# Case Report

## AN AUTOPSY CASE OF PORTOPULMONARY HYPERTENSION ASSOCIATED WITH ALCOHOLIC LIVER CIRRHOSIS

HIROSHI MARUYAMA[1], YUKI TOYODA-HIRANA[2] and TAKAHITO NAKAMURA[2]
*Departments of [1]Pathology and [2]Respiratory Medicine, Hoshigaoka Koseinenkin Hospital*

YASUNORI ENOMOTO[3], KAORU HAMADA[4] and HIROSHI KIMURA[4]
*Departments of [3]Diagnostic Pathology and [4]Respiratory Medicine, Nara Medical University*
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*Abstract* : We report an autopsy case of pulmonary plexogenic arteriopathy associated with portal hypertension due to alcoholic liver cirrhosis, termed portopulmonary hypertension (PPHT). A 49-year-old man who has had alcoholic liver cirrhosis for 10 years complained of severe dyspnea (Fletcher-Hugh-Jones V). Chest CT revealed marked enlargement of bilateral hilar pulmonary arteries and cardiomegaly associated with right ventricular hypertrophy. The patient died from hepatic encephalopathy and respiratory failure. Autopsy clearly revealed the wall thickness of pulmonary small vessels diffusely in peripheral fields on cut surfaces and marked dilatation of the main pulmonary artery, together with liver cirrhosis. Microscopically, the pulmonary small arteries demonstrated grade 5 pulmonary plexogenic arteriopathy including plexiform lesions and a micronodule resembling an arachnoid granulation or meningioma throughout the lungs. This case suggested that a typical plexogenic arteriopathy morphologically and definitely contributed to confirm PPHT, although the patient was clinically suspected of hepatopulmonary syndrome (HPS).

**Key words** : portopulmonary hypertension, alcoholic liver cirrhosis, plexiform lesion, associated pulmonary arterial hypertension, hepatopulmonary syndrome

## INTRODUCTION

The plexiform lesion is the cardinal histological finding of plexogenic pulmonary arteriopathy. The lesion is observed in primary plexogenic pulmonary arteriopathy, pulmonary hypertension (PH) secondary to congenital cardiac malformations associated with shunting, and the drug aminorex fumarate. Furthermore, it is rarely found with liver cirrhosis or portal vein thrombosis. It is well-known that a moderate degree of PH is common in patients with portal hypertension due to liver cirrhosis, corresponding to morphological change of classic plexogenic pulmonary arteriopathy[1]. The portopulmonary hypertension (PPHT) is defined as a pulmonary arterial hypertension associated with portal hypertension in the presence or absence of liver disease[2]. It was initially reported by Mantz and Craige[3] in 1951 that the coexistence of PH as a consequence of hepatic dysfunction

caused by portal axis thrombosis was found via a postcaval shunt, resulting in cor pulmonale. The prevalence is relatively low in PPHT, and its frequency observed to a greater extent in alcoholic liver cirrhosis. Especially, the incidence of pulmonary arterial hypertension in cases of biopsy-proven liver cirrhosis was between 0.61-2.0%[2].

We report here on an autopsy case of plexogenic pulmonary arteriopathy associated with alcoholic liver cirrhosis, termed PPHT. Concerning CT findings, the differentiation between PPHT and hepatopulmonary syndrome (HPS) is briefly discussed.

## CASE REPORT

A 49-year-old man complained of severe dyspnea (Fletcher-Hugh-Jones V) and was admitted to our hospital because of the marked enlargement of bilateral hilar shadows on chest X-ray (Fig. 1). He had a history of heavy alcohol intake (mainly, 5 x 180ml/day x 25 years of Japanese Sake) and was diagnosed with alcoholic liver cirrhosis since 10 years before. Brinkman index was approximately 400. In the past before admission, he underwent a sclerotherapy for esophageal varix. At the time of admission, blood pressure was elevated to 190/110 mmHg, with pulse rate of 86/min., respiration rate of 18 times/min, and oxygen saturation (SpO2) of 92%. Electrocardiography revealed mild right ventricular hypertrophy and right bundle branch block. Echocardiography did not show any cardiac valvular abnormality, or clear right ventricular dilatation. His consciousness was somnolent, suggesting hepatic encephalopathy of grade II, reflected by high serum ammonia value of 160$\mu$g/dl . The skin appeared icteric. Clubbed finger and flapping tremor were also

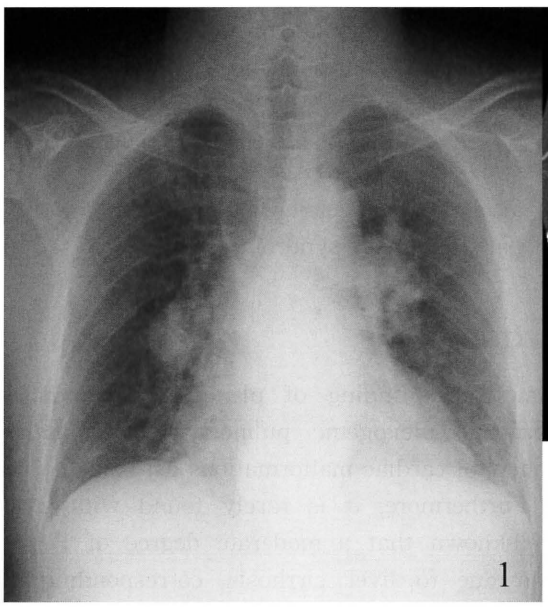


Fig. 1. Chest x-ray showed the enlargement of bilateral hilar shadows and elevation of cardio-thorax ratio (CTR).

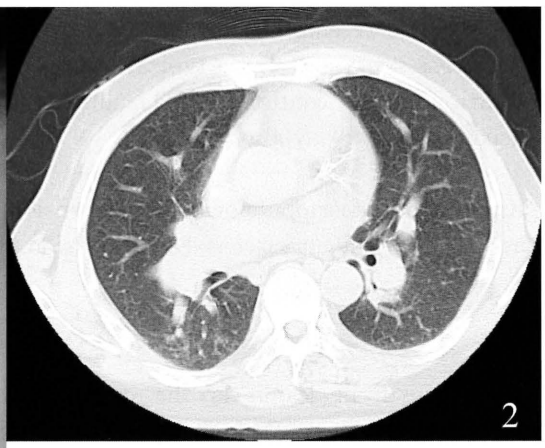


Fig. 2. Thoracic CT revealed marked enlargement of bilateral hilar pulmonary arteries and venous dilatated appearance in the peripheral lung fields.

Table 1. Laboratory data on admission

Blood : RBC 449×104 / μ L, HB 16.4 g/dL, HcT 46.8 %, WBC 7100 / μ L, PLT 4.9×104 / μ L

Hemostasis : PT 30.8 sec, PT 24.8%, PT-INR 2.42, APTT 81.5 sec, Fibrinogen 82 mg/dL, FDP 6.2 μ g/mL

Biochemistry/Immunology : T-Bilirubin 12.5 mg/dL, D-BIL 5.6 mg/dL, TP 5.2 g/dL, Alb 2.6 g/dL, AST 105 IU/L, ALT 57 IU/L, ALP 1243 U/L, γ-GTP 68 U/L, LDH 589 IU/L, Glucose 131 mg/dL, NH3 160 μ g/dL, BUN 15.7 mg/dL, Creatinine 0.56 mg/dL, Na 140 mEq/L, K 3.0 mEq/L, Cl 106 mEq/L, BNP 96.1pg/mL, CRP 0.18 mg/dL, HBs-Ag : (−)、HCV-Ab : (−), Anti-mitochondria Ab : (−)

Tumor marker : CEA 6.0 ng/mL, CA19-9 112.43 U/mL, AFP 14 ng/mL, PIVKA-II 829 mAU/mL, SCC0.5 ng/mL, NSE7.6 ng/mL, sIL-2R 345U/MI

Underline: abnormal values

recognized. Laboratory findings are shown in Table 1, and briefly summarized as thrombocytopenia, decrease in prothrombin time and total protein, increase in total bilirubin (12.5mg/dl), and HB-Ag, HCV and anti-mitochondria antibody were negative. Tumor markers were elevated as CA19-9 value: 112.4 U/ml, PIVKA-II: 829 and CEA: 6.0 (<5.0). Thoracic CT revealed marked enlargement of bilateral hilar pulmonary arteries and right ventricles, and moreover marked peripheral pulmonary veins (Fig. 2). Abdominal CT showed liver cirrhosis without space occupying lesion, nor obstruction of portal vein, accompanied with splenomegaly and esophageal varices. The clinical diagnosis denied lung cancer on CT findings with negative sputum cytology, and he was suspected of pulmonary hypertension associated with liver cirrhosis. Blood gas sample was not taken, and right heart catheterization was also not performed because of a refusal by the family. The patient died from hepatic encephalopathy four weeks after admission and was autopsied two hours later.

## PATHOLOGIC FINDINGS AT AUTOPSY

Grossly, the liver was very small, 630g in weight, and diffusely micorgranular in approximately 3 mm in diameter (Fig. 3). The cut surface did not show any liver tumors. There were yellowish ascites (600ml), jaundice, splenomegaly (270g) and esophageal varices with mild erosion of gastric cardiac portion. The heart weighed 590g, with 100 ml of pericardial yellowish effusion. There was marked left and right ventricular hypertrophy, with the wall thickness of 17 mm (<10 mm in normal) and 8 mm (<5 mm in normal), respectively. Especially, the girth of PA valve in 8cm was larger than that of aortic valve in 7cm. The right lung weighed 430g and the left 420g, almost without congestion and

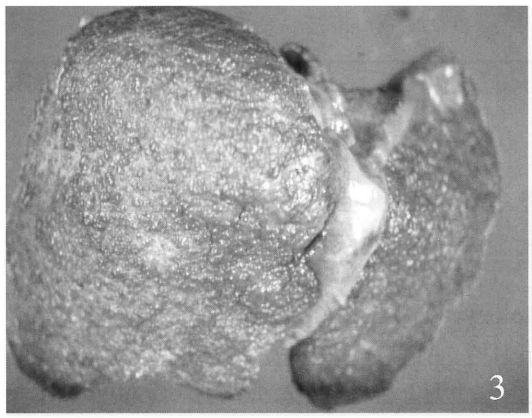

Fig. 3. Gross appearance of the liver weighing 630g showed diffuse micorgranules in approximately 3 mm in diameter.

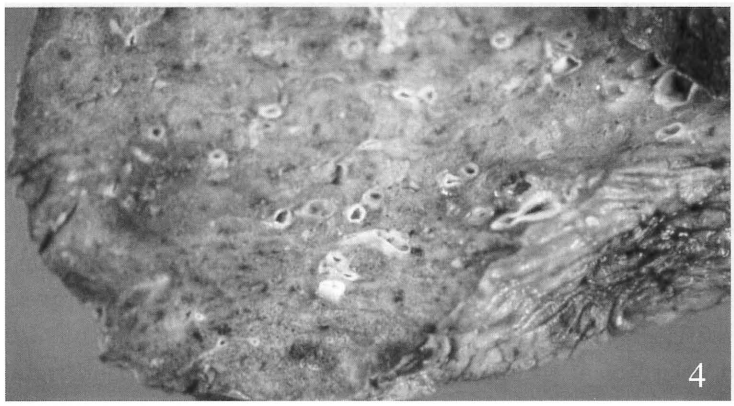

Fig. 4. At autopsy, after formalin-fixation, the cut surface of the lung showed the wall thickening of small pulmonary arterial vessels.

hemorrhage. There was pleural effusion (rt: 250ml, lt: 400ml). The cut surface of lung clearly revealed wall thickness of small blood vessels in the periphery, in addition to enlargement of the central pulmonary artery (Fig. 4). The hilar lymph nodes were slightly swollen with softness.

Microscopically, the liver revealed micronodular cirrhosis with only a little fatty change and Mallory body (Fig. 5). Because HBs-Ag and HCV were negative in serum, alcoholic liver cirrhosis was considered. The splenomegaly was observed as congestion associated with cirrhosis. The cardiac muscles of left and right ventricles were histologically hypertrophic, probably due to systemic and PH. In the histologic sections of the lung, the small pulmonary arteries from 200 to 500$\mu$m mostly demonstrated all types of hypertensive changes, ranging from muscular medial hypertrophy (Grade 1 in Heath-Edwards' classification of plexogenic pulmonary arteriopathy) to intimal fibrosis (Fig. 6), plexiform lesions (approximately 300$\mu$m in diameter) with peripheral dilatation lesions (Grade 4) (Fig. 7) and a micronodule

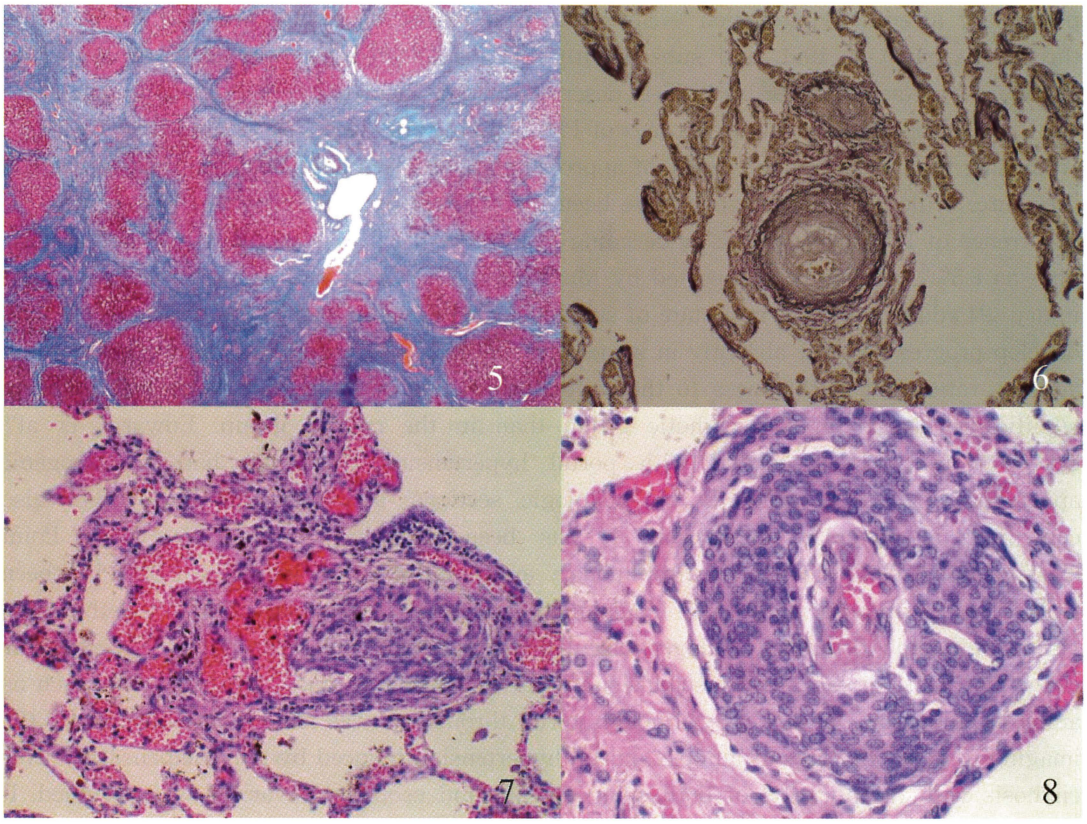


Fig. 5. Microscopically, the liver showed pseudolobules, suggesting the alcoholic liver cirrhosis (Masson trichrome stain, x20).
Fig. 6. Microscopically, the small pulmonary arteries of approximately 200-300$\mu$m demonstrated intimal fibrosis (Grade 2-3 in Heath-Edwards' classification) (EVG, x40), suggesting hypertensive change.
Fig. 7. A small vessel (approximately 300$\mu$m in diameter) in the lung microscopically formed the plexiform lesion (Grade 4) with peripheral capillary dilatation (HE, x40).
Fig. 8. Another small vessel in the lung microscopically demonstrated a micronodule resembling an arachnoid granulation or meningioma (Grade 5) ( HE, x100).

resembling an arachnoid granulation or meningioma (Grade 5) (Fig. 8). But necrotizing arteries of pulmonary arteries (Grade 6) were not observed at histologic sections examined. In central area, the pulmonary artery demonstrated intimal and medial wall thickness. The lymph nodes of pulmonary hilum showed nonspecific findings such as sinus histiocytosis and silicoanthracosis, without tumor.

## DISCUSSION

The present case was morphologically confirmed to show PPHT associated with non-compensatory phase of alcoholic liver cirrhosis, although valuable clinical examinations concerning on pulmonary hypertension were insufficient, such as a direct pulmonary arterial pressure and arterial blood oxygen pressure. That is, plexiform pulmonary arteriopathy was considered as the hallmark of primary pulmonary hypertension[4] (recently re-termed

pulmonary arterial hypertension[5]). Since the first report by Mantz and Craige[3] (a portal thrombosis case) in 1951, and subsequently PH complicated by liver cirrhosis was first described by Naeye[6] in 1960. PPHT is described in low incidence of 0.61-2%[2]. In Japan, Ito et al[7] (1987) reported two autopsy cases of PH in hepatitis B virus- associated liver cirrhosis. According to Nakatani et al[8], PPHT of approximately 60 cases have been reported in English literature, while 32 cases in Japan have been reported up to 1985, respectively. Recently, the occurrence of PPHT in patients undergoing evaluation for liver transplant has increased as high as 8.5%[9]. It has been reported by Matsubara et al[10] that patients with severe hepatic injury (94 adult cases) are in a state of subclinical PH and that symptoms of severe PH may develop progressively or abruptly in some of them. They suggested that the wall thickening and the ratio of wall thickness to the anatomical radius of small pulmonary arteries were significantly larger in the cirrhotic group than in the control group. Edwards et al[11] described that PH associated with portal hypertension commonly had a plexogenic appearance (10 of 12 patients) on histologic sections, and that thrombus might also contribute to vascular obstruction. It has been recently described by Dana Point classification (2008) that Plexiform pulmonary arteriopathy (PAH) including PPHT has been reclassified as an associated type of pulmonary arterial hypertension (APAH), together with various etiologic disorders, collagen-vascular disease, HIV infection, portal hypertension, congenital heart disease, schistosomiasis, chronic hemolytic anemia, and drug/toxin such as aminorex fumarate. In our case, although portal thrombosis was neither recognized with CT imaging or gross findings at autopsy, portal hypertension induced by non-compensatory liver cirrhosis with complication of both splenomegaly and esophageal varices was assumed. It has been indicated that portal hypertension and portosystemic shunting, rather than the hepatic disorder itself including cirrhosis, are most likely to be the determinant risk factor for developing PH.

On the other hand, another pulmonary vascular complication in liver dysfunction, hepatopulmonary syndrome (HPS)[12], is recently important for respiratory clinicians to differentiate from PPHT. HPS is defined by liver disease, intrapulmonary vasodilation and impaired arterial oxygenation. HPS is usually present with dyspnea without any abnormal shadows on chest x-ray, but occasionally with an increase in interstitial markings in the lower lung fields on CT imaging. Infrequently, HPS is not easily distinguished from portopulmonary hypertension because of similar clinical features, such as dyspnea, anemia, ascites, hepatic hydrothorax, and muscle wasting. In our case, oxygen saturation (SpO2) was lower at 92%, and there was some difficulty before the death in differentiating between PPHT and HPS showing the imaging of pulmonary vasodilation in peripheral zone of lung on CT[13]. However, chest x-ray of the present patient showed marked enlargement of bilateral hilar shadows and elevation of cardio-thorax ratio (CTR), suggesting some features of PPHT.

Microscopically, PPHT shows pulmonary vasoconstriction, intima proliferation, media-hypertrophy and plexiform lesions, but HPS shows capillary and pre-/post-capillary pulmonary vasodilation with lower pulmonary vascular resistance, and right to left shunt formation, in spite of fewer autopsy cases. In western countries, orthotopic liver transplantation is recently recommended in these two pulmonary vascular complications of end-stage liver disease[14]. It has already been described in 1999 that a case of PPHT following

HPS in a patient with liver cirrhosis showed 25-62 mmHg of mean pulmonary artery pressure on right-sided catheterization after more than 2-year clinical course, being still alive[15].

In conclusion, the present case suggests PPHT based on plexogenic pulmonary arteriopathy at autopsy associated with non-compensatory alcoholic liver cirrhosis, in spite of clinically differentiating from HPS. The pulmonary complications of end-stage liver disease include PPHT and HPS, and the etiologic pathogenesis of these conditions will need more elucidation in the near future.

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