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Spontaneous Regression of Massive Infiltrative Hepatocellular Carcinoma with Change in Hepatic Contour: A Case Report with Literature Review

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Spontaneous regression of hepatocellular carcinoma (HCC) is associated with alcohol abstinence, herbal medication, radiation, ischemia and immune reaction against systemic or local infections. Herein, we report a case of 67-year-old man with spontaneous disappearance of HCC after local infection as a rare cause. The patient had no clinical symptoms except for markedly increased tumor marker of HCC (protein induced by vitamin K absence or antagonist-II: 731 mAU/mL). On computed tomography (CT) and magnetic resonance imaging, massive infiltrating HCC with portal vein invasion was confirmed. During conservative treatment, he was admitted due to suppurative diabetic foot. After medical treatment, HCC disappeared on follow-up CT scans, along with change in hepatic contour. The disappearance of HCC might be a result of immune response by treatment of the diabetic foot and that of ischemia by portal vein tumor thrombosis secondarily. We summarized case reports regarding spontaneous regression of HCC by infection and ischemia. (*J Liver Cancer* 2018;18:55-62)

Keywords: Carcinoma, Hepatocellular; Neoplasm regression, Spontaneous; Infection; Ischemia

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INTRODUCTION

Over the last 50 years, several physicians have reported spontaneous regression of hepatocellular carcinoma (HCC). In the hope of discovering better therapeutic methods for HCC, many authors have attempted to explain spontaneous

regression of HCC with immune reaction against infection, alcohol abstinence, ischemia, herbal medication and radiation.¹ Although no definite mechanisms were documented in the several reports and studies, two major mechanisms such as ischemia and immune reaction were suggested as the possible mechanisms for spontaneous regression of HCC. However, among the published case reports on spontaneous regression of HCC, very few cases showed complete regression of massive infiltrative HCC induced by immune reaction. Herein, we report a case of spontaneous regression of a massive infiltrative HCC that showed a dramatic change in hepatic contour, accompanied with tumor regression after treatment against a local infection.

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To the best of our knowledge, this is the first case report, which not only demonstrated spontaneous tumor regression at the liver parenchyma, but also revealed an alteration in hepatic contour after control of a local infection. Based on this possibility, we have also summarized previous published case reports regarding spontaneous regression of HCC related to immune response against infections through the review of literature.

CASE REPORT

1. Clinical findings

A 67-year-old male patient with type 2 diabetes and hypertension presented with elevated serum gamma-glutamyl transpeptidase (γ -GTP) level, which was detected through a regular health check-up. The patient did not have any clinical symptoms. There was no family history regarding malignancy or liver-related diseases. The patient was a heavy drinker who had been consuming 100 grams of alcohol per day for the past forty years (two bottles of Korean raw rice wine per day). He was not taking any other medications including oriental herbal medicines or dietary supplements, except for oral hypoglycemic agent and antihypertensive drug. His body weight was 76 kg, height 1.75 m, and body mass index was 24.8 kg/m^2 . Initial vital signs were stable. The patient seemed to be relatively well-being. On physical examination, a soft and flat abdomen with no tender points was revealed. Laboratory values from a routine health screening performed a month earlier showed hemoglobin 12.4 g/dL, platelet count $1.17 \times 10^5 \text{ cells}/\mu\text{L}$, aspartate aminotransferase (AST) 40 IU/L, alanine aminotransferase (ALT) 25 IU/L, γ -GTP 698 IU/L (reference range: 0–50 IU/L), and alpha-fetoprotein (AFP) 6.8 ng/mL. Plain radiologic exams including chest x-ray and simple abdomen were non-specific. The ultrasonographic findings revealed diffuse nodular coarse liver echo-textures with lobular contours. With these findings, the patient was suspected to have alcoholic liver cirrhosis.

For further evaluation of alcoholic liver cirrhosis, additional laboratory examination was performed, which revealed alkaline phosphatase (ALP) 85 IU/L, lactate dehydrogenase

(LDH) 435 IU/L, albumin 4.0 g/dL, total protein 7.8 g/dL, total bilirubin 1.3 mg/dL, and international normalized ratio of prothrombin time (PT-INR) 1.13. An earlier exposure to hepatitis B with seroclearance was observed by positive hepatitis B surface antibodies and immunoglobulin G hepatitis B core antibodies, and negative hepatitis B surface antigen. Antibody against hepatitis C was negative. Initial renal function revealed blood urea nitrogen 9.0 mg/dL, and creatinine 0.7 mg/dL. The level of serum protein induced by vitamin K absence or antagonist II (PIVKA-II) was markedly elevated to 731 mAU/mL (reference range 0–40 mAU/mL).

2. Image findings

A liver dynamic computed tomography (CT) was performed and showed a massive HCC, replacing most of the left lateral segment with bulging-out contour, revealing as a diffuse infiltrating tumor with hypervascularity at arterial phase, and wash-out at portal venous and delayed venous phase (Fig. 1). A tumor thrombus was noted in the left portal vein. Splenomegaly and presence of small amount of ascites were pointed out. Multifocal calcified atherosclerotic lesions were also noted in the abdominal aorta. Contrast-enhanced liver dynamic magnetic resonance imaging (MRI) showed diffuse infiltrating mass of the left lobe of the liver with high signal intensity on T2 weighted imaging and diffuse weighted imaging (Fig. 2). In addition, the mass presented arterial enhancement and wash-out sign during dynamic phase, and the lesion showed low signal intensity on hepatobiliary phase.

3. Diagnosis and treatment progress

The massive tumor was diagnosed as HCC according to the diagnostic criteria of HCC of American Association for the Study of Liver Diseases (AASLD).² The HCC stage of the patient was evaluated as Barcelona Clinic Liver Cancer (BCLC) stage C and modified the International Union for Cancer Control (UICC) stage III.³ The patient was referred to a tertiary hospital for investigation of further treatment modality. However, the patient refused systemic chemotherapy using sorafenib due to its side effects and high cost. The patient

Figure 1. Liver dynamic computed tomography scans. (A) A massive infiltrative hepatocellular carcinoma replaced most of the left lateral segment with a bulging-out contour with hypervascularity at arterial phase (white arrows). Left portal vein tumor thrombosis was also noted (black arrow). (B, C) The lesion showed wash-out or hypointensity at portal venous phase and delayed venous phase. (D) Multi-focal atherosclerotic calcified lesions were observed at the abdominal aorta (black arrowheads).

Figure 2. Initial liver dynamic magnetic resonance imaging scans. Infiltrative massive hepatocellular carcinoma at the left lobe of the liver was noted (A) at arterial enhancement with portal vein thrombosis (black arrow), (B) T2 weighted imaging, (C) diffusion weighted imaging, and (D) hepatobiliary phase, respectively.

discontinued alcohol consumption and received conservative treatments at the outpatient clinic. His liver function continued to exacerbate and the amount of ascites increased. The follow-up laboratory results were aggravated as AST 130 IU/L, ALT 124 IU/L, ALP 211 IU/L, LDH 658 IU/L, albumin 2.7 g/dL, total bilirubin 8.2 mg/dL, γ -GTP 211 IU/L, and PT-INR 1.65. To relieve his pain and refractory ascites, fentanyl patch was administered and repeated large volume paracenteses were

performed. The follow-up CT after three months did not show any interval change in tumor size and appearance.

At six months after initial diagnosis of HCC, the patient was hospitalized with pus formation in the fourth web of the right foot due to exacerbation of diabetic foot. For approximately one month, he was treated with intravenous antibiotics (1st generation cephalosporin-cefazolin) and proper wound dressings; moreover, serum glucose level was kept un-

der control. Owing to antibiotics treatment and dressing for 1 month, the patient was discharged after the diabetic foot was completely healed.

After the treatment for diabetic foot, the patient's clinical condition improved dramatically. He did not complain of pain, and his refractory ascites was well controlled by diuretics. Routine laboratory examinations for HCC after discharge revealed AST 36 IU/L, ALT 31 IU/L, albumin 3.3 g/dL, total bilirubin 1.2 mg/dL, and PT-INR 1.34. The follow-up liver dynamic CT revealed a marked reduction in the massive HCC in the left lobe with normalization of liver contour without any specific treatments for HCC (Fig. 3). However, new lesions in the right lobe of segment 7 and 8 with the size less than 1 cm were noted. In addition, tumor thrombosis in the main and left portal vein were noted and cavernous transformation developed. The spontaneous regression of infiltrative HCC in the left lobe of the liver and development of new HCC in the right lobe of the liver were also confirmed by liver-specific MRI (Fig. 4). AFP was still within the normal limits (8.0 ng/mL), and PIVKA-II as an elevated tumor marker of HCC had sharply decreased from 731 mAU to 27 mAU/mL (Fig. 5). Thus, the level of PIVKA-II was normalized together with remission of massive HCC of the left lobe.

However, at the time of fifteen months after the diagnosis

of HCC, the liver function of the patient gradually deteriorated as Child-Pugh class C. As a result, the patient's HCC was staged as BCLC stage D and as modified UICC stage III, but the patient continues to survive through conservative treatment. Although the levels of AFP and PIVKA-II have been slowly increasing, no relapse of massive infiltrating HCC has been observed in the left lobe of the liver and the size of small HCCs in the right lobe of the liver grow larger. The hepatic contour remains unchanged, and total occlusion of left portal vein with cavernous formation has been detected on serial CT scans

DISCUSSION

HCC is associated with high mortality as the disease is diagnosed mostly at a late stage and curative surgery is applicable for only thirty percent of HCC cases.^{4,5} Although many therapeutic modalities for HCC except surgery have been attempted, HCC still remains a problematic malignancy for achieving a complete cure or remission in clinical practice. Although spontaneous regression of neoplasm is a rare phenomenon, a few spontaneous regression cases in HCC have been reported since 1982.^{1,6} Spontaneous regression of a malignant tumor was defined by Everson and Cole as the disappearance of a

Figure 3. After medical therapy of one-month duration for diabetic foot, follow-up computed tomography scans. Spontaneous regression of massive hepatocellular carcinoma in the left lobe of the liver as well as alteration of hepatic contour were noted (A) at arterial phase and (B) at delayed phase (white arrows). Newly small malignant nodules in the right lobe of the liver were detected (C) at arterial phase and (D) at delayed phase (black arrows).

Figure 4. Follow-up liver dynamic magnetic resonance imaging scans. Disappearance of infiltrative hepatocellular carcinoma at the left lobe of the liver was detected (A) at T2 weighted imaging, (B) diffusion weighted imaging, and (C) hepatobiliary phase, respectively. (D) Newly small hepatocellular carcinoma at the right lobe of the liver was observed at hepatobiliary phase (black arrow).

Figure 5. Serial changes in serum alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist II (PIVKA-II) during the follow-up period.

tumor without any specific therapeutic interventions.⁷ The mechanism of this phenomenal event remains unclear. Several authors suggested possible explanations for spontaneous regression of a tumor that included alcohol abstinence, ischemia, herbal medication, the abscopal effect of radiation, and non-specific immune reaction.¹ An appropriate understanding of the accumulated cases of spontaneous regression in HCC may facilitate in developing better therapeutic modalities for HCC. In this case, after the diagnosis of HCC, the patient was kept under conservative management. At six months after the initial diagnosis, the patient experienced diabetic foot

related to bacterial infection in the fourth web of the right foot. After medical therapy, the massive HCC disappeared radiologically along with change in the hepatic contour.

According to the review of several articles, regression of HCC in our case may be explained by an immune reaction induced by infection.⁶ The CD8+ cytotoxic T lymphocytes (CTLs) are the principal cells in inducing anti-tumor immunity.⁸ Cirrhotic liver has an impaired immune function so that the liver cannot initiate a proper immune reaction against the malignant tumor.⁶ It is hypothesized that an immune reaction provoked by a bacterial infection in the diabetic foot, might

eventually activate CTLs through pro-inflammatory mediators such as tumor necrosis factor and interleukin-12, thus leading to an anti-tumor effect.^{1,9} In our case, the patient was a heavy alcoholic, consuming 100 grams of alcohol every day. He abstained from alcohol after diagnosis of HCC. Alcohol abstinence is important in the alcoholic as it improved systemic immune function. In this case, alcohol cessation improved systemic immune function, eventually leading to the regression of HCC.¹

Malignant tissues are known to be more susceptible to ischemic change than normal tissues.¹⁰ Hypervascularity of HCC is developed to compensate insufficient perfusion to the tumor mass, and so this character of HCC indicates the key role in spontaneous regression of HCC. In our case, although the enhanced abdominal CT scan at presentation showed tumor thrombosis at the only left portal vein, tumor thrombosis proceeded to the main portal vein and cavernous transformation developed at the time of resolution of HCC. Complete occlusion of portal vein with cavernous transformation was also noted according to disease progression. These findings suggest that ischemia can be related to the regression of our patient's massive infiltrative HCC. Alqutub et al. reported that radiologic spontaneous regression of a large HCC was associated with the atrophy of the hepatic lobe due to the vascular occlusion by portal vein thrombosis.¹¹ The authors stated that the tumor infarction due to disruption of the feeding artery or portal vein caused by subintimal injury, thrombus, and tumor invasion could result in tumor necrosis and regression of HCC. This opinion may support our hypothesis that ischemia is one of causes of spontaneous regression of HCC. In addition, on abdominal CT scans, the abdominal aorta of our patient showed multifocal atherosclerotic and calcified lesions due to diabetes and hypertension. Vascular atherosclerosis might induce the ischemia of tumor cells partially. It is possible to hypothesize that ischemia with lack of perfusion may be the secondary cause of spontaneous regression of HCC in our patient.

Above all, our case is important in the respect of documenting a change of the hepatic contour as well as in the respect of spontaneous regression of HCC developed through an immune reaction and ischemia. The change of contour in

the left lobe of the liver may be associated with the decrease of liver volume according to progression of fibrosis and tumor necrosis. At the time of spontaneous regression of HCC, CT images showed the marked shrinkage of the liver, compared with initial CT scans.

Especially, in our case, although the infiltrative HCC of the left lobe of the liver showed spontaneous regression due to local infection and ischemia, newly small HCCs developed in the right lobe of the liver simultaneously. Considering regression of HCC and development of newly HCC happened at the same time, we hypothesize that synergic effect of immune reaction and ischemia by portal vein invasion can be more critical for spontaneous regression of HCC. Previously published case reports on infection-related spontaneous regression of HCC were retrieved from PubMed and Google Scholar, and were summarized. We carefully analyzed each case report and selected 9 case reports, which included an episode of infection prior to spontaneous regression of HCC. In Table 1,^{1,6,12-16} the etiology, tumor size, the status of cirrhosis and metastasis, AFP and PIVKA-II levels, therapeutic interventions, types of HCC, and types of infection from the selected 10 cases including our case were analyzed. In addition, as a secondary cause of spontaneous regression of HCC except immune response, we investigated the factors related to ischemia. Most of the cases presented the nodular type of HCC. No surgical intervention on HCC was applied, but appropriate medical managements such as antibiotics treatment against episodes of infection were carried out. Compared with our case, the other 9 cases in Table 1 presented systemic infectious conditions such as sepsis caused by pneumonia, cholangitis, and peritonitis. In contrast, our case presented a local infection due to a diabetic foot. In addition, radiologic alteration of hepatic contour was only observed in our case. In 3 case reports of cases from Table 1, an increase in interleukin-18 levels, a cytokine involved in the pro-inflammatory reaction, was observed.¹ This increase in cytokine demonstrates that an inflammatory reaction by infection may be related to spontaneous regression of HCC through activation of CTLs as mentioned above. Five case reports including our case showed that ischemia such as bleeding and portal vein tumor thrombosis might be a secondary cause of sponta-

Table 1. Summary of cases of spontaneous regression of HCC induced by infection

References	Age (yr)/sex	Etiology	Cirrhosis	Size (cm)	HCC Type	Metastasis	AFP (ng/mL)/PIVKA-II (mAU/mL)	Infection	Factor related to ischemia	Intervention
Johnson et al. ¹²	5/F	Androgenic-anabolic steroid	No	6	Nodular	No	NA/NA	Sepsis	NA	NA
Lam et al. ¹³	50/M	HBV	No	NA	NA	Lung	NA/NA	Broncho-pneumonia	None	IV antibiotics
Markovic et al. ¹⁴	62/M	HBV	Yes	13	Infiltrative	No	11/NA	Persistent fever	Hemorrhage following liver biopsy	NA
Stoelben et al. ¹⁵ #1	56/M	Unknown	No	6	Nodular	No	3.7/NA	Liver abscess	None	Puncture
Stoelben et al. ¹⁵ #2	74/M	Past HBV infection	No	6	Nodular	No	3,850/NA	Liver abscess	None	NA
Blondon et al. ⁶ #1	64/M	Alcohol	Yes	8	Nodular	No	915/NA	Peritonitis	Intraperitoneal bleeding	Acetaminophen/Propoxyphene
Blondon et al. ⁶ #2	70/F	Alcohol	Yes	NA	Nodular	No	4,205/NA	Pertontitis	Esophageal variceal bleeding	Tamoxifen
Ohta et al. ¹⁶	74/M	Unkonwn	No	6	Nodular	Intrahepatic	2.7/8,450	Cholangitis due to choledocholithiasis	None	Endoscopic removal
Randolph et al. ¹	56/M	HCV, Alcohol	NA	7.5	Nodular	Intrahepatic, Portal vein	2,854/NA	Pneumonia	Partial obstruction of portal vein thrombosis	NA
Our case	67/M	Past HBV infection, Alcohol	Yes	NA	Infiltrative	Portal vein	6.8/731	Diabetic foot	Partial obstruction of portal vein thrombosis	IV antibiotics/Dressing

HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist II; F, female; M, male; NA, not available; HBV, hepatitis B virus; IV, intravenous; HCV, hepatitis C virus.

neous regression of HCC.

Our observations from the present case guide us in further research on developing therapeutic modalities for HCC. Augmentation of the immune ability of the body may play an important role in the treatment of HCC. Triggering and fortifying a specific immune system may be a great therapeutic option for patients with inoperable HCC. In addition, synergic effect of immune reaction and ischemia will be more important for achieving better therapeutic goals of HCC.

AUTHOR CONTRIBUTIONS

Dr. Lee and Dr. Oh made substantial contributions in reviewing the case and the medical literature, and compiling the clinical data. Dr. Lee drafted the manuscript. Dr. Oh contributed to the discussion and reviewed the manuscript.

Conflicts of Interest

The authors have no conflicts to disclose.

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