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Pulmonary Resection for Lung Cancer in Patients with Liver Cirrhosis

Takashi Iwata
Department of Thoracic and Cardiovascular Surgery, Kansai Rosai Hospital,
Department of Thoracic Surgery,
Osaka City University Graduate School of Medicine,
Japan

1. Introduction

Liver cirrhosis is characterized by an advanced irreversible fibrotic change in hepatic tissue as a terminal stage of the chronic progressive injury of the liver.(1) The cause of the liver injury is various, and most common causes are chronic viral infection and alcoholism. In non-endemic area of hepatitis B and C virus such as the United States and European countries, the most frequent cause is long-term alcohol consumption. In the endemic area, especially among Asian and African countries including Japan, chronic infection of hepatitis B or C virus is the most common cause of liver cirrhosis.(2-5) Prognosis is not significantly different according to the cause of cirrhosis, such as alcoholic or viral due to hepatitis B or C virus, however, development of hepatocellular carcinoma is more likely to complicate in hepatitis C virus (HCV) infected-patients than in alcoholic patients.(6, 7) Today, HCV infection is spreading worldwide, even in non-endemic area such as the United States or Europe.(8-12) In these non-endemic areas, the main cause of viral infection has been blood transfusion and healthcare-related transmission. But the prevalence of blood test before transfusion and improvement of healthcare environment are decreasing the risk of HCV infection in daily medical practice. However, continuous increase of intravenous drug user and immigration from endemic countries are now bigger risks for HCV infection in these countries. Because HCV is strongly associated with the development of hepatocellular carcinoma, incidence of hepatocellular carcinoma is also increasing all over the world along with the increasing incidence of HCV-related cirrhosis.

On the other hand, incidence of lung cancer is still epidemic worldwide.(13-18) In some area of industrialized countries such as the United States, the various effort to educate the public about harmfulness of tobacco and importance of quitting smoking, and another effort to decrease air pollution and exposure of workplace carcinogenetic agents are successfully decreasing the incidence of lung cancer declining in the last decade. However, in the rest majority of the countries, incidence of lung cancer is still increasing especially in the developing countries. Thus, opportunity to encounter patients with lung cancer comorbid with liver cirrhosis will be increasing. These two diseases are both lethal. We will face the difficult question how to treat these patients with the both critical conditions.

In this chapter, I describe about pathophysiology of liver cirrhosis, its effect upon pulmonary function, and safety, risk and feasibility of pulmonary resection for lung cancer in cirrhotic patients, introducing my recent three cases with a review of the literature.

2. Pathophysiology of liver cirrhosis

The patients with mild to moderate liver cirrhosis are usually asymptomatic and look very well for years. But the fibrotic change in the liver is irreversible and progressing gradually. Common symptoms of such early-staged disease are non-specific, as general fatigue, loss of appetite, and body weight loss. Degrade of estrogen is performed in the liver and this estrogen metabolism is impaired in patients with liver cirrhosis. As a result of emphasized effect of estrogen, gynecomastia and testicular atrophy could be demonstrated in male patients. Severe fibrosis in the liver causes congestion of blood flow in the portal vein, so-called "portal hypertension." Portal hypertension complicates gastroesophageal varices. The rupture of gastroesophageal varices is an important cause of death in patients with liver cirrhosis. Portal congestion also evokes splenomegaly. Splenomegaly leads chronic anemia by destroying the blood cells. Platelet cell count is also decreased in the advanced cases. Congestion of the small intestine may cause malabsorption of various nutrient and moreover, increased susceptibility of infection due to decay of mucosal barrier, so-called "bacterial translocation" which allowed intraluminal microorganism in the intestine to move into the portal blood flow. Dilatation of the skin vessels is also seen; "vascular spider" is a small capillary dilatation mainly seen in the anterior chest, caput medusa is a sign of venous congestion in the abdominal wall. The flow of biliary juice is also interrupted. Chronic stasis of bile can lead to jaundice, itching, and xanthoma in bilateral eyelids. Decrease of biosynthesis of bile acid results malabsorption of fat and fat-soluble vitamins. Lowered production of coagulating factor increases a risk of bleeding. Palmer erythema, Dupuytren's contracture, muscular atrophy, swelling of salivary glands, axillary alopecia, peripheral nerve disorder are another sign of liver cirrhosis. When the liver congestion gets so severe, ascites and/or pleural effusion are also seen. Impaired synthesis of albumin in the liver also accelerates the production of ascites and/or pleural effusion. Finally, interruption of nitrous metabolism are occurred and leads encephalopathy.

3. Severity of the disease and its evaluation methods

Severity of the disease is evaluated and graded according to various physical and clinical parameters. Modified Child-Pugh classification is widely used all over the world, and the detail of its grading is shown in Table 1.(19-22) Patients with 8 – 9 points of Child-Pugh score are likely to die within a year. Patients with more than 10 points are likely to die within 6 months. Table 2 shows the details of Liver damage class that is another more useful method than Child-Pugh class to evaluate the severity of liver injury. This was made by the Liver Cancer Study Group of Japan, and is also widely used in Japan.(23) Liver damage class was developed for the diagnosis and treatment for hepatocellular carcinoma, and it is very useful to expect the patient's life expectancy because the result is more correlated with clinical outcome than Child-Pugh class.(23, 24)

Model for End-Stage Liver Disease (MELD) score is a new system that exclude the uncertainty and subjectivity from the evaluation process because it is based on mathematical

calculation by the results of three blood tests, such as serum value of total bilirubin (mg/dL), prothrombin test and international normalized ratio; PT-INR, and serum value of creatinine (mg/dL).(25-27) The MELD score is calculated using the following equation:

$$3.8\times\log(e)(\text{bilirubin mg / dL})+11.2\times\log(e)$$
$$(\text{PT}-\text{INR})+9.6\log(e)(\text{creatinine mg / dL})+6.43\,*$$

*This 6.43 points should not be added if the cause of liver damage is alcoholic or biliary stasis. If not, i.e. the liver damage is due to hepatitis virus infection, 6.43 points should be added.

MELD score is useful to predict short-term prognosis and for its fairness and accuracy it is used for the waiting list of the patients who wishes liver transplantation for end-stage cirrhosis.

Clinical and laboratory findings	Scores		
	1 point	2 points	3 points
Encepalopathy	None	Mild	Coma, occasionally
Ascites	Absent	Slight	Moderate
Serum bilirubin (mg/dL)	<2.0	2.0-3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time (sec. prolonged)	1-4	4-6	>6
or Prothrombin time INR*	<1.7	1.7 - 2.3	>2.3
Child-Pugh class is determined due to total score for all findings according to the chart below.			
	Total scores	Grade	
Child-Pugh	5-6	A	
	7-9	B	
	10-15	C	

INR; international normalized ratio.
from Pugh RNH, et. al. Brit. J. Surg. 60: 646-654, 1973.
*Lucey MR, et al. Liver Transpl Surg, 3: 628-637, 1997.
This table is modified with permission from #23 and #32

Table 1. Child-Pugh classification

	Grade		
Clinical and laboratory findings	A	B	C
Ascites	None	Controllable	Uncontrollable
Serum bilirubin (mg/dL)	<2.0	2.0-3.0	>3.0
Serum albumin (g/dL)	>3.5	3.0-3.5	<3.5
$ICGR_{15}$ (%)	<15	15-40	>40
Prothrombin activity (%)	>80	50-80	<50

Degree of liver damage is recorded as A, B, or C, based on the highest grade containing at least 2 clinical or laboratory findings liseted above in the chart. ICGR15; indocyanine green retention rate at 15 min.
This table is modified with permission from #23 and #32

Table 2. Liver damage classification by Liver Cancer Study Group of Japan

4. Effect of liver cirrhosis upon pulmonary function

Dysfunction of the liver could lead abnormality in pulmonary function and gas exchange. Aller and coworkers reported that mean partial pressure of O_2 in arterial blood in patients with cirrhosis was not significantly different from those in healthy control.(28) However, more than 70% of cirrhotic patients showed hypocapnea in arterial blood gas analysis. Mean partial pressure of CO_2 in arterial blood was 32.2 torr. Abnormality in the result of pulmonary function test was observed in 38%, and hypoxia and decreased diffusing capacity of carbon monoxide were significant in these patients. Pulmonary vasodilatation was also observed in approximately 30% of the patients, and was associated with hypocapnea and higher grade of Child-Pugh class. Yigit and coworkers also reported that hypoxia was not significantly affected by severity of liver dysfunction but diffusing capacity was.(29) These abnormalities of pulmonary function are called as Hepatopulmonary syndrome.(30) In patients with severely impaired liver function, the clearance of vasodilator substances is interrupted in the liver. As the result, excess vasodilator substances stay longer in pulmonary circulation, resulting pulmonary capillary vasodilatation in alveoli or formation of pulmonary arteriovenous shunting in the lung parencyma, or both. These changes could occur and get worse along with the progression of liver dysfunction. Increased amount of pulmonary arteriovenous shunting leads hypocapnea. Because the blood flow is too fast in the dilated pulmonary capillary or simply due to increased shunting flow, without getting enough oxygenation, hyperventilation is occurred to compensate hypoxemia, and resulted hypocapnea. Oxygenation is maintained in the most of the cases, because alveolar membrane itself is not damaged by liver dysfunction. Dilated capillary in the alveoli and/or increased flow of pulmonary shunt also lead decrease in diffusing capacity.

5. Feasibility of pulmonary resection in patients with liver cirrhosis

Feasibility of thoracic surgery in patients with liver cirrhosis is little known. There are only a few reports about this issue in the literature.(31-33) Iwasaki and coworkers reported a series of 17 patients with liver cirrhosis underwent pulmonary resection for primary lung cancer in 2006.(33) Pulmonary resection showed no mortality and morbidity in 4 patients with cirrhosis graded Child-Pugh class A. In 13 patients with cirrhosis graded Child-Pugh class B, morbidity was 4 out of 13 and mortality was 1. This one patient with Child-Pugh class B was died on the day 11 due to pneumonia and multiple organ failure secondary to acute liver failure. We also reported that one patient with Child-Pugh class A and one with class B died of sepsis on the day 6 and 46, respectively, in the series of 37 patients that included 28 patients with class A and 9 with class B.(31)

In 2006, 26,351 patients with lung cancer were surgically treated in Japan and 230 of them died in hospital.(34) The overall in-hospital mortality rate of surgically treated patients with primary lung cancer was 0.9%. Overall postoperative in-hospital death after pulmonary resection in patients with liver cirrhosis was reported as 5.8% and 5.4%, by Iwasaki and us, respectively. The mortality rate is approximately 5 or 6 times higher than the entire result of lung cancer surgery in Japan.

6. Early complications of pulmonary resection associated with liver cirrhosis

We also reported the details of early postoperative complications and their affecting factors from the results of these 37 patients with lung cancer comorbid with liver cirrhosis in

2007.(31) Cirrhosis-related early postoperative complication had occurred in 7 patients of 37 (18.9%). Intrathoracic bleeding was complicated in 4 patients (10.8%) that needed perioperative blood transfusion, and one of them had another bleeding from gastroduodenal ulcer simultaneously (2.7%). All could be saved by blood transfusion only in 3 cases and one needed successive thoracotomy. Liver failure was complicated in 2 patients (5.4%) and both of them had been recovered by liver supporting therapy. In another 2 patients (5.4%), sepsis was occurred and they all died. Preoperative serum value of total bilirubin was the only independent factor predicting postoperative liver failure. The complication of postoperative sepsis was associated with preoperative nutrition status. We could not find any useful factors predicting postoperative bleeding in this study. To prevent postoperative complications, it seems essential to improve preoperative systemic status, especially liver function and nutrition status.

Iwasaki and coworkers also reported perioperative complications, as well. They reported 9 patients (52.9%) out of 17 complicated intra- or postoperative bleeding so that they needed perioperative blood transfusion. Liver failure was complicated in 1 patient (5.9%) who was simultaneously complicated with pneumonia and die on the day 11. Infectious disease, such as pneumonia, was complicated in 2 patients (11.8%) including 1 already mentioned. Prolonged air leak from pulmonary fistula was complicated in 1 patient (5.9%).

7. Postoperative intrathoracic bleeding

According to the depletion of platelets counts and decreased synthesis of coagulation factor in the liver, a risk of postoperative bleeding is increased in cirrhotic patients.(35, 36) Rate of complication with postoperative intrathoracic bleeding that needed blood transfusion were from 10.8% to 52.9%, as described.(31, 33) In our previous report, of 4 patients with intrathoracic bleeding, 1 patient needed re-thoracotomy to control persisted bleeding on the day 1. These four patients showed remarkable decrease in platelet count, preoperatively. However, statistical analysis did not demonstrate that the preoperative platelet count was not a significant risk factor for postoperative bleeding. On the other hand, the size of the tumor was significantly associated with postoperative bleeding. Bigger tumors might have required wider dissections. Performance of wedge resection was correlated with the bleeding, also. This would be because we had selected the less risk operative method, such as wedge resection, than standard lobectomy for patients with comparatively higher risk among advanced cirrhotic patients. Perioperative blood transfusion, including platelet and fresh frozen plasma, should be considered when the patient seemed to complicate severe coagulopathy.(31, 33)

8. Upper gastrointestinal bleeding

We have also reported a case (0.3%) of acute gastrointestinal bleeding complicated after pulmonary resection in the same series of patients.(31) This patient also complicated with intrathoracic bleeding simultaneously. This patient was successfully saved by blood transfusion and endoscopic intervention. However, cirrhotic patients that complicated variceal bleeding have high risk of rebleeding or death and poor prognosis.(37, 38) Preoperative gastrointestinal endoscopy is recommended and sclerotherapy should be performed if needed. Administration of perioperative histamine H_2 blocker or proton pump inhibitor is also essential to prevent bleeding from acute gastrointestinal ulceration.(39)

9. Liver failure

Liver failure is another concern for patients with liver cirrhosis after surgery. This usually occurred in comparatively late period, such as several days or weeks after the surgical intervention. Hepatic encephalopathy could be developed by accumulation of intrinsic neurotoxic substances.(40) Ammonia is the most common cause of hepatic encephalopathy. Administration of oral branched chain amino acid, improvement of intestinal bacterial flora to decrease toxic substance production and absorption, and shunt obliteration are treatment options. However, the cirrhotic patient with encephalopathy has poor prognosis.

Ascites is another critical concern in patients with liver failure. Especially after abdominal surgery, control of postoperative increase of ascites or lymphorrhea is sometimes difficult.(41, 42) Interestingly, we did not experienced uncontrollable lymphorrhea or overproduction of pleural effusion after pulmonary surgery, even with mediastinal dissection. Probably lymphangitic stasis would be less in thoracic cavity than in abdominal cavity in cirrhotic patients. Perioperative maintenance with decreased transfusion and proper usage of diuretics would be important.

Jaundice is another important symptom of liver failure, and is clinically manifested with serum value of total bilirubin 3 mg/dL or more. When the value is between 1 to 3 mg/dL, it is called latent jaundice. Serum value of total bilirubin reflects the severity of liver dysfunction very well. Our studies revealed that preoperative serum value of total bilirubin was useful to predict both postoperative liver failure and long-term survival of the cirrhotic patients who underwent pulmonary surgery.(31, 32)

10. Complications associated with malnutrition and infectious diease

Cirrhotic patients sometimes complicated with malnutrition. Malnutrition is mainly evaluated with hypoalbuminemia, lower serum value of total cholesterol. Damaged tissue by surgical intervention would not be quickly repaired in such poor nutrition status. Delay of the healing of surgical site may lead prolonged air leakage or complication of bronchopleural fistula; those would finally invite intractable infection. Malnutrition also affects immunological insufficiency. Thus, a risk of infectious disease would be increased in such patients. This is more problematic when the patient undergoes surgical intervention.(35, 43, 44) In our study, 2 of 37 patients died of sepsis, postoperatively. Iwasaki and coworkers lost 1 of all 17 patients due to liver failure complicated with pneumonia. Severe infectious disease would be critical in cirrhotic patients after pulmonary resection. Not only perioperative antibiotics administration, preoperative improvement of nutrition status is essential.

11. Long-term outcome of lung cancer surgery in cirrhotic patients

We also reported the long-term outcome after pulmonary surgery in cirrhotic patients with lung cancer in 2007, analyzing 33 cases.(32) Mean survival time was 44.8 months. Overall 5-year survival rate after pulmonary surgery in patients with lung cancer comorbid liver cirrhosis was 37.6% (Fig. 1). During the observation period, lung cancer death had occurred in 9 patients. Mean survival time until lung cancer death was 33.5 months and 5-year survival rate from lung cancer death was 59.7%. Hepatic death had been occurred in 6 patients. Mean survival time until hepatic death was 60.1 months and its 5-year survival was 62.9%. Within 3 years after surgery, main cause of death was secondary to lung caner.

After 3 years, the main reason of death was hepatic cause, as shown in Fig. 1. Factors influencing lung cancer death were nodal extension and limited surgery, and factors influencing hepatic death were preoperative serum values of total bilirubin, choline esterase and alpha-fetoprotein, platelet count, and the result of prothrombin test. Local extensiveness of the tumor, limited surgery, mediastinal dissection, and pathological stage of the disease also affected the occurrence of hepatic death in the long-term period. However pulmonary resection itself might affect liver function in long-term, pulmonary resection for lung cancer is still beneficial also in patients with comorbid liver cirrhosis.

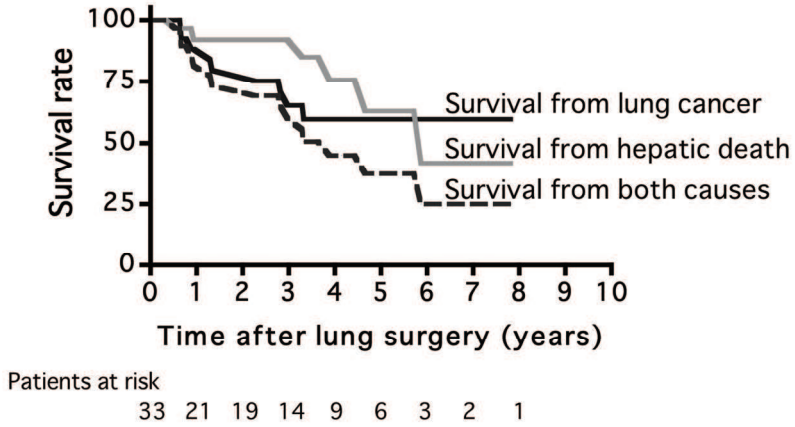

Fig. 1. Survival curves after lung cancer surgery in 33 patients with comorbid liver cirrhosis for lung cancer death (black solid line), hepatic death (gray solid line), and deaths from both causes (broken line). (This figure is taken from the article #32 with permission of Elsevier)

Iwasaki and coworkers also described long-term outcome, shortly. Of all 17 patients, 4 patients died of liver failure, 3 patients died of lung cancer recurrence, 1 died of cardiac event, and 1 died of unknown cause. The rest 8 patients were reported alive.

12. Complication with hepatocellular carcinoma and lung cancer surgery

Hepatocellular carcinoma (HCC) is another critical condition that is commonly found in patients with liver cirrhosis.(7) We also investigated the result of pulmonary surgery performed in 11 patients with both lethal malignancies, lung cancer and hepatocellular carcinoma, all comorbid with liver cirrhosis.(45) As early postoperative complication, liver failure occurred in 2 patients, intrathoracic bleeding did in 2 patients. One of them complicated gastrointestinal bleeding simultaneously. There was no postoperative in-hospital death. Five-year survival rate from lung cancer death was 74.1%, whereas 5-year survival from hepatic death was 39.8% (Fig. 2). Five-year survival from overall death was 29.5%. Complication of hepatocellular carcinoma showed worse long-term outcome than comorbidity of simple liver cirrhosis compared with the previous study.(32) Factors influencing survival in patients with both lung cancer and HCC were preoperative serum values of total bilirubin here again, choline esterase, platelet count, and the result of prothrombin test.

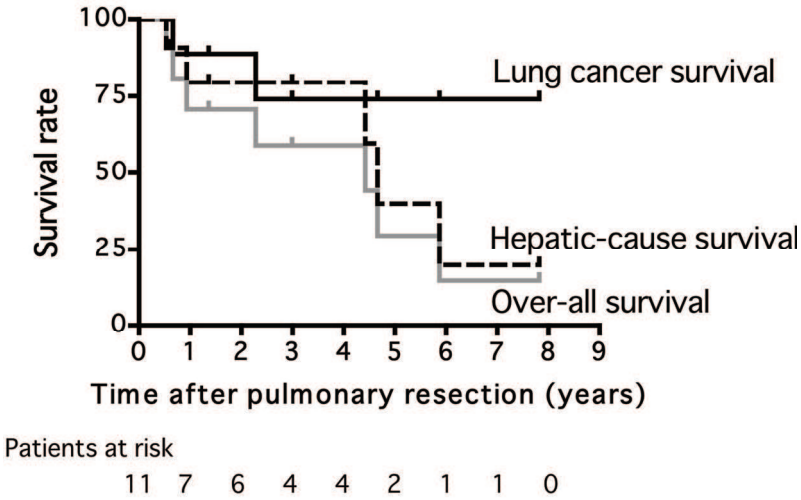

Fig. 2. Survival curves after pulmonary resection for non-small cell lung cancer in patients with hepatocellular carcinoma. Survival from lung cancer (black line), survival from hepatic causes, including both hepatocellular carcinoma and liver cirrhosis (broken line), and overall survival (gray line). (This figure is taken from the article #45 with permission of Springer-Verlag)

13. Decision making; Which patient would tolerate pulmonary resection?

From our previous data, regardless of comorbidity of HCC, if the life expectancy is predicted as more than 3 years according to the liver function, lung cancer surgery should be considered.(32, 45) Modified Child-Pugh grading system is reported to be useful to predict postoperative outcome by multiple investigators, including our results.(22, 41, 42) We have also investigated MELD score to predict postoperative complications and outcome, however, from our unpublished data, we could not find that the usefulness of MELD score for such purpose. The operative method is another problem in patients with cirrhosis; which is better, limited surgery or lobectomy with mediastinal dissection? Our previous data showed that mediastinal dissection, tumor size, and pathological stage have some impact on hepatic death in long-term.(32) Therefore minimal invasive method is favorable to preserve liver function. However, death from lung cancer mainly occurred within 3 years after surgery, and hepatic death after that. Thus, when the extensiveness of the lung cancer is advanced, usual standard operation with lobectomy and/or mediastinal dissection is recommended, while the patient's general status is tolerated for the surgical invasiveness. Basically we would take standard surgical strategy for patients with lung cancer comorbid with Child-Pugh class A cirrhosis. Operative method will be determined upon the extensiveness of the disease and pulmonary function. For patients with Child-Pugh class B cirrhosis, operative method will be determined upon symptoms and the result of blood chemical study, but limited surgery is recommended basically. And for patients with Child-Pugh class C cirrhosis, we recommend another substitution methods, such as stereotactic radiation therapy or radiofrequency abrasion.

14. Case reports and discussions

We are introducing our recent cases that underwent pulmonary resection for primary lung cancer comorbid with liver cirrhosis.

Case 1.

A 79-year-old woman who had diagnosed with chronic type C hepatitis at the age of 72 and was also diagnosed with Child-Pugh class B liver cirrhosis last year, was referred to our department for incidentally-discovered abnormal shadow on a chest radiograph (Fig. 3).

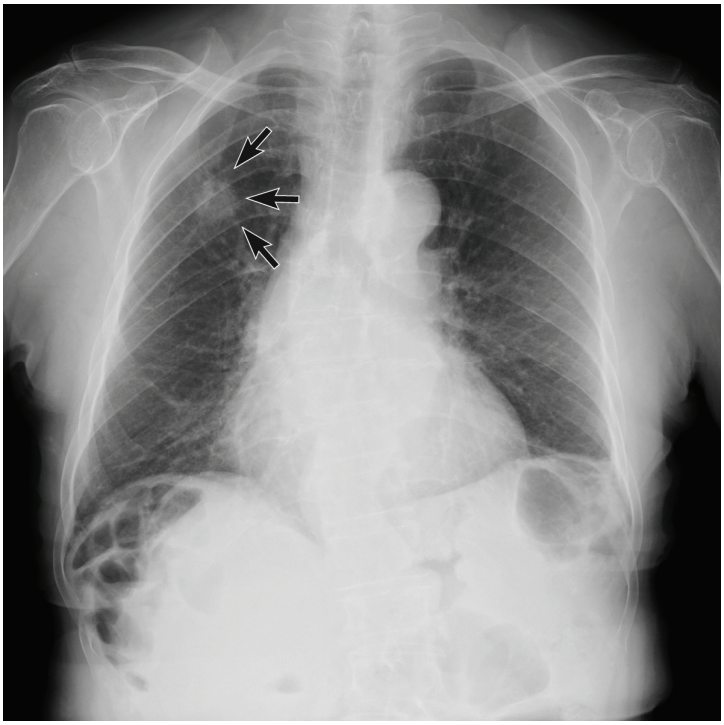

Fig. 3. A chest radiography demonstrates a spiculated mass of approximately 2cm in diameter, in the right upper field of the lung.

Chest computed tomography (CT) demonstrated a spiculated mass with cavity formation, of 23mm in diameter in the posterior segment in the right upper lobe of the lung. Maximum standardized uptake value (SUVmax) of the lesion was 19.19 by 18-fluoro-2-deoxy-D-glucose positron emission computed tomography (PET/CT). Nodal extension was not demonstrated both in chest CT and PET/CT scans. Brain magnetic resonance imaging did not show any metastatic lesions. Dynamic multi-detector-row CT demonstrated high-stained low-density area of 20 mm in diameter, suspecting hepatocellular carcinoma in posterosuperior segment and a typical hemangioma stain in posterosuperior segment of the right hepatic lobe. Ultrasonic scan showed irregular surface and nodular pattern of the liver and very small amount of ascites, a low echoic mass lesion that had partial hyper echoic lesion inside in posterosuperior segment of the right lobe. The lesion that was suspected as

hemangioma could not be detected by CT. Esophageal varices were observed without red color signs by Fiberoptic gastroscopy. She had currently smoked 50 cigarettes a day since 23 years old of age. Branched chain amino acid, spironolactone, folic acid, and menatetrenone (vitamin K2) had been orally administrated for a year. Result of blood chemical study showed in Table 3. Result of pulmonary function test revealed vital capacity as 2.39L, forced expiratory volume in 1 sec as 1.78L/sec, forced expiratory volume in 1 sec % as 75.74%, and diffusing capacity of carbon monoxide was 59.4%. She showed a good performance status so that she could climb up the stairs to the third floor all by herself. Right lung cancer of clinical T1aN0M0 stage 1A disease was suspected. Child B cirrhosis was confirmed and needle biopsy of the liver mass was planned after pulmonary surgery by a hepatologist. Thus, wedge resection of the right upper lobe was carried out via video-assisted thoracoscopic approach. Operative time was 1 hr 27 min. Blood loss was 20 g. The histopathology was squamous cell carcinoma without nodal extension, and she was diagnosed with p-T1bN0M0 p-stage 1B disease. The result of postoperative blood chemical study on the day 2 was also shown in Table 3. The patient was uneventfully discharged on the day 5. However, approximately 50 days after surgery, the patient noticed abdominal fullness and visited the out-patient. The hepatologist diagnosed her with liver failure by Child-Pugh class C cirrhosis, according to the result of blood chemical study (Table 3) and increased amount of ascites shown by ultrasonography. The patient was treated with liver supporting therapy, and the ascites was subsequently disappeared and the laboratory data got improved also (Table 3). Needle biopsy of the liver was performed 4 months from pulmonary surgery, and revealed only necrotic tissue, nor metastatic or primary malignancy. The patient is well without recurrent disease or exacerbation of cirrhosis 13 months after the surgery.

Discussion

Case 1 demonstrated a late onset of liver failure after pulmonary surgery, mainly developed as acute increase of ascites. The patient had been graded as Child-Pugh class B cirrhosis due to hepatitis C virus infection, preoperatively. She needed treatment for liver failure 60 days after pulmonary surgery, and she was then diagnosed as liver failure with Child-Pugh class C cirrhosis at that time. There was no other possible cause of acute exacerbation of the liver function for her. We have learned that late onset of liver failure could develop even 60 days after pulmonary resection.

Case 2.

A 61-year-old man presented with leukocytosis and elevation of c-reactive protein level in the serum by regular check up for alcoholic cirrhosis of Child-Pugh class A and chronic pancreatitis. His father and mother died of hepatocellular carcinoma and liver cirrhosis, respectively. A chest radiograph demonstrated a mass lesion of 7cm in diameter in the right upper lung field (Fig. 4). Bronchoscopic biopsy was not diagnostic. He lost 5kg of weight during the past 2 months. Systemic check up did not reveal metastatic disease. Result of blood chemical study showed in Table 3. Pulmonary function tests revealed vital capacity as 4.09L, forced expiratory volume in 1 sec as 2.49L/sec, forced expiratory volume in 1 sec % as 62.18%, and diffusing capacity of carbon monoxide was 56.9%. Preoperatively, delirium, offensive behavior, and hallucination that was related to small insects or dwarfs crawling on the ceiling, were developed suddenly 3 days after the hospitalization. We diagnosed him with alcohol withdrawal syndrome from the typical symptoms including weird hallucinations associated with insects and dwarfs, lack of flapping tremor, and low serum level of ammonia. Thus, surgical treatment was carried out as scheduled by maintaining the

Table 3. Results of preoperative blood chemical studies

					Case 1				Case 2		Case 3	
					Preop	2POD	60POD	79POD	Preop	6POD	Preop	2POD
Child-Pugh class					B	B	C	B	A	A	A	A
Ascietes					Trivial	None	Yes	None	None	None	None	None
WBC	9	-	4	10^3/μL	3.2	6.3	3.6	4.0	15.3	5.7	5.4	4.4
RBC	5.4		3.8	10^6/μL	2.56	2.10	2.61	2.57	3.89	2.91	4.29	3.79
Hb	15	-	11.5	g/dl	9.7	8.2	10.1	9.9	13.6	10.2	14.3	12.6
Ht	45	-	35	%	28.6	23.6	29.7	28.9	39.9	29.3	42.2	37.6
Plt	350	-	150	10^3/μL	59	32	75	87	311	362	109	103
PT-INR					1.21		1.30	1.18	1.30		1.06	
PTsec				sec	13.2		14.4	13.1	14.4		11.8	
PT%	70	-	140	%	71.0		62.0	78.0	63.0		91.0	
APTT	40	-	25	sec	43.6		41.3	37.7	41.1		37.9	
HCV	-				+				-		+	
HBVag	-				-				-		-	
CEA	5	-	0	ng/mL	11.6				4.3		5.7	
AFP	10	-	0	ng/mL				7			144	
CA19-9	37	-	0	U/mL	45.0				<10.0		130.0	
T-Bil	1.2	-	0.2	mg/dL	1.1	1.8	1.8	1.2	0.7	0.3	0.7	0.4
D-Bil	0.4	-	0	mg/dL	0.8				0.5		0.2	
AST	35	-	12	U/L	56	32	40	39	40	51	45	26
ALT	30	-	5	U/L	35	21	18	31	12	18	37	24
ALP	344	-	109	U/L	372	184	285	581	636	343	220	144
ChE	249	-	97	U/L	49		73	68	58		306	
LDH	240	-	110	U/L	225	199	225	217	150		276	169
γ-GTP	35	-	7	U/L	31		18	21	357		46	
T-Cho	219	-	120	mg/dL	92		90	83	107		190	
Na	147	-	136	mmol/L	140	131	138	132	137	132	142	
Cl	110	-	98	mmol/L	110	101	110	101	97	98	102	
K	5	-	3.5	mmol/L	5	4.2	4.3	4.2	4.0	4.0	4.1	
BUN	20	-	8	mg/dL	12.1	25.8	8.8	19.2	6.4	11.1	13.4	13.3
Cre	0.8	-	0.4	mg/dL	0.85	0.99	0.76	0.71	0.72	0.58	0.61	0.55
AMY	120	-	30	U/L	107		100	157	41		160	
Alb	5	-	3.2	g/dL	2.7	1.9	2.3	2.5	2.5	2.0	4.6	3.0
T-P	8.1	-	6.1	g/dL	6.1	4.5	6.0	6.0	7.4	5.8	8.6	6.2
NH3	60	-	15	μg/dL	18		39	59				
CRP	0.3	-	0	mg/dL	0.1	4.1	0.2	0.1	13.6	3.6	<0.1	1.1
type4 collagen 7s	6	-	0	ng/mL	7.3		12	12				

WBC; white blood cell counts, RBC; red blood cell counts, Hb; hemoglobin, Ht; hematcrit, Plt; platelet counts,

symptoms with risperidone. Because the tumor was growing rapidly, we thought that the patient had no time to overcome alcoholism before pulmonary resection. Limited resection was planned at first, but we thought that adjuvant chemotherapy would be difficult due to his mental disorder and liver dysfunction. Therefore, right upper lobectomy of the lung, combined resection of the chest wall, and hilar dissection were carried out. Total fibrous adhesion was observed in the right pleural cavity. Operative time was 4 hrs 6 min. Blood loss was 205 g. He was singing loudly just after extubation. Histopathology revealed pleomorphic carcinoma with chest wall invasion of p-T3N0M0 p-stage 2B disease. Malnutrition status was persisted and serum level of albumin was around 2.0 mg/dL for a week (Table 3). Bronchopleural fistula was also persisted and surgical direct closure of the fistula was performed two weeks after the first surgery. The clinical course after the second surgery was uneventful and he was transferred to a psychiatric hospital for treatment of alcoholism. After 5 months, his nutrition was dramatically improved then postoperative adjuvant chemotherapy with carboplatin and paclitaxel was introduced. After the adjuvant chemotherapy, by too much nutrition and improved liver function, he got 14kg of weight and subsequently developed diabetes mellitus. However, he is well without recurrent disease 13 months after lung cancer surgery.

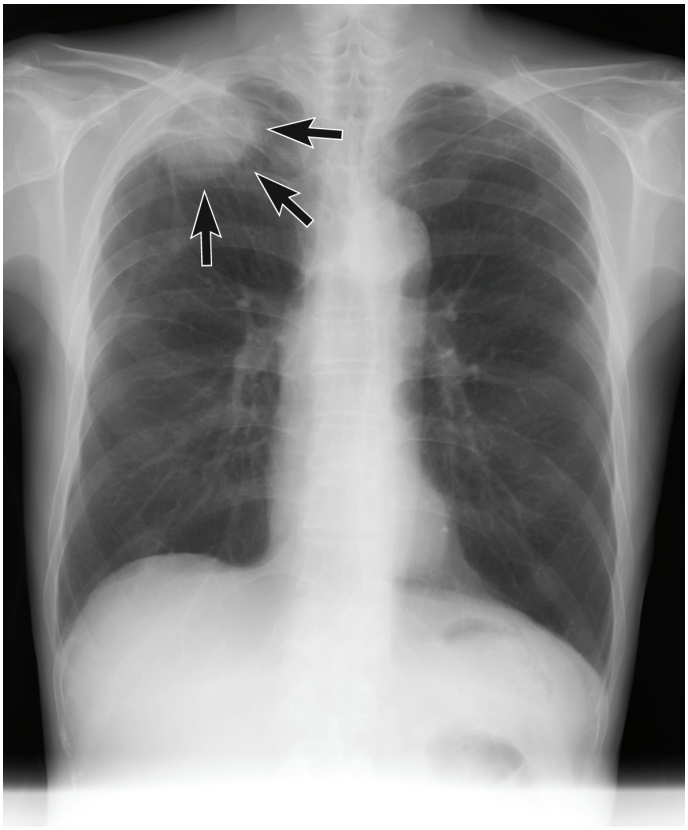

Fig. 4. A chest radiography demonstrates a large mass adjacent to the chest wall in the right apical area.

Discussion

Case 2 developed alcohol withdrawal syndrome preoperatively and persistent bronchopleural fistula that was also occurred due to malnutrition complicated with liver dysfunction. In such cases, differential diagnosis with hepatic encephalopathy is important. Typical symptoms including wired hallucinations associated with insects and dwarfs, lack of flapping tremor, and low serum level of ammonia were useful to exclude hepatic encephalopathy from alcohol withdrawal syndrome. Liver cirrhosis sometimes complicated with malnutrition, especially if it was due to alcoholism. Malnutrition would prolong the healing process at the operated site.

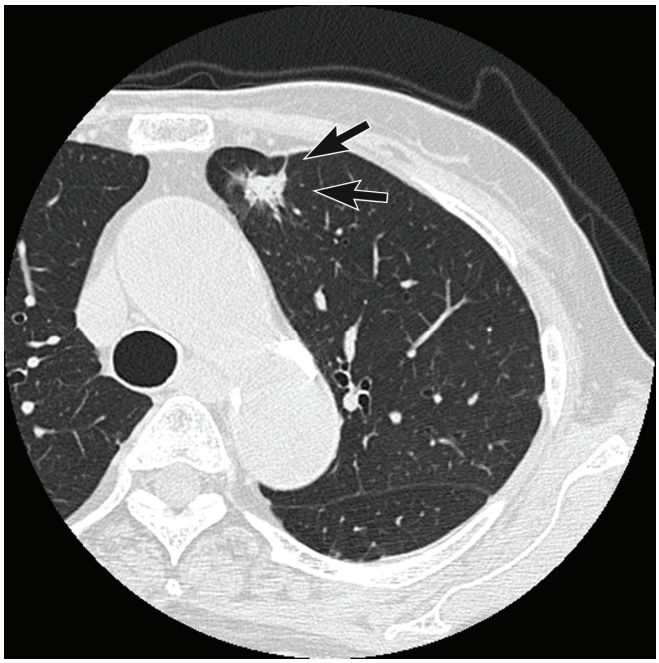

Fig. 5. Computed tomography demonstrates a small spiculated lung mass periphery in the left upper lobe of the lung.

Case 3.

A 77-year-old woman presented with high serum level of carcinoembryonic antigen during observation for Child-Pugh class A cirrhosis with type C hepatitis virus infection. A chest radiograph and chest CT demonstrated a spiculated mass of 1cm in diameter in the anterior segment of left upper lobe (Fig. 5). SUVmax of the lesion was 2.08 by PET/CT. The result of preoperative laboratory test was shown in Table 3. Abdominal ultrasonography revealed irregular-surfaced atrophic liver and multiple high echoic lesions were drawn within. Two of them were suspected as hepatocellular carcinoma and others were diagnosed as hemangiomas. Ascites was not visualized. Result of other systemic check-up did not demonstrate metastatic disease. The patient was never-smoker and the results of pulmonary function test were within normal ranges. Thus, excisional biopsy via video-assisted thoracoscopic approach and subsequent left upper lobectomy with mediastinal dissection

were carried out after confirmation of malignancy by frozen sectioning. The operative time was 1 hr 57 min and the blood loss was 5 g. Histopathology revealed adenocarcinoma with mixed subtype of p-T1bN0M0 p-stage 1A disease. She was uneventfully discharged on the day 5. Exacerbation of the liver function was not shown with regular check-up by a hepatologist. She is well without recurrent disease 7 months after the surgery and surgical treatment for hepatocellular carcinoma is now scheduled.

Disucssion

Case 3 was complicated with HCC. Prognosis from liver function and that from lung cancer should be compared to determine the therapeutic strategy, but sometimes it is not easy. Even after successful pulmonary resection, prediction of the patient's life expectancy is very difficult, and we will face another difficult problem if metastatic disease is developed in future.

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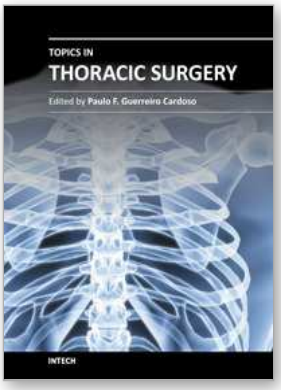

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