

Hemoperitoneum Secondary to Rupture of a Hepatic Metastasis from Small Cell Lung Cancer during Chemotherapy: A Case with a Literature Review

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Abstract

A 65-year-old man was diagnosed with small cell lung cancer with multiple liver metastases. Three days after initiating chemotherapy, he experienced abdominal discomfort with hypotension. Computed tomography revealed a ruptured liver metastasis and the presence of hemorrhagic ascites. Transcatheter arterial embolization to the appropriate hepatic artery in concomitant with supportive therapies successfully stabilized his condition. Unlike with hepatocellular carcinoma, the rupture of a liver metastasis and associated hemoperitoneum is very rare in patients with lung cancer. We comprehensively reviewed the literature and found 10 similar cases with this serious condition. Physicians should therefore be aware of the risk of hemoperitoneum caused by ruptured liver metastases in patients with lung cancer.

Key words: hemoperitoneum, chemotherapy, hepatic metastasis, lung cancer, transcatheter arterial embolization

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Introduction

Lung cancer is one of the most common neoplasms, and liver metastasis occurs frequently during the clinical course. Unlike hepatocellular carcinoma (HCC), in which the rupture of subcapsular tumors is relatively frequent, metastatic liver tumors are less likely to rupture, particularly those from lung cancer. We herein present a case of a ruptured liver metastasis and associated hemoperitoneum from small cell lung cancer during antitumor chemotherapy. This case is an important reminder for physicians who work on lung cancer of this relatively infrequent, but serious complication.

Case Report

A 65-year-old man with a 45-year history of cigarette smoking visited our hospital for the diagnosis of an abnor-

mal chest shadow on X-ray. He did not have any remarkable medical history and had not been prescribed anticoagulants or antiplatelet agents. A computed tomography (CT) scan revealed a huge mass in the left upper lobe (maximum size: 11.0 cm in diameter) that subsequently expanded to the left hilum and mediastinum, as well as an intrapulmonary metastasis located in the left lower lobe, pleural effusion on the left side, and multiple liver tumors ranging from 0.5 to 4.7 cm in diameter (Fig. 1). Of note, some of the liver metastases were located subcapsularly, and the liver surface was irregularly distorted. The laboratory findings were as follows: white blood cell count 11,900/mm³, hemoglobin 14.8 g/dL, platelet count 214,000/mm³, aspartate transaminase 31 IU/L, alanine transaminase 19 IU/L, and lactate dehydrogenase (LDH) 749 IU/L. No coagulation abnormalities were found. A subsequent histological examination of a tumor specimen obtained by bronchoscopy confirmed the diagnosis of small cell carcinoma. On considering the clinical diagnosis, per-

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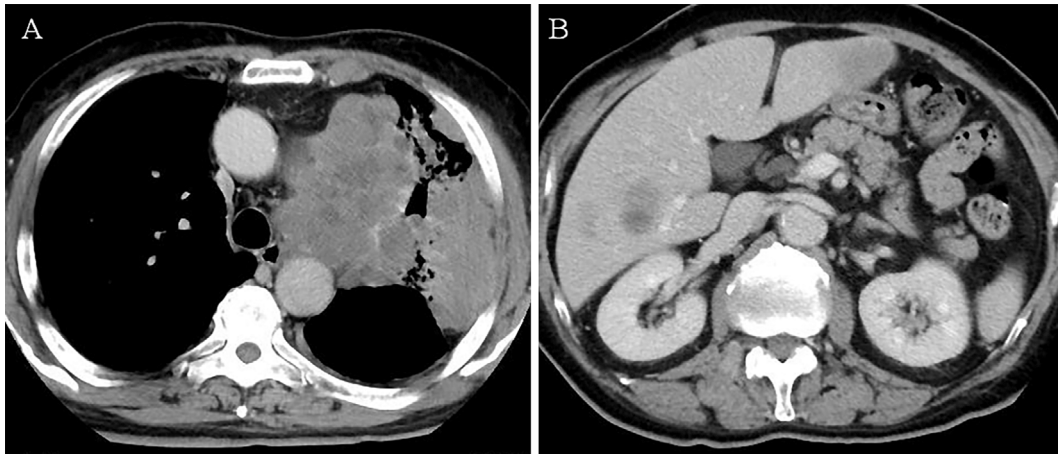


Figure 1. Computed tomography images at the time of diagnosis. A huge mass was noted in the left upper lobe, expanding to the left hilum and mediastinum (A). Multiple liver tumors were located in the left and right lobes of the liver (B).

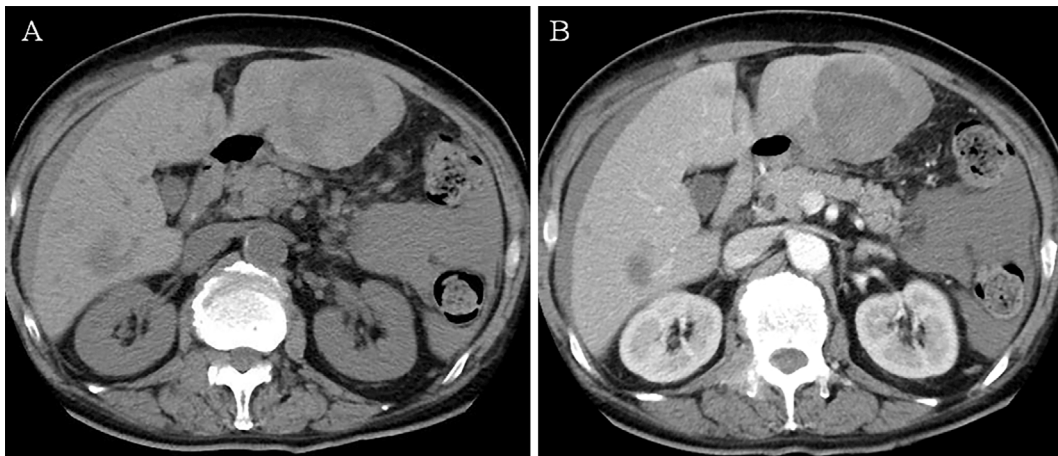


Figure 2. Computed tomography images on Day 3 after initiating chemotherapy. The plain scan revealed an enlarged hepatic tumor in the left lobe containing a high-density area and ascites showing relatively high density (A). A contrast-enhanced scan was negative for extravasation (B).

formance status, and age of the patient, we decided on a regimen of antitumor chemotherapy consisting of cisplatin (60 mg/m^2 body surface area on Day 1) and etoposide (100 mg/m^2 body surface area on Days 1-3). On a day after 2 weeks from the initial CT scan, he started his first chemotherapy session.

On Day 3 after initiating chemotherapy, he complained of abdominal discomfort, and his vital signs showed tachycardia (120 beats per minute) and hypotension (85/55 mmHg). A hematological examination showed severe anemia (hemoglobin 6.7 g/dL) that had dramatically dropped from 14.8 g/dL over 10 days. We attempted to identify the bleeding site on gastrointestinal endoscopy, to no avail, but a CT scan revealed the rapid enlargement of a liver tumor in the left lobe, which contained partial high-density areas on the plain scan, and also a novel finding of ascites showing higher density than usual, all suggesting a ruptured liver metastasis and associated hemorrhagic ascites (Fig. 2). A subsequent contrast-enhanced CT image was negative for extravasation. He underwent angiography for the left and right hepatic ar-

teries, but we only observed obscure tumor vessels in the left hepatic lobe without extravasation (Fig. 3A). We suspected this might be due to the hypovascularity of the metastatic tumors and inactive bleeding at the time.

Although the benefit of therapeutic embolization of the hepatic artery was uncertain based on the findings on angiography, we performed transcatheter arterial embolization (TAE) of the left main hepatic artery using gelform particles to prevent future re-bleeding. Post-embolization angiography revealed a slowed blood flow in the left hepatic artery, and the peripheral vessels were weakly visualized (Fig. 3B). After the embolization concomitant with supportive therapies, including RBC transfusions of 6 U in total, the clinical course of the patient stabilized. His blood pressure remained around 120/70 mmHg, tachycardia disappeared, and the anemia was improved after transfusion and did not progress again. Liver dysfunction did not appear. A month after the embolization, he was in relatively good health and re-started his antitumor chemotherapy, which he continued (first-line regimen) for six courses. A good partial response was

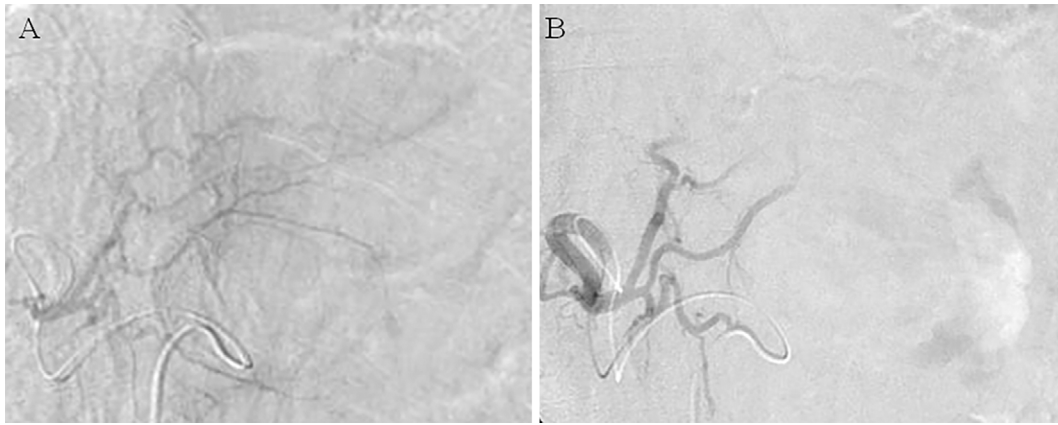


Figure 3. Angiography of the left hepatic artery before (A) and after (B) transcatheter arterial embolization. No obvious tumor stains or extravasation was observed in the left hepatic lobe (A). After embolization, the blood flow was slowed, and the peripheral vessels were visualized weakly (B).

gained after chemotherapy for both the lung and liver lesions.

Discussion

We herein describe a case of hemoperitoneum that occurred during an initial course of antitumor chemotherapy for extended disease of small cell lung cancer. The hemoperitoneum was thought to have been secondary to the rupture of a subcapsular liver metastasis from the lung cancer. Although angiography did not show obvious tumor staining or extravasation, TAE of the hepatic arteries and supportive therapy successfully stabilized the patient's condition.

A rupture of a metastatic liver tumor is a rare complication (1) compared with that of HCC (2). The putative cause of the relatively high incidence of HCC rupture is the hypervascularity of the neoplasm and decreased coagulation factors due to underlying liver cirrhosis. In contrast, lung cancer infrequently accompanies a ruptured liver metastasis despite a high incidence of liver metastasis (3-6). In this regard, we believe that the present case is very educational for physicians treating primary lung cancers, emphasizing this rare but severe complication.

We searched for cases of hemoperitoneum caused by a ruptured liver metastasis from lung cancer in the English literature using the PubMed website between 1960 and 2016, and found only four cases: two cases of adenocarcinoma, one squamous cell carcinoma, and one small cell carcinoma. Hemoperitoneum is a lethal condition for cancer patients, and indeed, three of the four patients died after conservative treatment (4, 6) or emergent operation (5). Only one of the adenocarcinoma patients survived, after being treated with TAE (3).

We further found an additional Japanese paper and five proceedings that described similar cases, after searching the website of the Japanese database *Ichushi* (7-11). We consequently counted 11 cases in total (including the present case) and summarized the characteristics of each case in Ta-

ble. The ages ranged from 57 and 79 years old, and male predominance (10 men vs. 1 woman) was observed. The pathological type of the cancer was as follows: 4 adenocarcinoma cases, 2 squamous cell carcinoma cases, 4 small cell carcinoma cases, and 1 large cell carcinoma case. The fraction of the cases with small cell carcinoma was relatively high, given the general distribution of each pathological type in primary lung cancers, probably due to the natural tendency of small cell carcinoma to have distant metastases from an earlier stage. The clinical sign most frequently found at the diagnosis was abdominal pain/discomfort (7 cases) followed by hypotension and tachycardia. A combined abdominal symptom and abnormal vital sign(s) was particularly important for suggesting an event in about a half of the cases (5 out of 9 cases describing initial symptoms). Regarding the treatment options, TAE was carried out in 2 patients, and both survived for a long period and successfully received antitumor chemotherapies. In contrast, 2 patients, who underwent emergency operation died as a result. The other 7 patients were given conservative care only, and they all died within a few days to a few months.

Although treatment with TAE might be associated with a better prognosis than other approaches, patients with a relatively good condition might be the most promising candidates for this treatment. In our case, angiogram did not depict apparent tumor vessels or extravasation, but we expected the beneficial role of TAE to reduce the risk of lethal re-bleeding. There are also some cases reporting successful treatment with TAE for ruptured liver metastases from renal cell carcinoma (12), esophageal leiomyosarcoma (13), choriocarcinoma (14), and scalp melanoma (15). Further studies are obviously required to determine the therapeutic role of TAE in this condition, so at present, the patient selection for TAE should be determined on a case-by-case basis.

Assessing the potential risk for tumor rupture in lung cancer patients with liver metastases is important. While the factors associated with tumor rupture remain unclear, several contributing factors have been proposed, including vascular-

Table. Reported Cases of Hemoperitoneum Resulting from a Ruptured Liver Metastasis in Patients Lung Cancer.

| Pathology | Age (years-old) | Sex | Latest treatment | Initial symptoms | Treatment | Survival | Time to death | Ref. |
|------------|--------------------|-----|-----------------------------------|--|--------------|----------|---------------|------|
| adeno | 64 | M | none | abdominal discomfort hypotension | TAE | Yes | - | 3 |
| adeno | 57 | M | none | confusion tachycardia hypotension | conservative | No | 6 days | 4 |
| small cell | 62 | M | none | abdominal pain back pain tachycardia | operation | No | <1 day | 5 |
| squamous | 72 | M | none | abdominal pain tachycardia hypotension | conservative | No | 2 months | 6 |
| small cell | 69 | M | amrubicin (8 weeks prior) | dizziness nausea abdominal pain | conservative | No | 3 days | 7 |
| adeno | 65 | F | erlotinib (current) | abdominal pain | conservative | No | 3 months | 8 |
| small cell | 79 | M | amrubicin (current) | N.D. | conservative | No | 2 months | 8 |
| adeno | 60 | M | enterectomy (6 days prior) | shock | operation | No | 7 days | 9 |
| squamous | 72 | M | none | abdominal pain hypotension | conservative | No | 2 months | 10 |
| large cell | 74 | M | lung lobectomy (4 weeks prior) | N.D. | conservative | No | 2-3 weeks | 11 |
| small cell | 65 | M | CDDP+ETP (current) | abdominal discomfort hypotension | TAE | Yes | - | - |

Ref: reference number, M: male, F: female, CDDP: cisplatin, ETP: etoposide, N.D.: no data, TAE; transarterial embolization,

ity, necrotic tendency, a subcapsular location, congestion of the local hepatic vein, increased intra-abdominal pressure, and impaired coagulation (12). In addition, rapid growth of the tumor was suggestively associated with ischemic necrotic and tumor bleeding (7). In the present case, the factors associated with a higher risk included rapid growth, a subcapsular location, and potentially tumor necrosis by anti-tumor chemotherapy for highly chemosensitive small cell carcinoma. According to a review by Marinella, tumor lysis syndrome should be considered a complication during chemotherapy of small cell carcinoma, especially in cases with relatively high pretreatment levels of LDH and hepatic metastases (16). In our case, the pretreatment LDH level was extremely high (749 IU/L). Two other cases of lung adenocarcinoma and small cell carcinoma were reported to develop hemoperitoneum during molecular-targeted antitumor therapy with erlotinib and antitumor chemotherapy with amrubicin, respectively (8).

We herein reported a case of a ruptured metastatic liver tumor and associated hemoperitoneum in patients with small cell lung cancer. This was not a unique case, but we learned some important points: i) a ruptured metastatic liver tumor and hemoperitoneum are rare but severe complications for lung cancer patients; ii) a prior assessment of the risk is im-

portant, especially for patients with subcapsular metastases of the liver; iii) careful observation of the physical and vital signs is required for high-risk patients, and iv) TAE might be an optional treatment for some patients.

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

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