Case Report

Fulminant Hepatic Failure as the Initial Manifestation of Small-Cell Lung Cancer: Report of 2 Cases

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Abstract

In this report, we describe two cases of small-cell lung cancer (SCLC) presenting with fulminant hepatic failure as the initial manifestation. Neither of the patients had a previous history of liver disease, evidence of viral infection, or exposure to hepatotoxins. Both presented with hepatomegaly and an increase in the serum LDH level. Although they had a history of smoking and respiratory symptoms such as dyspnea on exertion, their most striking initial symptoms were those of hepatic failure, which made it difficult to suspect the underlying primary lung cancer. In one case, contrast-enhanced CT of the abdomen revealed hypovascular nodules that were not visible on plain CT. After a rapidly deteriorating course, both patients died, 8 and 13 days after admission, respectively. Autopsy revealed diffuse infiltration of the hepatic sinusoids and extensive replacement of the liver parenchyma by metastatic small-cell carcinoma. We conclude that metastatic SCLC should be considered in the differential diagnosis in patients of advanced age with a smoking history presenting with rapidly progressive liver failure associated with hepatomegaly and elevation of the serum LDH.

Keywords: fulminant hepatic failure, small-cell lung cancer, liver metastasis, sinusoid

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Introduction

Fulminant hepatic failure (FHF) is characterized by the acute onset of severe hepatic dysfunction caused by massive liver necrosis¹⁾. The syndrome is described as a sudden severe impairment of hepatic function in patients with no prior evidence of liver disease, associated with the development of jaundice and hepatic encephalopathy within one week (hyperacute FHF), one month (acute FHF), or three months (subacute FHF) of the onset of symptoms²⁾. Viral hepatitis or drug-induced hepatotoxicity is reported to be the underlying cause in the majority of patients³⁾. FHF has also been reported as a rare complication of metastatic liver disease⁴⁾.

Small-cell lung cancer (SCLC) is an aggressive cancer that metastasizes to other organs early in its course. At the time of diagnosis, liver involvement is found in 25 to 26% of the patients^{5,6)}. Metastatic cancer of the liver usually manifests as multiple nodular lesions. Although the liver is one of the most common sites of metastases in patients with SCLC, mild to moderate disorder of the

liver chemistry is all that is encountered and the patients are most often asymptomatic. SCLC manifesting as acute hepatic failure is extremely rare. The clinical course is usually very short after the development of hepatic failure, with rapid deterioration of the liver function and the development of multiorgan failure⁷⁻⁹⁾. Making a diagnosis of hepatic infiltration in patients presenting with FHF in such cases is difficult and requires a high degree of suspicion if no evidence of the underlying primary disease is present, as usually is the case. In this report, we describe the cases of two patients who presented with FHF as the initial manifestation of hepatic infiltration by SCLC.

Report of the cases

Case 1. A 57-year-old man sought medical advice with a 3-weeks' history of progressive anorexia, generalized fatigue, dyspnea on exertion, back pain, jaundice, and dark-colored urine. Two days before his admission to the hospital, his local physician had detected an enlarged tender liver on physical examination. At that time, laboratory studies had revealed a 5-fold elevation of the serum alkaline phosphatase (ALP) and 10-fold elevation of the serum transaminases relative to the respective normal ranges. The patient had no history of

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blood transfusion, hepatitis, intravenous drug use, or alcohol abuse. There was also no history of liver disease or of exposure to any hepatotoxins. He gave a history of smoking 1-pack-day of cigarettes. He also had a history of gastric ulcer, for which he was under treatment with famotidine and ecabet sodium. On physical examination, the liver was palpable up to 4 cm below the costal margin and was tender to palpation. The patient was fully alert. The significant laboratory abnormalities at admission are listed in Table 1. Serological tests for hepatitis A, B, and C, cytomegalovirus, and Epstein-Barr virus were all negative. A plain computed tomography (CT) of the abdomen showed massive hepatomegaly and an inhomogeneous parenchymal pattern of the liver, without any evident nodular lesions. Contrast-enhanced CT of the abdomen revealed hepatomegaly with multiple hypovascular lesions throughout the liver (Fig. 1A). The chest roentgenogram and CT revealed a mass in the left lower lobe of the lung and left hilar and mediastinal lymphadenopathy (Fig. 1B). The serum levels of tumor markers for SCLC examined on the third hospital day were as follows: neuron-specific enolase (NSE) 1,020 ng/mL; progastrin-releasing peptide (Pro-GRP) 8,630 U/mL. On the sixth day of hospitalization, the patient's condition began to deteriorate due to progressive hepatic failure (total bilirubin (TB), 9.8 mg/dL; prothrombin time (PT), 12.7 seconds; 59.5%). His dyspnea worsened and he developed oliguria associated with further deterioration of the liver function (TB 21.8 mg/dL; aspartate aminotransferase (AST) 15,075 IU/L; alanine aminotransferase (ALT) 3,900 IU/L; lactate dehydrogenase (LDH) 24,490 IU/L; ALP 6,440 IU/L; PT 22.6 seconds (21.3%)). He died of severe liver dysfunction and multiple organ failure on the eighth hospital day. Postmortem examination showed a markedly enlarged liver, weighing 3,200 g, that showed a coarse micronodular surface. The cut surfaces revealed multiple tumor nodules of varying sizes. Microscopic examination of these nodules revealed metastatic small-cell carcinoma. Extensive infiltration of the hepatic sinusoids by tumor cells and replacement of the hepatic parenchyma in many areas by sheets of tumor cells were observed (Fig. 1C). The autopsy examination also revealed small-cell carcinoma involving the left lower lobe of the lung arising from the left lower bronchus (Fig. 1D) with multiple pulmonary metastases.

Case 2. An 86-year-old woman admitted to our hospital with a 2-weeks' history of progressive anorexia, cough and dyspnea on exertion. She had no history of blood transfusion, hepatitis, intravenous drug use, or alcohol abuse. There was also no history of liver disease or of exposure to hepatotoxins. She had a history of smoking half-pack-day of cigarettes, and a history of osteoporosis. Her daily medication included vitamin K, alfacalcidol, and etidronate disodium. On physical examination, the liver was palpable up to 7 cm below the costal margin.

Table 1 Initial Laboratory Findings

Laboratory test	Normal range	Case 1	Case 2
Hemoglobin (mg/dL)	Male 13.5-17.0 Female 11.5-15.0	14.1	14.3
BUN (mg/dL)	8-23	15	12
Creatinine (mg/dL)	Male 0.61-1.04 Female 0.47-0.79	0.76	0.68
Calcium (mg/dL)	8.4-10.4	8.9	9.1
Uric acid (mg/dL)	<7.0	5.7	8.4
AST (IU/L)	10-40	399	198
ALT (IU/L)	5-45	440	107
Total bilirubin (mg/dL)	0.2-1.1	5.3	3.9
LDH (IU/L)	115-250	2658	1355
ALP (IU/L)	115-380	1902	1208
PT (%)	70-140	79.0	44.4

BUN= blood urea nitrogen; AST= serum aspartate aminotransferase; ALT= serum alanine aminotransferase; LDH= serum lactate dehydrogenase; ALP= serum alkaline phosphatase; PT= prothrombin time.

The patient was alert. The significant laboratory abnormalities at admission are listed in Table 1. Viral markers for hepatitis (B and C) were negative. Chest roentgenography revealed an opacity in the right lower lobe of the lung suggestive of pneumonia. Abdominal ultrasound examination revealed hepatomegaly with numerous small nodules distributed diffusely throughout the liver. A CT of the abdomen revealed an enlarged liver with multiple nodular lesions (Fig. 2A). A chest CT revealed a right hilar mass with probable right paratracheal and subcarinal adenopathy, and right pleural effusion (Fig. 2B). The serum levels of tumor markers for SCLC examined on the day of admission were as follows: NSE 2,180 ng/mL; Pro-GRP 14,600 U/mL. Cytological examination of sputum specimens suggested a diagnosis of small-cell carcinoma. On the fifth day of hospitalization, the patient became increasingly drowsy and exhibited abnormal behavior. At that time, the serum chemistry profile showed elevation of the TB to 5.7 mg/dL, AST to 188 IU/L, ALT to 89 IU/L, and LDH to 1786 IU/L. She died of severe liver dysfunction associated with multiple organ failure on the thirteenth hospital day. Autopsy revealed an enlarged liver diffusely infiltrated by metastatic tumor. More than 80% of the hepatic parenchyma was replaced by the tumor. Microscopically, diffuse invasion of the sinusoids by the tumor cells was evident throughout the liver, along with extensive replacement of hepatocytes by the tumor cells (Fig. 2C). The autopsy examination also revealed small-cell carcinoma involving the right lower lobe of the lung arising from the right lower lobe bronchus (Fig. 2D) with multiple pulmonary and mediastinal lymphnode metastases.

Discussion

Our two cases had several common features. Neither of the patients had a previous history of liver disease

Fig. 1 A: Contrast-enhanced CT of the abdomen, showing marked hepatomegaly with multiple lesions. B: CT scan of the chest, showing a mass in the left lower lobe of the lung and left hilar lymphadenopathy. C: Photomicrograph of a section of the liver, showing extensive infiltration by metastatic small-cell carcinoma cells. The sinusoids of the hepatic lobules are filled with tumor cells. In some areas, the hepatic parenchyma is diffusely replaced by large sheets of tumor cells. D: Histological examination of the lung, showing extensive infiltration by small-cell carcinoma.

Fig. 2 A: CT scan of the abdomen, showing an enlarged liver with multiple nodular lesions. B: CT scan of the chest, showing a right hilar mass with subcarinal lymphadenopathy. C: Photomicrograph of a section of the liver, showing extensive infiltration of the sinusoids and blood vessels by small-cell carcinoma cells. Extensive replacement of the hepatic parenchyma by metastatic small-cell carcinoma is seen. D: Histological examination of the lung, showing extensive infiltration by small-cell carcinoma.

or exposure to hepatotoxins, or evidence of viral infection. Hepatomegaly was detected both on physical examination and by imaging studies. Although both had a smoking history and respiratory symptoms such as dyspnea on exertion, the most striking initial symptoms were those of hepatic failure, which made it difficult to suspect the underlying primary lung cancer. Laboratory findings showed elevation of the serum LDH level. In addition, both patients died after a rapidly deteriorating course complicated by multiple organ failure. Previous case reports also show several similarities to the two cases reported herein, including the presence of massive hepatomegaly and an increase in the serum LDH⁷⁻¹³. The diagnosis could only be confirmed at postmortem examination in most of the reported cases also. The plausible reasons for the difficulty in the diagnosis before death were: imaging studies showed hepatomegaly but no discrete nodules, failure to consider the possibility of a neoplastic process in the differential diagnosis, or rapid progression that precluded a diagnostic bronchoscopy or liver biopsy.

Among the laboratory findings, the serum LDH may be the most useful indicator of an underlying neoplastic diseases^{7,8}. In the two cases reported herein and also the previously reported patients, there was an at least fivefold increase above the normal⁷. It has been suggested that an elevation of the serum LDH can be used as a prognostic indicator in SCLC patients with disturbed liver chemistry with hepatic failure and impending FHF⁷. Extremely high serum LDH levels represent diffuse replacement of the liver parenchyma and are associated with a higher risk of development of acute liver failure^{7,8}. These findings are supported by the results of the liver chemistry tests in our case 1, who showed extremely elevated serum LDH levels before death.

Imaging studies often fail to reveal a malignant process in a significant number of patients with FHF because of the diffuse hepatic involvement^{4,8-10}. In case 1, a contrast-enhanced CT of the abdomen revealed hypovascular nodules, which were not visible on plain CT. Thus, contrast-enhanced CT may be helpful in the evaluation of diffuse hepatomegaly. Magnetic resonance imaging has been reported to be useful for detecting hepatic nodules in cases where it is difficult by ultrasound examination to differentiate between diffuse intrasinusoidal metastasis and other diseases such as fatty infiltration of the liver or hepatitis⁸. Postmortem examination revealed diffuse and extensive replacement of the hepatic parenchyma or sinusoidal infiltration by the small-cell carcinoma. This may explain why the imaging studies of the liver did not reveal any metastatic tumor.

FHF is reportedly due to viral infection or exposure to hepatotoxins in the majority of the cases. In a French study, viral hepatitis accounted for 72% and drug toxicity for 15% of all the cases³. In another series of 4,020

cases with FHF of various causes, malignant hepatic infiltration accounted for only 0.44% (18 cases)⁴. As seen in the present cases, FHF may be the first clinical manifestation of hepatic metastasis from an unrecognized carcinoma; furthermore, in some patients with diffuse small hepatic metastases, imaging studies may only show homogeneous liver enlargement. Because malignant liver infiltration is a rare cause of FHF, the diagnosis may remain obscure until autopsy is performed. It is important to consider metastatic involvement of the liver in the differential diagnosis in patients with hepatic failure with no history of viral hepatitis or exposure to hepatotoxins.

Metastatic liver involvement in patients with SCLC is common, but most often, the patients are asymptomatic. Elevation of ALP and LDH is common, but liver failure is extremely rare. In our two cases, postmortem examination showed diffuse invasion of the hepatic sinusoids by the tumor cells with extensive destruction of the liver parenchyma. Massive sinusoidal infiltration and obliterative invasion of the hepatic vessels by malignant cells may result in ischemia and necrosis of hepatocytes. Alternatively, rapid replacement of vast areas of the normal liver parenchyma by tumor cells may result in the destruction of large hepatocyte populations, sufficient to induce FHF.

SCLC manifesting as acute hepatic failure is a rare but challenging clinical situation. The treatment of this entity differs considerably from that of hepatic failure due to more common causes. For this reason and because of the high likelihood of rapid deterioration of the patient's condition, a correct diagnosis must be established in a brief period of time. Underlying primary cancer must be borne in mind in the differential diagnosis of acute hepatic failure associated with hepatomegaly and elevated serum LDH in patients of advanced age with a smoking history, especially when viral hepatitis and drug-induced hepatotoxicity are excluded.

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