,000 individuals (95% CI=18-76). There was a tendency for PAVMs to be more prevalent in females than in males (p=0.07).

The characteristics of the eight PAVMs patients are sum-

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**Table 1. Characteristics of the Participants**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Male Subjects</th>
<th>Female Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial Screening</td>
<td>Repeat Screening</td>
</tr>
<tr>
<td>Age, yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>170</td>
<td>42</td>
</tr>
<tr>
<td>40-49</td>
<td>409</td>
<td>175</td>
</tr>
<tr>
<td>50-59</td>
<td>2,510</td>
<td>1,263</td>
</tr>
<tr>
<td>60-69</td>
<td>4,991</td>
<td>2,950</td>
</tr>
<tr>
<td>70-79</td>
<td>1,775</td>
<td>1,418</td>
</tr>
<tr>
<td>80+</td>
<td>156</td>
<td>159</td>
</tr>
<tr>
<td>total</td>
<td>10,011</td>
<td>6,007</td>
</tr>
</tbody>
</table>

*Data are presented as number of participants unless otherwise indicated.*
Table 2. Characteristics of the PAVM Patients Detected by Thoracic CT Screening

<table>
<thead>
<tr>
<th>Patient</th>
<th>Year</th>
<th>Age</th>
<th>Sex</th>
<th>Related Disease</th>
<th>Number of PAVMs</th>
<th>Location of PAVMs</th>
<th>Maximal Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2002</td>
<td>44</td>
<td>female</td>
<td>none</td>
<td>single</td>
<td>Rt. S⁷</td>
<td>5.0</td>
</tr>
<tr>
<td>2</td>
<td>2003</td>
<td>60</td>
<td>female</td>
<td>none</td>
<td>single</td>
<td>Lt. S⁷</td>
<td>8.0</td>
</tr>
<tr>
<td>3</td>
<td>2004</td>
<td>56</td>
<td>female</td>
<td>none</td>
<td>single</td>
<td>Lt. S⁷</td>
<td>4.0</td>
</tr>
<tr>
<td>4</td>
<td>2004</td>
<td>68</td>
<td>female</td>
<td>brain abscess</td>
<td>single</td>
<td>Rt. S⁷</td>
<td>5.5</td>
</tr>
<tr>
<td>5</td>
<td>2005</td>
<td>67</td>
<td>male</td>
<td>none</td>
<td>single</td>
<td>Rt. S⁷⁹</td>
<td>12.0</td>
</tr>
<tr>
<td>6</td>
<td>2006</td>
<td>65</td>
<td>female</td>
<td>none</td>
<td>single</td>
<td>Lt. S⁷</td>
<td>6.0</td>
</tr>
<tr>
<td>7</td>
<td>2007</td>
<td>62</td>
<td>female</td>
<td>none</td>
<td>single</td>
<td>Rt. S⁷</td>
<td>6.2</td>
</tr>
<tr>
<td>8</td>
<td>2007</td>
<td>63</td>
<td>female</td>
<td>none</td>
<td>multiple</td>
<td>Rt. S⁷, Rt. S⁹</td>
<td>5.0, 8.0</td>
</tr>
</tbody>
</table>

PAVMs: Pulmonary Arteriovenous Malformations

Figure 1. Low-dose CT images of PAVMs: 4 representative cases. PAVMs are indicated by arrows.

The eight patients were examined for an association with HHT at Akita University Hospital. Two patients, patient 4 who had had a brain abscess, and patient 8 who had multiple PAVMs, were diagnosed with possible HHT based on Curacao criteria, as both patients had visceral lesions (PAVMs) and episodes of repeated epistaxis. The detection rate of PAVMs not associated with HHT was 0.028%, and that associated with HHT was 0.009%. The prevalence of PAVMs not associated with HHT was estimated as 28 per 100,000 (95% CI=11-63), and that associated with HHT was 9 per 100,000 (95% CI=0.2-37).

Discussion

In our study, we detected PAVMs in eight patients out of 21,235 thoracic CT initial screening participants over a seven-year period, which represents a detection rate of 0.038%. The two institutions, HMC and HGHCC, used a different type of CT scanner and different scanning parameters. However, the observed prevalence of PAVMs was similar between the two institutions. This suggests that the different techniques exerted almost no influence on the detec-
tion of small PAVMs.

PAVMs are reported to occur twice as often in females as in males (8). However, in our study, seven out of the eight patients were female, even though there was a slight bias in the sex ratio of the participants. From the recent questionnaires regarding PAVMs, performed in many Japanese institutions, approximately 80% of patients not associated with HHT were female (9). Compared to previous reports, this suggests that the female predominance of PAVMs is greater in Japan than in Western countries. Furthermore, in the present study, the female patients were all multiparae, and there was a tendency for older females to have larger PAVMs. During pregnancy, increases in systemic circulation, cardiac output, and the secretion of progesterone can cause the diameter of PAVMs to expand (10, 11). Approximately 25% of PAVMs can enlarge gradually in size between 0.3-2.0 mm each year in about 25% of cases (12). This may explain the increased prevalence in females and the increased size in older patients.

The prevalence of PAVMs in the general population has not been previously reported for the following reasons: it is a very uncommon disorder; asymptomatic patients rarely visit medical institutions; and small PAVMs are difficult to detect on chest X-rays. The prevalence of HHT is estimated to be between 13 and 20 per 100,000 among European, U.S., and Japanese populations; this has been calculated based on the family members of HHT patients (1-3). Approximately 70% of patients with PAVMs have HHT (1), and 30-50% of patients with HHT have PAVMs (3, 13, 14). Based on these data, the prevalence of PAVMs associated, or not associated, with HHT is estimated as 5 and 14 per 100,000 individuals, respectively. In some geographical areas, there is a high prevalence of HHT; HHT is estimated to be present in 61 per 100,000 in the County of Fyn, Denmark (15), and in 76 per 100,000 in the Afro-Caribbean population of the Netherlands Antilles (16). In these areas, the prevalence of PAVMs is estimated to be between 26 and 56 per 100,000. In the area where we performed CT screening, the estimated prevalence of PAVMs was 38 per 100,000, which is much higher than that reported in previous epidemiologic studies, and is closer to the value in the high-prevalence areas. The screening test commonly used for PAVMs in HHT patients is transthoracic contrast echocardiography (TTCE), which has a high sensitivity and low risk (2). However, CT is not recommended as a screening test due to radiation exposure (2). CT screening for PAVMs has not been previously reported. Thus, our estimated prevalence of PAVMs could not be compared accurately with previous studies due to different screening tools. Considering that low-dose CT could detect small PAVMs, of approximately 4 mm in size in our study, the sensitivity of low-dose CT for detection of PAVMs would be high. However, TTCE can detect subtle PAVMs which CT cannot (17). This implies that the real prevalence of PAVMs in the area we studied may be slightly higher than our original estimation. Furthermore, as most of the participants in our study were between 50 and 80 years old, our estimated prevalence of PAVMs does not truly reflect that in the general population. However, because we performed a large-scale screening with over 20,000 participants, we believe that our data are valuable to estimate the prevalence of PAVMs in the general population.

Among the present eight patients, only two (25%) were diagnosed with HHT, which is a lower incidence than in previous reports. However, a recent Japanese questionnaire reported that 24.8% of patients with PAVMs have HHT (9), which is closer to our data. Furthermore, the prevalence of PAVMs associated with HHT in our study, 9 per 100,000, is close to the prevalence noted in the above-mentioned reports (1-3, 12, 13). Considering that CT screening could detect small PAVMs in asymptomatic patients, which could not have been detected by chest X-ray, the prevalence of PAVMs not associated with HHT is likely to be higher than previously thought.

Conclusion

The detection rate of PAVMs by CT screening was 0.038%. Based on these data, we estimate the prevalence of PAVMs to be 38 per 100,000 individuals. This is more prevalent than has been previously reported, especially among females.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

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