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Association of deep vein thrombosis type with clinical phenotype of chronic thromboembolic pulmonary hypertension

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ABSTRACT

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) has been considered to be caused by single or recurrent pulmonary embolism (PE) arising from deep vein thrombosis (DVT). In Japan, female predominance and association of HLA-B*5201 with CTEPH unrelated to DVT were reported. In acute PE residual proximal DVT is associated with larger obstruction of pulmonary arteries. However, it remains uncertain whether DVT and the type of DVT are associated with clinical phenotype of CTEPH.
Purpose: To clarify the association of DVT and DVT type with clinical phenotype of CTEPH.
Methods: Among 98 consecutive patients who underwent 16 or 64-slice multidetector CT angiography and indirect venography, 91 patients (66% female, age: 56 ± 3years) with adequate images were enrolled. The associations of DVT and DVT type with pulmonary hemodynamics, CT obstruction index and other clinical parameters were analyzed.
Results: DVT was found in 45 patients (49.5%) (distal: 12, proximal: 33), and was significantly associated with male gender and recurrent type. Furthermore, it was more frequent in HLA-B*5201-negative, and D-dimer positive patients. Compared with distal DVT, proximal DVT was associated with male gender, larger CT obstruction index (48.6 ± 13.0 vs. 34.1 ± 13.2%, $p = 0.004$), and higher mean pulmonary arterial pressure (48.2 ± 12.8 vs. 40.8 ± 7.9 mm Hg, $p = 0.03$). Proximal DVT was significantly associated with the central type of CTEPH only in HLA-B*5201-negative patients.
Conclusions: The existence and type of DVT were associated with clinical phenotype of CTEPH, and proximal DVT might contribute to the central type of CTEPH in only HLA-B*5201-negative patients.

1. Background

Chronic thromboembolic pulmonary hypertension (CTEPH) has been considered to be caused by single or recurrent pulmonary embolism (PE) arising from deep vein thrombosis (DVT) [1]. However, 40% of patients with CTEPH do not have a history of PE or DVT [2]. In situ thrombosis in the pulmonary artery and pulmonary vascular remodeling might be involved in the pathogenesis of CTEPH [3,4].

Recurrent venous thromboembolism was shown to be associated with residual DVT [5], and the risk of recurrence was higher in men than women [6]. Jamieson reported a female predominance in type 3 disease (distal segmental arteries only type) [7] and our group also confirmed that CTEPH in females was associated with the peripheral type in only HLA-B*5201-negative patients (Western type) [8]. On the other hand, a female predominance in the central type of CTEPH unrelated to DVT was reported in Japan, and this specific type was associated with HLA-B*5201-positive patients [8].

In acute PE, DVT, especially proximal DVT is thought to be associated with the larger and proximal obstruction of pulmonary arteries [9,10]. However, it remains uncertain whether the existence and type of residual DVT are associated with the clinical phenotype of CTEPH, especially the central extent of thrombi in the pulmonary arteries.

Recently, indirect multi-detector CT venography (MDCTV) has made it possible to detect DVT even in CTEPH [11,12], and we used this method in the present study to investigate the existence and proximal extent of DVT and its association with the clinical phenotype of CTEPH.

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2. Methods

2.1. Subjects

Between Jan 2003 and Dec 2010, 98 consecutive CTEPH patients underwent 16- or 64-slice multidetector CT angiography (MDCTA) and indirect venography (MDCTV). Seven patients including 4 patients that had DVT confirmed by other modalities had images judged as poor image quality; thus 91 patients with adequate images were enrolled in this study. CTEPH was defined as mean pulmonary arterial pressure (PAP) >25 mm Hg with normal wedge pressure in patients with symptoms for >6 months [2,8]. In addition, lung perfusion scans were required to demonstrate segmental or larger defects concomitant with a normal ventilation scan. Chronic thromboembolic findings were confirmed by pulmonary angiography [13]. All patients had blood gas analysis, D-dimer test (Mitsubishi Medience, Japan), right-heart catheterization, pulmonary angiography and MDCTA–MDCTV. Furthermore, other than simultaneous MDCTA–CTV images at diagnosis of CTEPH, previous MDCTV images during after acute embolic episodes in our hospital were included to determine the proximal site of DVT in 5 of 91 patients.

2.2. CT protocol

CT was performed with a 16-slice multidetector row CT scanner (LightSpeed Ultra, GE Medical Systems, Milwaukee, WI) and a 64-slice multidetector row CT scanner (Aquillion One or Aquillion 64, Toshiba, Tokyo, Japan). Digital scout CT images of the chest, abdomen, and lower extremities to the middle calf level were obtained. For MDCTA, a total of 100–150 ml (≥600 mg I/kg) of non-ionic contrast material was injected into the antecubital vein via intravenous catheter at a rate of 3 ml/s with a power injector. MDCTA scanning was started during the phase peak of main pulmonary arterial enhancement, and the scanning delay was 25–35 s. MDCTA was scanned from the lung apex to the level of the diaphragm. The patients were instructed to hold their breath for the duration of the scan (9–20 s in 16-slice CT and ~4 s in 64-slice CT). Gantry rotation time was 0.5 s. The imaging parameters were 0.625-mm collimation with a pitch of 13.75 in 16-slice CT and 0.5-mm collimation with a pitch of 53.0 in 64-slice CT using the fast mode. Images were reconstructed from raw data set at 2.5-mm intervals and 1.25-mm thickness in 16-slice CT and at 0.5-mm intervals and 0.5-mm thickness in 64-slice CT.

MDCTV was performed 3.5 min after the initial injection of contrast media. Axial venous images were obtained from the level of middle calves to the level of the diaphragm during breath-holding (~20 s in 16-slice CT and ~8 s in 64 slice CT). The imaging parameters were 1.25-mm collimation with a pitch of 27.5 in 16-slice CT and 0.5-mm collimation with a pitch of 75.0 in 64-slice CT using the fast mode. Images were reconstructed from the raw data set at 5-mm intervals and 2.5-mm thickness in 16-slice CT and at 2-mm intervals and 2-mm thickness in 64-slice CT.

2.3. Image interpretation

MDCTA–CTV images of all patients were reloaded from optic disks to a workstation for retrospective review by 2 trained pneumologists that specialized in CT, and the final evaluations were achieved by consensus.

2.4. CT obstruction index

To quantify pulmonary arterial obstruction by thrombi, the CT obstruction index was calculated according to Qanadli [14]. In brief, this index is defined as the number of segmental artery branches that are blocked and corrected by a factor of one for partial blockage or a factor of two for completely obstructive PE. With this scoring system, the highest possible score is 40 (thrombus completely obstructing the pulmonary trunk), which corresponds to a 100% obstruction index.

2.5. Assessment of central extent of thrombi

Using MDCTA, central arteries were defined as vessels proximal to the segmental branches and were divided into four portions based on the method of Bergin [15]. These portions included the right and left main pulmonary arteries proximal to the upper lobe branches and the right and left descending portions of the central arteries between the upper lobes and the segmental branches. The central disease score was determined by adding up the number of abnormal central portions in each patient up to a maximum score of 4.

2.6. Classification of DVT

Thrombi were defined as low-attenuating partial or complete intraluminal filling defects surrounded by a high-attenuating ring of enhanced blood seen on at least two consecutive transverse images (10 mm) in 16-slice CT and 4 consecutive transverse images (8 mm) in 64-slice CT. Streaking artifacts were distinguished from clots in several ways according to Cham [11]. The upper level of DVT (caval, iliac, femoral, popliteal, or calf) was investigated in each patient. DVT proximal to the popliteal artery was defined as proximal DVT and DTV at the calf as distal DVT [9]. Findings of chronic DVT (calcification of venous walls, shrunken veins, or collateral vessels) were not included in the definition of DVT [12,16]. Although lower extremity venography or ultrasonography was also performed in 88% of the patients according to their medical records, the classification of DVT type was based only on CT venography.

The associations of DVT and DVT type with pulmonary hemodynamics, CT obstruction index and other clinical parameters were analyzed. Since the presence of a Japanese-specific type of CTEPH may influence the association between DVT and the phenotype of CTEPH, the patients were stratified by HLA-B*5201. HLA-B*5201-positive patients have the Japanese-specific type of CTEPH, whereas HLA-B*5201-negative patients have the usual Western type of CTEPH [8,17].

The study protocol for HLA typing was approved by the Research Ethics Committee of Chiba University School of Medicine, and written informed consent was obtained from all patients.

2.7. Statistical analysis

Results are expressed as the mean ± SD for continuous variables and as the number or percentage for categorical variables. Comparison of two groups was performed by an unpaired t-test when the variables were continuous, and by a chi-square test or Wilcoxon test when the variables were categorical. A p value <0.05 was considered significant. All statistical analyses were performed using commercially-available software (JMP9.0.0, Japanese version, SAS Institute Inc. Tokyo, Japan).

3. Results

As shown in Table 1, there were more females (n = 60) than males (n = 31) in the 91 cases that were enrolled in the study. The age at catheterization and CT ranged from 16 to 78 years (56.3 ± 12.8 years). Forty-five patients (49.9%) had a history of deep vein thrombosis (DVT), and 33 patients were classified as central type (iliac: 1, femoral: 25, popliteal: 7) and 12 patients were distal (calf) type. Thirty patients (33.0%) showed abnormalities in the screening for coagulopathy, 24 (26.4%) had antiphospholipid antibodies. The mean PAP and pulmonary vascular resistance (PVR) were 46.5 ± 12.0 mm Hg and 861 ± 409 dyn s cm^{-5}, respectively. Arterial oxygen tension (PaO_2) while breathing room air was 57.2 ± 9.7 Torr. The number of patients in WHO functional classes 1, 2, 3 and 4 were 1, 25, 61 and 4, respectively. There were 24 patients (26.4%) that had D-dimer >1.0 μg/ml during anticoagulation treatment (Table 1). Forty-one patients underwent pulmonary endarterectomy.

The DVT-positive group had a significantly greater proportion of males and a more frequent history of acute embolic episodes than the DVT-negative group (Table 2). Compared with the DVT-negative group, the DVT-positive group had fewer HLA-B*5201-positive cases but more D-dimer positive cases (Table 2). There were no significant

Table 1
Clinical characteristics of enrolled patients with CTEPH (n = 91).

Age	years	56.3 ± 12.8
Female versus male	n	60 vs 31
Duration of symptoms	months	38.6 ± 39.4
DVT	%	49.9
Proximal site, distal:central	n	12:33
Side, right only:left only:bilateral	n	14:8:23
Coagulopathy	%	33.0
Anti-cardiolipin antibody	%	26.4
Acute embolic episodes	%	51.6
HLA-B*5201 posotive	%	32.6
Cardiorespiratory data		
Mean Pra	mm Hg	6.2 ± 4.4
Mean PAP	mm Hg	46.5 ± 12.0
Cardiac index	L min^{-1} m^{-2}	2.55 ± 0.67
PVR	dyn s cm^{-5}	861 ± 409
PaO_2	Torr	57.2 ± 9.7
D-dimer >1 μg/ml	%	26.4
WHO functional class		1:25:61:4
I:II:III:IV	%	45.3 ± 12.4
CT obstruction index		
Central disease score		27:31:22:9:2
0:1:2:3:4		

Values are presented as mean ± SD or n (%).
CTEPH: chronic thromboembolic pulmonary hypertension; Pra: right atrial pressure; PAP: pulmonary arterial pressure; PVR: pulmonary vascular resistance; PaO_2: arterial oxygen tension.