Pathological Evidence of the Cause of Spontaneous Regression in a Case of Resected Hepatocellular Carcinoma

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Abstract

A 67-year-old man presented for an evaluation after experiencing right hypochondrial pain lasting for two months. Abdominal ultrasonography showed a hepatic tumor in the right liver and extremely mild hepatic steatosis. The imaging findings indicated that the tumor (43 mm in size) was ischemic, and the lesion was surgically resected and examined. The histopathological findings demonstrated 95% necrosis with moderately differentiated hepatocellular carcinoma (HCC). The diagnosis was HCC with spontaneous regression. There was also pathological evidence of thrombus formation in the peripheral arteries and portal veins. In addition, the non-cancerous regions of the liver were diagnosed as exhibiting non-alcoholic steatohepatitis. The pathological findings obtained after resection of the HCC lesion showed spontaneous regression.

Key words: hepatocellular carcinoma (HCC), spontaneous regression, arterio-portal thrombi, non-alcoholic steatohepatitis (NASH)

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Introduction

Approximately 85% of cases of hepatocellular carcinoma (HCC) are thought to be caused by virus-induced chronic liver diseases. In recent years, however, the number of non-hepatic B virus (HBV)- and non-hepatic C virus (HCV)-related cases has been increasing. Reports of HCC resulting from non-alcoholic steatohepatitis (NASH) are particularly noticeable. In addition, although rare, there are reports each year of cases of HCC with spontaneous regression. In almost all of these cases, the HCC lesions are the result of virus-induced hepatic disease. Concerning HCC with spontaneous regression involving the peripheral blood vessels, many reports have provided evidence of arterial thrombosis, with a few noting evidence of portal vein thrombosis. However, there are no reports of cases in which both types of thrombi have been observed. In this report, we describe a case of HCC resulting from NASH in which the pathological evidence indicated spontaneous regression caused by the presence of both arterial and portal vein thrombi.

Case Report

A 67-year-old man complained chiefly of right hypochondriac pain. He had been receiving oral treatment with amlodipine in addition to colestimide and Glufast in the hospital for hypertension and diabetes mellitus, respectively. Due to his obese status, the patient had begun a diet three years earlier and had succeeded in reducing his weight by approximately 5 kg. The mild hypochondriac pain was not related to dietary intake, and he presented to our hospital for his first examination after his symptoms had persisted for two months. On the first examination, only mild hepatic dysfunction and hypercholesterolemia were observed. However, since abdominal ultrasonography showed an approximately 42-mm neoplastic lesion in segment S6 of the right lobe of the liver, the patient was hospitalized for further examinations and treatment. He had a past medical history of hypertension at 48 years of age and diabetes mellitus and...
hepatic dysfunction due to hepatic steatosis at 55 years of age, with no history of transfusion. He had no history of alcohol consumption or smoking and no family history of note. At the time of hospitalization, his height was 152 cm, his body weight was 59 kg and his body mass index (BMI) was 25.5. In addition, his body temperature was 36.7°C, his blood pressure was 152/94 mmHg and his pulse rate was 76 beats/min. The palpebral conjunctiva showed no signs of anemia, and there were no palpable superficial lymph nodes or yellowing of the bulbar conjunctiva. No rales or murmurs were detected. Mild tenderness was confined to the right hypochondrium. There was no pretibial edema.

The patient’s laboratory findings on admission were as follows (Table): total bilirubin (T-Bil) =0.8 mg/dL, aspartate aminotransferase (AST) =35 IU/L, alanine aminotransferase (ALT) =43 IU/L, alkaline phosphatase (ALP) =185 IU/L, lactic acid dehydrogenase (LDH) =236, γ-glutamyl transpeptidase (γ-GTP) =52 IU/L. In addition, mild hepatic dysfunction was observed, with a total cholesterol (TCHO) level of 231 mg/dL. Known hepatitis viral markers, including those for hepatic B virus (HBV) and hepatic C virus (HCV), were negative. The concentrations of antinuclear antibodies and antimitochondrial antibodies were elevated at 40x and less than 5x, respectively. The hemoglobin A1c (HbA1c) value was 5.1%, thus indicating favorable glycemic control, and other fibrosis markers and ferritin parameters were within the normal ranges. Tests of tumor markers showed an alpha fetoprotein (AFP) level of 11 ng/mL (normal: 20 or less) and a mildly elevated AFP-Lectin 3 fraction of 25%, while other test results were normal.

The abdominal ultrasonography (B mode) findings are shown in Fig. 1. The size of the liver was normal, although the slightly irregular surface and blunt borders indicated a pattern of chronic liver dysfunction. A 42-mm ×45-mm solid tumor was observed protruding down from the right posterior inferior segment of the liver, with an echo-poor mild mosaic pattern. There were no halos, and no spleen enlargement, ascites fluid or collateral circulation were noted. There were also no biliary, pancreatic or renal abnormalities, and no lymphadenopathy was observed in abdominal areas.

The patient’s clinical course after admission was evaluated using contrast-enhanced ultrasonography of the hepatic mass, in which early vascular phase images showed no contrast enhancement, whereas post-vascular phase images showed a deficiency (Fig. 2). As on contrast-enhanced ultrasonography, contrast-enhanced abdominal computed tomography (CT) showed no dense staining on arterial phase images (Fig. 3). In addition, the abdominal angiography findings showed no dense staining in the cancerous portions of the liver on early vascular phase images (Fig. 4). Based on these imaging and hematological findings, the possibility of atypical HCC, intrahepatic bile duct carcinoma or Hodgkin’s disease was considered. However, no definitive diagno-
Figure 2. Contrast-enhanced ultrasonography of the hepatic mass: Early vascular phase images showed no contrast enhancement (A), while post-vascular phase images showed a deficiency (B).

Figure 3. Contrast-enhanced abdominal CT showed no dense staining on arterial phase images (A), while dense ring-shaped staining was observed at the periphery of the mass on portal images (B).

Figure 4. Abdominal angiography findings showing no dense staining in the cancerous portion of the liver on early vascular phase image.

sias was made, and segment 6 subsegmental resection was subsequently performed on day 18 of hospitalization.

The macroscopic findings of the resected specimen are shown in Fig. 5A. The tumor measured 42 mm ×43 mm in size, was brown-green in color and exhibited capsule formation. Most of the tumor appeared to be necrotic. On a magnified image (Fig. 5B), the tumor was observed to be touching the capsule. Subsequent findings indicated that most of the lesion was necrotic due to coagulative necrosis, and portal vein thrombi had formed, as shown in the schematic figure (Fig. 5C). Liver injury in the non-cancerous portion was caused by chronic hepatitis.

The pathological findings showed capsular invasion with a trabecular pattern of structural atypia in the viable tumor, with poorly differentiated HCC and pseudotubules in some parts (Fig. 6A). Necrosis was detected in most of the regions thought to be cancerous, and ghost cells suggesting hepatocytes were observed, as well as granulation tissue formation due to the proliferation of fibroblasts, collagen fibers and macrophages (Fig. 6B).

In the non-cancerous portions, fat deposition in hepatocytes was observed in less than 30% of the whole specimen, and there was very mild inflammatory cell infiltration in the portal vein and hepatic mesenchyme. The lobular architecture showed deformation due to the effects of fibrosis between the central veins and the central and portal veins (Fig. 6C).

The pathological diagnosis was moderately differentiated HCC type eg, fc (+), fc-inf (+), sf (+), s1, vp1, v0, va0, b0, im0, sm (-), ch. Pericellular and perivenular fibrosis was also observed, in addition to slight ballooning degeneration. Fibrosis, ballooning and other factors, such as a NASH activity score (NAS) of 4 points, Matteoni classification of type 4 and Brunt classification of grade 1, led to a diagnosis of stage 3 NASH (Fig. 6D). The intratumoral vessels contained fresh blood (→) and organizing thrombi (▲).
Figure 5. Macroscopic appearance of the resected right liver tumor. A: The uneven irregular surface of the non-neoplastic portion of the liver showing chronic hepatitis and capsule formation with a large 42mm×43mm green-brown tumor containing blood vessels. B: Magnified image showing the tumor touching the capsule, with findings of coagulation necrosis in most of the tumor. Blood vessels corresponding to thrombi formation in the portal vein. C: Schematic figure of B.

Figure 6. Histopathological findings. A: Moderately differentiated HCC with a viable tumor exhibiting capsular invasion, a trabecular pattern of structural atypia and pseudotubules in various locations. B: Necrosis in most of the area thought to be the tumor, with ghost cells suggesting HCC. Fibroblasts, collagen fibers and granulation tissue resulting from an increased number of macrophages were observed. C: Distortion of the lobular architecture due to the presence of fibrosis between the central veins (CV and between the central and portal veins). D: Very mild inflammatory cell infiltration in the portal area and parenchyma of the liver, with slight ballooning degeneration (↑). E: Fresh thrombi (→) and organized thrombi (▲) in the portal vein in the tumor. F: Elastica van Gieson (EV) staining in the same in location. G: Narrowing of the peritumoral arterioles (▲). H: Narrowing of the peritumoral portal vein branches (▲).
(Fig. 6E). In addition, Elastica van Gieson staining (EV stain) of the same site demonstrated narrowing of peritumoral arterioles (▲) (Fig. 6F, G), and pre-cirrhotic changes were observed in peritumoral cells (Fig. 6H). Consequently, the diagnosis was confirmed to be HCC due to chronic liver disease against a background of NASH with necrosis in most of the tumor (95%) as a result of thrombosis in the surrounding hepatic arteries and intrahepatic portal veins, leaving just 5% of the tumor viable. The patient’s postoperative course was favorable, and he was discharged from the hospital 11 days after undergoing surgery. He has since visited the hospital regularly for over three years, with no signs of recurrence.

Discussion

In a majority of cases of HCC, there is a background of chronic liver disease caused by HBV or HCV. Recently, however, there have been many reports of cases resulting from NASH. The present case involved non-B and non-C HCC with presumed coexisting NASH based on the patient’s clinical course and medical history that included abnormal glucose tolerance, hyperlipidemia, hypertension and obesity. The patient’s NAS was 4 points, his Matteoni classification was type 4 and his Brunt classification was grade 1, stage 3 (1-3). Fibrosis was more conspicuous than fat deposition. According to the preoperative blood platelet and indocyanine green (ICG) values, he was thought to have a non-cirrhotic liver; however, cirrhosis was verified pathologically. There are several previous reports of coexisting HCC in cases of non-cirrhotic NASH (4). In the present case, the findings showed necrosis in most of the tumor, with just a small portion remaining in the capsule, indicating partial spontaneous regression of the HCC. In addition, the histological findings showed the presence of fibroblasts, histiocytes and other granulation tissue surrounding an extensive and organized necrotic focus. We therefore conjectured that this observation was reflective of a response to the progression of necrosis over time by biological processes reacting to the development of coagulation necrosis. Theories have been put forward concerning the role played by embolism and factors of infection, immunology and the spontaneous regression of HCC. For example, Imaoka et al. expressed the pathological opinion that spontaneous regression in resected HCC is due to nutrient vessel embolism caused by the accumulation of coagulation necrosis debris (5). In addition, Yano et al. reported a total of 28 cases of spontaneous regression of HCC, including one treated by their group. The cause of regression was unknown in 16 of the cases, whereas, in four cases, the cause was identified to be a blood flow disorder, with pathological proof of arterial embolism only in the study by Imaoka et al. (6). In the present case, although the macroscopic findings did not show fresh and organized thrombi in the thick portal vein penetrating the tumor, such lesions were observed in the pathological findings. Organized thrombi and recanalization were also observed in the peritumoral arterioles and portal vein. Furthermore, the histopathological findings showed no necrosis of normal hepatocytes in the necrotic portions, although hepatocyte ghost cells and findings suggestive of postoperative hepatic artery embolism were noted. However, no angiographic techniques were performed in this case; therefore, such procedures could not possibly have caused the patient’s symptoms. We speculate that the necrosis in most of the HCC mass was the result of the formation of thrombi in nutrient vessels for an unknown reason. In other words, it was strongly presumed that, rather than being a spontaneous clinical condition caused by the mixture of old thrombi with tissue, the necrosis was the product of gradual thrombi formation in the peritumoral arteriolar walls, causing luminal narrowing that led to ischemic changes. In this case, thrombus formation was observed in a branch of the portal vein, and the peritumoral hemodynamics were estimated to be extremely complex. The schematic drawing presented in Fig. 5C shows the areas of necrosis, granulation tissue and viable tumor tissue, with conspicuous granulation tissue in the region with numerous thrombi. In addition, irregular regeneration was observed in hepatocytes in the non-cancerous areas. The generation of morphologically different cell populations due to chronic liver injury resulting from HCV has been hypothesized. In other words, that a process of repeated necrosis and regeneration lies at the heart of carcinogenesis (7, 8). However, there have been no reports of this issue concerning NASH patients. The relationship between irregular regeneration and NASH should therefore be examined in the future. The cause of gradual thrombus formation over time is unknown; however, the possible influence of oral medications and cytokines secreted by the tumor itself has not been determined. In general, terms such as spontaneous recovery and spontaneous remission are used to describe the spontaneous regression of a tumor, although it has been reported that spontaneous recovery occurs in only approximately one in 10,000 cases. Renal cell carcinoma, neuroblastoma, choriocarcinoma, malignant melanoma, bladder carcinoma, leukemia and some forms of Hodgkin’s disease, as well as breast and other cancers, account for 70% of these cases. Although theories of immune activation, hormonal effects, apoptosis, differentiation and other factors have been proposed, no definitive answers have been found; opinions concerning HCC are particularly scarce.

This report describes a case of resected HCC with a background of NASH involving 95% tumor necrosis. The coexistence of old and new arterio-portal thrombi has been pathologically verified, and this phenomenon is thought to be a potential cause of the spontaneous regression of HCC. The etiology of thrombi formation is unknown. However, if it can be proven that these lesions are the result of the actions of oral medications and/or cytokines, such findings would suggest the need to switch to molecular-targeted therapeutic agents as a treatment method.

In this report, we described a case of HCC that resulted
from non-alcoholic steatohepatitis in which pathological evidence indicated spontaneous regression due to the presence of both arterial and portal vein thrombi.

The authors state that they have no Conflict of Interest (COI).

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