Rupture of a Small Hepatocellular Carcinoma in a Stable Disease State in a Patient Receiving Sorafenib Treatment

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To the Editor: Sorafenib, a multikinase inhibitor of cell proliferation and angiogenesis, is expected to cause intratumoral necrosis and maintain stable disease in hepatocellular carcinoma (HCC). HCC rupture during treatment of sorafenib is rare.[1] We describe a male patient who was treated with sorafenib and experienced a comparatively small HCC rupture during a stable disease state.

A 72-year-old man presented with upper abdominal pain. When he was 65-years old, he was diagnosed with HCC and underwent subsegmentectomy of S6 and S8 of the liver. Thereafter, he had repeated HCC recurrences and underwent transcatheter arterial chemoembolization (TACE) nine times and radiofrequency ablation twice. He had undergone the last TACE against segment 5 at 15 months before the rupture. When his HCC became refractory to the treatments, he started taking sorafenib 400–600 mg/day since 14 months before the rupture. The vascularity of HCC was decreased by sorafenib, and there was no significant change in size. Dynamic computed tomography (CT, Canon Medical Systems, Tokyo, Japan) revealed six small HCCs a month before, and stable disease indicated therapeutic efficacy. He has no history of abdominal trauma. He had hypertension since he was 60 years old, and his blood pressure was usually controlled to about 130/80 mmHg (1 mmHg = 0.133 kPa) with amlodipine 10 mg orally. He did not take antiplatelet drugs or anticoagulants.

Physical examinations revealed abdominal distention and upper abdominal tenderness. Blood pressure was 65/52 mmHg, and heart rate was 96 beats/min. Laboratory data showed a hemoglobin level of 68.0 g/L, total bilirubin level of 41.0 mg/L, alanine aminotransferase level of 89 IU/L, prothrombin time/international normalized ratio of 0.92, alpha-fetoprotein level of 5.9 ng/ml, and des-gamma-carboxy prothrombin (DCP) level of 2280 mAU/ml. Tumor marker DCP showed fluctuation but decreased at just before HCC rupture compared to one month before (7244 mAU/ml) and three months before (4949 mAU/ml) [Table 1]. Enhanced CT revealed a large hematoma from the hilum of the liver to the intraperitoneal region and extravasations at S4. Previous abdominal CT performed a month before revealed a hepatic tumor 2.6 cm in diameter, with hypovascularity [Figure 1]. Then, he was diagnosed with HCC rupture.

Abdominal angiography revealed extravasations from the branch of the middle hepatic artery and a densely stained mass. We performed transcatheter arterial embolization, which was effective and improved his general status. His hepatic function was damaged by hypovolemic shock, and ascites and pleural effusion were increased. Conservative management gradually improved his hepatic dysfunction, without a sign of rebleeding on CT 2 months later.

Table 1: Changes of tumor markers of the patient

Tumor markers	Time before the tumor rupture (month)					
	15	8	4	3	1	0
AFP (ng/ml)	5.8	3.3	5.0	5.1	5.6	5.9
DCP (mAU/ml)	31	2041	869	4949	7244	2280

AFP: Alpha-fetoprotein; DCP: Des-gamma-carboxy prothrombin.

We found uncommon but important clinical issues. First, the ruptured tumor was effectively controlled and maintained in a stable and hypovascular state by sorafenib, and tumor viability was decreased. Second, the tumor was smaller than 3 cm in diameter, without rapid growth. The presence of HCC rupture, in this case, suggested that treatment with sorafenib might be associated with HCC rupture.

Spontaneous HCC rupture is observed in 2.3% of cases in Japan.[2] The exact mechanism that leads to rupture is not clearly defined but is more frequent when the tumor diameter is more than 7 cm or the tumor protrudes from the surface of the liver.[3] In this case, the ruptured tumor was smaller than 3 cm in diameter and had no rapid growth. Thus, a relatively uncommon mechanism should be considered.

Sorafenib is a small-molecule inhibitor of multiple tyrosine kinase receptors involved in both angiogenesis and tumor cell proliferation including vascular endothelial growth factor receptor (VEGFR)-2, VEGFR-3, platelet-derived growth factor receptor-β, and RAF kinase. Common adverse effects are hand-foot skin reaction,

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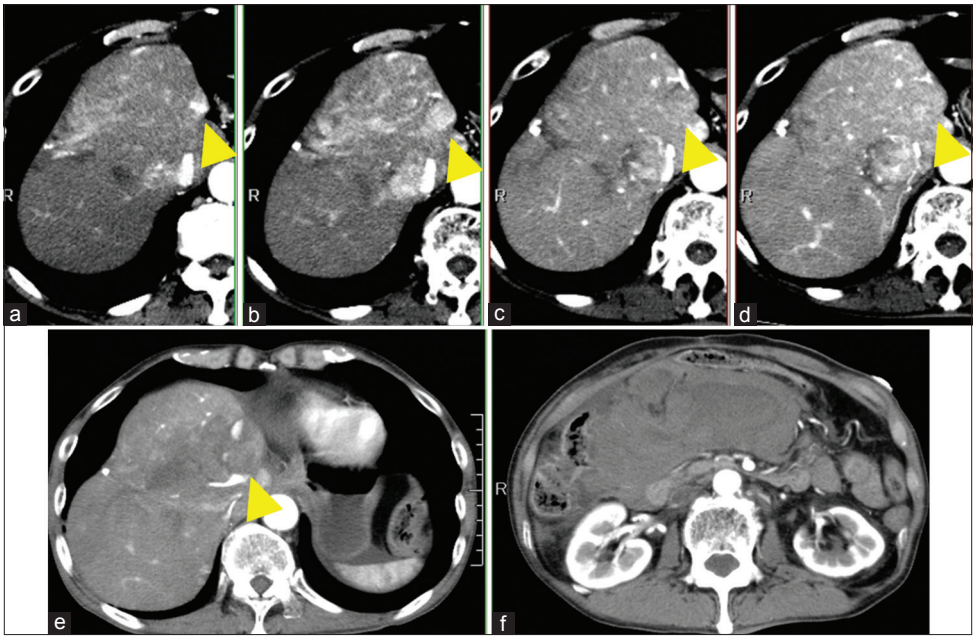

Figure 1: Enhanced CT showed HCC in the liver S4. (a) 15 months, (b) 8 months, (c) 4 months, (d) 1 month before the tumor rupture. The ruptured tumor was indicated by arrows. Sorafenib was started at 14 months before the rupture. The vascularity of the tumor was gradually decreased. The size of tumor was within stable disease. (e) Enhanced CT showed HCC rupture in the liver S4. The extravasation from tumor (arrow), (f) intraperitoneal hematoma. HCC: Hepatocellular carcinoma; CT: Computed tomography.

diarrhea, rash, hypertension, and bleeding. HCC rupture treated with sorafenib is also rare, with an incidence of about 0.2%.[1] The reason for the low incidence is considered to be the decreased intratumoral pressure after tumor necrosis through sorafenib administration. However, elevated blood pressure due to side effects of sorafenib might also contribute to vascular fragility.

Immunohistochemical study suggested that underlying vascular dysfunction might play a role in HCC rupture. The mechanism of bleeding by sorafenib is considered to involve not only the impairment of endothelial cell proliferation and maintenance of vascular integrity by the VEGF inhibitor[4] but also the weakening of the wall of major vessels by tumor erosion, necrosis, cavitation, or other concurrent pathological conditions. In systematic reviews and meta-analysis, the VEGFR tyrosine-kinase inhibitors such as sorafenib and sunitinib are associated with a significantly increased bleeding risk in HCC patients, similar to that noted in renal cell cancer patients. Although the incidence of high-grade bleeding events was increased only slightly, awareness of the possibility of increased bleeding is important.[4,5] Sorafenib possibly induces fragility of tumor vessel endothelial cells, tumor capsule, and hepatic capsule and leads to HCC rupture. Although reports of HCC rupture with sorafenib treatment are few, the risk of HCC rupture or bleeding should always be considered during chemotherapy with sorafenib.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initial will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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