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Single Case

Spontaneous Pathological Complete Regression of Hepatocellular Carcinoma

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Keywords
Hepatocellular carcinoma · Spontaneous regression

Abstract
Several possible mechanisms for spontaneous regression of hepatocellular carcinoma (HCC) have been reported. Spontaneous complete regression of HCC is extremely rare. We herein report a case of spontaneous pathological complete regression of HCC following decrement of elevated serum alpha-fetoprotein (AFP). The serum AFP of a 74-year-old man who underwent hepatic resection for HCC twice increased up to 7,529 ng/mL and then spontaneously decreased to 404 ng/mL in 2 months. Computed tomography, magnetic resonance imaging, and angiography revealed a liver tumor in segment 7 without early enhancement. With a diagnosis of recurrent HCC, partial hepatic resection was performed. The resected specimens revealed no HCC macroscopically, and pathological examination revealed only a small area with cell dysplasia. The patient remains well with normal serum AFP and protein induced by vitamin K absence or antagonist-II (PIVKA-II) levels for 29 months after the third hepatic resection without recurrence of HCC. We describe a case of spontaneous pathological complete regression of HCC following decrement of elevated serum AFP. Further studies are needed to identify the mechanism(s) of spontaneous regression of HCC.

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Introduction

Spontaneous regression of neoplasm is a rare event, which has been reported especially in renal cell carcinoma, neuroblastoma, malignant melanoma, and choriocarcinoma [1]. The incidence of regression of hepatocellular carcinoma (HCC) is calculated to be 0.4% [2], and spontaneous complete regression of HCC is extremely rare. Several possible mechanisms for spontaneous regression of HCC have been reported. However, the definitive mechanism of this phenomenon is unknown. We herein report a case of spontaneous pathological complete regression of HCC following decrement of elevated serum alpha-fetoprotein (AFP).

Case Report

A 74-year-old man had been followed up for elevated serum liver enzymes without medication since the age of 44 years. At the age of 65, the patient underwent anterior segmentectomy of the liver for HCC in segment 8. At the age of 69, the patient underwent medial segmentectomy for recurrent HCC in segment 4. At 44 months after the second hepatic resection, the serum AFP increased up to 7,529 ng/mL, and ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) and gadoxetic acid-enhanced magnetic resonance imaging (MRI) revealed a liver tumor compatible with HCC in segment 7. Laboratory data were as follows; AFP 7,529 ng/mL, AFP-lectin 3 (AFP-L3) fraction 26.4%, and protein induced by vitamin K absence or antagonist-II (PIVKA-II) 20 mAU/mL. Liver enzymes were slightly elevated. Hepatitis virus markers were negative except for positive anti-hepatitis B core antibody. However, serum AFP level spontaneously decreased to 404 ng/mL 2 months later. FDG-PET revealed a tumor with accumulation of FDG in segment 7 of the liver (Fig. 1a). Abdominal enhanced computed tomography (CT) revealed a low-density tumor in segment 7 in the delayed phase without early enhancement (Fig. 1b). Also, MRI with contrast enhancement showed a low-intensity tumor in segment 7 in the delayed phase without early enhancement (Fig. 1c). The CT during hepatic arteriography (CTAP) revealed a low-density tumor in segment 7 (Fig. 1d) without enhancement by CT during hepatic arteriography (CTHA) (Fig. 1e). With a diagnosis of recurrent HCC, the patient underwent partial hepatic resection of segment 7. At first, we detected the tumor near the right hepatic vein by intraoperative ultrasonography and performed partial resection of the liver including the tumor. However, no tumor was identified in the resected specimen by intraoperative pathological examination using frozen section. Therefore, we performed additional hepatic resection of the right hepatic vein reflux area, because the patient had an inferior right hepatic vein. In macroscopic findings, both the first and additional resected specimens revealed no HCC, and showed only regenerative nodules (Fig. 2). Pathological examination revealed normal hepatocytes in most of the specimen (Fig. 3a, b), but part of the specimen revealed high cell density and slight nuclear atypia, described as small cell dysplasia (Fig. 3c, d). There was no sign of necrosis and vascular embolism. The patient made a satisfactory recovery without postoperative complication and was discharged on postoperative day 14. He remains well with normal serum AFP and PIVKA-II levels 29 months after the third hepatic resection.

Discussion

Spontaneous regression of HCC was first reported by Johnson FL et al. [3] in 1972. This report suggested that the cessation of steroid treatment was one of the possible mechanisms for spontaneous regression of HCC. Since this report, several reports on spontaneous regression of HCC have been published, and several mechanisms of this phenomenon have been suggested. Possible mechanisms of tumor regression are divided into three categories: impairment of blood supply, immune reaction, and others such as the administration of herbal remedies, or the withdrawal of alcohol, tobacco, or exogenous androgens [4].

The reasons for the impairment of blood supply were as follows: occlusion of the portal vein, hepatic artery thrombosis, large arterioportal shunt, and chronic hypotension [4]. This mechanism is used for HCC treatment such as transcatheter arterial chemoembolization (TACE) [5] and sorafenib [6]. In the current case, pathological findings revealed no necrotic tissue nor vascular thrombosis.

In several reports of spontaneous regression of HCC, the elevated levels of cytokines such as IL-18 [7], IL-2, IL-6, IL-12, and interferon (IFN)-gamma [8] have been documented. Measurement of inflammatory cytokines may help to elucidate the mechanism(s) of this phenomenon. In the present case, pathological findings revealed no evidence of immune response activation such as the proliferation of macrophages or lymphocytes.

AFP and AFP-L3 are useful tumor markers for the early detection of HCC. Serum AFP has a sensitivity of 41–65% and specificity of 80–94% when the cut-off value is 20 ng/mL [9]. Moreover, serum AFP-L3 fraction has a sensitivity of 96.9% and specificity of 92% when the cut-off value is 15% [10]. In the present case, tests of tumor markers revealed serum AFP level of 7,529 ng/mL and AFP-L3 fraction of 26.4% at 2 months before his admission, and serum AFP level 2 months later decreased to 404 ng/mL on admission. Close follow-up of these tumor markers may be important for selecting appropriate treatment for HCC in such cases. We described a case of spontaneous pathological complete regression of HCC following decrement of elevated serum AFP. Further studies are needed to identify the mechanism(s) of spontaneous regression of HCC.

Statement of Ethics

Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

Disclosure Statement

The authors declare that they have no competing interest. No funding was received for this study.

Author Contributions

T.T., Y.S., H.S., T.S., and K.F. drafted the manuscript. K.Y. gave the final approval of the version to be published. All authors read and approved the final manuscript.

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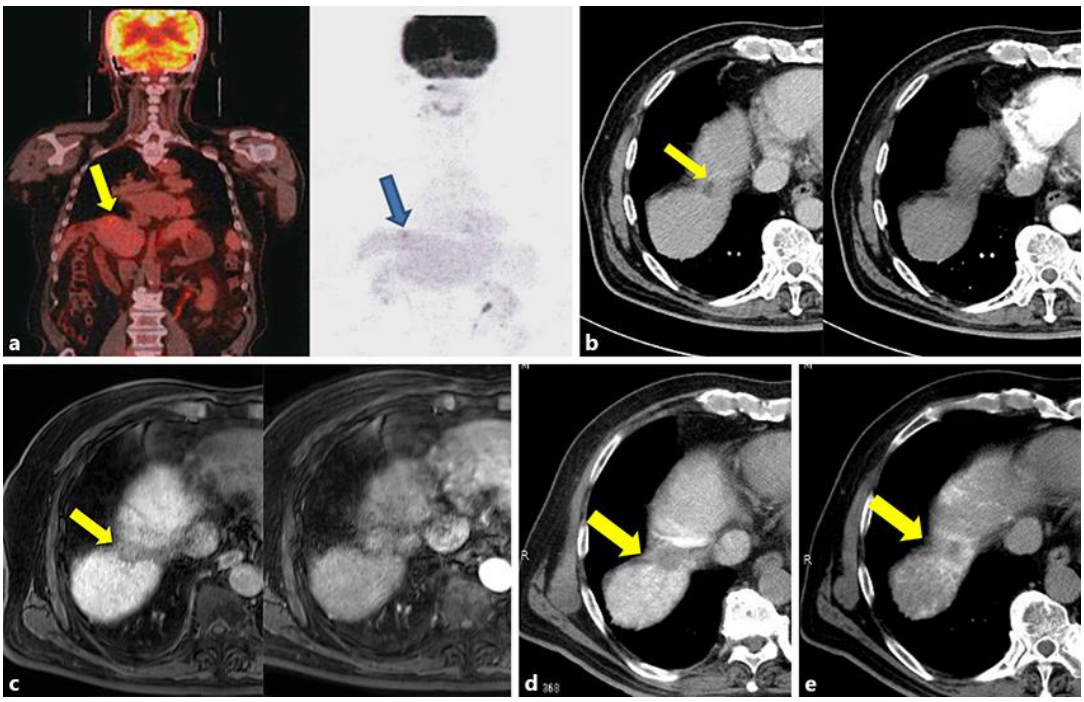

Fig. 1. **a** FDG-PET revealed a tumor with accumulation of FDG in segment 7 of the liver. **b** Enhanced CT demonstrated a low-density tumor in segment 7 in the delayed phase without early enhancement. **c** Enhanced MRI showed a low-intensity tumor in segment 7 in the delayed phase without early enhancement. The CT during CTAP (**d**) revealed a low-density tumor in segment 7 without enhancement in the CT during CTHA (**e**).

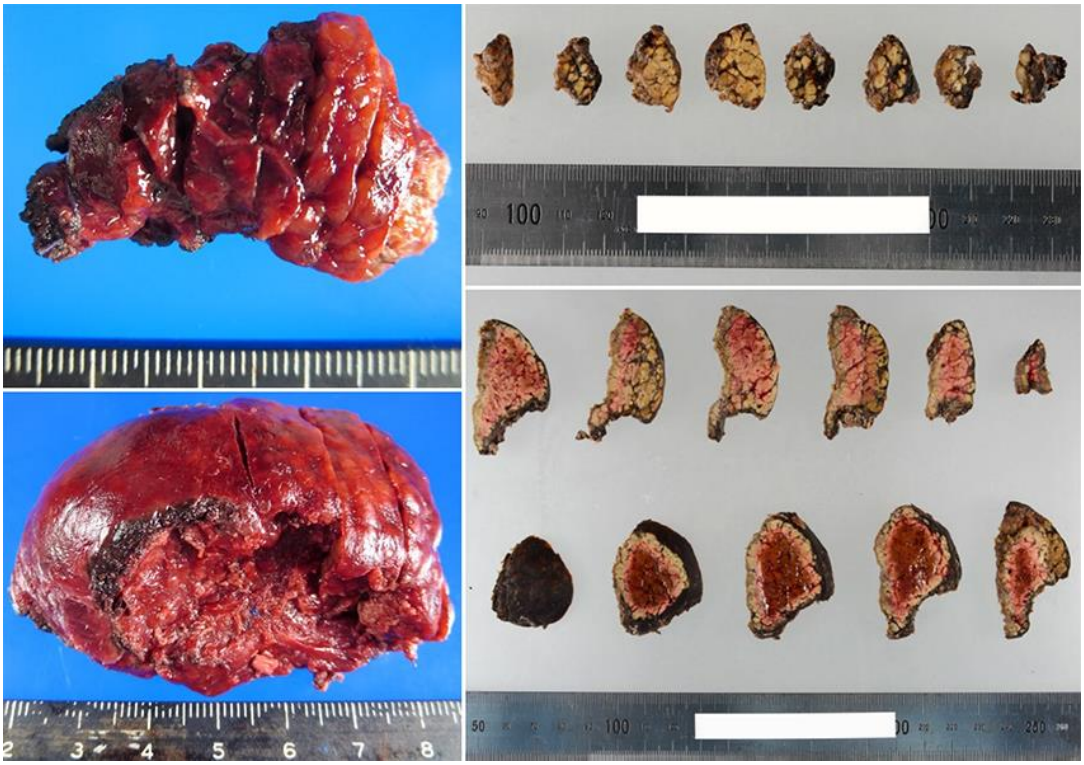

Fig. 2. In macroscopic findings, both the first and additionally resected specimens revealed no HCC, and only regenerative nodules could be seen.

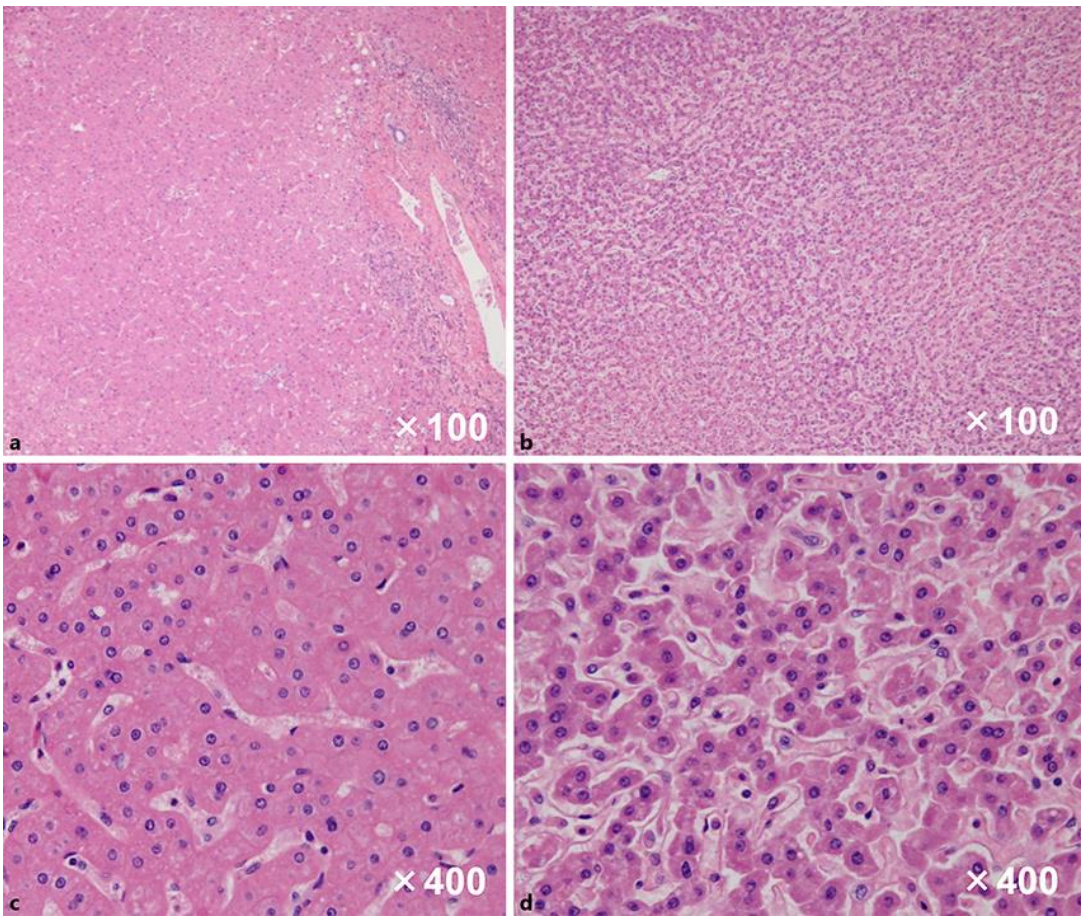

Fig. 3. Pathological examination revealed normal hepatocytes in most of the specimens (**a**, **b**), but a part of the specimens revealed high cell density and slight nuclear atypia, described as small cell dysplasia (**c**, **d**).