

[CASE REPORT]

Acute Liver Failure Due to Severe Hepatic Metastasis of Small-cell Lung Cancer Producing Adrenocorticotrophic Hormone Complicating Ectopic Cushing Syndrome

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Abstract:

A 72-year-old man was admitted to a general hospital with progressive liver dysfunction, hypokalemia, hyperglycemia, and nodules in the lung and liver and then transferred to our institution on the seventh hospital day. Plasma levels of adrenocorticotrophic hormone (ACTH), cortisol, and neuron-specific enolase concentrations were extremely high. He developed acute liver failure, his consciousness and general condition deteriorated rapidly, and he died on Day 11. At the postmortem examination, he was found to have extensive metastases from small-cell lung cancer, including advanced hepatic metastases. This is the first reported case of acute liver failure caused by metastases derived from an ACTH-producing pulmonary small-cell carcinoma.

Key words: liver failure, small-cell lung cancer, ACTH-producing tumor, ectopic Cushing syndrome

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Introduction

Patients with prothrombin times that are $\leq 40\%$ of the standardized value or international normalized ratios (INRs) of ≥ 1.5 caused by severe liver damage within 8 weeks of the onset of symptoms and in whom blood laboratory data and imaging indicate that the liver function was normal prior to the current acute episode are classified as having acute liver failure (ALF) (1).

Although liver metastases commonly occur in individuals with cancer, diffuse liver infiltration rarely results in ALF. Only 7.2% of patients with metastatic liver disease develop ALF-related coma, and their metastases mainly originate from breast, gastric, or colon cancer, or lymphoma (2). ALF caused by hepatic parenchymal metastases from small-cell lung cancer (SCLC) is extremely rare, and the prognosis is poor, with death usually occurring within several days (3).

SCLC cells rarely but occasionally produce adrenocorticotrophic hormone (ACTH) or cause severe paraneoplastic Cushing syndrome (4).

We herein report, to our knowledge, the first reported case of ALF caused by extensive hepatic metastases from an ACTH-producing SCLC.

Case Report

A 72-year-old man was admitted to a general hospital (Day 1) because of general fatigue and excessive thirst for 6 days. He had no history of blood transfusion, hepatitis, or alcohol abuse, but had smoked an average of 1 pack of cigarettes a day for 52 years. Blood tests showed hypokalemia (K 2.5 mEq/L), high blood glucose (521 mg/dL), and mild hepato-renal dysfunction (total bilirubin 1.6 mg/dL, aspartate transaminase 81 IU/L, alanine aminotransferase 88 IU/L, and creatinine 1.95 mg/dL) (Table). The prothrombin time

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Table. Summary of Laboratory Data.

	Day 1	7	8		Day 1	7	8
WBC (μL)	13,660	11,500	10,000	Ca (mEq/L)	8.3		
RBC ($\times 10^4 \mu\text{L}$)	476	462	434	Glu (mg/dL)	521	125	130
hemoglobin (g/dL)	15.7	15.2	14.5	NH ₃ ($\mu\text{g/dL}$)		113	126
platelet ($\times 10^4 \mu\text{L}$)	9.3	9.9	9.8	AFP (ng/mL) (<8.8)		1.6	
albumin (g/dL)	3.8	2.58	2.2	PIVKA-II (mAU/mL) (<40)		68	
total bilirubin (mg/dL)	1.6	7.6	9.2	neuron specific enolase (ng/mL) (<16.3)			1,210
direct bilirubin (mg/dL)	0.8	5.0	6.3	pro-gastrin releasing peptide (pg/mL) (<81)			20,500
AST (IU/L)	81	541	581	cortisol ($\mu\text{g/dL}$) (5-17)			147
ALT (IU/L)	88	554	656	adrenocorticotrophic hormone (pg/mL) (7.2-63)			1,042
LDH (IU/L)	743	1,812	1,597	HBsAg		2.6 (+)	
Alkaline phosphatase (IU/L)	321	1,258	1,355	HBsAb		(-)	
γ -GTP (IU/L)	370	1,975	1,949	HBcAb		(-)	
PT INR	1.02	1.73	1.88	HBV-DNA		(-)	
FDP ($\mu\text{g/mL}$)	2	3.5		HCVAb		(-)	
D-Dimer ($\mu\text{g/mL}$)		1.26		HTLV-1		14.1(+)	
BUN (mg/dL)	44.3	32.7	36.6	ANA		20 \times (-)	
Cre (mg/dL)	1.95	1.41	1.58	Urinalysis			
Na (mEq/L)	144	143	142	protein		3+	
K (mEq/L)	2.5	2.5	2.9	occult blood		3+	
Cl (mEq/L)	93	99	99	glucose		3+	
				bilirubin		+	

RBC: red blood cell, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, γ -GTP: γ -glutamyl transpeptidase, PT: prothrombin time, INR: international normalized ratio, FDP: fibrin degradation products, BUN: blood urea nitrogen, Cre: creatinine, Na: sodium, K: potassium, Cl: chlorine, Ca: calcium, Glu: glucose, NH₃: ammonia, AFP: α -fetoprotein, PIVKA-II: protein induced by vitamin K absence or antagonist-II, HTLV-1: human T-cell leukemia virus type 1, ANA: anti-nuclear antibody

was within the normal range [International Normalized Ratio (INR) 1.02].

Plain computed tomography (CT) (Fig. 1) revealed nodular lesions in the peripheral region and hilum of the left lung. The liver was enlarged, and there were some low-density nodules in both lobes. Because of the patient's renal dysfunction, no contrast was administered.

After admission, insulin therapy was instituted, and supplementary potassium administered. Although the plasma glucose and serum potassium concentrations gradually normalized, the aspartate and alanine aminotransferase concentrations increased rapidly, and he was transferred to our institution on Day 7.

On admission to our institution, the patient was alert. Jaundice was noted. The significant laboratory abnormalities on Days 1 (in previous hospital) and 7 are listed in Table. By Day 7, he had developed acute liver failure (ALF) (total bilirubin 7.6 mg/dL, INR 1.73, NH₃ 113 $\mu\text{g/dL}$). Serological tests for hepatitis A and C viruses were negative. Although hepatitis B (HB) surface antigen was weakly positive, HBV-DNA and HB core antibody were negative; thus, the weakly positive surface antigen was considered a false positive.

Given the findings of pulmonary nodules on chest CT and his severe hypokalemia and hyperglycemia, lung cancer and some endocrine disorder, most likely an ACTH-producing SCLC, was suspected.

The serum concentrations of tumor markers for SCLC on Day 8 were as follows: neuron-specific enolase (NSE) 1,210

ng/mL and progastrin-releasing peptide (Pro-GRP) 20,500 pg/mL. Plasma cortisol and ACTH concentrations were both extremely high (Table). Taken together, these findings resulted in a diagnosis of paraneoplastic Cushing syndrome.

Because of the patient's renal dysfunction, enhanced abdominal CT and magnetic resonance imaging (MRI) could not be performed. Abdominal ultrasonography (US) revealed multiple, small, poorly demarcated nodules in both lobes of the liver. Contrast enhancement using perflubutane microbubbles (Sonazoid; Daiichi Sankyo, Tokyo, Japan) showed circularly enhanced peripheral nodules on re-perfusion images in the post-vascular phase (5) and markedly heterogeneous liver parenchymal enhancement in the post-vascular phase (Fig. 2). These findings indicate liver metastases. A liver biopsy was performed on Day 8, and a rapid pathological examination resulted in a provisional diagnosis of metastatic small-cell carcinoma. Thus, a diagnosis of ACTH-producing SCLC and ALF caused by hepatic metastases from that SCLC was made on Day 9.

Although the patient's general condition was good on Day 7, he gradually lost consciousness and developed a flapping tremor. His hepatic and renal dysfunction progressed rapidly, and he died on Day 11.

A postmortem examination (Fig. 3) showed a markedly enlarged liver (2,005 g), the cut surfaces of which revealed nodules of varying sizes distributed diffusely throughout the liver tissue. A microscopic examination revealed massive diffuse replacement of the liver parenchyma by SCLC cells.

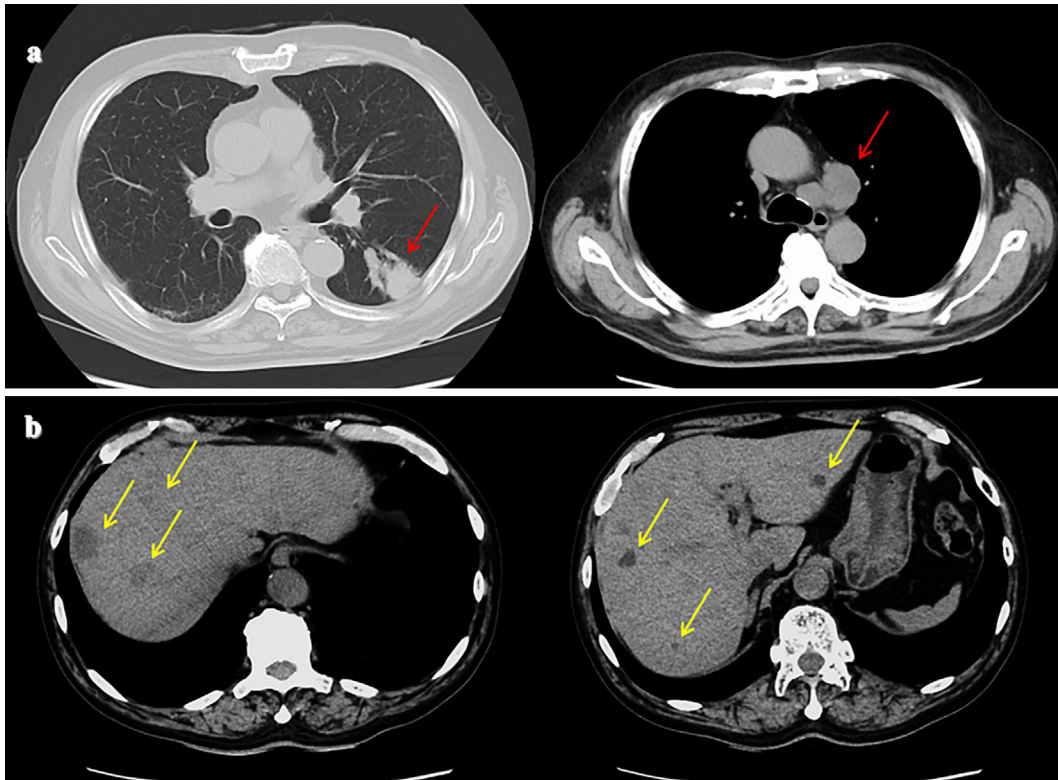


Figure 1. Plain computed tomography image on the seventh hospital day showing nodules in the periphery of the left lung and the mediastinum (a, red arrows) and some low-density nodules in the liver (b, yellow arrows).

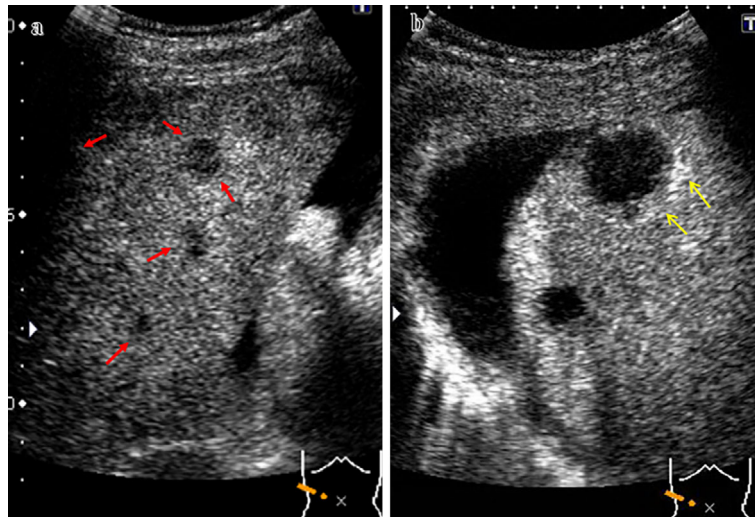


Figure 2. Contrast-enhanced abdominal ultrasonography (Aplio XG; Toshiba, Tokyo, Japan) using perflubutane microbubbles. (a) Multiple perfusion defects are apparent (red arrows), and there is extremely heterogeneous hepatic parenchymal enhancement in the post-vascular phase. (b) Defect re-perfusion image showing rim enhancement around the nodules (yellow arrows).

No hepatic fibrosis was seen. The primary lesion was identified in the left lower lobe of the lung, and metastases were detected in the left chest wall, lumbar vertebrae, sternum, dura, and pituitary gland; these metastases had not been diagnosed while the patient was alive. Immunohistochemical staining of the SCLC cells was positive for synaptophysin, chromogranin A, CD56, and, partially, ACTH.

Discussion

Patients with prothrombin times that are $\leq 40\%$ of the standardized value or INRs of ≥ 1.5 caused by severe liver damage within 8 weeks of the onset of symptoms and in whom blood laboratory data and imaging indicate that the

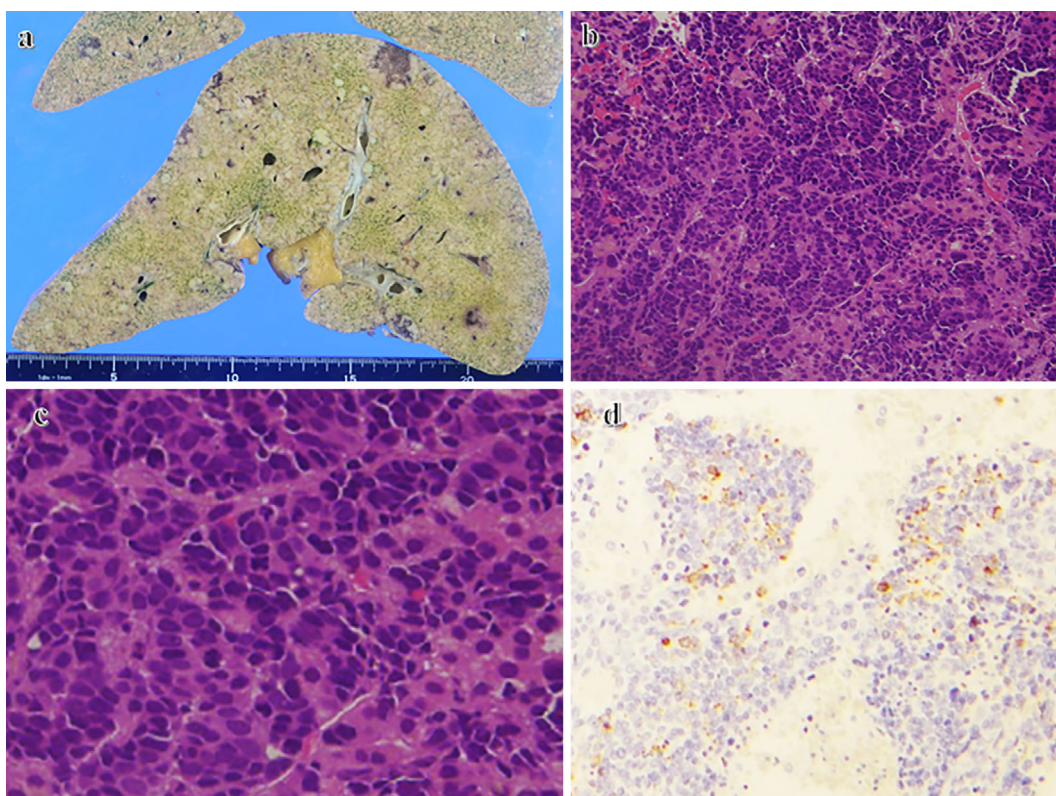


Figure 3. Findings of a postmortem examination. (a) Nodules of varying size are diffusely scattered throughout the hepatic parenchyma. (b, c) Photomicrograph showing extensive cancer infiltration of the hepatic sinusoids and replacement of the hepatic parenchyma by SCLC [Hematoxylin and Eosin staining, (b) 100 \times , (c) 200 \times]. (d) Immunohistochemistry: primary SCLC cells are partially positive for ACTH (100 \times).

liver function was normal prior to the current acute episode are classified as having ALF (1). These Japanese criteria for ALF were introduced in 2011. Patients without hepatic encephalopathy but with an INR of ≥ 1.5 are also classified as having ALF.

The present patient had no history of liver disease and no evidence of chronic liver disease or fibrosis at the postmortem examination. He had thrombocytopenia of undetermined cause. His SCLC had not invaded his bone marrow, and drug toxicity was unlikely. The INR of the prothrombin time was prolonged. The concentrations of fibrin degradation products and D-dimers (Table) were normal, and there was no evidence of disseminated intravascular coagulation at the autopsy. Although alkaline phosphatase and γ -glutamyltranspeptidase concentrations were high, suggesting biliary congestion, the duration of such congestion was too brief to have resulted in vitamin K deficiency. In addition, the concentration of protein induced by vitamin K absence/antagonist-II was just above the upper limit of normal, excluding vitamin K deficiency. We considered his coagulopathy to be attributable to liver failure. Based on these findings, we diagnosed him with ALF.

Our patient developed a disturbance in consciousness of indeterminate cause 3 days prior to his death. Serum concentrations of electrolytes were close to normal. Although pituitary and dural metastatic lesions were detected at the

autopsy, they did not seem large or numerous enough to have caused the patient's coma. Based on his NH_3 concentration and flapping tremor, we speculated that our patient's coma was due to hepatic encephalopathy. However, we did not check his arterial blood gases, so could not exclude acidosis.

The liver is the most common site for metastases; however, ALF secondary to metastases is rare. In one reported series, only 21 (7.2%) of 292 patients with metastatic liver disease developed ALF-related coma, and this occurred mainly in patients with breast, gastric, or colon cancer or lymphoma (2). According to a nationwide survey in Japan, infiltration by malignant cells was responsible for ALF and late-onset hepatic failure (LOHF) in only 29 of 1,603 patients (1.8%) with these conditions (6); however, that report did not detail the origins of the malignant cells.

ALF caused by hepatic invasion by SCLC is extremely rare, with a search of published reports yielding only 24 such patients (3, 7-19). These reports highlighted the difficulty in making a diagnosis and the extremely poor prognosis of this condition. Most such patients have rapidly progressive liver failure and a deteriorated general condition and die within a day to a month. In older patients in particular, the diagnosis of metastatic cancer is rarely made during life.

SCLC is an aggressive tumor, with liver involvement be-

ing found in 22% to 29% of patients at the time of the diagnosis (17). It usually presents as macroscopic nodules associated with patchy infiltration of the parenchyma. How this causes ALF is unclear; however, in all reported cases, tumor cells had massively invaded and destroyed the liver parenchyma. Some strong genetic mutation promoting severe invasion or progression may occur in SCLC tumor cells, including in the present patient.

Imaging findings (CT, US, or MRI) vary among patients, with some showing only hepatomegaly with no distinct nodules or masses in the liver. The use of contrast material is often contraindicated because of these patients' impaired renal function, as was the case with our present patient. Unenhanced CT revealed only some nodules in the liver. Because our patient's renal function was deteriorating rapidly, contrast-enhanced US using perflubutane microbubbles was performed as a substitute for enhanced CT. It clearly revealed multiple tumors in our patient's liver with typical enhancement of the rims of the nodules (20). It also showed markedly heterogeneous hepatic parenchymal enhancement in the post-vascular phase, indicating diffuse malignant invasion. The case reports mentioned above did not document the use of contrast-enhanced US so the present report is, to our knowledge, the first such report. Contrast-enhanced US using perflubutane microbubbles should be considered in patients with renal dysfunction or allergy to contrast media because this procedure does not affect the renal function and causes allergic reactions only in patients with egg allergy.

As is true of previously reported patients, our patient's condition deteriorated so rapidly that chemotherapy or liver support could not be provided, and he died within a few days of presentation. Only two previously reported patients received chemotherapy despite their liver failure; both responded dramatically and survived for over 150 days (8). Chemotherapy should therefore be considered provided the diagnosis is made quickly enough.

Our patient presented with hypokalemia and marked hyperglycemia without a history of diabetes and was therefore suspected of having Cushing syndrome. His cortisol and ACTH concentrations were checked promptly after his transfer to our institution and found to be extremely high. These findings along with those of lung nodules on chest CT, abdominal CT, and US and positive tumor markers (NSE and pro-GRP), a provisional diagnosis of ACTH-producing SCLC and Cushing syndrome was made.

On a postmortem examination, the tumor cells were immunopositive for the markers of SCLC and ACTH. No pituitary adenoma was detected. Although urine had not been collected for measuring the cortisol and dexamethasone levels because of the rapid clinical course, a final diagnosis of ACTH-producing SCLC and Cushing syndrome was made on the basis of the postmortem findings, including the histopathologic findings, together with the strong clinical evidence and firm laboratory findings of hypercortisolism.

Ectopic Cushing syndrome (ECS) is a paraneoplastic syndrome that occurs in 1-5% of patients with SCLC (21). Pa-

tients with SCLC and ECS have a poor prognosis because of their advanced stage, poor response to chemotherapy, high susceptibility to serious infections, and high incidence of thromboembolic phenomena. Most patients present with electrolyte disturbances and muscle weakness rather than the typical clinical features of Cushing syndrome (4). Our patient presented with hypokalemia and hyperglycemia but had not developed the typical buffalo hump or central obesity.

To our knowledge, this is the first reported case of ALF caused by an ACTH-producing SCLC. Cushing syndrome caused by an ACTH-producing tumor may be misdiagnosed because hyperglycemia and hypokalemia without the typical Cushingoid appearance mentioned above often occur in association with other conditions, such as dehydration, primary diabetes, hepatic cirrhosis, and malnutrition. If these abnormalities are detected in patients with ALF and/or with some type of cancer, plasma hormone concentrations should be checked in order to investigate the possibility of Cushing syndrome.

It is unclear how his severe hypercorticism affected our patient's clinical course. He had no serious infections or evidence of thromboembolism in life or on the autopsy examination, with the only relevant finding being mild esophageal erosion caused by herpes simplex virus infection of his tongue, pharynx, and esophagus. We speculate that his hypercorticism may have contributed to his rapid tumor progression by suppressing anticancer immunity; however, we found no evidence that that was the case. More experience and more data on such patients are needed to clarify this point.

We failed to immediately administer metyrapone, which inhibits glucocorticoid synthesis, because the hypertension and electrolyte abnormalities were well-controlled, and we predicted an extremely poor prognosis due to his SCLC. As a result, we speculated that the primary cause of his death was likely the systemic and, in particular, liver invasion by SCLC, and the administration of metyrapone may well have failed to alter his prognosis. However, in general, the severe hypercorticism (serum cortisol >40 or 51 µg/dL or 24-hour urinary free cholesterol >4-fold the upper limit of normal), is a life-threatening condition that mandates immediate treatment because it may cause severe infection, consciousness disturbance, and other severe manifestations, and the administration of the metyrapone should thus be considered (22).

On a postmortem examination, our patient's liver was found to be enlarged and to have been extensively replaced by tumor cells, causing his ALF, as has been reported by others (3, 9, 19). ALF in patients with diffuse intrasinusoidal liver metastases is attributable to the destruction of liver cells by diffuse carcinomatous infiltration, ischemia caused by occlusion of the portal vein, or non-occlusive infarction of the liver caused by shock from other causes, such as sepsis or cardiac dysfunction (3).

In conclusion, we herein report, to our knowledge, the first case of ALF caused by extensive metastases from an

ACTH-producing SCLC and the first account of the helpfulness of contrast-enhanced US with perflubutane in a patient whose impaired renal function precluded the use of conventional contrast medium.

The authors state that they have no Conflict of Interest (COI).

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References

1. Sugawara K, Nakayama N, Mochida S. Acute liver failure in Japan: definition, classification, and prediction of the outcome. *J Gastroenterol* **47**: 849-861, 2012.
2. Bernuau J, Rueff B, Benhamou JP. Fulminant and subfulminant liver failure: definitions and causes. *Semin Liver Dis* **6**: 97-106, 1986.
3. Miyaaki H, Ichikawa T, Taura N, et al. Diffuse liver metastasis of small-cell lung cancer causing marked hepatomegaly and fulminant hepatic failure. *Intern Med* **49**: 1383-1386, 2010.
4. Zhang H, Zhao J. Ectopic Cushing syndrome in small-cell lung cancer: a case report and literature review. *Thorac Cancer* **8**: 114-117, 2017.
5. Kudo M. The 2008 Okuda lecture: management of hepatocellular carcinoma: from surveillance to molecular targeted therapy. *J Gastroenterol Hepatol* **25**: 439-452, 2010.
6. Nakao M, Nakayama N, Uchida Y, et al. Nationwide survey for acute liver failure and late-onset hepatic failure in Japan. *J Gastroenterol* **53**: 1-18, 2017.
7. Spechler SJ, Esposito AL, Koff RS, Hong WK. Lactic acidosis in oat cell carcinoma with extensive hepatic metastases. *Arch Intern Med* **138**: 1663-1664, 1978.
8. Kaira K, Takise A, Watanabe R, Mori M. Fulminant hepatic failure resulting from small-cell lung cancer and dramatic response of chemotherapy. *World J Gastroenterol* **12**: 2466-2468, 2006.
9. Terashima T, Matsuzaki T, Ogawa R, et al. Fulminant hepatic failure as the initial manifestation of small-cell lung cancer: report of 2 cases. *Ann Cancer Res Ther* **16**: 16-20, 2008.
10. Ojeda VJ. Metastatic oat cell carcinoma simulating liver cirrhosis. *N Z Med J* **86**: 480-481, 1977.
11. Athanasakis E, Mouloudi E, Prinianakis G, Kostaki M, Tzardi M, Georgopoulos D. Metastatic liver disease and fulminant hepatic failure: presentation of a case and review of the literature. *Eur J Gastroenterol Hepatol* **15**: 1235-1240, 2003.
12. Krauss EA, Ludwig PW, Sumner HW. Metastatic carcinoma presenting as fulminant hepatic failure. *Am J Gastroenterol* **72**: 651-654, 1979.
13. Harrison HB, Middleton HM, Crosby JH, Dasher MN. Fulminant hepatic failure: an unusual presentation of metastatic liver disease. *Gastroenterology* **80**: 820-825, 1981.
14. Lin MS, Donati RM. "Mottled" liver scan in giant hepatomegaly due to intrasinusoidal metastasis of small-cell lung cancer. *Clin Nucl Med* **6**: 496-497, 1981.
15. Wesbey G. Lactic acidosis in oat cell carcinoma with extensive hepatic metastases. *Arch Intern Med* **141**: 816-817, 1981.
16. Sheriff DS. Lactic acidosis and small-cell carcinoma of the lung. *Postgrad Med J* **62**: 297-298, 1986.
17. McGuire BM, Cherwitz DL, Rabe KM, Ho SB. Small-cell carcinoma of the lung manifesting as acute hepatic failure. *Mayo Clin Proc* **72**: 133-139, 1997.
18. Galus M. Liver failure due to metastatic small-cell carcinoma of the lung. *Mayo Clin Proc* **72**: 791, 1997.
19. Ihara N, Yashiro N, Kinoshita T, et al. Diffuse intrasinusoidal liver metastasis of small-cell lung cancer causing fulminant hepatic failure: CT findings-a case report. *Radiat Med* **19**: 275-277, 2001.
20. Tochio H, Sugahara M, Imai Y, et al. Hyperenhanced rim surrounding liver metastatic tumors in the postvascular phase of sonazoid-enhanced ultrasonography: a histological indication of the presence of kupffer cells. *Oncology* **89**: 33-41, 2015.
21. Mayer S, Cypess AM, Kocher ON, et al. Uncommon presentations of some common malignancies: case 1. Sequential paraneoplastic endocrine syndromes in small-cell lung cancer. *J Clin Oncol* **23**: 1312-1314, 2005.
22. Nieman LK, Nieman LK, Biller BM, et al. Endocrine society: treatment of Cushing's syndrome: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* **100**: 2807-2831, 2015.

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