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# Gastroesophageal Variceal Hemorrhage Induced by Metastatic Liver Tumor of Lung Cancer

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## Key Words

Gastroesophageal varix · Lung cancer · Gefitinib · Bevacizumab

## Abstract

Gastroesophageal variceal hemorrhage is a lethal complication of portal hypertension. Liver cirrhosis is often the principal cause of the portal hypertensive state. Malignant tumors coexist with portal hypertension in some cases. Non-small-cell lung cancer (NSCLC) is likely to become metastatic. Liver is a frequent site of cancer metastasis, but diffuse hepatic sinusoidal metastasis is uncommon as a metastatic form of NSCLC. This report describes a patient with gastroesophageal variceal hemorrhage owing to a metastatic liver tumor of NSCLC. The patient, a male smoker with stage IV NSCLC, was free of any hepatitis viral infection and had no alcohol addiction. Liver dysfunction and liver disease had never been pointed out in his medical history. His tumor harbored an L858R epidermal growth factor receptor mutation. Gefitinib was initiated but had to be ceased because of interstitial lung disease. Sequential steroid therapy was effective and bevacizumab-containing chemotherapy was commenced. Both chemotherapy regimens produced favorable effects against the metastatic liver tumor, eliciting atrophic change regardless of the chemotherapy-free interval. One day the patient was admitted to our hospital because of black stool and hypotension. Upper gastrointestinal endoscopy revealed a beaded appearance of the gastroesophageal varix with bloody gastric contents. The portal hypertension might have been caused by changes in portal vein hemodynamics induced by the conformational changes underlying the favorable response of the liver tumor to molecular targeted chemotherapy and notable regression.

## Case Report

A 48-year-old man was admitted to our hospital because of fever and chills. His past medical history was not notable. He had imbibed 1–2 beers per day for the last 20 years and had a smoking history of 30 pack-years. He was initially diagnosed with pneumonia and prescribed antibiotics, but his symptoms persisted and a thorough examination was performed.

Enhancement computed tomography (CT) imaging showed a mass lesion in the right middle lobe of the lung and hilar and mediastinal lymphadenopathy (fig. 1a, b). The abdominal image revealed hypertrophic change of hepatic left lobe with inhomogeneous enhancement of sinusoidal metastasis and lymphadenopathy along the common hepatic artery (fig. 2a). The portal vein was narrowed but seemed to be patent, and no collateral circulation was observed. A bronchoscopy revealed tumor invasion into the right middle bronchus and a sample taken was positive for adenocarcinoma. Positron emission tomography CT imaging showed intense uptake in the same region pointed out by the chest CT and in some of the vertebrae. No evidence of metastasis was found in brain magnetic resonance imaging, and the patient was diagnosed as stage IV lung adenocarcinoma with liver and bone metastasis.

The tumor was found to harbor an epidermal growth factor receptor (EGFR) mutation of L858R, so he was subsequently treated with gefitinib (250 mg/day) and his general condition immediately improved. One month later, he was admitted to the emergency department after experiencing fever and progressive dyspnea on exertion for several days. Chest CT images showed shrinkage of the primary tumor and lymph nodes, but diffuse gland-grass opacity was also found in both lung fields (fig. 1c). An abdominal CT revealed atrophic changes in the hepatic left lobe (fig. 2b). Gefitinib, the most likely cause of the interstitial lung disease, was immediately discontinued. The patient was then given 500 mg/day of methylprednisolone for 3 days, followed by 30 mg/day of prednisolone as a maintenance therapy. His respiratory condition gradually improved and the prednisolone was tapered. CT scans were performed 2 months after the start of the steroid therapy to re-evaluate his lung condition and the extent of his tumor. The primary tumor and lymph nodes were still shrunken (fig. 1d) but the tumor of hepatic left lobe had regrown. The residual hepatic right lobe showed compensatory enlargement (fig. 2c).

Second-line chemotherapy with carboplatin (AUC 5) plus pemetrexed (500 mg/m<sup>2</sup>) plus bevacizumab (15 mg/kg) was initiated. This therapy produced a good response and no serious adverse event occurred. Ten days after the administration of the 4th course of this chemotherapy, the patient had black stool and hypotension. He was readmitted to the emergency department and was found to have anemic conjunctiva on physical examination. Laboratory data showed normocytic anemia (hemoglobin 9.8 mg/dl), mildly elevated blood urea nitrogen [38.4 mg/dl (upper limit of normal: <20.0 mg/dl)] and no hepatic viral infection. Mild elevation of transaminase was also noted, but no other findings were suggestive of liver failure. Upper gastrointestinal endoscopy revealed beaded esophagus varices and gastric varix in the distal site with bloody gastric contents (fig. 3). Beaded esophageal varix suggested the existence of portal hypertension. An enhancement CT depicted an inhomogeneous enhancement of liver hepatic parenchyma that could have reflected an imbalance of the portal vein blood flow, but no evidence of ascites, collateral vein circulation, or splenomegaly was observable. A blood transfusion and elective endoscopic variceal ligation were successfully performed. The patient was discharged 1 week after this. Follow-up upper gastrointestinal endoscopy showed varix regression and a smooth mucosal surface.

## Discussion

Lung cancer is the leading cause of cancer-related death worldwide. Compared to other types of cancer, the long-term survival rate remains poor in lung cancer [1]. Many factors contribute to the high mortality of this cancer. One major factor is the advanced state of the lung cancer and presence of metastatic lesions by the time of diagnosis. The most frequent sites of metastasis of this tumor are brain, bone, adrenal gland and liver. All of these extrathoracic organs should be screened by imaging modalities for pretreatment evaluation [2].

Liver metastasis, with its high blood flow, is frequent not only in lung cancer but also cancers of the stomach, colon, breast, etc. Primary or metastatic liver tumors sometimes cause complications. Metastatic liver tumor has been reported, for example, to cause liver failure and extrahepatic biliary obstruction [3, 4]. Portal hypertension is usually caused by liver cirrhosis, but portal vein invasion by hepatocellular carcinoma, by other tumors, or by tumor emboli to the vein may lead to the hypertensive state in some cases. The three major complications of portal hypertension are gastroesophageal varix, ascites, and hypersplenism. Patients with liver cirrhosis routinely undergo upper gastrointestinal endoscopy to screen for gastroesophageal varices because the first of these complications, gastroesophageal variceal hemorrhage, can be fatal. Endoscopic variceal ligation and other prophylactic endoscopic treatments are recommended for patients with gastroesophageal varices [5].

The progression from chronic hepatitis to cirrhosis usually takes place over a period of years. The development of collateral circulation is accompanied by portal hypertension induced by hepatic fibrosis. Distended and engorged epigastric veins (caput medusae) are a typical sign found in physical examination, and CT scanning is a suitable evaluation for the portal venous system [6]. Yet no features of liver cirrhosis were found in any of our examinations or in the patient's medical history. The evidence suggested that his portal circulation had changed rapidly and drastically, and the formation of gastroesophageal varix seemed to be caused subacutely by an abrupt increase of his portal vein pressure. The patient's metastatic liver tumor was the most likely cause of his portal hypertension. Diffuse hepatic sinusoidal metastases and the notable conformational changes brought about by chemotherapy might have induced the gastroesophageal varix hemorrhage by altering the hemodynamics of his portal circulation.

Recent progress in molecular targeted therapy now enables clinical oncologists to tailor therapeutic drugs to the biological profiles of the patients. The reported evidence singles out EGFR as the strongest biomarker for NSCLC and as the biomarker most predictive of prognosis. A recent clinical trial in Japan has shown that gefitinib, a well-known EGFR-tyrosine kinase inhibitor, can prolong progression-free survival and overall survival in patients positive for the EGFR mutation [7]. The frequency of the EGFR mutation in NSCLC is high in the Japanese population, especially in adenocarcinoma histology [8]. The Japan Cancer Society guideline recommends first-line use of gefitinib for EGFR mutation-positive patients. Bevacizumab is the monoclonal antibody against vascular endothelial growth factor (VEGF). It modifies intratumoral angiogenesis and facilitates drug delivery to tumor cells [9]. Adding bevacizumab to cytotoxic chemotherapy may bring about a higher response rate and better overall survival than what will normally be achieved by chemotherapy without the antibody [10]. Bevacizumab should be considered an option for patients who clear exclusion criteria such as squamous histology, etc. [11].

Gefitinib shows great therapeutic efficiency in the subpopulation of so-called 'super-responders' [12]. The agent generally achieves notable tumor regression and improved performance status at an early stage in super-responders. Our patient responded well not only to gefitinib, but also to bevacizumab-containing chemotherapy. Some reports argue that bevacizumab has the possibility of dramatic therapeutic effects [13]. Our experience supports this. VEGF confers strong effects on liver sinusoidal endothelial cells as proliferative stimulation *in vitro* and supports the maintenance of sinusoidal

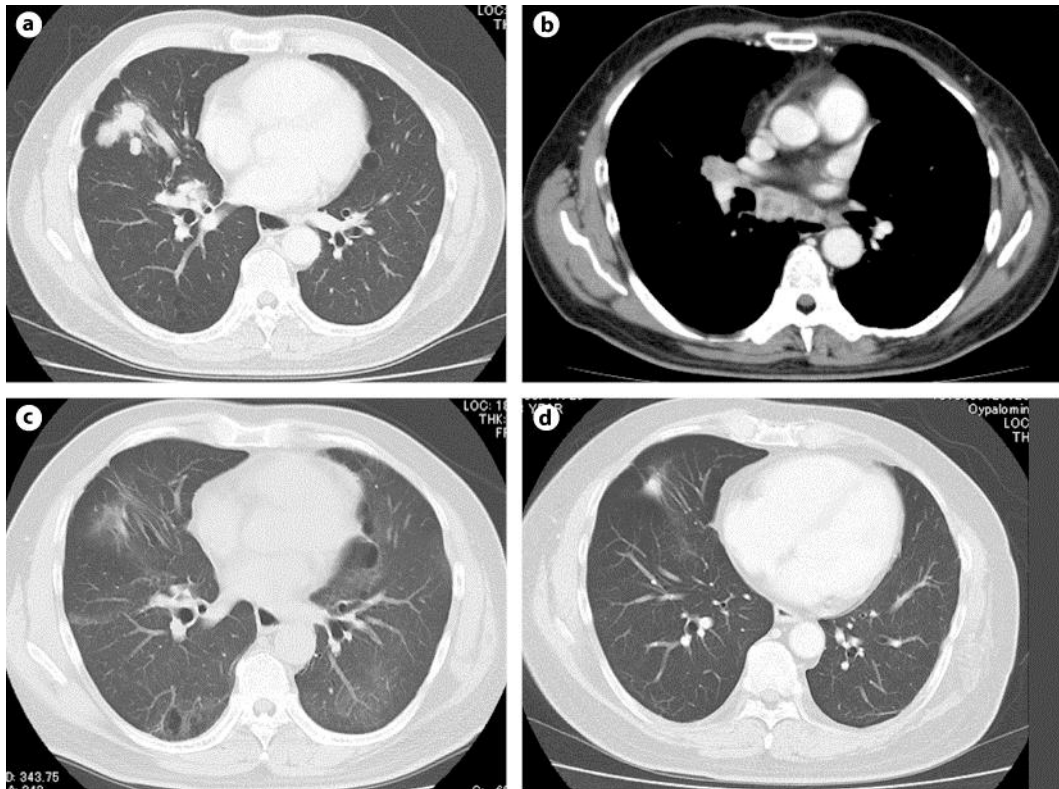
endothelial cells [14]. The organ-specific action in our patient may have reflected the discrepancy in his response, that is, the dramatic regression of his metastatic liver tumor versus the unchanging tumor volume in his lung.

### Conclusion

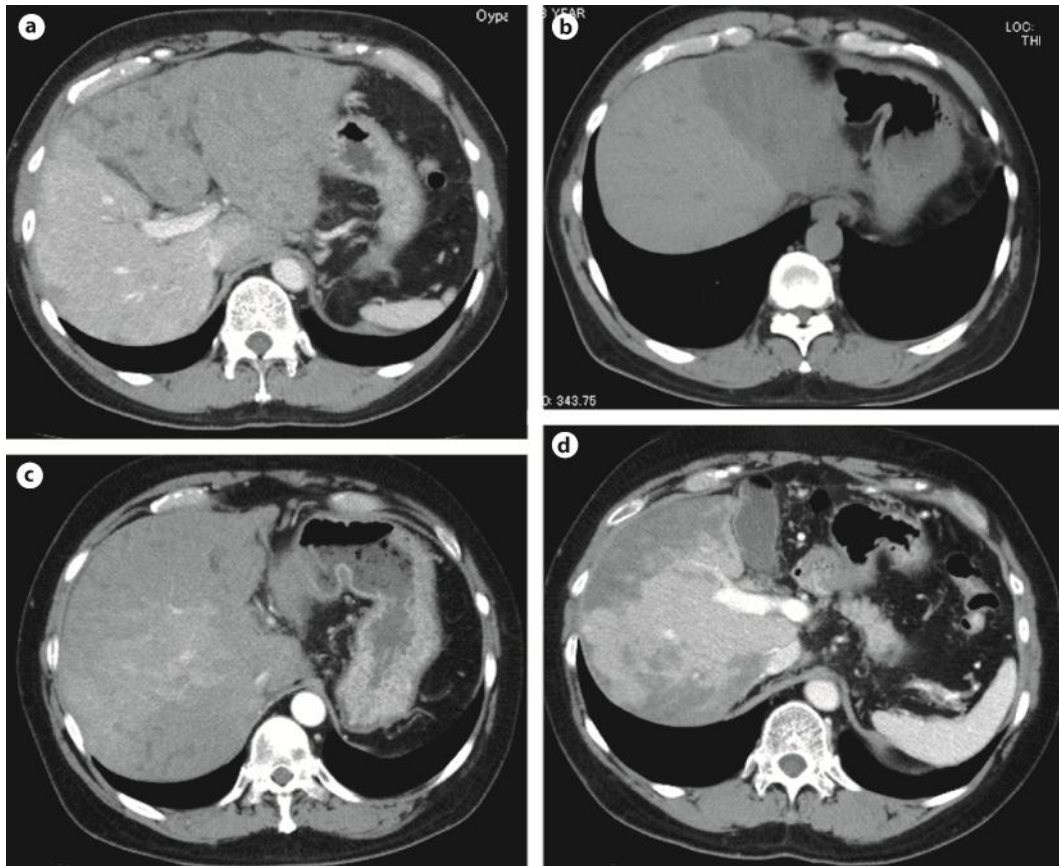
We treated a case of gastroesophageal variceal hemorrhage in a patient with metastatic liver tumor of NSCLC. The patient responded well to both gefitinib and bevacizumab-containing chemotherapy. Chemotherapy in series brought about a dramatic regression of his metastatic liver tumor but might have caused the patient's gastroesophageal varix by subacutely inducing the hemodynamics of portal hypertension. While molecular targeted therapy generally achieves significant improvement, the strong and rapid pharmaceutical action sometimes causes unexpected adverse events.

### Disclosure Statement

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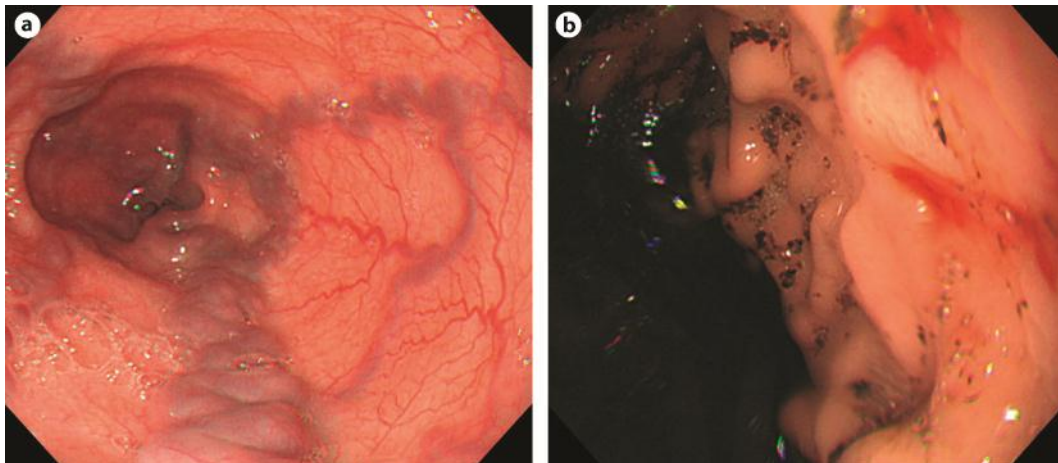


**Fig. 1.** Chest computed tomography of this patient. The chest images at diagnosis show a lobulated irregularly shaped tumor in the right middle lobe (a) and hilar and mediastinal lymphadenopathy (b). The chest image 1 month after initiation of gefitinib shows tumor shrinkage and diffuse gland-grass opacities in both lung fields (c). Computed tomography at the time of gastroesophageal hemorrhage shows shrinkage of the primary tumor (d).



**Fig. 2.** Abdominal computed tomography of the patient. The abdominal image at diagnosis shows a hypertrophic left hepatic lobe occupied by low-density lesions with inhomogeneous enhancement, and narrowed but still patent portal vein (**a**). The abdominal image taken after detection of interstitial lung disease shows notable atrophic regression in the hepatic left lobe (**b**). The computed tomography image at the re-evaluation 2 months after steroid therapy shows hepatic left lobe tumor regrowth and compensatory enlargement in the residual right lobe (**c**). The abdominal image at the time of gastroesophageal hemorrhage shows atrophic regression in both hepatic lobes, but no apparent splenomegaly or collateral vein development (**d**).





**Fig. 3.** Upper gastrointestinal endoscopy reveals beaded and dilated esophageal varices with partial redness (a). Bloody gastric contents are seen, but his gastric mucosa is not ulcerative (b).

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