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Case Report

Spontaneous Regression of a Poorly Differentiated Hepatocellular Carcinoma: A Case Report

Omameuda T*, Miyato H, Sakuma Y, Sata N and Kawarai Lefor A

Department of Surgery, Division of Gastroenterological, General and Transplant Surgery, Jichi Medical University, Shimotsuke, Tochigi, Japan

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ABSTRACT

Hepatocellular carcinoma (HCC) is the most common histological type of primary liver cancer, and spontaneous regression of HCC is rare. We report the case of a 76-year-old male diagnosed with poorly differentiated HCC that spontaneously regressed. Although the patient did not undergo any treatment or invasive diagnostic tests, such as angiography, before surgery, the resected tumor showed complete necrosis similar to that seen after transcatheter arterial embolization. The main cause of the necrosis in the present case was thought to be the occlusion of nutrient vessels and tumor hypoxia. Tumor hypoxia and immunological reactions are reported to be the main causes of spontaneous HCC regression, although the underlying mechanisms remain unclear. In this case report, we provide additional insights into this phenomenon.

Introduction

Hepatocellular carcinoma (HCC) often develops in patients with underlying chronic liver diseases such as chronic viral hepatitis, alcohol-induced liver injury, and metabolic disorders including non-alcoholic steatohepatitis. Spontaneous regression of a malignant tumor is a rare phenomenon and is defined as the partial or complete disappearance of a malignant tumor in the absence of any treatment [1]. Although few cases of spontaneous regression of HCC have been reported in the literature, the main causes can be categorized into two types: i) tumor hypoxia and ii) systemic immunological reaction [2].

Here, we describe a case of a poorly differentiated hepatocellular carcinoma that exhibited spontaneous regression, possibly owing to tumor hypoxia. This report provides an additional perspective on the underlying causes of the spontaneous regression of HCC.

Case Presentation

A 76-year-old male with chronic obstructive pulmonary disease (COPD) diagnosed more than 20 years ago underwent routine annual surveillance computed tomography (CT), which revealed a space-occupying lesion in the lateral segment and a nodular opacity in the middle lobe of the right lung (Figure 1). The patient had no history of hepatic disorders, hepatitis B, hepatitis C, or alcohol consumption. He had quit smoking 20 years prior, although his Brinkman index had reached 1050 when he was a smoker. The patient was diagnosed with IgA nephropathy 30 years previously and had renal dysfunction at that time. Transbronchial lung biopsy (TBLB) was performed to examine the nodular lesion of the lung; however, no malignant findings were detected.

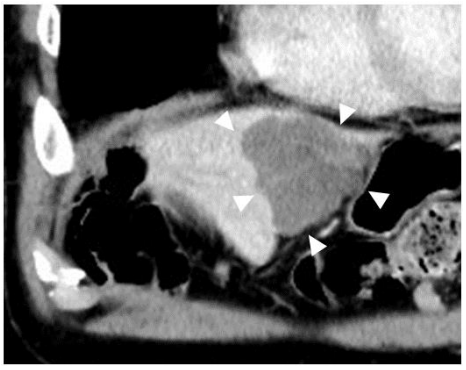

Figure 1: Contrast-enhanced computer tomography (CT) performed for the surveillance of chronic obstructive pulmonary disease (COPD). A space-occupying lesion measuring 55×50 mm was found in the lateral segment of the liver (arrowheads). The majority of the area of the tumor was enhanced only slightly or not at all, indicating necrotic tissue. An artery penetrated the tumor.

Correspondence to: Takahiko Omameuda, Department of Surgery, Division of Gastroenterological, General and Transplant Surgery, Jichi Medical University, Tochigi, 329-4421 Japan; Tel: +81285442111; Fax: +81285443234; E-mail: r1711ot@jichi.ac.jp

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The same CT showed that the majority of the hepatic lesion lacked enhancement (Figure 1), which was suspected to be necrotic tissue. The levels of the tumor markers CA19-9 and IL-2R were elevated, while the levels of AFP and PIVKAII were within the normal range (Table 1). Needle biopsy and subsequent histological examination revealed that the hepatic lesion consisted of necrotic tissue. Therefore, no treatment was administered, and no surgery was performed. The patient was then followed-up. After six months, the volume of the hepatic lesion remained almost unchanged, while a solid portion of the tumor could be seen protruding from the liver surface (Figure 2A-2C). Magnetic resonance imaging (MRI) revealed that the tumor was composed of two parts. The central region displayed elevated signal intensity on T1-weighted images and reduced signal intensity on T2-weighted images. In contrast, the peripheral region of the tumor displayed reduced signal intensity on T1-weighted images and elevated signal intensity on T2-weighted images (Figure 3A-3C). Laparoscopic lateral hepatectomy was performed for diagnosis and treatment.

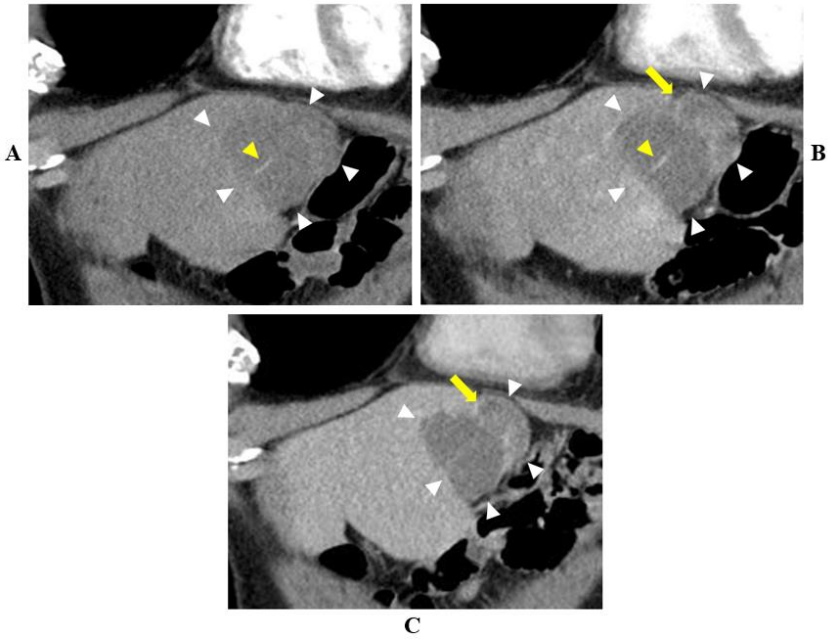

Figure 2: Contrast-enhanced computer tomography (CT) performed preoperatively. The tumor measured 57×52 mm. While the total volume of the tumor showed only a slight change, the solid portion of the tumor protruded from the liver surface and gradually became stained with contrast agent (arrow). An artery penetrated the tumor (yellow arrowhead). **A)** Arterial phase, **B)** portal phase, and **C)** delayed phase.

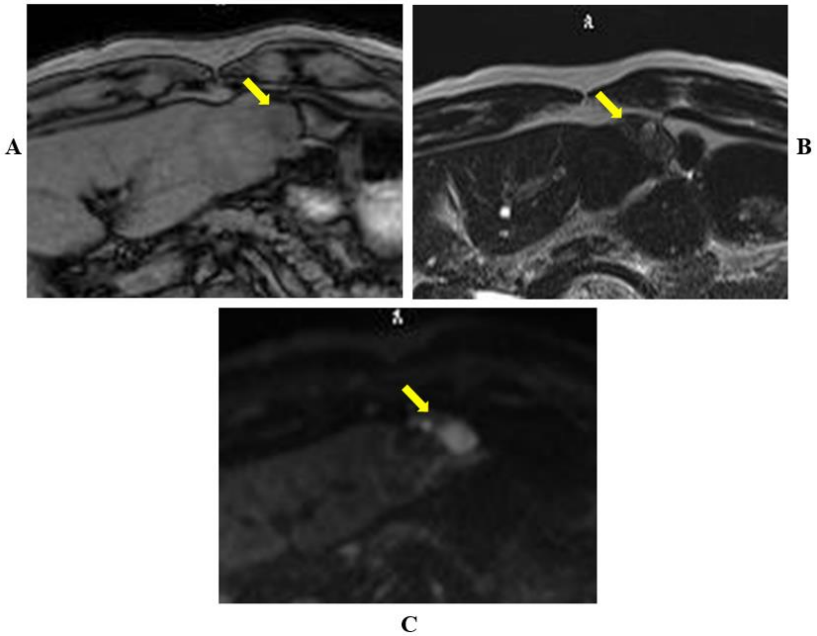

Figure 3: Magnetic resonance imaging (MRI) performed preoperatively. The central region of the tumor displayed elevated signal intensity on T1-weighted images and reduced signal intensity on T2-weighted images. The peripheral region displayed reduced signal intensity on T1-weighted images and elevated signal intensity on T2-weighted images, with reduced diffusion (arrow). **A)** T1-weighted image, **B)** T2-weighted image, and **C)** diffusion-weighted image.

Table 1: Results of the preoperative blood tests.

Peripheral blood		Biochemistry		Serology	
White blood cells	$5.5\times10^3/\mu L$	C-reactive protein	0.19 mg/dL	HBs-Ag	(-)
Neutrophils	63.80%	Total protein	7.0 g/dL	HCV-Ab	(-)
Eosinophils	1.70%	Albumin	3.6 g/dL	HIV-Ab	(-)
Basophils	0.80%	Total bilirubin	0.99 mg/dL	Tumor markers	
Monocytes	7.60%	Alkaline phosphatase	181 IU/L	PIVKA-II	26 AU/mL
Lymphocytes	26.10%	γ-Glutamyl transpeptidase	32 IU/L	CEA	4.4 ng/mL
Red blood cells	$458\times10^4/\mu L$	Aspartate aminotransferase	19 IU/L	CA19-9	107 U/mL
MCV	95.3 fL	Alanine aminotransferase	11 IU/L	AFP	1 ng/mL
MCH	30.9 pg	Lactate dehydrogenase	190 IU/L	sIL-2R	816 U/mL
MCHC	32.40%	Blood-urea-nitrogen	25 mg/dL		
Haemoglobin	14.1 g/dL	Creatinine	1.79 mg/dL		
Hematocrit	43.70%	Uric acid	mg/dL		
Platelet count	$1.73\times10^4/\mu L$	Na	139 mEq/L		
Coagulation		K	5.3 mEq/L		
PT-INR	1.18	Cl	106 mEq/L		
APTT	32.8 seconds	Ferritin	193.5 ng/mL		

AFP: alpha-fetoprotein; APTT: activated partial thromboplastin time; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; HBs Ag: hepatitis B surface antigen; HCV-Ab: hepatitis C virus antibody; HIV-Ab: human immunodeficiency virus antibody; MCV: mean corpuscular volume; MCH: mean corpuscular haemoglobin; MCHC: mean corpuscular haemoglobin concentration; PIVKA-II: protein induced by vitamin K absence-II; PT-INR: prothrombin time-international normalized ratio; sIL-2R: soluble interleukin-2 receptor.

On gross examination of the resected specimen, the hepatic tumor was occupied by a vast area of necrotic tissue, with a distensible solid component in the peripheral region covered with thick fibrous capsules (Figure 4A). Pathological examination revealed that necrotic tissue had spread throughout the central region of the tumor (Figure 4B), whereas the peripheral solid region was composed of a mixture of poorly differentiated carcinoma and necrotic tissues (Figure 4C). In addition, lymphocytes infiltrated the stroma of the peripheral region (Figure 4D). Based on the presence of some tumor cells expressing glypican-3 (Figure 4E) and structures considered to be hepatic cords, as visualized by silver impregnation staining (Figure 4F), the tumor was finally diagnosed as poorly differentiated HCC with spontaneous regression.

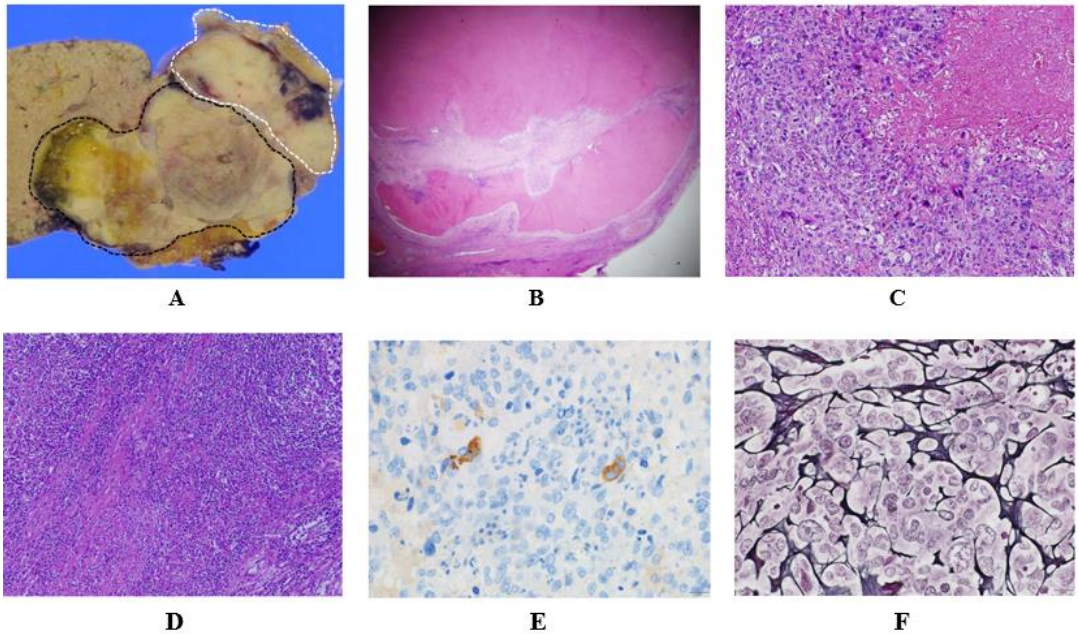

Figure 4: The macroscopic **A)** and histological images **B-F)** of the resected specimen. **A)** The hepatic tumor was occupied by a vast area of necrotic tissue, with a solid component in the peripheral region covered by thick fibrous capsules. The black dotted line delineates the central region of the tumor, while the white dotted line delineates peripheral region of the tumor. **B)** Complete necrosis spreading throughout the central region of the tumor (hematoxylin-eosin staining). **C)** The peripheral region of the tumor was composed of a mixture of poorly differentiated carcinoma and necrotic tissue (hematoxylin-eosin staining). **D)** Crowds of lymphocytes infiltrating the stroma in the peripheral region (hematoxylin-eosin staining). **E)** Some of the tumor cells were positive for glypican3 by immunohistochemical staining. **F)** Silver impregnation staining revealed the presence of structures considered to be hepatic cords.

The patient had a favourable postoperative course and was discharged on the sixth postoperative day. However, two months later, rapid expansion of the lung lesion was observed and TBLB revealed the presence of a primary squamous cell carcinoma. A metastatic bone tumor developed in the left femur, and chemotherapy was administered. However, the patient eventually died of disease progression 14 months postoperatively.

Discussion

Spontaneous regression of HCC was first described in 1972 as regression of HCC without any therapy [3]. Spontaneous regression of HCC is exceedingly rare with recently reported incidence of <1% of those with disease in a large center study [4]. Many factors, alone or in combination, have been suggested to be involved in the spontaneous regression of HCC and the causes can be categorized into two main types: tumor hypoxia (such as thrombosis, hepatic angiography, rapid tumor growth, hepatic arterioportal shunts, massive gastrointestinal hemorrhage, and capsule formation) and systemic immunological reaction (such as abstinence from alcohol and smoking, the use of herbal medicine, prolonged fever, and antidiabetic drugs) [2, 5-14]. Sakamaki *et al.* reviewed 16 cases in which the potential mechanisms were reported and summarized them as follows: hypoxia in three cases, systemic immunological reaction in nine cases, and the combination of both in four cases [2].

In this case, complete necrosis spread throughout the central region of the tumor and resembled a change seen after transcatheter arterial embolization (TAE), suggesting that the main cause of regression may have been the occlusion of nutrient vessels and tumor hypoxia. However, the possibility that arterial blood flow was preserved remains because preoperative CT revealed penetration of the artery in the tumor, and histological examination did not detect any findings of blood vessel occlusion. In addition, the possibility of an immunological reaction remains because crowds of lymphocytes were observed infiltrating the stroma of the peripheral region.

It is unclear which types of HCC can undergo spontaneous regression. HCC is dependent on arterial blood flow and has a low incidence of necrosis compared to other types of tumors. Asayama *et al.* reported that the arterial blood supply significantly decreased as the histologic grade progressed in the late stage of HCC development [15]. This suggests that the lack of blood supply in poorly differentiated HCC may be involved in tumor necrosis and spontaneous regression. However, this association is unclear and further evidence is needed.

In summary, we encountered a case of poorly differentiated HCC with spontaneous regression resembling complete necrosis after TAE.

Conflict of Interests

None.

Date Access Statement

The authors confirm that the data supporting the findings of this study are available in the article and the supplementary material.

Ethics Statement

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

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Author Contributions

Conceptualization: Takahiko Omameuda, Hideyo Miyato. Drafting the manuscript: Takahiko Omameuda, Hideyo Miyato. Resources: Takahiko Omameuda, Hideyo Miyato. Supervision: Hideyo Miyato. Writing: Original draft: Takahiko Omameuda, Hideyo Miyato. Writing: Review & editing: Hideyo Miyato, Sakuma Yasunaru, Naohiro Sata, Alan Kawarai Lefor. All authors have read and agree to publication of the manuscript.

Abbreviations

CT: Computed Tomography
COPD: Chronic Obstructive Pulmonary Disease
HCC: Hepatocellular Carcinoma
MRI: Magnetic Resonance Imaging
TBLB: Transbronchial Lung Biopsy
TAE: Transcatheter Arterial Embolization

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