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Original Article

Different sizes of centrilobular ground-glass opacities in chest high-resolution computed tomography of patients with pulmonary veno-occlusive disease and patients with pulmonary capillary hemangiomatosis

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ABSTRACT

Background: Centrilobular ground-glass opacity (GGO) is one of the characteristic findings in chest high-resolution computed tomography (HRCT) of patients with pulmonary veno-occlusive disease (PVOD) and patients with pulmonary capillary hemangiomatosis (PCH). However, clinical differential diagnosis of these two diseases is difficult and has not been established. In order to clarify their differences, we compared the sizes of GGOs in chest HRCT and the sizes of capillary assemblies in pulmonary vascular casts between patients diagnosed pathologically with PVOD and PCH.
Methods: We evaluated chest HRCT images for four patients with idiopathic pulmonary arterial hypertension (IPAH), three patients with PVOD and three patients with PCH, and we evaluated pulmonary vascular casts of lung tissues obtained from those patients at lung transplantation or autopsy.
Results: Centrilobular GGOs in chest HRCT were observed in patients with PVOD and patients with PCH but not in patients with IPAH. We measured the longest diameter of the GGOs. The size of centrilobular GGOs was significantly larger in patients with PCH than in patients with PVOD (5.60±1.43 mm versus 2.51±0.79 mm, $P<.01$). We succeeded in visualization of the 3-dimensional structures of pulmonary capillary vessels obtained from the same patients with PVOD and PCH undergoing lung transplantation or autopsy and measured the diameters of capillary assemblies. The longest diameter of capillary assemblies was also significantly larger in patients with PCH than in patients with PVOD (5.44±1.71 mm versus 3.07±1.07 mm, $P<.01$).
Conclusion: Measurement of the sizes of centrilobular GGOs in HRCT is a simple and useful method for clinical differential diagnosis of PVOD and PCH.

1. Introduction

Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) are rare diseases that are classified as a subgroup of pulmonary arterial hypertension (PAH) [1–3]. PVOD is histologically characterized by intimal fibrosis that narrows and occludes pulmonary veins and it accounts for 5–10% of cases initially thought to be idiopathic PAH (IPAH) [4]. PVOD occurs in a wide range of ages. Among adult patients, the incidence in men is about twice that in women. PCH is histologically characterized by localized capillary proliferation within the lung in which capillaries invade the pulmonary interstitium, vessels and, less commonly, airways [5]. PCH has been reported to be much less frequent than PVOD [6]. PCH and PVOD have similar clinical presentations with poor prognosis.

In recent years, PAH-targeted drugs including epoprostenol have improved the survival of patients with IPAH [3,7,8], but no medical treatment to improve the survival of patients with PVOD or PCH has been established. Several investigators have reported the possible efficacy of cautious application of epoprostenol [9,10], but incautious administration of vasodilators including epoprostenol sometimes causes massive pulmonary edema and can be fatal in these patients.

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Therefore, the establishment of methods for medical treatment in these patients is required. To that end, accurate diagnosis of PVOD and PCH is also needed.

Histological proof is required for a definitive diagnosis of PVOD and PCH. Since surgical lung biopsy is too invasive and is a high risk for patients with PVOD or PCH, a noninvasive approach is preferable. High-resolution computed tomography (HRCT) of the chest is one of the diagnostic tools for PVOD and PCH. Centrilobular ground-glass opacities (GGOs), septal lines and mediastinal lymph node enlargement are characteristic findings in chest HRCT of patients with PVOD or PCH [6,11,12]. However, clinical differential diagnosis of these diseases has not been established.

We previously reported success in visualization of the 3-dimensional structures of pulmonary capillary vessels in patients with PAH, PVOD and PCH using scanning electron microscopy of blood vascular casts [13]. Study of blood vascular casts revealed differences in the three diseases. PAH was characterized by a deficient capillary network, PVOD was characterized by swollen capillary vessels and PCH was characterized by tumor-like outgrowth of capillaries. These differences in capillaries might reflect differences in the sizes of GGOs in chest HRCT since centrilobular GGOs reflect thickening of interstitial tissues, local fluid accumulation in airspaces, local alveoli collapse and increased capillary blood volume [14,15]. Thus, we compared the sizes of centrilobular GGO in chest HRCT and the sizes of capillary assemblies in pulmonary vascular casts in patients diagnosed pathologically with PVOD and patients diagnosed pathologically with PCH in order to clarify their differences.

2. Methods

2.1. Subjects

We obtained lung tissues from 27 patients clinically diagnosed with PAH by living-donor lobar lung transplantation (LDLLT), cadaveric lung transplantation (CLT) or autopsy between 1999 and 2011 in our institution. Twenty patients were diagnosed with pulmonary arteriopathy, four patients were diagnosed with PVOD and three patients were diagnosed with PCH by pathological examination. We could obtain findings of chest HRCT from four patients with idiopathic PAH (IPAH), three patients with PVOD and three patients with PCH before or just after the start of specific treatment for pulmonary hypertension. For non-pulmonary hypertension control experiments, samples of pulmonary arteries were also obtained at autopsy from a patient with cerebral infarction (male, 43 years old) who showed no evidence of PAH.

All human subject protocols were approved by the Human Ethics Committee of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, and written informed consent was obtained from all patients before the procedure. The investigation also conforms to the principles outlined in the Declaration of Helsinki.

2.2. Histological analysis

Lung tissue was fixed in 10% formalin. Hematoxylin and eosin stain and elastica-van Gieson stain were used for all histological specimens to characterize pulmonary abnormalities. The pathologic hallmark of pulmonary arteriopathy was defined as medial hypertrophy, intimal thickening and plexiform lesions. The pathologic hallmark of PVOD was defined as an extensive and diffuse obstruction of pulmonary venules and veins of various sizes. The pathologic hallmark of PCH was defined as localized capillary proliferation within the lung in which capillaries have invaded the pulmonary interstitium, vessels and, less commonly, airways as previously described [5,16].

2.3. Pulmonary vascular casts

To visualize the 3-dimensional structures of pulmonary vessels, we made vascular casts as previously described [13,17]. In brief, lungs were isolated from patients undergoing lung transplantation or at autopsy, and their pulmonary arteries were cannulated. The pulmonary arteries were then perfused with saline and methacrylate resin (Mercox CL; Oken Shoji, Tokyo, Japan). These resin-injected lungs were placed in a hot water bath to completely polymerize the resin. The lungs with polymerized resin were immersed in a hot 10% NaOH solution and washed in water. This series of maceration and washing was repeated several times until tissue elements had been completely removed. The blood vascular casts of lungs were air-dried, coated with gold, and observed with a scanning electron microscope (S-2300, Hitachi) using an acceleration voltage of 5 kV. Digital images were also obtained with a digital camera (Canon IXY Digital 800IS), and the longest diameter of 14−16 capillary assemblies in the pulmonary vascular casts in each patient were measured.

2.4. Clinical and functional assessment

We obtained clinical data at HRCT of the chest including clinical diagnosis, World Health Organization functional class, pulmonary function test results and PAH-specific treatment from medical records as previously described [13,18–21]. Diffusion capacity of the lung for carbon monoxide (DLco) was measured by the single-breath method and expressed as %DLco (% predicted). We collected hemodynamic data from right heart catheterization performed within one month of HRCT of the chest examination. Event-free survival period was from

Table 1
Patients` characteristics

No.	Age (years old)	Sex	Histological diagnosis	WHO FC	mean PAP (mmHg)	%DLco (%)	Survival (years)	Outcome
1	10	F	IPAH	IV	84	59	0.8	LDLLT
2	27	M	IPAH	IV	50	58	4.0	Autopsy
3	16	M	IPAH	IV	106	79	11.7	CLT
4	20	F	IPAH	IV	58	81	3.7	LDLLT
5	41	M	PVOD	IV	39	24	2.0	Autopsy
6	32	F	PVOD	IV	57	23	1.2	LDLLT
7	26	M	PVOD	IV	57	31	0.4	Autopsy
8	11	M	PCH	IV	52	64	3.1	Autopsy
9	17	F	PCH	IV	NA	NA	0.1	Autopsy
10	25	F	PCH	IV	55	36	0.4	LDLLT

Age, age at chest CT examination; WHO FC, World Health Organization classification of functional status of patients with pulmonary hypertension; PAP, pulmonary artery pressure; %DLCO, diffusion capacity of the lung for carbon monoxide expressed as % predicted; survival, period between diagnosis and outcome; CLT, cadaveric lung transplantation; LDLLT, living-donor lobar lung transplantation; F, female; M, male; PAH, pulmonary arterial hypertension; PVOD, pulmonary veno-occlusive disease; PCH, pulmonary capillary hemangiomatosis; NA, not available.