

CASE REPORT

## 간세포암종의 자연퇴행

김성배<sup>1</sup>, 강원석<sup>1,3</sup>, 신승환<sup>1</sup>, 이희승<sup>1</sup>, 이상훈<sup>1</sup>, 최기홍<sup>2,3</sup>, 박준용<sup>1,3</sup>

연세대학교 의과대학 내과학교실 소화기병연구소<sup>1</sup>, 외과학교실<sup>2</sup>, 세브란스병원 연세간암전문클리닉<sup>3</sup>

### Spontaneous Neoplastic Remission of Hepatocellular Carcinoma

Sung Bae Kim<sup>1</sup>, Wonseok Kang<sup>1,3</sup>, Seung Hwan Shin<sup>1</sup>, Hee Seung Lee<sup>1</sup>, Sang Hoon Lee<sup>1</sup>, Gi Hong Choi<sup>2,3</sup>, and Jun Yong Park<sup>1,3</sup>

Department of Internal Medicine, Institute of Gastroenterology<sup>1</sup>, Department of Surgery<sup>2</sup>, Yonsei University College of Medicine, Yonsei Liver Cancer Special Clinic, Severance Hospital<sup>3</sup>, Seoul, Korea

We report on a case of a 57-year-old male who underwent a curative resection for hepatocellular carcinoma (HCC) with histological confirmation of a spontaneously necrotized tumor. Initial serum AFP level was 4,778 ng/mL. A 3.7 cm hyperechoic mass in segment 6 of the liver was observed on ultrasonography and dynamic contrast-enhanced liver MRI showed a 3.7×3.1 cm sized HCC. He was scheduled to undergo curative surgical resection under the clinical diagnosis of an early stage HCC (Barcelona Clinic Liver Cancer stage A). Without treatment, the serum AFP level declined rapidly to 50 ng/mL over five weeks. He underwent curative wedge resection of segment 6 of the liver. Histology revealed complete necrosis of the mass rimmed by inflamed fibrous capsule on a background of HBV-related cirrhosis with infiltration of lymphoplasmic cells. Exact pathophysiology underlying this event is unknown. Among the proposed mechanisms of spontaneous neoplastic remission of HCC, circulatory disturbance and activation of host immune response offer the most scientific explanation for the complete histologic necrosis of HCC in the resected mass seen in our patient. (*Korean J Gastroenterol* 2015;65:312-315)

**Key Words:** Spontaneous neoplasm regression; Liver neoplasms; Spontaneous neoplasm remission

### INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most prevalent cancer and the third most frequent cause of cancer-related death worldwide.<sup>1</sup> Approximately 80% of HCC is reported in Eastern Asia and sub-Saharan Africa, and is commonly associated with chronic hepatitis B (CHB).<sup>1</sup> Spontaneous neoplastic remission of HCC is an interesting, yet extremely rare phenomenon. The presumed overall incidence is one in every 140,000.<sup>2</sup> Approximately 86 cases of spontaneous remission of HCC have been reported.<sup>3</sup> We present a case of a Korean male who had undergone a curative re-

section for HCC, followed by histological confirmation of a spontaneously necrotized tumor.

### CASE REPORT

In January 2012, a 57-year-old male with HBV-related cirrhosis was referred for an elevated serum AFP level and a liver mass found on regular surveillance ultrasonography. Two years prior to referral, he had been diagnosed as HBeAg-positive CHB and had since been on entecavir therapy. He had no history of alcohol drinking or medical disease, but had a family history of HBV-related HCC. He had no symptoms such

Received August 3, 2014. Revised October 25, 2014. Accepted October 28, 2014.

© This is an open access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited. Copyright © 2015. Korean Society of Gastroenterology.

교신저자: 박준용, 120-752, 서울시 서대문구 연세로 50-1, 연세대학교 의과대학 내과학교실 소화기병연구소

Correspondence to: Jun Yong Park, Department of Internal Medicine, Institute of Gastroenterology, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Korea. Tel: +82-2-2228-1994, Fax: +82-2-393-6884, E-mail: drpjy@yuhs.ac

Financial support: None. Conflict of interest: None.

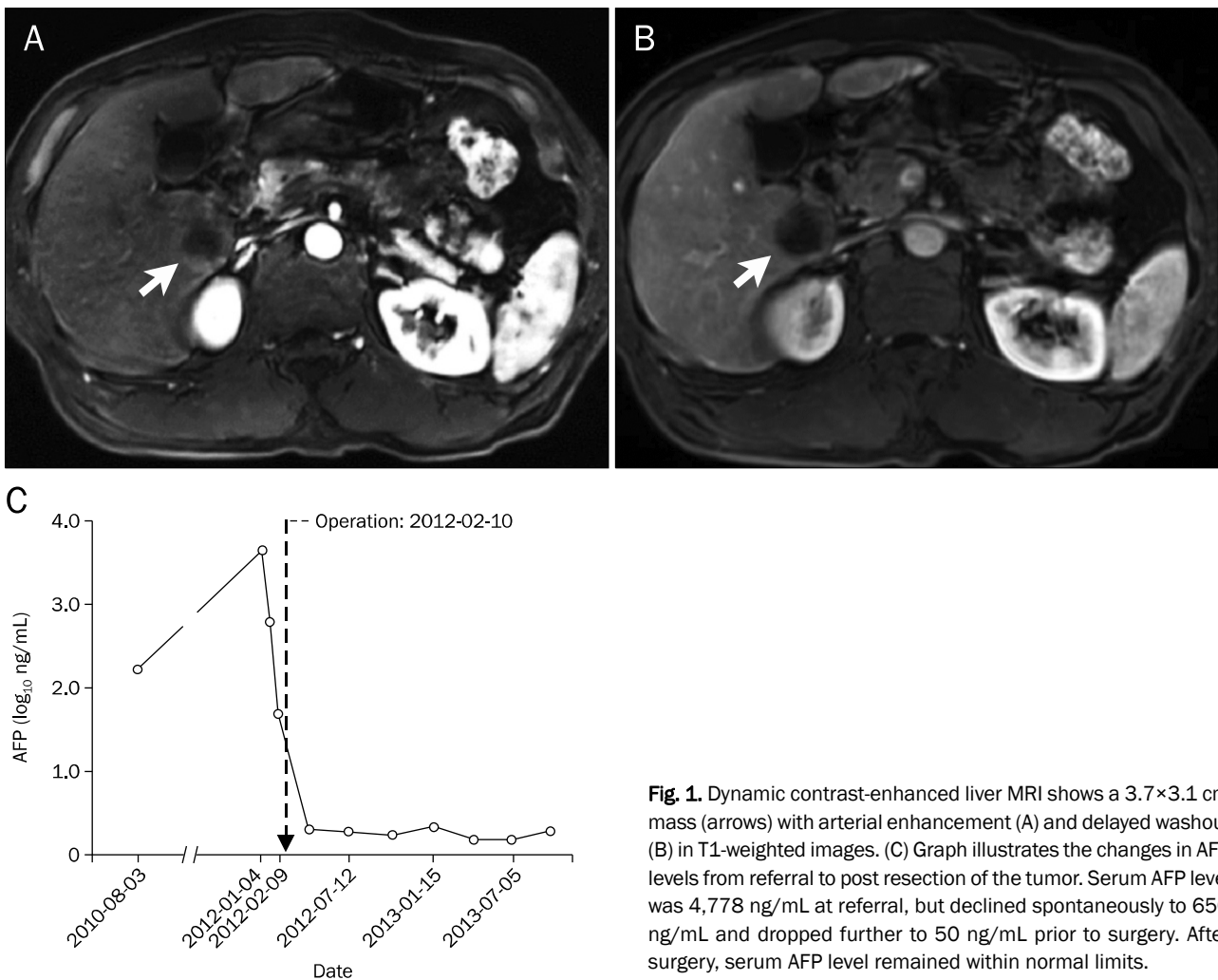
as abdominal pain, discomfort, weight loss, or fever. His mental status was alert and no icteric sclera or direct and rebound abdominal tenderness was observed during the physical examination.

Laboratory tests showed a normal complete blood count and well-preserved liver function (Child-Pugh class A) without evidence of acute flare up of underlying CHB: white blood count 7,680/ $\mu$ L, hemoglobin 15.2 g/dL, platelet 153,000/ $\mu$ L, AST 29 IU/L, ALT 41 IU/L, total bilirubin 0.9 mg/dL, total protein 7.0 g/dL, albumin 4.1 g/dL, INR 0.95, HBeAg positive, and undetectable HBV DNA (< 20 IU/mL). The serum AFP level was 4,778 ng/mL (reference range, 0-9 ng/mL) and des-gamma carboxyprothrombin level was 22 mAU/mL (reference range, 0-35 mAU/mL).

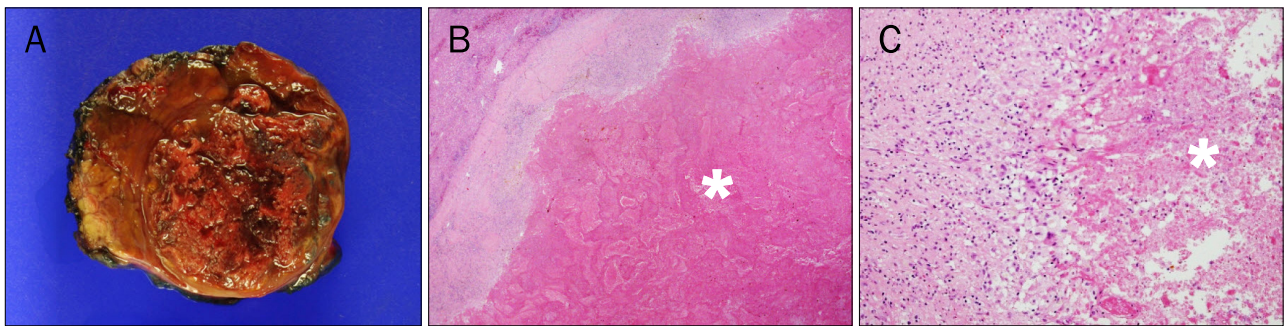
Ultrasonography performed prior to referral showed a blunted liver margin with coarse and heterogeneous echo-

texture of the parenchyma. A 3.7 cm-sized well-defined hyperechoic nodule with central hypoechogenicity was observed in segment 6 of the liver.

On dynamic contrast-enhanced liver MRI, the lesion measured 3.7 $\times$ 3.1 cm and showed arterial enhancement with delayed washout, consistent with the vascular pattern of HCC (Fig. 1A, B). No portal vein thrombosis or splenomegaly was observed on MRI. Based on radiological findings and elevated serum AFP level, an early stage HCC (Barcelona Clinic Liver Cancer stage A) was diagnosed and the patient was scheduled to undergo curative surgical resection. Without treatment, the serum AFP level declined rapidly to 650 ng/mL during the cancer stage work-up and dropped further to 50 ng/mL within five weeks, prior to the surgery (Fig. 1C). Subsequently, the patient underwent curative wedge resection of segment 6 of the liver. The surgical specimen



**Fig. 1.** Dynamic contrast-enhanced liver MRI shows a 3.7 $\times$ 3.1 cm mass (arrows) with arterial enhancement (A) and delayed washout (B) in T1-weighted images. (C) Graph illustrates the changes in AFP levels from referral to post resection of the tumor. Serum AFP level was 4,778 ng/mL at referral, but declined spontaneously to 650 ng/mL and dropped further to 50 ng/mL prior to surgery. After surgery, serum AFP level remained within normal limits.



**Fig. 2.** (A) Gross appearance of the resected tumor shows an expanding type of mass with necrotic features. (B, C) Histology reveals complete necrosis of hepatocellular carcinoma (asterisks) rimmed by inflamed fibrous capsule with lymphoplasmacytoid cell infiltration (H&E stain; B:  $\times 12.5$ , C:  $\times 100$ ).

showed an expanding type of mass with necrotic features (Fig. 2A). Histology revealed complete necrosis of the mass rimmed by inflamed fibrous capsule. Background of the mass showed HBV-related mixed micro and macronodular cirrhosis, with infiltration of lymphoplasmacytoid cells and focal granulomatous inflammation (Fig. 2B, C). Anti-hepatocyte and cyokeratin immunohistochemical stain were negative. Additional Periodic acid-Schiff-diastase, Gomori-Grocott methenamine silver, and Ziehl-Neelsen stain revealed no microorganism. The patient was followed up for 18 months in our clinic without recurrence.

## DISCUSSION

Spontaneous regression of a malignant tumor was originally described in 1959 by Everson and Cole,<sup>4</sup> as a complete or partial clearance of malignant cells in the absence of all treatment, or in the presence of therapy which is considered inadequate to exert a significant influence on the neoplastic disease. Spontaneous neoplastic remission of HCC is an unusual phenomenon with estimated incidence of approximately 0.4%; the exact pathophysiology underlying this event is unknown.<sup>5</sup> Among the proposed mechanisms of spontaneous HCC regression, circulatory disturbance with tumor hypoxia and activation of host immune response offer the most scientific explanation for the complete histologic necrosis of HCC.

Because HCC is a highly vascularized and oxygen-sensitive tumor, rapid tumor growth, occlusive portal vein thrombosis, spontaneous hepatic arterial thrombosis, thick fibrous capsule and/or poor arterial supply in the cirrhotic liver may be associated with circulatory disturbance and ischemic injury

causing the necrosis of the tumor.<sup>6-10</sup> However, in this case vascular occlusion or tumor necrosis along the specific hepatic artery was not observed on MRI or histology. Thus, tumor hypoxia caused by circulatory disturbance may be less likely. Lymphoplasmacytoid cell infiltration with granulomatous inflammation in histopathology was a characteristic finding in the presented case. Therefore, in the current case, we consider the host immune response as the mechanism of spontaneous HCC regression. Previous case reports have suggested that various events including persistent febrile illness, such as viral or bacterial infections, may give rise to systemic inflammatory responses. Subsequent production of pro-inflammatory cytokines such as tumor necrosis factor- $\alpha$  and interferon- $\gamma$  would lead to activation of innate and/or adaptive immune responses against the tumor cells and may lead to regression of the tumor.<sup>11,12</sup> Two cases of pathologically confirmed spontaneous HCC regression with massive infiltrating inflammatory cells, mainly composed of CD4+ T cells, have been reported.<sup>13,14</sup> And, the fact that patients with HCC showing massive infiltration of lymphocytes generally have a better clinical outcome also supports host immune response mechanism hypothesis.<sup>15</sup>

It is still controversial whether or not surgical resection is required in patients with spontaneous HCC regression in imaging, laboratory study. A case of HCC with complete regression in imaging study but with a viable tumor histologically has been reported.<sup>5</sup> Therefore, despite the decline in level of AFP after 5 weeks, we decided to perform a curative wedge resection.

To summarize, we present an unusual case of spontaneous regression of HCC. Although the underlying mechanism of spontaneous regression of HCC is thought to be com-

plex and largely uncertain, circulatory disturbance and activation of host immune response are considered the two major factors. Further understanding of the mechanism behind this rare phenomenon may provide new strategies for management of HCC.

## REFERENCES

1. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet* 2012;379:1245-1255.
2. Cole WH. Efforts to explain spontaneous regression of cancer. *J Surg Oncol* 1981;17:201-209.
3. Huz JI, Melis M, Sarpel U. Spontaneous regression of hepatocellular carcinoma is most often associated with tumour hypoxia or a systemic inflammatory response. *HPB (Oxford)* 2012;14:500-505.
4. Everson TC, Cole WH. Spontaneous regression of malignant disease. *J Am Med Assoc* 1959;169:1758-1759.
5. Sasaki T, Fukumori D, Yamamoto K, Yamamoto F, Igimi H, Yamashita Y. Management considerations for purported spontaneous regression of hepatocellular carcinoma: a case report. *Case Rep Gastroenterol* 2013;7:147-152.
6. Okano A, Ohana M, Kusumi F, Nabeshima M. Spontaneous regression of hepatocellular carcinoma due to disruption of the feeding artery. *Case Rep Oncol* 2013;6:180-185.
7. Oquiñena S, Iñarrairaegui 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.
8. Ohtani H, Yamazaki O, Matsuyama M, et al. Spontaneous regression of hepatocellular carcinoma: report of a case. *Surg Today* 2005;35:1081-1086.
9. Iiai T, Sato Y, Nabatame N, Yamamoto S, Makino S, Hatakeyama K. Spontaneous complete regression of hepatocellular carcinoma with portal vein tumor thrombus. *Hepatogastroenterology* 2003;50:1628-1630.
10. Morimoto Y, Tanaka Y, Itoh T, Yamamoto S, Mizuno H, Fushimi H. Spontaneous necrosis of hepatocellular carcinoma: a case report. *Dig Surg* 2002;19:413-418.
11. Stoelben E, Koch M, Hanke S, et al. Spontaneous regression of hepatocellular carcinoma confirmed by surgical specimen: report of two cases and review of the literature. *Langenbecks Arch Surg* 1998;383:447-452.
12. Lam KC, Ho JC, Yeung RT. Spontaneous regression of hepatocellular carcinoma: a case study. *Cancer* 1982;50:332-336.
13. Yoo JJ, Lee JH, Lee KB, et al. Pathologically confirmed spontaneous partial regression of hepatocellular carcinoma. *Korean J Med* 2014;86:198-203.
14. 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.
15. Wada Y, Nakashima O, Kutami R, Yamamoto O, Kojiro M. Clinicopathological study on hepatocellular carcinoma with lymphocytic infiltration. *Hepatology* 1998;27:407-414.