—Case Reports—

Spontaneous Complete Necrosis of Advanced Hepatocellular Carcinoma

Tadashi Yokoyama[1,2], Hiroshi Yoshida[1,2], Atsushi Hirakata[1,2], Hiroshi Makino[1,2], Hiroshi Maruyama[1,2], Seiji Suzuki[1,2], Takeshi Matsutani[1,2], Tomohiro Hayakawa[1,2], Masaru Hosone[3] and Eiji Uchida[1]

[1]Surgery for Organ Function and Biological Regulation, Graduate School of Medicine, Nippon Medical School
[2]Department of Surgery, Nippon Medical School Tama Nagayama Hospital
[3]Department of Pathology, Nippon Medical School Tama Nagayama Hospital

Abstract

We present a rare case of hepatocellular carcinoma (HCC) in which spontaneous complete necrosis was confirmed with surgical resection. An 80-year-old man with HCC was referred to Nippon Medical School Tama Nagayama Hospital. The medical history included hypertension, managed with medication, and partial lobectomy of the lung owing to a lung schwannoma. A previously untreated abdominal aortic aneurysm, 51 mm in maximum diameter, was detected. The serum concentration of proteins induced by vitamin k antagonism or absence (PIVKA-2) was 14,300 mAU/mL, and that of alpha-fetoprotein was 184.2 ng/mL. Antibodies against hepatitis B surface antigens and hepatitis C virus were not detected in the serum. Computed tomography (CT) demonstrated a hypervascular tumor, 68 mm in diameter, in the left paramedian sector of the liver with washout of contrast medium in the delayed phase. An HCC in the left paramedian sector was diagnosed. Laparotomy was performed 40 days after CT scanning. Intraoperative ultrasonography showed that the HCC had shrunk to 30 mm in diameter. A left paramedian sectionectomy was performed. On macroscopic examination the surgical specimen was a firm mass, 30 mm in diameter, with a fibrous capsule. Histologic examination showed that the tumor in the cirrhotic liver had been completely replaced by central coagulative necrosis, circumferential fibrosis, and dense infiltrates of inflammatory cells. No viable HCC cells were observed in the coagulative necrosis. Organized thrombi in the hepatic artery were detected in the tumor. The tumor also contained multiple foci of old hemorrhage, ductular proliferation, and granulation tissue. The patient was discharged 10 days after the operation. After 1 month, the serum concentrations of PIVKA-2 (25 mAU/mL) and alpha-fetoprotein (5.9 ng/mL) had decreased to within their normal ranges.
(J Nippon Med Sch 2012; 79: 213–217)

Key words: spontaneous, necrosis, hepatocellular carcinoma

Introduction

Spontaneous necrosis or regression of a neoplasm is a rare event occurring with a frequency of 1 per 60,000 to 100,000 tumors[1]. Spontaneous regression has also been reported in hepatocellular carcinoma (HCC)[2–9].

Correspondence to Hiroshi Yoshida, MD, Department of Surgery, Nippon Medical School Tama Nagayama Hospital, 1–7–1 Nagayama, Tama, Tokyo 206–8512, Japan
E-mail: hiroshiy@nms.ac.jp
Journal Website (http://www.nms.ac.jp/jnms/)

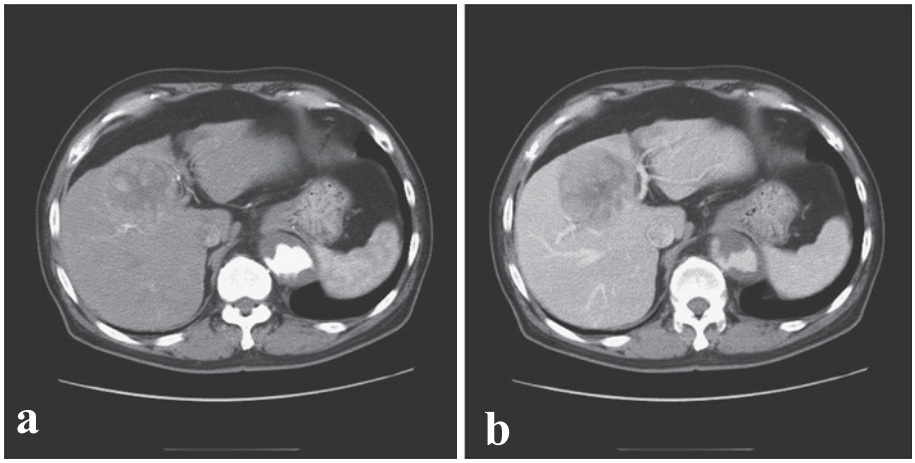

Fig. 1 Computed tomography demonstrated a hypervascular tumor, 68 mm in diameter, in the left paramedian sector of the liver (a) with washout of contrast medium in the delayed phase (b).

We present a rare case of spontaneous complete necrosis of HCC, as confirmed with surgical resection.

Case

An 80-year-old man with HCC was referred to Nippon Medical School Tama Nagayama Hospital. The medical history included hypertension, managed with medication, and partial lobectomy of the lung secondary to a lung schwannoma. A previously untreated abdominal aortic aneurysm, 51 mm in maximum diameter, was detected.

Initial laboratory tests revealed the following values: serum aspartate aminotransferase, 60 IU/L (normal, <38 IU/L); serum alanine aminotransferase, 186 IU/L (normal, <44 IU/L); serum alkaline phosphatase, 243 IU/L (normal 104 to 338 IU/L); serum lactic dehydrogenase, 294 IU/L (normal, 180 to 460 IU/L); serum gamma glutamic transpeptidase, 254 IU/L (normal, 16 to 73 IU/L); total serum bilirubin, 0.8 mg/dL (normal, 0.2 to 1.2 mg/dL); serum albumin, 3.9 g/dL (normal, 3.8 to 5.5 g/dL); serum C-reactive protein, 0.42 mg/dL (normal, <0.3 mg/dL); white blood cell count, 5,400/μL (normal, 4,000 to 9,000/μL); red blood cell count, 470 × 10^4/μL (normal, 427 to 570 × 10^4/μL); serum hemoglobin concentration, 13.9 g/dL (normal, 14 to 18 g/dL); serum platelet count, 19.6 × 10^4/μL (normal, 20 to 40 × 10^4/μL); and antithrombin, 89.4% (normal, >82%). The serum concentration of proteins induced by vitamin k antagonism or absence (PIVKA-2) was 14,300 mAU/mL (normal, <40 mAU/mL), and that of alpha-fetoprotein was 184.2 ng/mL (normal, <6.92 ng/mL). The indocyanine green clearance rate at 15 minutes was 9.5% (normal, <10%). Antibodies against surface antigens for hepatitis B and hepatitis C virus were not detected in the serum.

Computed tomography (CT) demonstrated a hypervascular tumor, 68 mm in diameter, in the left paramedian sector of the liver with washout of contrast medium in the delayed phase **(Fig. 1)**. Color Doppler ultrasonography revealed a hyperechoic tumor with vascular flow **(Fig. 2)**. Upper gastrointestinal endoscopy showed mild esophageal varices without gastric varices (Li, Cw, F_1, RC_0: according to the General Rules for Recording Endoscopic Findings of Esophagogastric Varices[10]). An HCC in the left paramedian sector was diagnosed.

Laparotomy was performed 40 days after the HCC had been demonstrated with CT. Intraoperative ultrasonography showed that the HCC had shrunk to 30 mm in diameter. Left paramedian sectionectomy was performed with intermittent clamping (Pringle maneuver)[11]. After resection, biliary leakage tests with the injection of saline and air were performed, and several leakage points were repaired with fine sutures. Hemostasis of the cut surface of the liver was achieved with

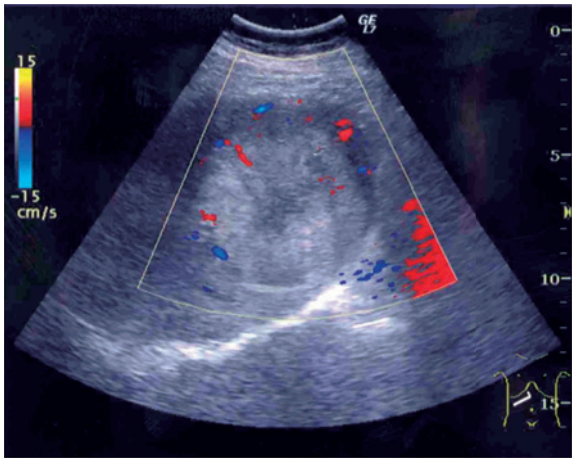

Fig. 2 Color Doppler ultrasonography revealed a hyperechoic tumor with vascular flow.

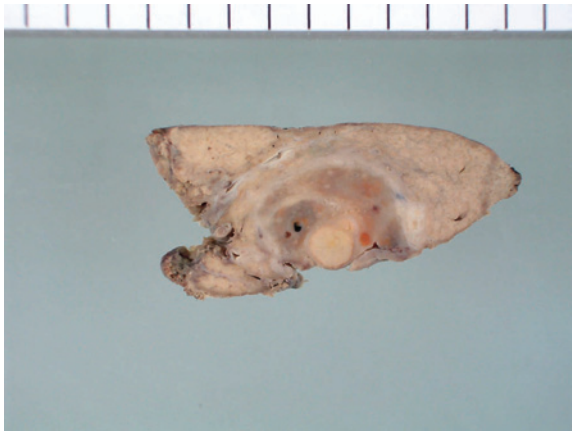

Fig. 3 On macroscopic examination the surgical specimen was a firm mass, 30 mm in diameter, with a fibrous capsule.

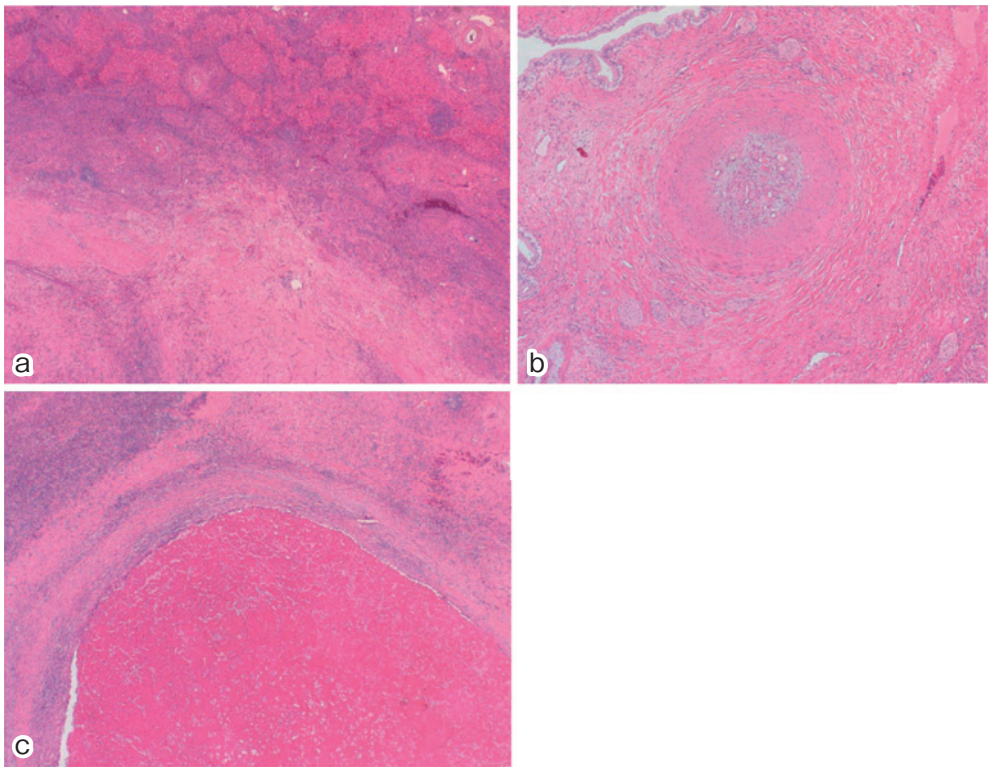

Fig. 4 Histologic examination showed that the tumor in the cirrhotic liver had been completely replaced by central coagulative necrosis, circumferential fibrosis, and dense infiltrates of inflammatory cells. No viable HCC cells were found in the coagulative necrosis. Organized thrombi in the hepatic artery were detected in the tumor. The tumor also contained multiple foci of old hemorrhage, ductular proliferation, and granulation tissue.

ligation and application of a fibrin glue spray (Bolheal; Chemo-Sero Therapeutic Research Institute, Kumamoto, Japan). The greater omentum was fixed to the peritoneum to prevent delayed gastric emptying[12,13]. An external drainage catheter (19-Fr. Blake Silicon Drain; Ethicon, Somerville, NJ, USA) was positioned in the space created by surgery.

On macroscopic examination the surgical specimen was a firm mass, 30 mm in diameter, with

a fibrous capsule (**Fig. 3**). Histologic examination showed that the tumor in the cirrhotic liver had been completely replaced by central coagulative necrosis, circumferential fibrosis, and dense infiltrates of inflammatory cells. No viable HCC cells were found in the areas of coagulative necrosis. Organized thrombi in the hepatic artery were detected in the tumor. The tumor also contained multiple foci of old hemorrhage, ductular proliferation, and granulation tissue (**Fig. 4**).

The patient was discharged 10 days after the operation. After 1 month, the serum concentrations of PIVKA-2 (25 mAU/mL) and alpha-fetoprotein (5.9 ng/mL) had decreased to their normal ranges. No recurrence has been detected 1 year after the operation.

Discussion

Spontaneous regression has been described for many types of tumors, especially renal cell carcinoma, melanoma, and neuroblastoma, which constitute nearly half of all reported cases. Spontaneous regression of HCC is a rare event, with a rate of 1 in 140,000 cases of HCC[14]. A review of cases of spontaneous regression of HCC has found that 65% of tumors show complete regression on either radiological or histological examination. On long-term follow-up, 77% of the patients were alive 1 to 20 years after diagnosis. However, because 12% of cases recurred after spontaneous regression[15], we performed hepatectomy in the present case.

Possible causes of spontaneous regression include thrombosis of feeding vessels[16], oxygen deprivation due to gastrointestinal[17,18] or intraperitoneal[19] bleeding, and cessation of exposure to noxious agents, such as androgens[20,21], alcohol, and tobacco smoke, that had sustained tumor growth[22,23]. The most likely mechanism for complete regression of a primary tumor and distant metastasis is a spontaneous immune response against tumor epitopes[24]. In our patient we confirmed the rapid regression of a fully developed HCC. The most common mechanism for spontaneous necrosis of HCC is ischemic damage, which has been described in several case reports[2,3]. It should be noted that ischemic damage has induced complete necrosis of even large tumors. Spontaneous ischemic damage of HCC can be compared to the response to therapeutic transarterial chemoembolization. Because our patient had hypertension and an aortic aneurysm, ischemic damage due to arteriosclerosis might have occurred.

References

1. Cole WH: Efforts to explain spontaneous regression of cancer. J Surg Oncol 1981; 17: 201–209.
2. Kato H, Nakamura M, Muramatsu M, Orito E, Ueda R, Mizokami M: Spontaneous regression of hepatocellular carcinoma: two case reports and a literature review. Hepatol Res 2004; 29: 180–190.
3. Lin TJ, Liao LY, Lin CL, et al.: Spontaneous regression of hepatocellular carcinoma: a case report and literature review. Hepatogastroenterology 2004; 51: 579–582.
4. Meza-Junco J, Montano-Loza AJ, Martinez-Benitez B, Cabrera-Aleksandrova T: Spontaneous partial regression of hepatocellular carcinoma in a cirrhotic patient. Ann Hepatol 2007; 6: 66–69.
5. Del Poggio P, Mattiello M, Gilardoni L, Jamoletti C, Colombo S, Zabbialini G: The mysterious case of spontaneous disappearance of hepatocellular carcinoma. Dig Liver Dis 2009; 41: e21–25.
6. Park HS, Jang KY, Kim YK, Cho BH, Moon WS: Hepatocellular carcinoma with massive lymphoid infiltration: a regressing phenomenon? Pathol Res Pract 2009; 205: 648–652.
7. Arakawa Y, Mori H, Ikegami T, et al.: Hepatocellular carcinoma with spontaneous regression: report of the rare case. Hepatogastroenterology 2008; 55: 1770–1772.
8. Heianna J, Miyauchi T, Suzuki T, Ishida H, Hashimoto M, Watarai J: Spontaneous regression of multiple lung metastases following regression of hepatocellular carcinoma after transcatheter arterial embolization. A case report. Hepatogastroenterology 2007; 54: 1560–1562.
9. Oquinena S, Inarrairaegui M, Vila JJ, Alegre F, Zozaya JM, Sangro B: Spontaneous regression of hepatocellular carcinoma: three case reports and a categorized review of the literature. Dig Dis Sci 2009; 54: 1147–1153.
10. Tajiri T, Yoshida H, Obara K, et al.: General rules for recording endoscopic findings of esophagogastric varices (2nd edition). Dig Endosc 2010; 22: 1–9.
11. Pringle JH: V. Notes on the Arrest of Hepatic Hemorrhage Due to Trauma. Ann Surg 1908; 48: 541–549.
12. Yoshida H, Mamada Y, Taniai N, et al.: Fixation of the greater omentum for prevention of delayed gastric emptying after left hepatectomy with lymphadenectomy for cholangiocarcinoma. J Hepatobiliary Pancreat Surg 2007; 14: 392–396.
13. Yoshida H, Mamada Y, Taniai N, et al.: Fixation of the greater omentum for prevention of delayed gastric emptying after left-sided hepatectomy: a

randomized controlled trial. Hepatogastroenterology 2005; 52: 1334–1337.
14. Chang WY: Complete spontaneous regression of cancer: four case reports, review of literature, and discussion of possible mechanisms involved. Hawaii Med J 2000; 59: 379–387.
15. Ohtani H, Yamazaki O, Matsuyama M, et al.: Spontaneous regression of hepatocellular carcinoma: report of a case. Surg Today 2005; 35: 1081–1086.
16. Imaoka S, Sasaki Y, Masutani S, et al.: Necrosis of hepatocellular carcinoma caused by spontaneously arising arterial thrombus. Hepatogastroenterology 1994; 41: 359–362.
17. Sato Y, Fujiwara K, Nakagawa S, et al.: A case of spontaneous regression of hepatocellular carcinoma with bone metastasis. Cancer 1985; 56: 667–671.
18. Tocci G, Conte A, Guarascio P, Visco G: Spontaneous remission of hepatocellular carcinoma after massive gastrointestinal haemorrhage. BMJ 1990; 300: 641–642.
19. Blondon H, Fritsch L, Cherqui D: Two cases of spontaneous regression of multicentric hepatocellular carcinoma after intraperitoneal rupture: possible role of immune mechanisms. Eur J Gastroenterol Hepatol 2004; 16: 1355–1359.
20. Johnson FL, Lerner KG, Siegel M, et al.: Association of androgenic-anabolic steroid therapy with development of hepatocellular carcinoma. Lancet 1972; 2: 1273–1276.
21. McCaughan GW, Bilous MJ, Gallagher ND: Long-term survival with tumor regression in androgen-induced liver tumors. Cancer 1985; 56: 2622–2626.
22. Gottfried EB, Steller R, Paronetto F, Lieber CS: Spontaneous regression of hepatocellular carcinoma. Gastroenterology 1982; 82: 770–774.
23. Grossmann M, Hoermann R, Weiss M, et al.: Spontaneous regression of hepatocellular carcinoma. Am J Gastroenterol 1995; 90: 1500–1503.
24. Jeon SW, Lee MK, Lee YD, et al.: Clear cell hepatocellular carcinoma with spontaneous regression of primary and metastatic lesions. Korean J Intern Med 2005; 20: 268–273.

(Received, September 24, 2011)
(Accepted, October 21, 2011)