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Complete spontaneous necrosis of hepatocellular carcinoma accompanied by portal vein tumor thrombosis: A case report

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ABSTRACT

INTRODUCTION: We report a rare case of complete spontaneous necrosis of a hepatocellular carcinoma (HCC) accompanied by portal vein tumor thrombosis (PVTT), as confirmed by resection.
CASE PRESENTATION: A 64-year-old man was referred to our hospital for suspected HCC. Contrast-enhanced computed tomography (CECT) findings before admission revealed a 53-mm tumor in the posterior segment of the liver and were suspicious for PVTT in the right posterior PV. Both alpha-fetoprotein (AFP) and proteins induced by vitamin K absence or antagonist-II (PIVKA-II) were elevated at 17,562 ng/mL and 153 mAU/mL, respectively. We diagnosed the findings as HCC with PVTT. Seven days after the first CECT scan, we performed CECT volumetry, which revealed that the tumor had regressed to 30 mm, along with regression of the PVTT. We performed portal vein ligation (PVL), and 10 days later, CECT revealed that the tumor had shrunk to 20 mm. AFP and PIVKA-II levels were 643 ng/mL and 14 mAU/mL, respectively. We suspected spontaneous regression of the patient's HCC, but performed a hepatectomy. Histopathology revealed a 22-mm tumor with a thin fibrous capsule and a tumor thrombus in the PV. Trabecular and pseudoglandular structures consisting of denucleated HCC epithelial cells made up both the tumor and thrombus, and the finding confirmed the spontaneous necrosis of HCC.
CONCLUSIONS: We present an extremely rare case of complete spontaneous necrosis of HCC with PVTT. When spontaneous necrosis is suspected, surgery should be considered because of the potential risk of residual viable cancer cells.

1. Introduction

Spontaneous massive necrosis of hepatocellular carcinoma (HCC) is observed about 2% of patients, especially those with large tumors; whereas spontaneous complete necrosis is extremely rare, with 1 case occurring per 6000–10,000 cases [1]. Only 17 English-language reports of spontaneous complete necrosis of HCC as confirmed by resected specimens were published between 1987 and 2017 [1–17]. Of these reports, only 1 described complete spontaneous necrosis of HCC with gross portal vein tumor thrombosis (PVTT) [10]. Herein, we present an extremely rare case of complete spontaneous necrosis of HCC with PVTT. This paper has been reported in line with the SCARE criteria [18].

2. Case presentation

A 64-year-old man with a liver tumor detected by abdominal ultrasonography (US) was referred to our hospital. The patient's past history included hepatitis C virus infection treated by interferon therapy 9 years previously. He achieved sustained virological response. The patient was negative for a history of alcohol consumption; smoking; excessive weight loss; and medications, including herbs. The patient's height and weight were 1.68 m and 52.6 kg, respectively with no specific physical abnormalities. Contrast-enhanced computed tomography (CECT) before admission revealed a 53-mm tumor in hepatic segments 6 and 7, and findings suggestive of PVTT in the right posterior portal vein (PV) (Fig. 1). The tumor and suspected PVTT were slightly enhanced during the early-phase CECT (Fig. 1A) and were washed out dur-

Abbreviations: AFP, alpha-fetoprotein; AFP-L3, *Lens culinaris* agglutinin-reactive AFP isoform 3; CECT, contrast-enhanced computed tomography; HCC, hepatocellular carcinomaPIVKA-II – proteins induced by vitamin K absence or antagonist-II; PV, portal vein; PVL, portal vein ligation; PVTT, portal vein tumor thrombosis; US, ultrasonography.

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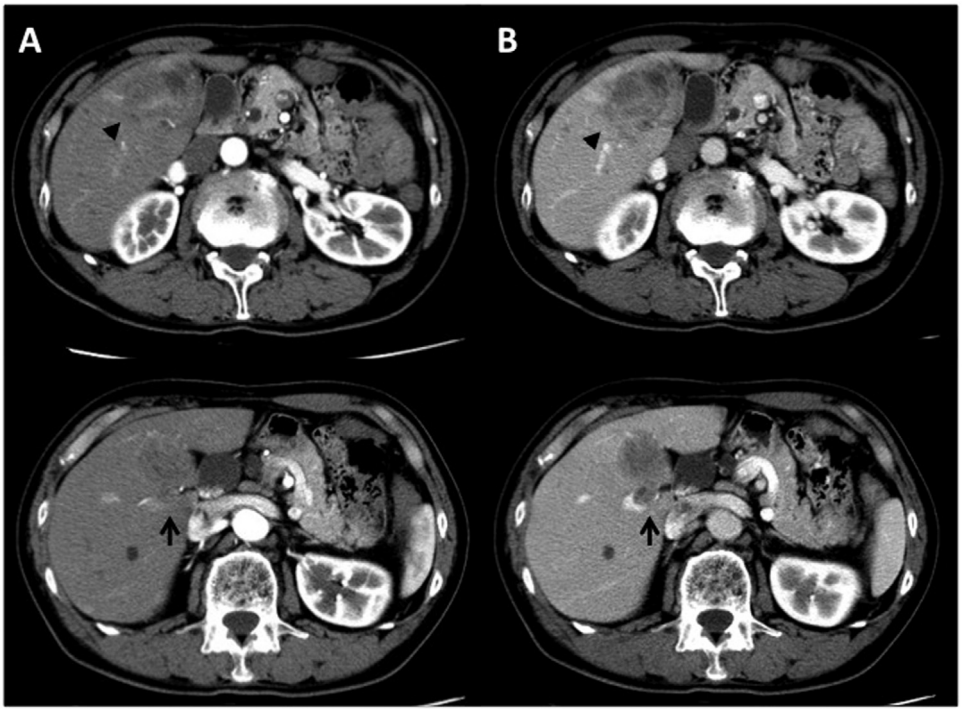

Fig. 1. Contrast-enhanced computed tomography (CECT) scan for initial diagnosis. The image shows a tumor 53 mm in size (arrowhead) and portal vein tumor thrombosis (PVTT) in the posterior branch of the portal vein (arrow). The tumor and suspected PVTT are slightly enhanced during the early-phase CECT (A) and are washed out during the equilibrium phase (B).

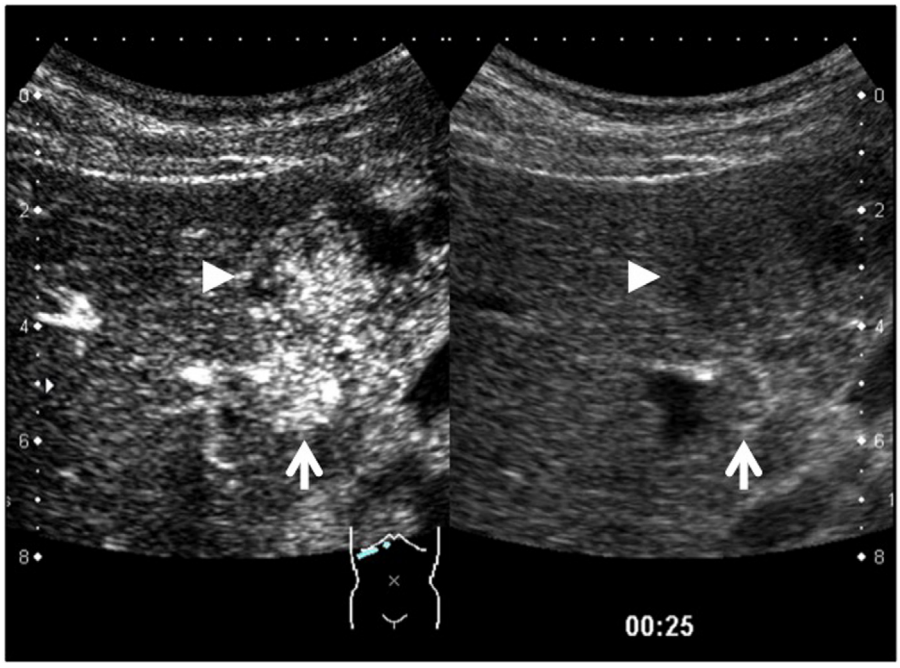

Fig. 2. Arterial phase of contrast-enhanced ultrasonography at diagnosis. Main tumor (arrowhead) and suspected portal vein tumor thrombosis (arrow) are well enhanced.

ing the equilibrium phase (Fig. 1B). However, both the tumor and suspected PVTT were well enhanced during the arterial phase and washed out in the postvascular phase on contrast-enhanced US (Fig. 2). Upper gastrointestinal endoscopy and colonoscopy revealed nonspecific findings. The results of preoperative laboratory testing were as follows: white blood cell count, 5300 cells/μL; red blood cell count, 463×10^4 cells/μL; serum hemoglobin concentration, 14.6 g/dL; serum platelet count, 19.5×10^4 platelets/μL; serum aspartate aminotransferase, 12 IU/L; serum alanine aminotransferase, 16 IU/L; serum alkaline phosphatase, 229 IU/L; serum gamma glutamic transpeptidase, 29 IU/L; total serum bilirubin, 1.2 mg/dL; serum albumin, 4.58 g/dL; serum C-reactive protein, <0.04 mg/dL; prothrombin time (%), 88%; hemoglobin A1c, 5.7%; indocyanin green retention rate after 15 min, 26.0%. The levels of serum alpha-fetoprotein (AFP) and proteins induced by vitamin K absence or antagonist-II (PIVKA-II) were elevated at 17,562 ng/mL and 153 mAU/mL, respectively, with a percentage of the *Lens culinaris* agglutinin-reactive AFP isoform 3 (AFP-L3) of

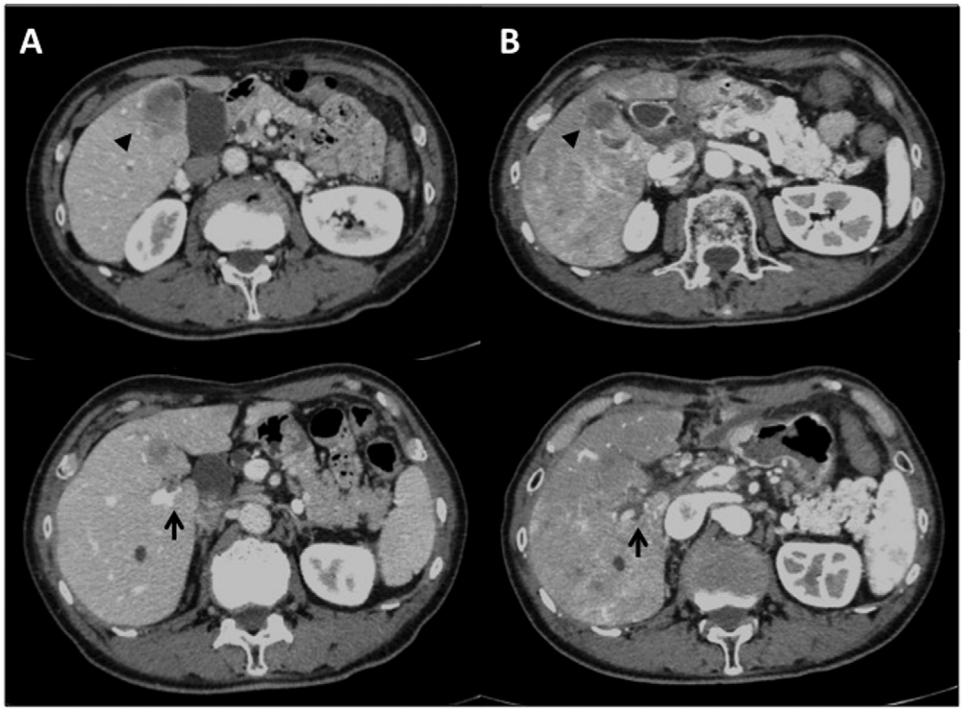

Fig. 3. A) Contrast-enhanced computed tomography (CECT) scan 7 days after the initial CECT reveals tumor regression to 30 mm (arrowhead) in diameter and regression of portal vein tumor thrombosis (arrow). B) CECT findings 10 days after ligation of portal vein (PV). Tumor regression to 20 mm (arrowhead). Tumor thrombosis is no longer evaluable as a result of ligation of PV (arrow).

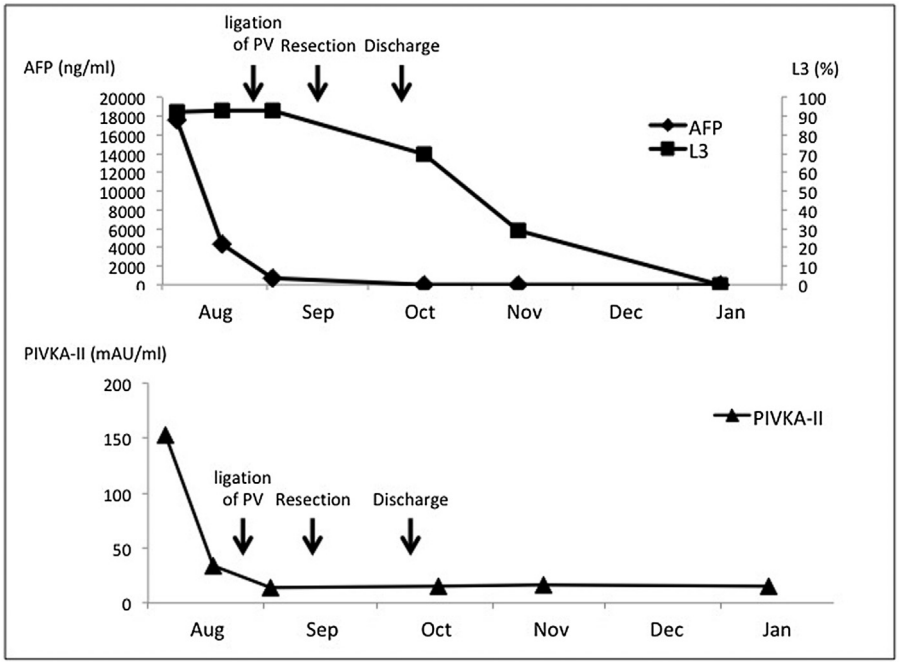

Fig. 4. The graph illustrates changes in alpha-fetoprotein (AFP), percentage of the *Lens culinaris* agglutinin-reactive AFP isoform 3 (AFP-L3) and proteins induced by vitamin K absence or antagonist-II (PIVKA-II) levels from initial diagnosis to post resection. Serum AFP and PIVKA-II levels at initial diagnosis were 17,562 ng/mL and 153 mAU/mL, respectively, and decreased to 643 ng/mL and 14 mAU/mL prior to hepatectomy. AFP-L3 levels were normalized 4 months after surgery. Tumor marker levels remained within normal range after surgery.

92.6%. We diagnosed the findings as HCC with PVTT in the right posterior PV. Because the right posterior PV was the first branch of the main PV, we classified the tumor thrombosis as Vp3. We planned to perform a posterior sectionectomy. We also performed preoperative multidetector thin-slice CT for liver volumetry 7 days after the first CT scan. Preoperative CT volumetry revealed that the tumor had shrunk to 30 mm and that the PVTT had regressed (Fig. 3A). The patient's serum AFP and PIVKA-II levels also decreased to 4329 ng/mL, 34 mAU/mL, respectively. The preoperative CT for liver volumetry also showed that the proportion of liver to be resected by a posterior sectionectomy would be 56.5% of the entire liver. We performed ligation of the right posterior PV before hepatectomy.

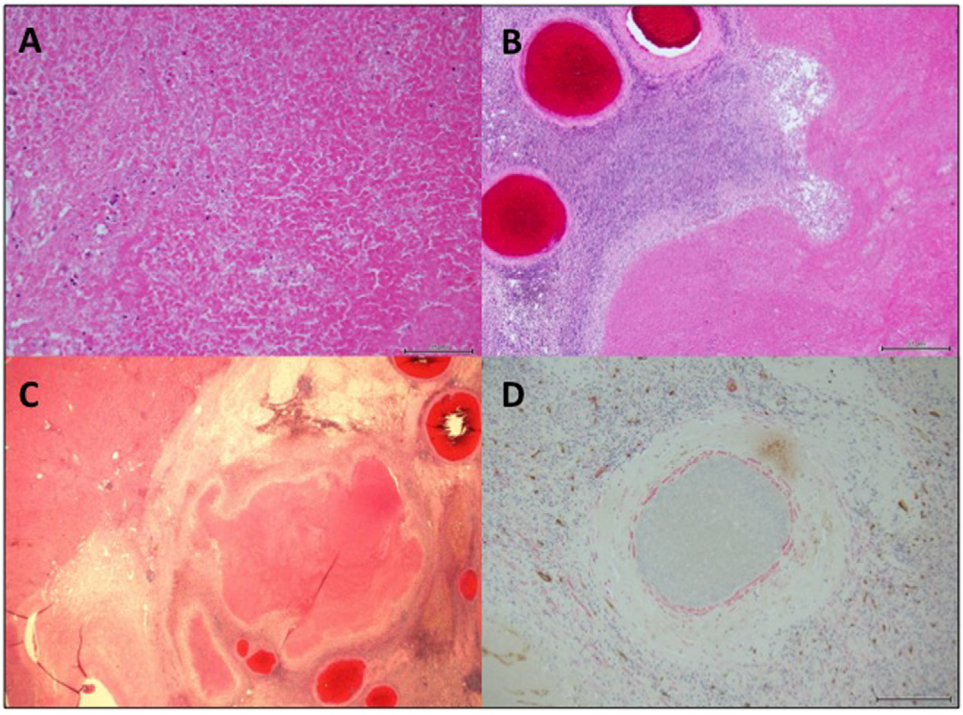

Fig. 5. Among the histopathological findings: grossly, the nodule was 22 × 20 mm with a thin fibrous capsule, and a thrombus was seen the right posterior portal vein (PV). The histological examination revealed that the nodule was mainly composed of granulation and necrotic tissue. A trabecular pattern and pseudoglandular structures of denucleated cells were reminiscent of moderately differentiated hepatocellular carcinoma. Viable tumor cells were not observed in either the nodule or tumor thrombus (A). Infiltrating inflammatory cells such as lymphocytes were observed both in the nodule and portal vein tumor thrombus (B). The PV around the nodule was filled with blood clot as a result of ligation of the PV (C). Immunohistochemical staining for alpha-smooth muscle actin revealed patency of the hepatic arteries and no arterial thrombosis (D).

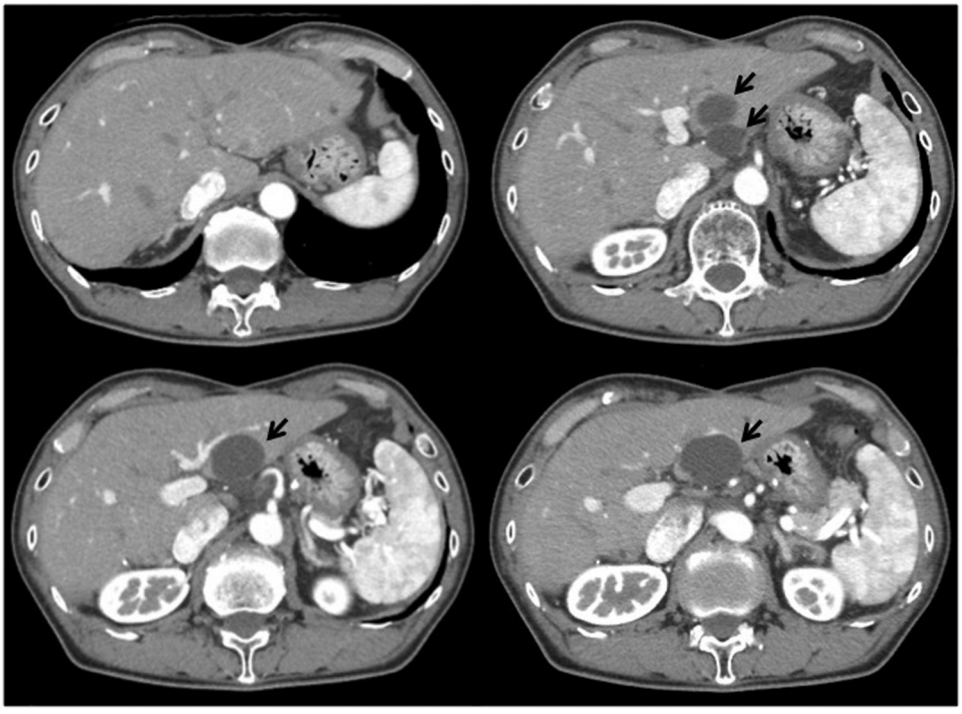

Fig. 6. Contrast-enhanced computed tomography scan at 24 months after surgery. The patient is alive without recurrence. The arrows indicate liver cysts.

The postoperative course of PVL was uneventful. CT volumetry performed 10 postoperative days after PVL revealed that the resection rate reduced to 29.7%. Additionally, the tumor shrank to 20 mm (Fig. 3B), along with the levels of tumor markers (AFP, PIVKA-II: 643 ng/mL, 14 mAU/mL, respectively). The findings were suggestive of spontaneous regression of the HCC, but we performed a posterior sectionectomy 1 month after the initial diagnosis. Intraoperative US showed the tumor as a hypoechogenic nodule with clear borders. Tumor thrombosis was not clearly demonstrated because of ligation of the PV. The procedure and patient's postoperative course

were uneventful. He was discharged on postoperative day 14. Both the AFP and PIVKA-II levels decreased to almost normal within 4 weeks after surgery (10 ng/mL and 15 mAU/mL, respectively). The AFP-L3 decreased to normal gradually, within 4 months after hepatectomy (Fig. 4). Grossly, the cut surface of the resected specimen revealed a 22 × 20 mm tumor with a thin fibrous capsule and a tumor thrombus in the right posterior PV. Histopathology revealed that the tumor mainly consisted of granulation and necrotic tissue, which appeared to resemble a trabecular pattern; and pseudoglandular structures that consisted of denucleated HCC epithelial cells, but no viable cancer cells in either the tumor or thrombus in the PV. Lymphocytic infiltration was seen in both the tumor and tumor thrombus in the PV. The final pathological diagnosis was total necrosis of an HCC. Immunohistochemical staining for alpha-smooth muscle actin revealed patency of the hepatic arteries without thrombosis (Fig. 5). The patient is alive without recurrence 24 months after surgery (Fig. 6).

3. Discussion

Spontaneous necrosis of malignant tumor without any treatment or with intervention ineffective at preventing tumor progression is further defined as partial or complete necrosis [17]. To the best of our knowledge, only 17 English-language reports of spontaneous complete necrosis of HCC as confirmed by resected specimens were published between 1987 and 2017 [1–17]. Of these reports, only 1 described complete spontaneous necrosis of HCC with gross portal vein tumor thrombosis (PVTT) [10]. Among these 17 cases, only 2 had PVTT, and regression of PVTT before hepatectomy was confirmed only in our case. PVTT is present in 10%–40% of patients with HCC at the time of diagnosis, and is strongly associated with poor outcome [19]. PVTT with HCC has sometimes been considered to be a contraindication for surgery, but our case along with the other cases had excellent outcomes; and surgery could be justified for patients with spontaneous tumor regression to confirm viability of residual tumor, even in the presence of gross tumor thrombosis.

The mechanism of spontaneous regression of HCC is poorly understood. Possible causes of spontaneous complete necrosis of HCC are as follows: 1) impairment of the hepatic circulation as a result of gastrointestinal bleeding [20], 2) PVTT [10], 3) blockage or reduced blood flow through arteries to the tumor as a result of a thick fibrous tumor capsule [1,17], 4) ischemia caused by abrupt enlargement of the tumor [1], 5) immune response [6,11,13,16], 6) cessation of heavy drinking or use of herbal medicine [21]. We believe that the immune response of our patient, as manifested by lymphocytic infiltration around the nodule observed on histopathology, was thought to be the main cause of total necrosis. The ligation of the PV may also have played a role in necrosis of the tumor, because tumor vascularization on CECT could not be observed after the ligation procedure, and had been present on images of the second CECT that had been performed before the ligation procedure. Ligation of the PV is probably not the main reason for regression, since the tumor had already shown regression before the procedure. In addition, the PVTT and ligation of the PV might not account for spontaneous necrosis of HCC, because HCC has been reported to be predominantly vascularized by arterial circulation [10]. Arterial injury possibly occurring during PVL might be a cause of tumor necrosis, but in our case, there was no evidence of arterial injury on the CECT performed after the ligation procedure and on histopathology of the resected specimen.

Despite advances in imaging modalities, the confirmation of complete necrosis of HCC on imaging remains impossible, and the potential for residual cancer cells must be taken into account. Ohtani et al. reported that 5 out of 40 patients with spontaneous regression of HCC later recurred [12]. To prevent tumor relapse, surgical intervention, as generally provided for patients with HCC, should also be considered for patients with suspected tumor necrosis.

4. Conclusions

In this case report, we described a patient with spontaneously regressed HCC that was confirmed to be complete necrosis by histopathological findings on the resected specimens. Although a definitive underlying mechanism for the complete necrosis was not determined for our patient, his immune response was thought to be a major reason for necrosis of the HCC with PVTT. Further understanding of mechanisms involved in cases of necrosis of HCC with PVTT, along with additional accrual of similar cases, might lead to new approaches to the treatment of HCC.

Conflicts of interest

All authors have no conflict of interest to disclose.

Funding

All authors have no funding to disclose.

Ethical approval

The ethics committee of Kurume University approved this case report (No. 2017-019).

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Yuichi Goto, Yoshihiro Uchino, and Nobuhisa Shirahama collected the data and wrote this paper.

Shin Sasaki and Yoriko Nomura reviewed the final manuscript.

Hiroto Ishikawa contributed to the study concept and review of the final manuscript.

Jun Akiba diagnosed HCC and reviewed the histopathological findings in this manuscript.

Yoshito Akagi, Hiroyuki Tanaka, and Koji Okuda reviewed the manuscript and provided the final approval of this article.

Registration of research studies

Not applicable.

Guarantor

Yuichi Goto is the guarantor of this study.

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