Case Report

Combined Hepatocellular-Cholangiocarcinoma Associated With Radiofrequency Ablation for Hepatocellular Carcinoma

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Abstract

The patient was a 70-year-old male with liver cirrhosis associated with viral hepatitis C. He underwent radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC) four times in the 3 years prior to this reported event. Although he was closely followed after RFA by imaging every 3 - 4 months, a hypovascular and ill-defined tumor was revealed in segment IV of the liver by enhanced CT. The tumor expanded from the necrotic area associated with RFA performed 2 years prior. Because the tumor rapidly enlarged and was accompanied by a progressive tumor thrombus that filled the left portal vein, left hepatectomy was urgently performed. Histopathological examination of the resected specimen demonstrated that the tumor was mostly composed of moderately differentiated HCC. However, it also included obvious glandular structures with mucin production, which were immunohistochemically positive for both cytokeratin 7 and 19. These features are characteristic of cholangiocarcinoma; therefore the tumor was diagnosed as an uncommon combined hepatocellular-cholangiocarcinoma (cHCC-CC). From both pathological investigation and retrospective review of imaging results, the present cHCC-CC was presumed to derive from a locally recurring tumor with morphologic changes to the biliary phenotype induced by RFA for HCC. Both distant and intrahepatic metastases appeared 4 months after surgery and the patient died of cancer 15 months after surgery in spite of anti-cancer treatments.

Keywords: Combined hepatocellular-cholangiocarcinoma; Radiofrequency ablation; Hepatocellular carcinoma; Local recurrence; Morphologic change; Biliary phenotype; Liver resection

Introduction

Combined hepatocellular-cholangiocarcinoma (cHCC-CC) is defined as a tumor comprised of both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC) within the same tumor [1]. It is quite uncommon and accounts for only approximately 1% of primary liver cancers [2-5]. Although the pathogenesis of cHCC-CC remains uncertain, it has been recently suggested that cHCC-CC may derive from a hepatic stem cell or hepatic progenitor cell [6,7].

Radiofrequency ablation (RFA) is established as an effective and less invasive treatment for small HCC, and is thus accepted as an alternative to surgery [8]. However, local recurrence or local tumor progression after RFA remains a significant problem with a reported incidence ranging from 0.9% to 12% [8-14]. Among the cases with local recurrences, few demonstrate rapid and aggressive progression associated with morphologic changes [15-18].

We herein report a rare case of cHCC-CC, which is presumed to derive from a local recurrence with morphologic changes to the biliary phenotype caused by RFA for small HCC.

Case Report

The patient was a 70-year-old male with a 20-year history of chronic liver disease associated with hepatitis C virus. He underwent RFA for HCCs three times between April 2007 and November 2009. Subsequently, an additional 1-cm tumor in segment IV of the liver showed arterial hyperenhancement and washout in the delayed phase of three-phase CT (Fig. 1). Because those enhancements agreed with the typical diagnostic characteristics of HCC, the tumor was diagnosed as a new HCC. Percutaneous RFA for this HCC was performed in July 2010 and complete necrosis was radiologically confirmed after RFA. He was subsequently monitored closely by imaging every 3 - 4 months. Slight intrahepatic bile duct dilatation, which was restricted adjacent to the necrotic area because of RFA, was observed by CT in November 2011 (Fig. 2). At that time, the finding was not interpreted as evidence of local recurrence. In May 2012, a hypovascular and ill-defined tumor, which expanded from necrotic area in segment IV of the liver, was revealed by CT (Fig. 3). Because the tumor rapidly enlarged and was accompanied by a progressive portal vein tumor thrombus that filled the left portal vein, left hepatectomy with removal of the portal vein tumor thrombus extending to the

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portal trunk was performed urgently. In macroscopic findings of the resected specimen, a white and unencapsulated tumor showed infiltrative growth and was accompanied by tumor thrombus that filled the left portal vein (Fig. 4). Pathological examination showed that the tumor consisted of mostly moderately differentiated HCC and partly well to poorly differentiated HCC. Furthermore, obvious glandular structures with mucin production were observed (Fig. 5). Immunohistochemical investigation demonstrated that the glandular component was positive for both cytokeratin (CK) 7 and CK19 (Fig. 6) and was regarded as CC; therefore, the tumor was diagnosed as cHCC-CC. The postoperative course was uneventful. Four
months after surgery, CT revealed multiple recurrent tumors in the remnant liver and distant metastases to lung and lymph nodes. Although the patient underwent systemic chemotherapy by orally administration of a standard dose of S-1 for recurrent disease, he died 15 months after surgery. Autopsy was not performed.

Discussion

RFA is established as an ablation therapy for HCC and is accepted as an alternative to surgical resection, especially for small HCC with impairment of hepatic functional reserve [8]. Nevertheless, local recurrence or local tumor progression remains a significant problem after RFA, and its incidence has recently been reported to range from 0.9% to 12% [8-14]. Local recurrence after RFA is generally considered to be due to regrowth of residual tumor cells. In fact, Pompili and colleagues [19] reported that only 47% (14/30) of HCCs treated by RFA obtained complete necrosis in their retrospective study using explanted livers. Furthermore, they also showed that 50% of all ablated tumors were still viable on pathological ex-

Figure 4. Macroscopic finding of the resected specimen. On a cross-section of resected specimen, there was a white and unencapsulated tumor with massive portal vein tumor thrombus (arrow) that filled the left portal vein.

Figure 5. Microscopic findings of the resected tumor (hematoxylin & eosin stain, × 100). (A) The tumor was mainly composed of moderately differentiated hepatocellular carcinoma, revealing a trabecular pattern. (B) The tumor included obvious glandular structures with mucin production and was regarded as cholangiocarcinoma.

Figure 6. Immunohistochemical findings (× 100). The glandular structure in the present tumor was composed of the cells staining positive for both cytokeratin 19 (A) and cytokeratin 7 (B).
amination, in spite of being assessed as achieving complete necrosis by CT before orthotopic liver transplantation.

The present case had already undergone RFA three times previously for HCCs that developed in cirrhotic liver associated with viral hepatitis C. A subsequent 1-cm tumor developed, which, by three-phase CT, showed two classic enhancements associated with HCC. It was clinically diagnosed as HCC, percutaneous RFA was performed, and it was assessed by imaging that complete necrosis had been achieved. Despite this, about 2 years later, a large tumor with a massive left portal vein tumor thrombus presented in the same segment of the liver. Although the resected specimen was macroscopically quite different from typical HCC, pathological investigation revealed that it mostly was composed of moderately differentiated HCC and surrounded necrotic tissue resulted from RFA. Therefore, the present tumor was presumed to be a locally recurring tumor after RFA for HCC.

Diagnosis of cHCC-CC is usually confirmed by the presence of both hepatocellular and cholangiocellular features by histopathological examination. Hepatocellular features are described as trabecular or pseudoglandular architecture of cells with prominent nucleoli, eosinophilic cytoplasm, and bile production, while cholangiocellular features include glandular structures with mucin production. Furthermore, immunohistochemical investigations have recently been established to verify the histopathological diagnosis. Namely, hepatocellular components express hepatocyte antigen (hepatocyte paraffin 1: Hep Par 1), CK8, and CK18; whereas cholangiocellular components are positive for CK7 and CK19 [5]. Although it has recently been suggested that cHCC-CC originates from hepatic stem cells or hepatic progenitor cells [6, 7], the pathogenesis of cHCC-CC remains uncertain.

On retrospective review of imaging results over the course of the patient’s follow-up, slight bile duct dilatation in the area adjacent to the RFA-induced necrosis was identified by CT at 16 months after treatment. Because bile duct dilatation peripheral to CC is often observed, this finding suggests that the CC component of this tumor already existed at that time. Hence we suspect that the pathogenesis of present cHCC-CC was associated with a morphologic change from moderately differentiated HCC to CC. It has been previously reported that some local recurrences after RFA can exhibit phenotypic conversion or malignant transformation [15-18]. These reports implied that the thermal effect of RFA increased the malignant potential of the tumor [18]. The results of the experimental studies also confirmed that both malignant transformation and enhancement of malignant potential were induced by sublethal or insufficient RFA [20, 21]. Dong and co-workers [22] described that insufficient RFA might promote the epithelial-mesenchymal transition, which is considered to be a key process of metastasis of cancer. Although Nishihara et al [23] described that transcatheter arterial chemoembolization induced the biliary phenotype of HCC, there has been no previous report that RFA has an impact on acquiring the biliary phenotype of HCC. Therefore, the present cHCC-CC is considered to be very rare.

The present cHCC-CC recurred as systemic disease rapidly after surgery and consequently resulted in a poor prognosis. Among reported locally recurring tumors after locoregional therapy for HCC, few demonstrated rapid and aggressive progression, and poor prognoses similar to the present case. Because it is important for recurring tumors that demonstrate malignant behavior to be identified early, close follow-up is necessary after locoregional therapy for HCC.

In conclusion, we herein report a rare case of cHCC-CC, which derived from the local recurrence of the tumor, accompanied by morphologic changes to the biliary phenotype caused by RFA for small HCC. Although RFA is an established and effective ablation therapy for small HCC, local recurrence remains a significant problem. Among locally recurrent tumors, few demonstrate rapid and aggressive progression and poor prognoses. Morphologic changes induced by RFA are believed to be the cause of such a clinical course. Close follow-up is therefore important after locoregional therapy including RFA for HCC, even if complete necrosis is reported using imaging procedures.

Disclosure

This case was already reported in International Surgical Week 2013 in Helsinki, Finland.

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Conflict of Interest

All of the authors declare that they have no conflicts of interest.

References


