Hepatopulmonary syndrome-discussion of cardiopulmonary parameters

Keisuke Miki, Tsutomu Shinohara*, Fumitaka Ogushi*, Saburo Sone*, Hirotsugu Yamada**, Yoshifumi Oishi**, Tetsuzo Wakatsuki**, Susumu Ito**, Shiro Yogita***, Seiki Tashiro***

*Department of Internal Medicine, Kochi Nokyo General Hospital, Nankoku, Kochi, Japan ; * Third Department of Internal Medicine, ** Second Department of Internal Medicine, and *** First Department of Surgery, The University of Tokushima School of Medicine, Tokushima, Japan*

Abstract: We report a 70-year-old man with hepatopulmonary syndrome (HPS) in C liver cirrhosis. Hypoxemia worsened markedly, especially on exertion, while the hepatic function was clinically stable. Contrast echocardiography, ^{99m}Tc macroaggregated albumin (^{99m}TcMAA) lung scan, and pulmonary angiography were performed. The findings suggested the presence of both intrapulmonary vascular dilatation and substantial right-to-left shunt. The contribution of intrapulmonary vascular abnormalities in patients with severe liver cirrhosis without abnormal chest radiography and spirometry tests when marked hypoxemia is present should be investigated. J. Med. Invest. 47 : 164-169, 2000

Key words **:** *Hypoxemia, liver disease, contrast echocardiography, pulmonary angiography, ^{99m}Tc macroaggregated albumin (^{99m}TcMAA) lung scan*

INTRODUCTION

Hepatopulmonary syndrome (HPS) was first suggested by Kenney and Knudson (1) in 1977 and has received attention recently because of the potential complications during liver transplantations in patients with severe hypoxemiam (2). HPS is defined as the triad of hepatic dysfunction, hypoxemia, and pulmonary vascular dilatation (1). Pulmonary angiography has shown, with hypoxemia in HPS, diffuse vascular abnormalities (type I) and discrete vascular lesions (type II). The former is seen as diffuse, spidery vessels during the arterial phase of the angiogram, and the latter is due to arteriovenous communications (3-5). Because of its unique pathophysiologic state, the hypoxemia may have a variable response to supplemental oxygenation. We report a cirrhotic patient who underwent a partial liver resection under the diagnosis of hepatocellular carcinoma (HCC) with refractory hypoxemia that could not be explained by the spirometry tests, and we discuss the cardiopulmonary functional tests.

CASE REPORT

In April 1998, a 70-year-old man was admitted to the third Department of Internal Medicine of Tokushima University hospital because of worsening of exertional dyspnea (Hugh-Jones IV) that first appeared 1 yr before. In 1992, he had undergone a partial liver resection (S6) under the diagnosis of HCC. He reported a smoking history (25/day ×45yr) and that he had given up smoking for 5 years. A physical examination showed significant digital clubbing, cyanosis, and cutaneous vascular spiders of chronic liver disease without bilateral ankle edema. There was no obvious ascites on abdominal examination, and the liver was enlarged to 2.5cm palpable

Abbreviations : $AaDo_2$=alveolar-arterial oxygen pressure difference ; DLco=single-breath diffusing capacity ; $FEV_{1.0}$=forced expiratory volume in one second ; FVC= forced vital capacity ; HCC=hepatocellular carcinoma ; HOT= home oxygen therapy ; HPS=hepatopulmonary syndrome ; $Paco_2$=arterial carbon dioxide pressure ; Pao_2=arterial oxygen pressure ; PCW=pulmonary capillary wedge ; Spo_2=arterial oxygen saturation ; ^{99m}TcMAA=^{99m}Tc macroaggregated albumin ; TTE=transthoracic echocardiography ; VC=vital capacity ; 6 WT=6 minute waking test.

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Address correspondence and reprint requests to Keisuke Miki, M. D., Department of Internal Medicine, Kochi Nokyo General Hospital, 1571 Oosone-kou Nankoku, Kochi 783-8509, Japan and Fax : +81-88-863-3720.

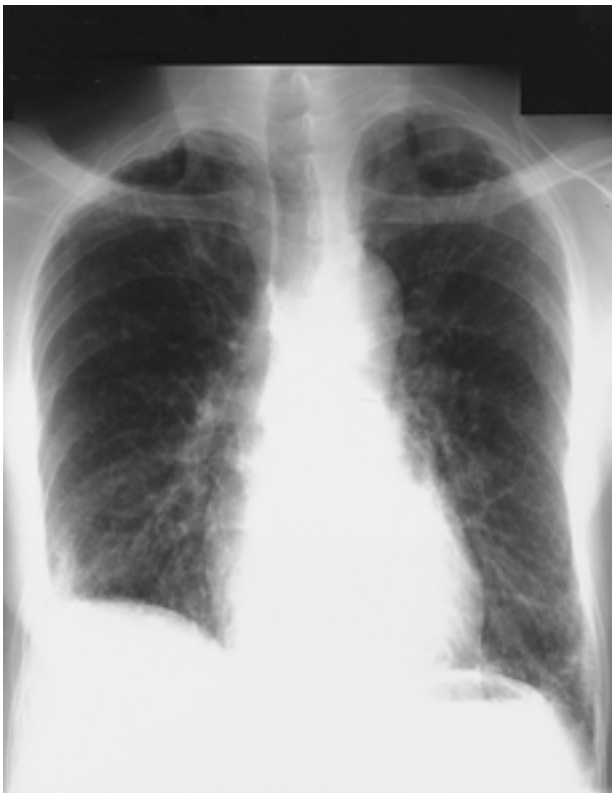


Fig. 1. Chest X-ray on admission showing a slightly post-inflammatory change in the right upper lung field and an elevated right diaphragm, without cardiac enlargement.

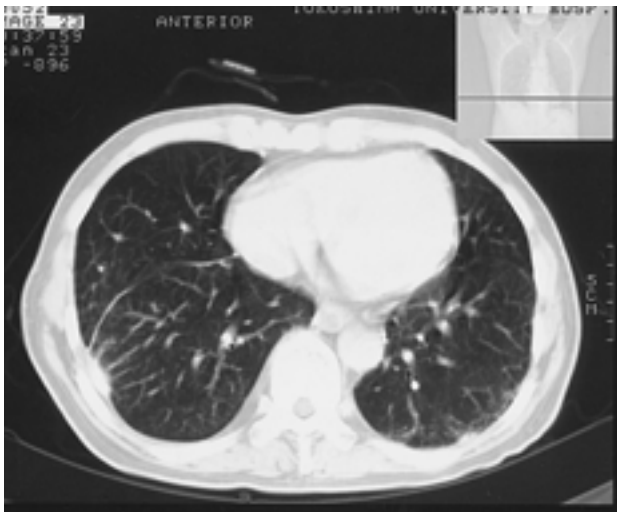
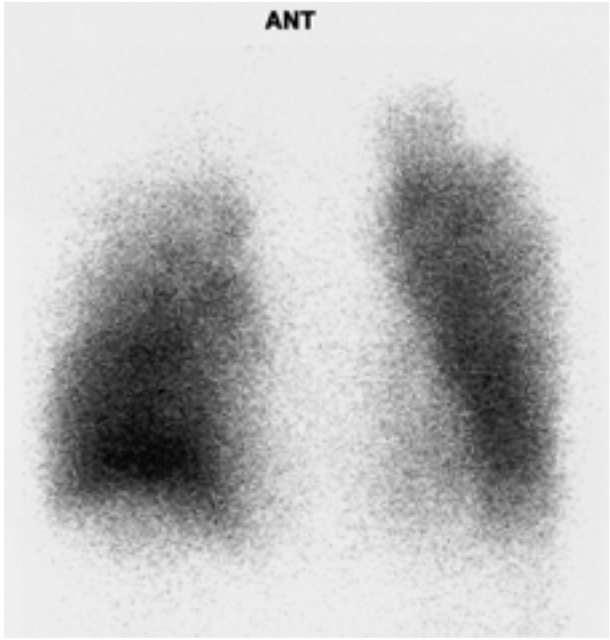
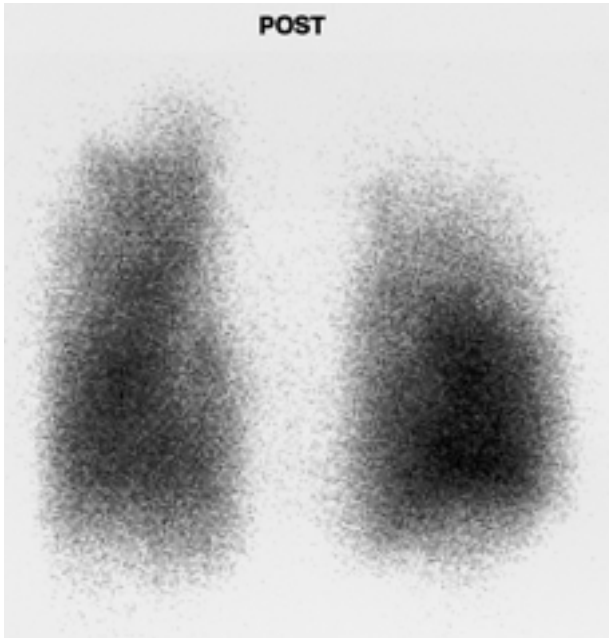


Fig. 2. Chest CT shows interlobular septal thickening in the right lower lung field.





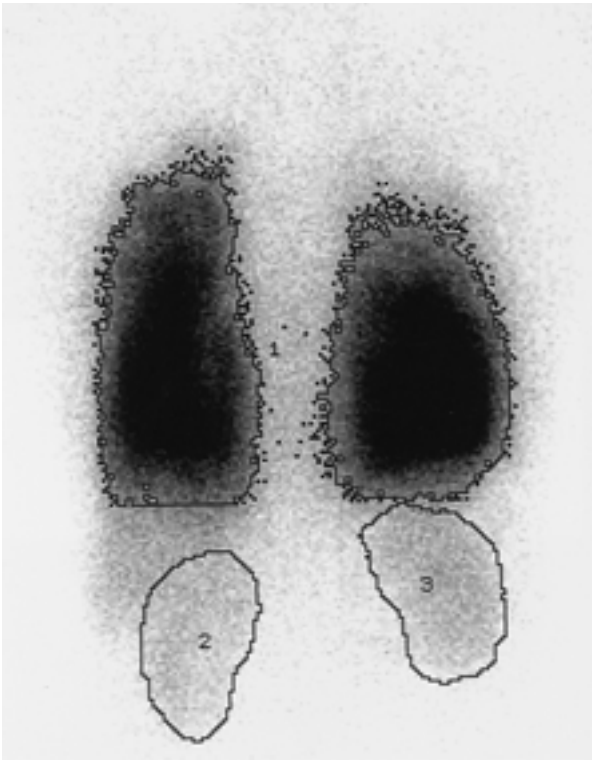


Fig. 3. Pulmonary perfusion scintigraphy with ^{99m}TcMAA performed on admission (A ; anterior, B ; posterior), showing the uptake over the kidneys (C). The shunt rate was 19.3% as measured by the ^{99m}TcMAA lung and kidney scan in the supine position.

Table 1. Data on Admission

Peripheral blood		
White blood cell	3,900	/μl
Red blood cell	452×10^4	/μl
Hemoglobin	14.3	g/dl
Hematocrit	45	%
Platelet	9.3×10^4	/μl
Blood chemistry		
Alanine aminotransferase	36	IU/l
Aspartate aminotransferase	27	IU/l
Total bilirubin	2.5	mg/dl
T-Cholesterol	112	mg/dl
Triglycerides	68	mg/dl
Choline esterase	124	U/l
Lactate dehydrogenase	367	IU/l
Total protein	7.4	g/dl
Albumin	2.6	g/dl
Blood urea nitrogen	20	mg/dl
Creatinine	0.86	mg/dl
Sodium	141	mEq/l
Potassium	3.7	mEq/l
Chloride	107	mEq/l
Lactate	19.2	mg/dl
C-reactive protein	0.09	mg/dl
Indocyanine green (15min)	31.5	%
Tumor marker		
Carcinoembryonic antigen	5.1	ng/ml
Alpha-fetoprotein	69	ng/ml
Infectional study		
Hepatitis B surface antigen	(−)	
Hepatitis C virus-antibody	(+)	
Sputum (smear culture)		
Mycobacterium tuberculosis	(−)	

Arterial blood gas (room air, at the supine)		
pH	7.5	
Pao_2	43.7	mmHg
$Paco_2$	32.5	mmHg
$AaDo_2$	51.8	mmHg
6 WT (Oxygen, by nasal cannula, 5 L/min) stopped, in 3 min		
	before	after
Spo_2 (%)	94	79
Heart rate (beats/min)	76	102
Pulmonary functional test		
VC	2.6	L
%VC	64.8	%
FEV1.0	1.4	L
FEV1.0/FVC	76.8	%
%DLco	34.2	%
Pulmonary perfusion scintigram by the ^{99m}TcMAA		
Shunt rate=19.3%		
Right heart catheterization		
Pressure study (mmHg)		
Pulmonary artery		23/8
Pulmonary artery, mean		13
PCW mean		8
Cardiac index (L/min/m 2)		3.08
Sampling(100% O_2 inhalation, mmHg)		
	Pao_2	$Paco_2$
Pulmonary artery	60.9	44.0
Femoral artery	376.5	37.9
Shunt rate =23%		

Pao_2, arterial oxygen pressure ; $Paco_2$, arterial carbon dioxide pressure ; Spo_2, arterial oxygen saturation ; $AaDo_2$, alveolar-arterial oxygen pressure difference ; 6 WT, 6 minute waking test ; VC, vital capacity ; FVC, forced vital capacity ; FEV 1.0, forced expiratory volume in one second ; %Dlco, single-breath diffusing capacity ; PCW, pulmonary capillary wedge ; ^{99m}TcMAA, ^{99m}Tc macroaggregated albumin.

below the costal margin. The laboratory findings on admission are shown in Table 1. Serological testing was positive for hepatitis C antibody. Chest roentgenography and computed tomography showed interlobular septal thickening in the right lower field (Fig.1,2). Chest roentgenography showed a slightly elevated right diaphragm, which was detected after the partial liver resection, but there were no other abnormal findings in the pulmonary field. A pulmonary functional test showed a single-breath diffusing capacity (DLco) of 34% of the predicted value, with a slightly abnormal ratio of vital capacity (VC) from the predicted value.

In the 6 minute walking test (oxygen by nasal cannula, 5 L/min), the patient was unable to continue the exercise after 3 min due to dyspnea, the Spo_2 decreased from 94% to 79%, and the pulse rate increased from76/min to102/min. Arterial blood gas analysis in room air showed deep hypoxemia with orthodeoxia, i.e., at rest Pao_2 decreased by as much as about 95% when the patient moved from the supine to the sitting position, which could not be estimated by the pulmonary functional test. The blood lactate, the presence of which is a marker of anaerobic metabolism (6), increased (19.2mg/dL). This may be due to the inability to provide enough oxygen to the peripheral muscles. A transthoracic

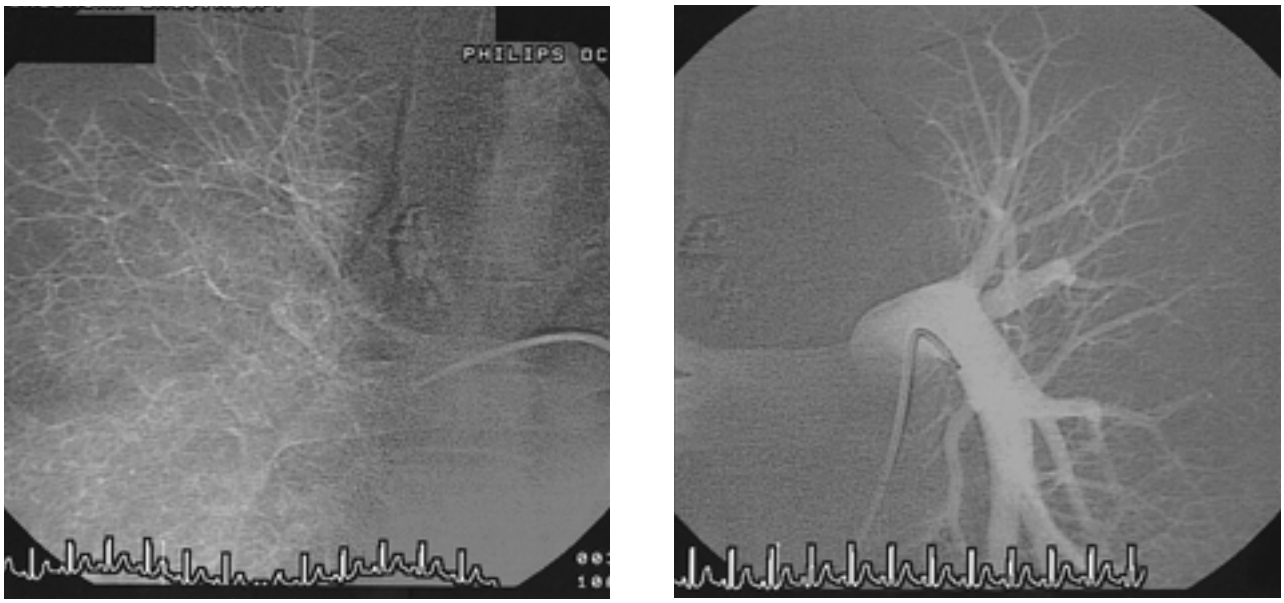


Fig. 4. Pulmonary angiography shows a diffuse spongy appearance (Type I) in the lower right lung. A, right; B, left. No arteriovenous communications can be seen. The shunt rate was calculated to be 23.3% by the 100% inspired oxygen method in the supine position.

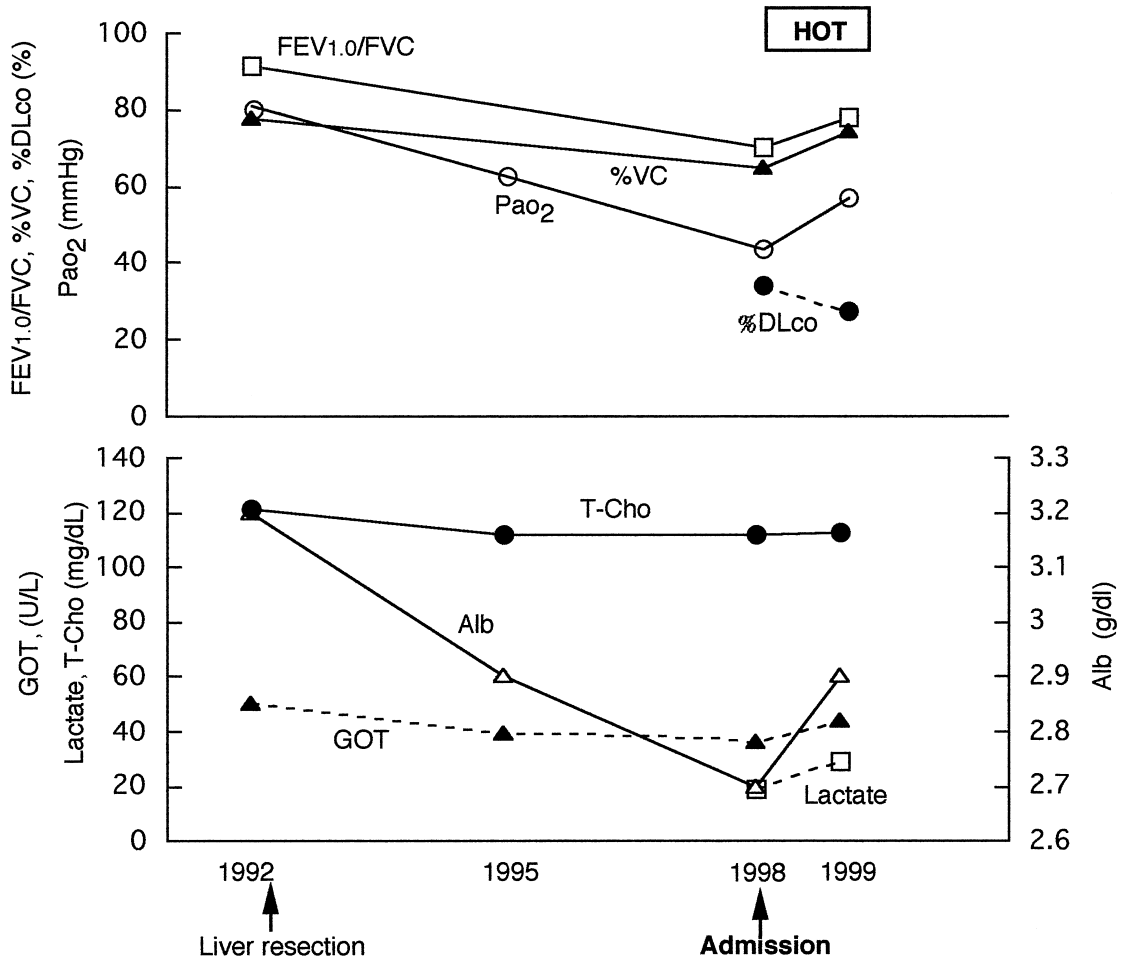


Fig. 5. Clinical course.
Alb, albumin; T-Cho, total cholesterol; GOT, Aspartate aminotransferase; HOT, home oxygen therapy: $FEV_{1.0}$ / FVC, % VC, Pao_2, and %DLco; see text for details.

contrast echocardiogram was suspiciously diagnostic for an intrapulmonary vascular dilatation and/or substantial right to left shunt with left atrial opacificationk 5 to 6 beats after the appearance of microbubbles in the right ventricle, using microbubbles generated by hand-agitation of saline. Color flow Doppler echocardiography and contrast studies demonstrated no evidence of an intracardiac right-to-left shunt.

A ^{99m}TcMAA lung scan showed an increased uptake by the kidneys suggesting that the ^{99m}TcMAA had passed through dilated intrapulmonary vessels or the substantial right-to-left shunt. The shunt rate was 19.3% measured by the ^{99m}TcMAA lung and kidney scann in the supine position (Fig.3, Table 1).

Right coronary catheterization showed a slightly high cardiac output and a normal mean pulmonary arterial pressure. The pulmonary angiogram (Fig.4) showed a subtle spongy-diffuse arterial phase (type I), which had spidery dilatations in the intrapulmonary vessels without discrete arteriovenous communication (type II) and, which was a direct, substantial intrapulmonary shunt. Then, using a face mask, the shunt rate was calculated at 23.3% by the 100% inspired oxygen method in the supine position, which was not lower than that measured by the ^{99m}TcMAA scanning. The Pao_2 on 100% inspired oxygen was 376.5mmHg (Table1). The above findings showed dilated intrapulmonary vessels and a substantial right-to-left shunt in both.

Taking into account the pathophysiologic state, age, and wishes of the patient, he was discharged on June 1998 with oxygen supplementation (nasal cannula, at rest ; 2.5L/min, on effort ; 5L/min), since the oxygen therapy had some beneficial effects on his activities of daily living. The clinical course is summarized in Fig.5. No significant changes in spirometry or the liver functional tests were found over his clinical course. However, the % DLco decreased from 34% to 27.5%, and the blood lactate level increased from 19.2 mg/dL to 29.0 mg/dL.

DISCUSSION

In this cirrhotic patient with near-normal chest roentgenography and pulmonary functional tests, severe hypoxemia was associated with evidence of intrapulmonary vascular dilatation and/or substantial right-left shunt by means of contrast echocardiography, ^{99m}TcMAA lung scanning and pulmonary angiography (5,7). Generally, the presence of other obvious concomitant pulmonary disorders such as an obstructive airway or restrictive disease, are excluded in the diagnosis of HPS.

Contrast transthoracic echocardiography (TTE) using a saline solution contrast that gives microbubbles of 24 to 180 μm, is currently used to identify HPS (8). Vedrinne et al. had reported that the benefit of using TTE is to detect not only an intracardiac shunt, but also an intrapulmonary shunt when bubbles appear in the left atrium. However, caution should be used with the intrapulmonary shunt because microbubbles may appear in left atrium of normal volunteers if the diameter of the normal pulmonary capillary beds (approximately 8 to 15μm in diameter) is larger than that of the saline-microbubbles with insufficient hand-agitation.

The purpose of pulmonary angiography in this case was to detect and visualize distinct arteriovenous communications. In this case, the angiographic pattern may be classified as a diffuse spongy appearance pattern (type I) as first reported by Hansoti and Shah (9) and demonstrated by Stoller *et al* (10). This pattern is associated with severe hypoxemia and a limited improvement in the shunt rate due to concentrated O_2 inhalation. However, our patient did not respond to this intervention and the shunt rate calculated by inspiration of 100% oxygen was not lower than that measured by ^{99m}TcMAA. Although the reason is unclear, it is speculated that substantial right-to-left shunting with intrapulmonary vascular dilatation may occur in this patient, while pulmonary angiography did not detect obvious arteriovenous communication.

The etiology of dilatation of the intrapulmonary vasculature and substantial right-to-left shunting has not been elucidated. However, it is reported that abnormal pulmonary vasodilatation occurs from the decreased hepatic metabolism of vasodilators because of either abnormal liver function or shunting of blood carrying these vasodilators away from the liver due to portal hypertension (2, 5, 8).

Krowaka *et al*. reported that HPS, suggested by contrast echocardiography, was not uncommon (from 13.2% to 47%) in consecutive liver transplant candidates (11, 12), and that 16% of patients with HPS, which has a poor prognosis, died within 3 months after transplantation. Moreover, they demonstrated that the degree of the Pao_2 at rest is the prognostic predictor for survival in HPS (13). Meanwhile, Krowka, et al. showed that the mortality rate for 2.5 years after the onset of dyspnea was 41% (4). In view of the above evidence, the estimation of the arterial oxygen pressure and the lactate, the presence of which is a marker of anaerobic metabolism, may

be useful for following this patient (6).

In summary, we showed a case of HPS with marked hypoxemia diagnosed by contrast echocardiography, ^{99m}Tc macroaggregated albumin (^{99m}TcMAA) lung scan, and pulmonary angiography, which are useful for determining the appropriate of therapeutic modality. Eventually, we found that intrapulmonary vascular abnormalities, such as cardiopulmonary concomitant with liver disease, can be recognized if the above examinations are performed on patients with HPS, taking it into account that hypoxemia is the prognostic predictor for survival in HPS.

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