

CASE REPORT

진행 간세포암종 환자에서 소라페닙 치료 후 발생한 간농양증

신승각, 정영걸, 윤현화, 권오상, 김연수, 최덕주, 김주현

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Liver Abscess in Advanced Hepatocellular Carcinoma after Sorafenib Treatment

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Hepatocellular carcinoma (HCC) is a critical global health issue and the third most common cause of cancer-related deaths worldwide. The majority of patients who present HCC are already at an advanced stage and their tumors are unresectable. Sorafenib is a multi-kinase inhibitor of the vascular endothelial growth factor pathway and was recently introduced as a therapy for advanced HCC. Furthermore, studies have shown that oral sorafenib has beneficial effects on survival. However, many patients experience diverse side effects, and some of these are severe. Liver abscess development has not been previously documented to be associated with sorafenib administration in HCC. Here, we report the case of a HCC patient that developed a liver abscess while being treated with sorafenib. (**Korean J Gastroenterol 2014;63:47-50**)

Key Words: Sorafenib; Hepatocellular carcinoma; Liver abscess

INTRODUCTION

Surgical resection and orthotopic liver transplantation are the best treatment options for select patients with hepatocellular carcinoma (HCC). However, the majority of patients who present HCC are already at an advanced stage and their tumors are unresectable. No effective systemic therapeutic modality has been established for patients with unresectable advanced-stage HCC. However, recent advances in our understanding of the molecular mechanisms underlying carcinogenesis have provided novel targets in advanced HCCs which are richly supplied with blood vessels.^{1,2}

Sorafenib is multi-tyrosine kinase inhibitor that targets Raf, vascular endothelial growth factor, platelet-derived growth factor, and c-kit.³ It is believed that the benefits of sor-

afenib are due to its anti-proliferative and anti-angiogenic effects. These benefits were demonstrated in the Sorafenib HCC Assessment Randomized Protocol (SHARP) study, in which sorafenib was found to increase median overall survival from 7.9 to 10.7 months in advanced HCC patients with Child-Pugh classification A cirrhosis.⁴ In addition, in the SHARP trial, drug-related adverse events of any grade were found to occur more significantly among sorafenib than did placebo recipients. Documented adverse events included diarrhea, hand-foot skin reactions, anorexia, alopecia, weight loss, dry skin, abdominal pain, voice changes, and other dermatological events.^{4,5}

However, no report has previously linked sorafenib with liver abscess development. Here, we report for the first time a case of liver abscess after sorafenib treatment in a patient

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with advanced HCC, and we include a review of the literature.

CASE REPORT

A 55-year-old male was admitted to our hospital with symptoms of dyspepsia. He did not report abdominal pain or weight loss. He had been diagnosed as a HBV carrier at 51 years of age, but had not been treated with antiviral agents. He had no family history of disease, was not obese, and presented no evidence of diabetes mellitus. The patient had a 30 pack-year smoking history but did not drink alcohol at all. His abdomen was soft, and no abdominal tenderness was observed. Laboratory data at admission were as follows: total bilirubin, 1.8 mg/dL; ALP, 203 IU/L; AST, 124 IU/L; ALT, 60 IU/L; PT, 14 seconds (INR 1.29); hemoglobin, 11.1 g/dL; white blood cells (WBC), 3,150/mm³ (51.4% segments); platelet, 80,000/mm³; hsCRP, 2.30 mg/dL; erythrocyte sedimentation rate (ESR), 24 mm/hr; HBeAg, positive; HBV DNA, 4,550,827 copies/mL; AFP level, 19,312 ng/mL; and protein-induced by vitamin K absence (PIVKA)-II, > 75,000 mAU/mL. Abdominal sonography showed a 9×8 cm-sized mass of slightly increased echogenicity in the right lobe of the liver with right portal vein thrombosis. A dynamic CT scan confirmed a mass located in the right lobe of liver, which showed enhancement during the arterial phase and washout during the portal venous phase with right portal vein thrombosis (Fig. 1). In addition, CT also revealed several masses of < 1 cm in the inferior lobe and a small amount of ascites.

Although no liver biopsy was performed, a diagnosis of HCC was made based on the following: HBsAg positivity; the

presence of liver nodules during abdominal sonography; an AFP of > 200 ng/mL; and specific dynamic liver CT findings such as mass enhancement during the arterial phase and washout in the portal venous phase. The stage of the HCC was American Joint Committee on Cancer (AJCC) TNM stage IIIB or Barcelona-Clinic Liver Cancer (BCLC) stage C.

The patient was administered oral sorafenib 400 mg twice daily without treatment of HBV, but after 4 days of treatment, he complained of right hypochondrial and epigastric pain. On examination, his body temperature was 39.5°C, pulse rate 100 per minute, and blood pressure 130/80 mmHg. In addition, his abdomen was soft, and right hypochondrial and epigastric tenderness were observed. Laboratory data were as follows: total bilirubin, 5.6 mg/dL; ALP, 209 IU/L; AST, 1,007 IU/L; ALT, 169 IU/L; PT, 19.3 seconds (INR 1.82); hemoglobin, 8.4 g/dL; WBC, 2,680/mm³ (segment form: 87.8%); platelet, 32,000/mm³; hsCRP, 17.47 mg/dL; and ESR, 35 mm/hr. An abdominal CT revealed a new necrotic lesion and newly developed air densities in the right liver lobe (Fig. 2). Sorafenib was immediately stopped, and broad spectrum intravenous antibiotic treatment (cefotaxime and metronidazole) was started for the liver abscess. We did not perform percutaneous catheter drainage or needle aspiration for the liver abscess. The fever promptly subsided, and, subsequently, *Peptoniphilus asaccharolyticus* was cultured from the blood.

After 20 days of antibiotic treatment, his symptoms were slightly improved, and he was discharged. Laboratory data at discharge were as follows: total bilirubin, 6.4 mg/dL; ALP, 183 IU/L; AST, 206 IU/L; ALT, 45 IU/L; PT, 17.5 seconds (INR

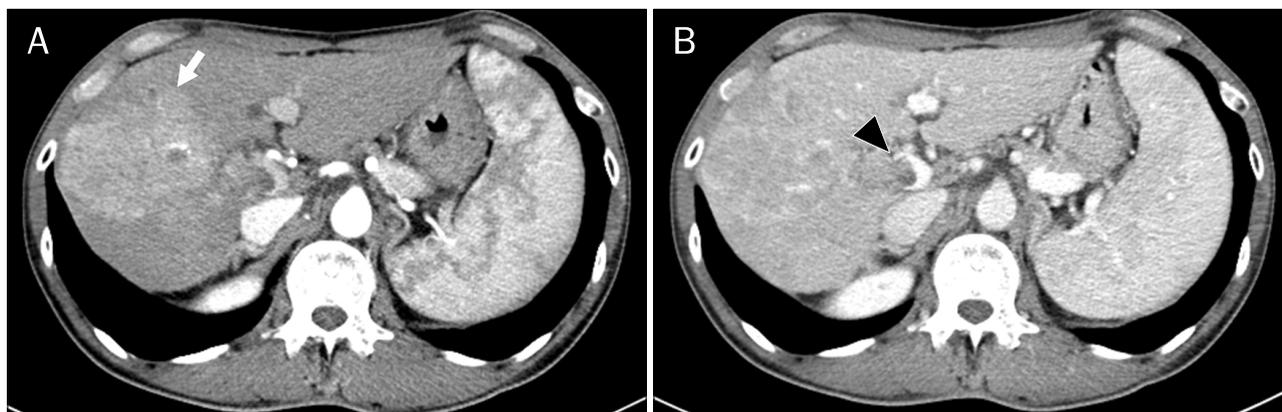


Fig. 1. Liver CT scan at the time of hepatocellular carcinoma diagnosis, showing a 10-cm sized high density mass in the arterial phase (arrow) and washout in the portal venous phase, with portal vein thrombosis (arrow head) in the right lobe of the liver. (A) Arterial phase. (B) Portal venous phase.



Fig. 2. CT scan after sorafenib commencement, showing newly developed air densities with necrosis.

1.64); hemoglobin, 10.6 g/dL; WBC, 7,860/mm³ (segment form: 78.6%); platelet, 180,000/mm³; hsCRP, 13.11 mg/dL; and ESR, 93 mm/hr.

However, one week after discharge, he was readmitted due to poor oral intake. A CT scan performed at the time showed the air densities had disappeared, but that the HCC had progressed (Fig. 3). He was subsequently discharged to a hospice center where he succumbed to liver failure.

DISCUSSION

Sorafenib has been reported to be well-tolerated with manageable side-effects, the most common of which are hand-foot skin reaction, diarrhea, alopecia, fatigue, rash or desquamation, and hypertension.^{4,5} However, we found that a liver abscess associated with tumor necrosis and gas formation developed after only 4 days of sorafenib use in an advanced HCC patient. Moreover, this link between sorafenib and liver abscess development has not been previously reported.

Liver abscesses can be caused by bacteria, parasites, and fungi, but the most common organisms to cause them are *Klebsiella pneumoniae* and *Escherichia coli*.⁶ In our case, *Peptoniphilus asaccharolyticus* (a gram positive anaerobic cocci) was cultured from the blood, and it is not a common pathogen in liver abscess. In 1998, it was reported that the predominant anaerobes in causes of liver abscesses were *Peptostreptococcus* spp. (18 isolates) that included *P. micros* (7), *P. prevotii* (4), *P. anaerobius* (3), *P. magnus* (2) and *P. asaccharolyticus* (2).⁷

One case of a liver abscess was attributed to bevacizumab,



Fig. 3. CT scan after antibiotic commencement, showing the disappearance of air densities, but hepatocellular carcinoma aggravation and massive ascites.

capecitabine, and oxaliplatin chemoimmunotherapy for adenocarcinoma of the cecum with liver and lung metastases, and in this case, *Bacteroides fragilis* (an anaerobic bacterium) was cultured from the blood. Bevacizumab inhibits vascular endothelial growth factor A, and the authors suggested that its use could cause necrosis due to the creation of an anaerobic environment which makes lesions more susceptible to anaerobic infection.⁸

On the other hand, liver abscess development after specific treatments for HCC has been reported extensively, for example, after radiofrequency ablation or embolization. Reported incidences of liver abscess formation after transcatheter arterial chemoembolization (TACE) ranged from 0% to 3.3%,^{9,11} and after radiofrequency ablation (RFA) range from 1.5% to 2.4%.¹¹⁻¹³ Gas-forming liver abscess development is even rarer and relatively few case reports have been issued on the topic. These abscesses are usually encountered after RFA, and are believed to be caused by bacterial contamination of ablated regions.¹¹ However, the mechanism involved has not been properly established. The pathogenic mechanism of liver abscess formation after TACE has been linked to biloma formation and biliary tract infection. The pathophysiology of biloma formation involves ischemic injury to the peribiliary capillary plexus, which is supplied by branches of the hepatic artery. As a result, the integrity of the biliary tree is disrupted, and biloma formation ensues.¹⁴ Bacterial seeding of bilomas can then produce hepatic abscesses. Another mechanism involves the development of an abscess within the necrotic center of a devascularized hepatic tumor. The major risk factors of biliary tract infection

are pneumobilia, portal vein thrombosis, bilo-enteric anastomosis, and biliary obstruction.¹⁵

Our patient had advanced HCC with portal vein thrombosis, and sorafenib might have caused an ischemic condition, tumor necrosis, and diminished capacity for removal of gas in necrotic tissue. Furthermore, portal vein thrombosis may have increased the risk of a biliary tree infection.

Of course, we need to distinguish a liver abscess after sorafenib treatment from the possibility of a spontaneous necrosis of HCC. Everson and Cole¹⁶ considered regression of cancer to be spontaneous if it occurred without the administration of anticancer drugs or surgical resection. In this case, although duration of the sorafenib treatment was relatively short, the event clearly occurred after the administration of the anticancer drug, and it was consistent with liver abscess in the imaging study and the results of the blood culture. Also, other causes of spontaneous necrosis of HCC, such as gastrointestinal bleeding and occlusion of feeding artery, did not occur. We could consider the liver abscess formation after sorafenib treatment in advanced HCC more likely than the possibility of spontaneous necrosis of HCC.

We report for the first time a case of liver abscess formation attributed to sorafenib in a patient with advanced HCC. Liver abscesses are almost uniformly fatal if left untreated. Accordingly, after initiating sorafenib in patients with HCC, and especially in patients with portal vein thrombosis, the advent of febrile illness, abdominal pain, liver function test changes, hsCRP, leukocytosis, or thrombocytopenia should raise suspicion of a liver abscess. Furthermore, the recently devised combination therapies of TACE or RFA with sorafenib for advanced HCC should also be considered to increase the risk of liver abscess development. More studies are needed to identify the risk factors and mechanism of liver abscess formation associated with sorafenib use in patients with HCC.

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