

Colon perforation during sorafenib therapy for advanced hepatocellular carcinoma. A case report

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ABSTRACT

There are no effective conventional systemic cytotoxic therapies for patients with unresectable or advanced hepatocellular carcinoma (HCC). Sorafenib, an oral multi-targeted tyrosine kinase inhibitor, was recently approved for the treatment of patients with HCC. Sorafenib is generally well tolerated and has an acceptable toxicity profile. Gastrointestinal perforation is a rare adverse event. We present a case of transverse colon perforation during sorafenib therapy for advanced HCC. A 68-year-old woman with advanced HCC was treated with sorafenib. Eight weeks later the patient presented with the sudden onset of sharp abdominal pain. Emergency surgery was performed for peritonitis and a perforation involving the transverse colon.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third most common cause of cancer-related deaths globally¹. For patients with unresectable or advanced disease, HCC is known to be highly refractory to conventional cytotoxic therapy. With no effective therapy, the prognosis is usually poor². Sorafenib is an oral, multi-targeted tyrosine kinase inhibitor and the first agent to produce a statistically significant survival gain in HCC patients with advanced disease³.

Case report

A 68-year-old woman with right upper quadrant abdominal pain for more than 3 days, general fatigue, and nausea for 3 months was admitted to our hospital. She was afebrile, and physical examination revealed right upper quadrant tenderness (without rebound tenderness) and organomegaly. The patient had had chronic hepatitis B for 20 years and irregular follow-up with a hepatologist.

The initial complete blood count was as follows: white blood cells (WBC), $4.13 \times 10^3/\mu\text{L}$; hemoglobin, 11.7 g/dL; platelets, $147 \times 10^3/\mu\text{L}$. Other laboratory findings included total bilirubin, 0.63 mg/dL (0.2-1.1 mg/dL); aspartate aminotransferase (SGOT), 140 U/L (5-40 U/L); alanine aminotransferase (SGPT), 47 U/L (5-40 U/L); alkaline phosphatase (ALP), 375 U/L (42-128 U/L); gamma-glutamyl transferase (γGT), 518 U/L (16-73 U/L); albumin, 3.43 g/dL (3.8-5.3 g/dL); partial thromboplastin time (PTT), 12.1 seconds (9.5-12.5 s); D-dimer, 1045 ng/mL (0-255 ng/mL); and C-reactive protein (CRP), 2.35 mg/dL (0-0.5 mg/dL). Viral and tumor markers were as follows: HBsAg(+), HBsAb(-), HBeAg(-), HBeAb(+), anti-HCV(-), and serum alpha-fetoprotein (AFP), 3245 ng/mL (<5 ng/mL). Abdominal computed tomography (CT) demonstrated a poorly defined infiltrating lesion, possibly HCC, in segment 4 to 8 with metastatic nodules in the left lobe of the liver, a left portal vein thrombus, cirrhosis, and a small amount of ascites (Figure 1).

Based on these findings the patient was diagnosed with HCC with multiple liver and lung metastases, left portal vein thrombosis, and Child-Pugh class B cirrhosis secondary to chronic hepatitis B. No local therapy (eg, transarterial chemoemboliza-

Key words: sorafenib, bowel perforation, hepatocellular carcinoma.

Financial support: This study was supported by a research fund from Chosun University, 2010.

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Received December 13, 2010; accepted March 4, 2011.

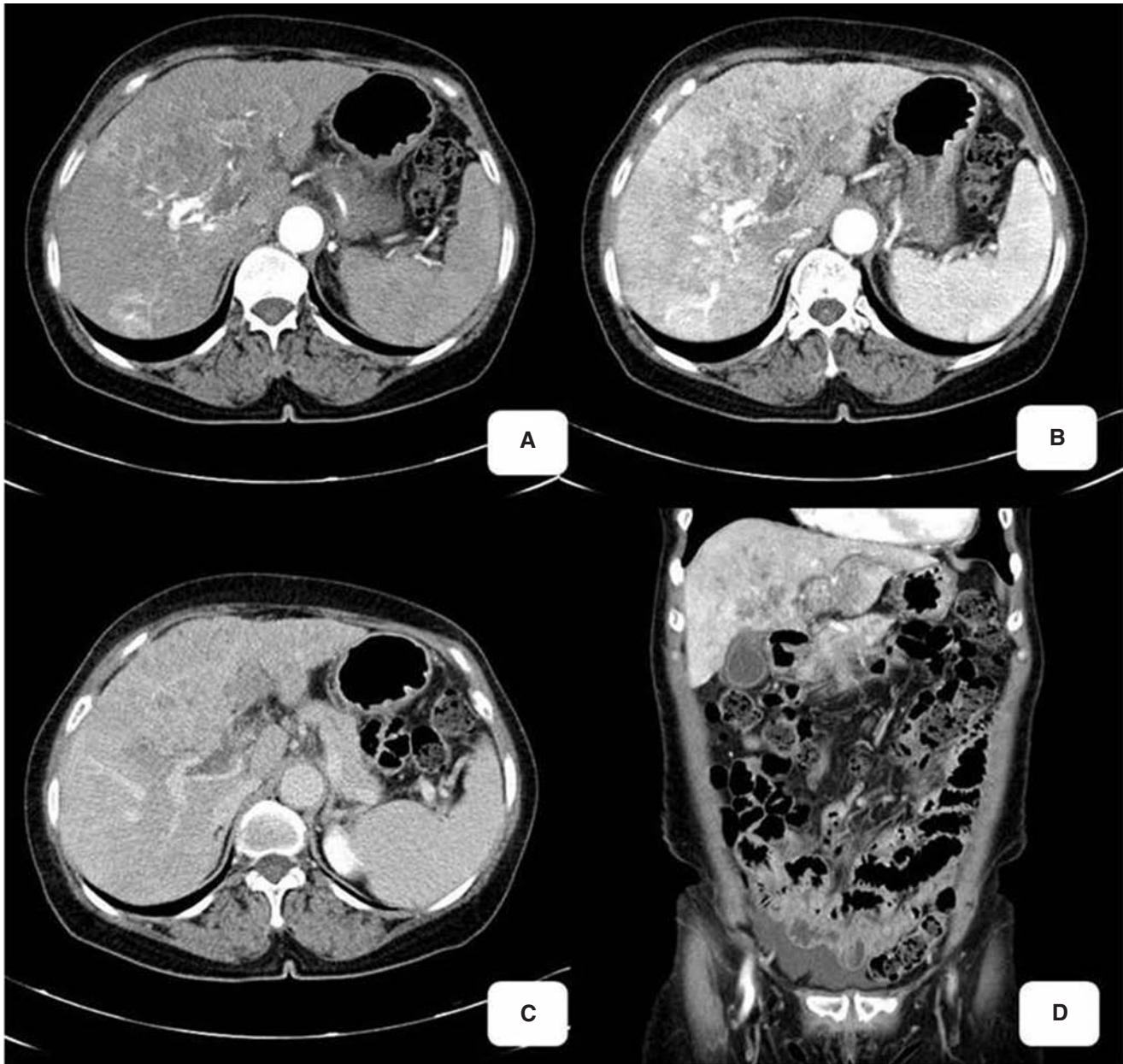


Figure 1 - Computer tomography of the abdomen showing a poorly defined infiltrating lesion in segments 4-8 of the liver with metastatic nodules in the left lobe, a left portal vein thrombus, liver cirrhosis, and a small amount of ascites.

tion) was given because of the large metastatic lesions and portal vein thrombosis. Instead, therapy with oral sorafenib was started.

Six weeks later, abdominal CT and AFP levels were repeated. The tumor size had not changed, but the ascites was slightly increased, and the AFP level was decreased to 2012 ng/mL. Sorafenib was well tolerated. The patient was still Child-Pugh class B (bilirubin, 1.9 mg/dL; PTT, 14.9 s; albumin, 3.15 g/dL; mild ascites; no encephalitis; WBC, $6.54 \times 10^3/\mu\text{L}$; hemoglobin, 10.1 g/dL; and platelets, $151 \times 10^3/\mu\text{L}$). Oral sorafenib was continued. Eight weeks later, the patient had sudden-onset sharp,

pan-abdominal pain. Physical examination revealed abdominal tenderness with rebound tenderness and decreased bowel sounds. An x-ray showed a pneumoperitoneum; WBC increased to $12.1 \times 10^3/\mu\text{L}$ with 85% neutrophils (Figure 2).

Sorafenib was discontinued and emergency surgery was performed. Intraoperatively, the abdominal cavity was noted to contain more than 1000 mL of turbid fluid with severe liver cirrhosis accompanied by a yellow nodule. Assessment of the stomach showed no evidence of perforation, and examination of the lesser sac found no evidence of saponification suggestive of pancreatitis.

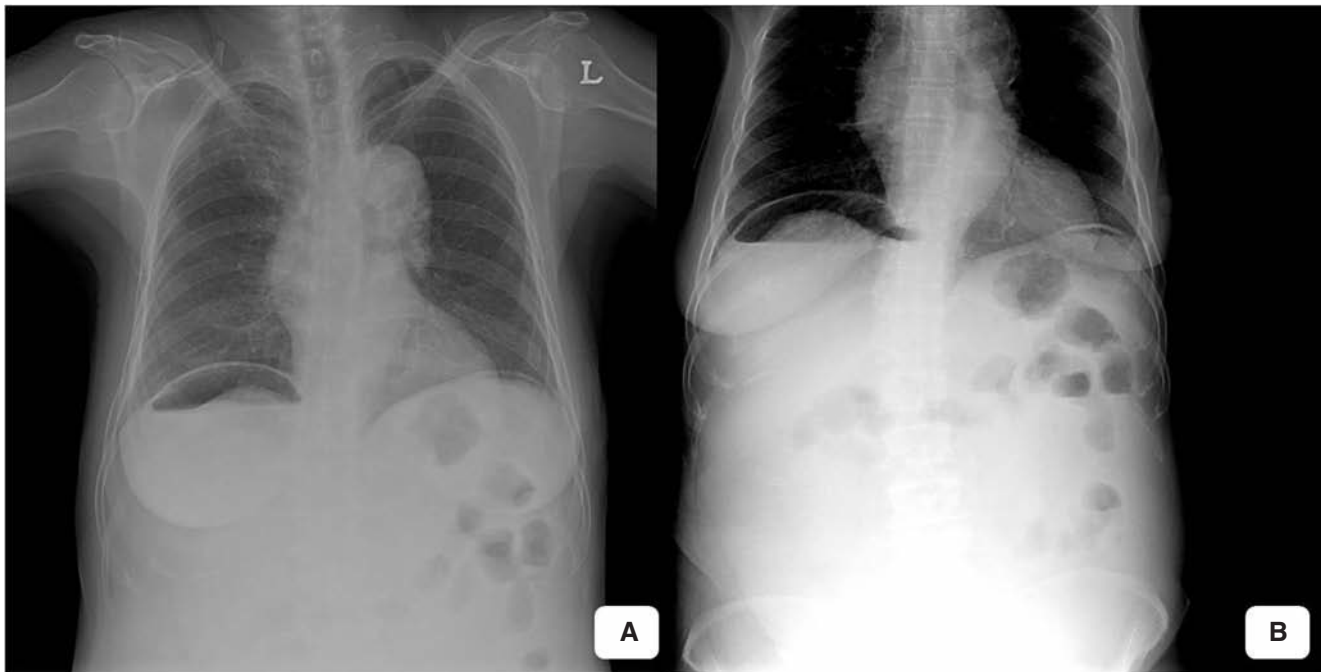


Figure 2 - Posteroanterior chest and abdominal erect x-ray. There is free gas under the diaphragm in both views.

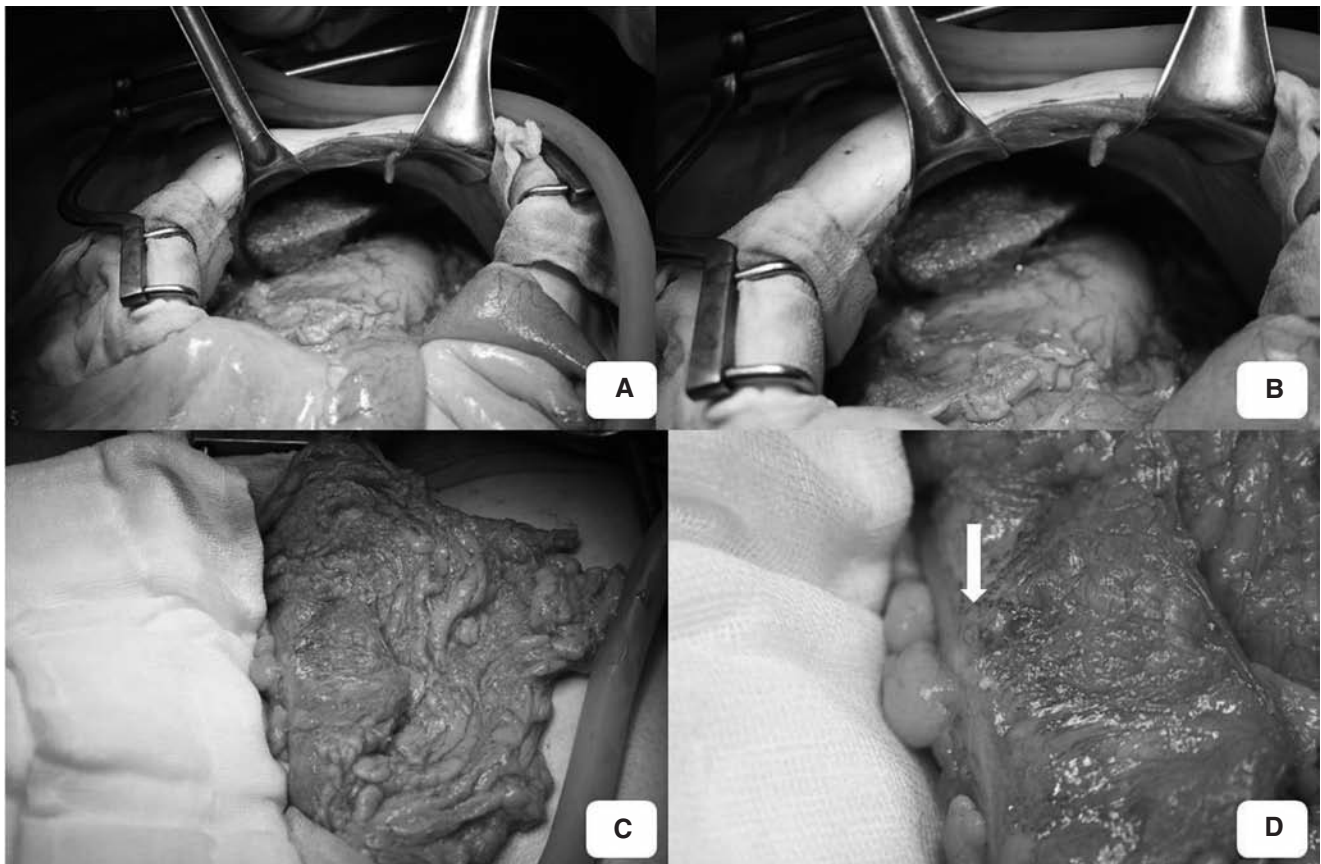


Figure 3 - Operation field. A) Severe liver cirrhosis accompanied by a yellow nodule. B) Examination of the stomach showed no evidence of perforation. C, D) Upon examination of the large and small bowel, a small perforation was identified in the transverse colon.

Upon examination of the large and small bowel, a small perforation was identified in the transverse colon. The perforation was resected widely, and reanastomosis was performed followed by warm saline irrigation (Figure 3). The pathological assessment of the resected bowel revealed transmural ischemic changes with small vessel thrombi (Figure 4).

Postoperatively, abdominal pain, WBC, and CRP level were all decreased. On the third postoperative day the patient complained of increased abdominal pain and distension. Urine output decreased (50 mL/day), and WBC ($26.93 \times 10^3/\mu\text{L}$ with 86% neutrophils), total bilirubin (3.73 mg/dL), and serum creatinine (2.53 mg/dL) increased. Examination of the ascitic fluid revealed a WBC count of 25,000/m² (polymorphonuclear cells, 87%), a pH of 7.10, and turbid color. We presumed panperitonitis due to reperforation at the colon anastomosis site

and recommended surgery; however, the patient's guardian declined the recommendation. The patient died from sepsis on postoperative day 5.

Discussion

Hepatocellular carcinoma is a highly vascularized tumor, dependent on neoangiogenesis for blood supply. Both cell proliferation and angiogenesis substantially contribute to the initiation and progression of HCC. Vascular endothelial growth factor (VEGF) is frequently expressed in HCC as a central mediator of angiogenesis. Sorafenib is an oral multi-targeted tyrosine kinase inhibitor that was originally developed as an inhibitor of Raf-1, which is vital for cell proliferation. Sorafenib is also an inhibitor of VEGFR, PDGFR, and FLT3³.

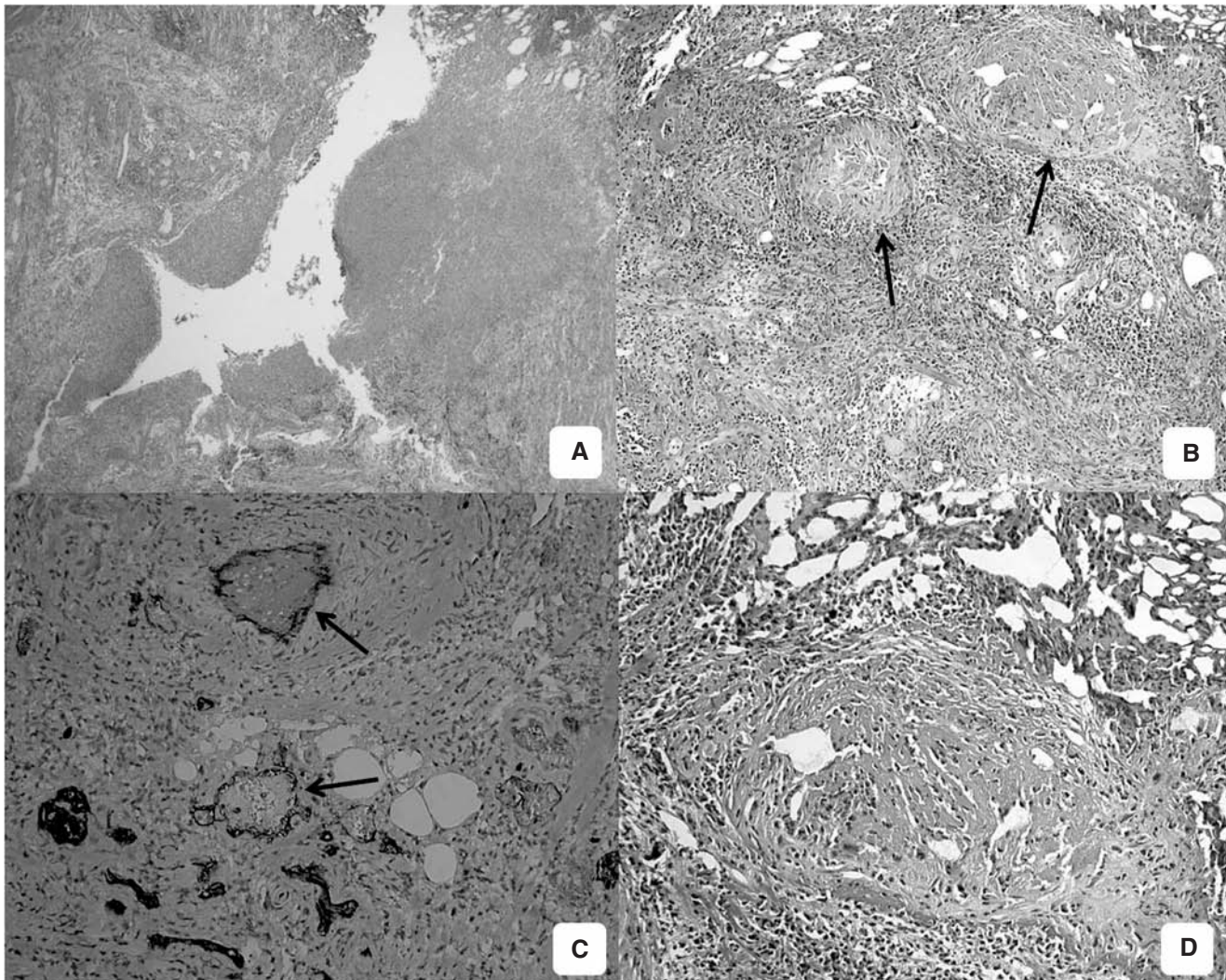


Figure 4 - Pathology findings. A) The resected bowel showed a transmural perforation with focal ischemic changes (HE, $\times 40$). B) Multiple small vessels with thrombi near ischemic zones (HE, $\times 200$). C) Vessels staining positively for CD34. D) It showed a small vessel filled with thrombi (HE, $\times 400$).

Sorafenib was the first agent to produce a statistically significant improvement in overall survival for HCC patients with advanced disease and was approved for this use by the US Food and Drug Administration in 2007. Common toxicities reported during clinical trials include skin changes (eg, rash, desquamation, and hand-foot skin reactions), diarrhea, and hypertension. Grade 4 toxicities have been reported in <1% of patients³.

Gastrointestinal perforation has been reported in <1% of patients taking sorafenib. Available published reports on gastrointestinal perforation have included patients postradiotherapy, with gastric ulcerations, or with tumor involvement. However, no patients with HCC treated with sorafenib have been reported to have a gastrointestinal perforation⁴. The exact mechanism of bowel perforation from sorafenib is unknown. However, sorafenib is also an inhibitor of VEGFR. Bevacizumab, a humanized monoclonal antibody of VEGF, was the first angiogenesis inhibitor to be developed and used clinically. A potentially serious adverse effect of bevacizumab is gastrointestinal perforation, with a reported rate of up to 1.7% based on data from a large, community-based registry⁵⁻⁷. The mechanism of bowel perforation with bevacizumab is also unknown.

Various theories have been proposed regarding the mechanisms by which antiangiogenic agents can lead to bowel perforation. Based on review of the few available cases and retrospective studies of patients given bevacizumab, proposed risk factors for gastrointestinal perforation include various local conditions, such as diverticulitis, bowel obstruction, chemotherapy-induced colitis, prior bowel irradiation, ulcer, tumor necrosis, and carcinomatosis⁶⁻⁹.

Another possible mechanism is that inhibition of VEGF signaling causes vascular regression of capillaries of the intestinal villi, and excessive VEGF inhibition contributes directly to gastrointestinal perforation by inducing regression of normal blood vessels in the gastrointestinal tract^{10,11}.

VEGF is also known to increase nitric oxide (NO) production by endothelial cells. Loss of NO release due to VEGF inhibition may lead to decreased blood flow and thrombosis, which may result in bowel infarction and perforation in areas with marginal blood supply^{4,11,12}.

Finally, Heinzerling *et al.*⁷ suggested that bevacizumab-related perforations are due to microembolic disease, which leads to ischemia and subsequent perforation. An increased risk of arterial and venous thromboembolic events has been a well-documented complication of bevacizumab therapy, as well as therapy with sunitinib and sorafenib¹³⁻¹⁵. It is well known that emboli, such as cholesterol atheromatous emboli, can lead to regional ischemia of the bowel and to perforation^{16,17}. This theory is supported by reports of bowel perforation with histologically confirmed evidence of ischemia and thrombus, and the fact that use of antiangiogenic agents has been associated with an increased risk of

thromboembolic events^{7,18-20}. In our case, the patient had no risk factors; however, the resected bowel revealed focal ischemic changes with thrombi in small vessels.

In conclusion, perforation of the transverse colon was seen after sorafenib therapy in a patient with HCC and evidence of thrombosis. Microthromboembolic events of the bowel may occur and lead to local ischemia, which in turn may lead to bowel perforation.

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