

## A Case of the Double Cancer Which Was Difficult to Distinguish Intrahepatic Cholangiocarcinoma From Multiple Hepatocellular Carcinomas

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A man in his 60s was introduced for a further examination of chronic hepatitis C virus infection, and two nodules were detected in the liver by abdominal ultrasonography (US). Serum alpha-feto-protein was elevated (56 ng/ml). The nodules were identified in various imaging examinations (abdominal US, contrast-enhanced US, contrast-enhanced CT and Gd-EOB-DTPA MRI) in segment 8 of the liver, both of which showed a typical contrast-enhanced pattern of hepatocellular carcinoma (HCC). Preoperatively diagnosed as HCC, a surgery was performed on these lesions. The pathological examinations of resected specimens showed of the two nodules were HCC and cholangiocellular carcinoma (ICC), respectively. There are only a few reports for double cancer complicated HCC and ICC at the same time. Then, it should be noted that many of them are preoperatively assumed as multiple HCC. Our case indicates that we need to take into consideration the likelihood of ICC even when multiple HCC are suggested from imaging diagnosis, because the treatment strategies for HCC and ICC are quite different.

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Key words: hepatocellular carcinoma (HCC), cholangiocellular carcinoma (ICC), double cancer

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### INTRODUCTION

There have been only a few reports of HCC and ICC complicated at the same time, and yet many of them are preoperatively diagnosed as multiple HCC [1]. Hepatitis B and C viral infection, excessive alcohol intake and background of diabetes mellitus effect a development of primary liver cancer, and a few small HCC with kept liver function is good indication of radiofrequency ablation (RFA) which achieves therapeutic effects almost equivalent to surgery. However, HCC and ICC should be sufficiently differentiated by imaging examination and US-guided aspiration biopsy because subsequent treatments and prognoses are different between HCC and ICC.

In this report, we present a case which had been preoperatively assumed as two nodules of HCC and finally diagnosed as duplication of HCC and ICC by histopathological examination after surgery.

### CASE REPORT

A 60s man with history that he had been having abnormal liver function from his 20s and diagnosed with chronic hepatitis C virus infection in 2002 was introduced to the department of Gastroenterology and Hepatology of Shimane University Hospital from a dermatologist of the same hospital who treated his psoriasis vulgaris for a further examination of chronic hepatitis C virus infection at the beginning of 2009. Also he had history of interferon treatment, but therapeutic effect was transient. Abdominal ultrasonographic examination detected two

Table 1. Laboratory date on admission

<CBC>		AST	59 IU/l
WBC	5260 / $\mu$ l	ALT	112 IU/l
RBC	445 $\times$ 10 <sup>4</sup> / $\mu$ l	Alp	203 IU/l
Hb	14.6 g/dl	LAP	32 IU/l
Plt	17.3 $\times$ 10 <sup>4</sup> / $\mu$ l	$\gamma$ -GTP	69 IU/l
<Coagulation>		ChE	262 IU/l
PT	106.4 %	T-Cho	152 mg/dl
APTT	36.7 sec	BUN	19.7 mg/dl
Fib	319 mg/dl	Crea	0.71 mg/dl
FDP	3.7 $\mu$ g/dl	FPG	86 mg/dl
<Biochemistry>		CRP	0.02 mg/dl
TP	6.7 g/dl	HCV Ab	(+)
Alb	4.2 g/dl	HBs Ag	(-)
T.Bil	1.2 mg/dl	<Tumor marker>	
		AFP	56 ng/ml
		PIVKA-II	24 mAU/ml

nodules in the liver, so he was hospitalized for a scrutiny of these two lesions.

On admission, his laboratory note showed abnormal liver function and elevated tumor markers for primary liver cancer (Table 1). Abdominal US on admission revealed two nodules in the liver. One lesion was a 21mm-sized hypoechoic nodule in segment 8 of the liver and contrast-enhanced US with Sonazoid<sup>®</sup> showed strong hypervascularity at the early arterial phase and a defect image at the post-vascular phase. Another 17mm-sized nodule in segment 8 of the liver was observed as defect image at the post-vascular phase of contrast enhanced US and

showed hypervascular at the early arterial phase by defect re-perfusion methods with Sonazoid<sup>®</sup> (Fig. 1).

In Gd-EOB-DTPA MRI, both of two nodules in segment 8 were hypervascular at the arterial phase, and showed defect image at the hepatobiliary phase, respectively (Fig. 2).

In CT during hepatic arteriography (CTHA), larger nodule was lobular-shaped and hypervascular and another nodule was hypervascular at the lateral part of the nodule. Both of them show defect images in CT during arterial portography (CTAP) (Fig. 3).

On the basis of these findings, we diagnosed these two intrahepatic nodules as HCC derived from chronic hepatitis C virus infection which is the highest risk factor of HCC. With the facts that the evaluation of liver reserve function is Child-Pugh grade A (score 5), the degree of liver damage is A. No extrahepatic lesion was detected by some imaging examinations. Therefore, we decided to undergo a surgical resection (wedge resection) in April, 2009.

#### Pathological Examination

Larger nodule is macroscopically showed as a multinodular-fused-type tumor with capsule and biliarygenesis (Figs. 4a and 4b). It is histologically diagnosed a common well differentiated hepatocellular carcinoma, some of whose cells revealed features of foamy cytoplasm or steatosis, and trabecular pattern

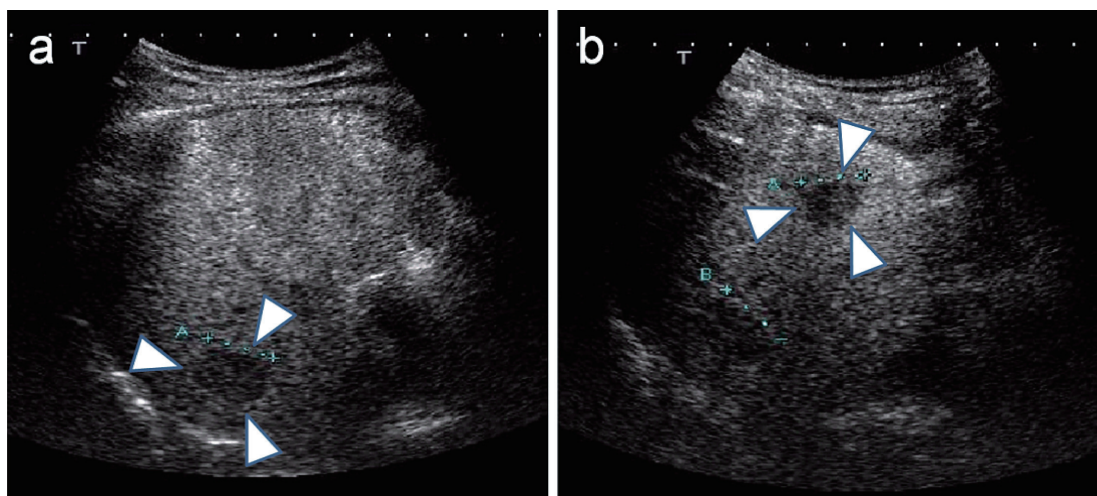


Fig. 1. Contrast-Enhanced Ultrasonography with Sonazoid<sup>®</sup> in the Post Vascular Phase  
 a: defect image in S8  
 b: another defect image near (a)

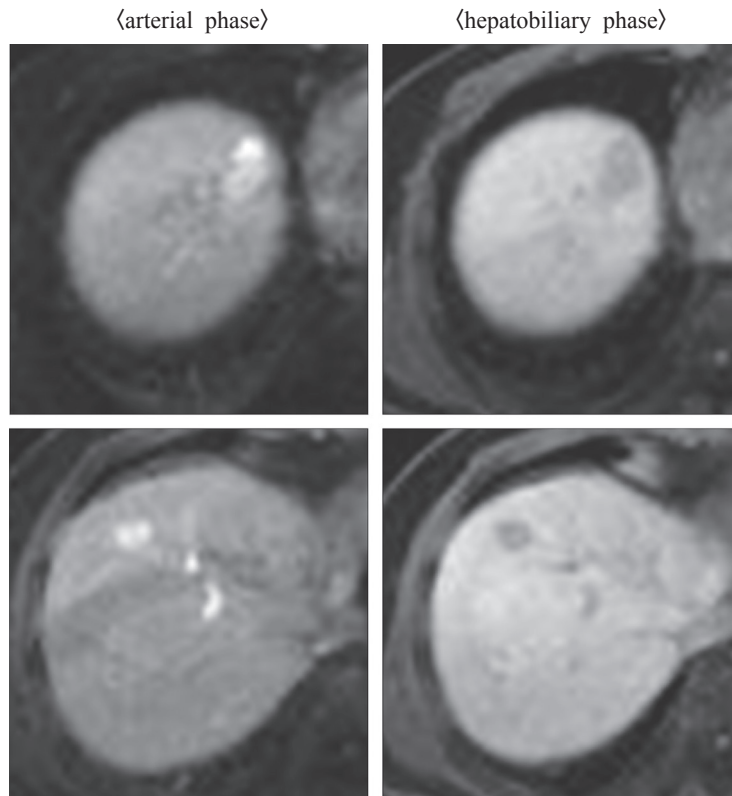


Fig. 2. Gd-EOB-DTPA MRI (upper images: lateral lesion in S8, lower images: medial lesion in S8)  
Both became hypervascular in the arterial phase and low signal in the hepatobiliary phase.

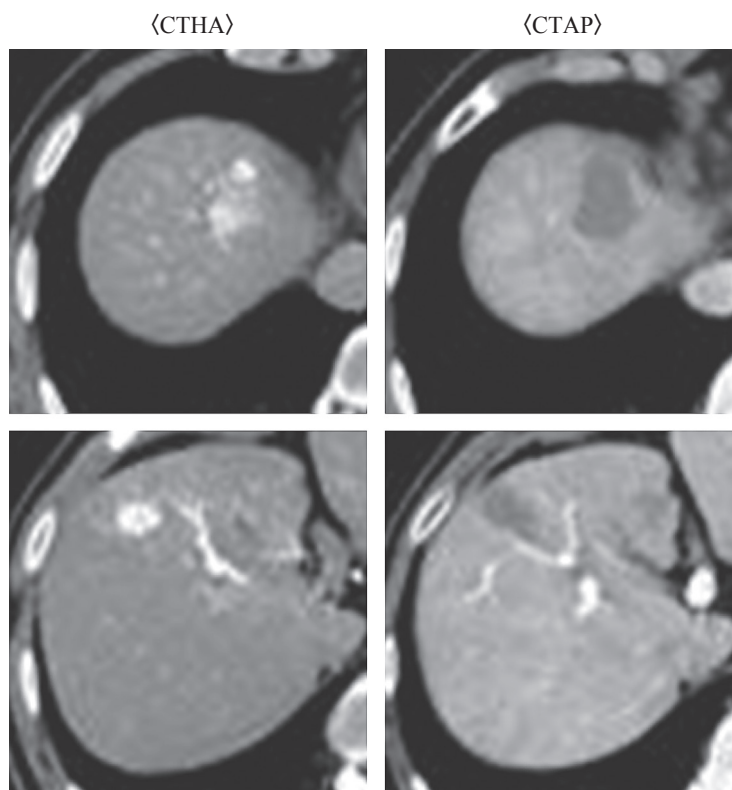


Fig. 3. CTHA, CTAP (upper images: medial lesion in S8, lower images: lateral lesion in S8)  
Both became hypervascular in CTHA, and show defect images in CTAP.



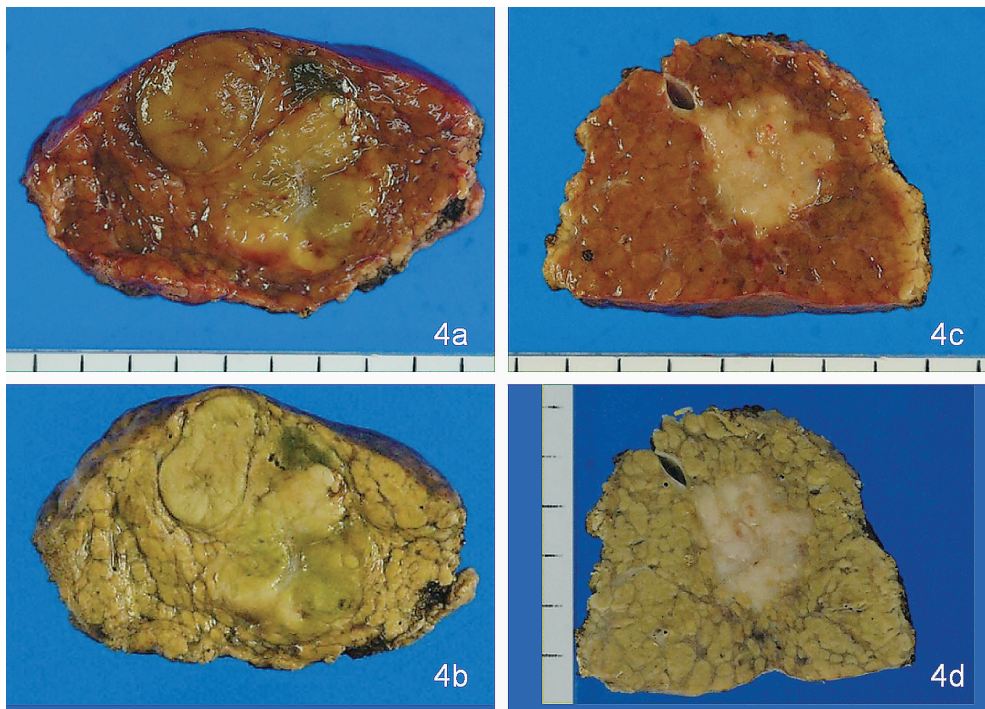


Fig. 4. Resected Specimen (macroscopic image)

4a: medial lesion in S8 (before fixation), 4b: medial lesion in S8 (after fixation), 4c: lateral lesion in S8 (before fixation), 4d: lateral lesion in S8 (after fixation)

Medial lesion is multinodular-fused-type tumor with capsule and biligenesis.

Lateral lesion is mass-forming-type white tumor without capsule nor biligenesis.

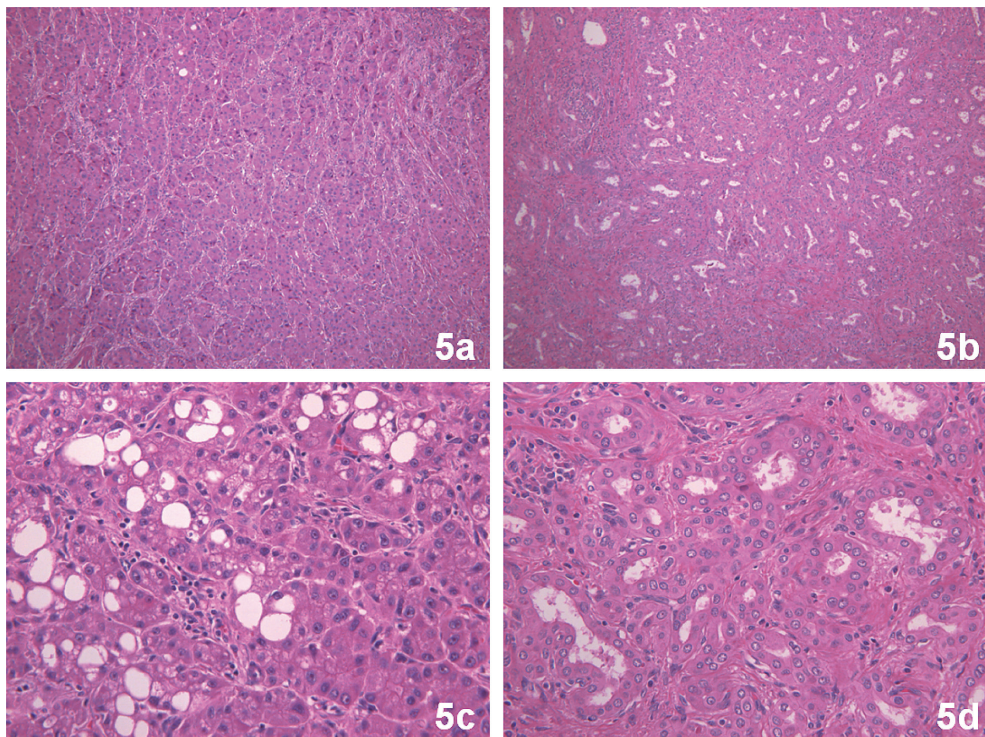


Fig. 5. Resected Specimen (microscopic image)

5a: medial lesion in S8 (low-power), 5b: medial lesion in S8 (high-power), 5c: lateral lesion in S8 (low-power), 5d: lateral lesion in S8 (high-power)

Medial lesion shows evidence of a pure hepatocellular carcinoma.

Lateral lesion shows evidence of well-differentiated or moderately-differentiated adenocarcinoma.

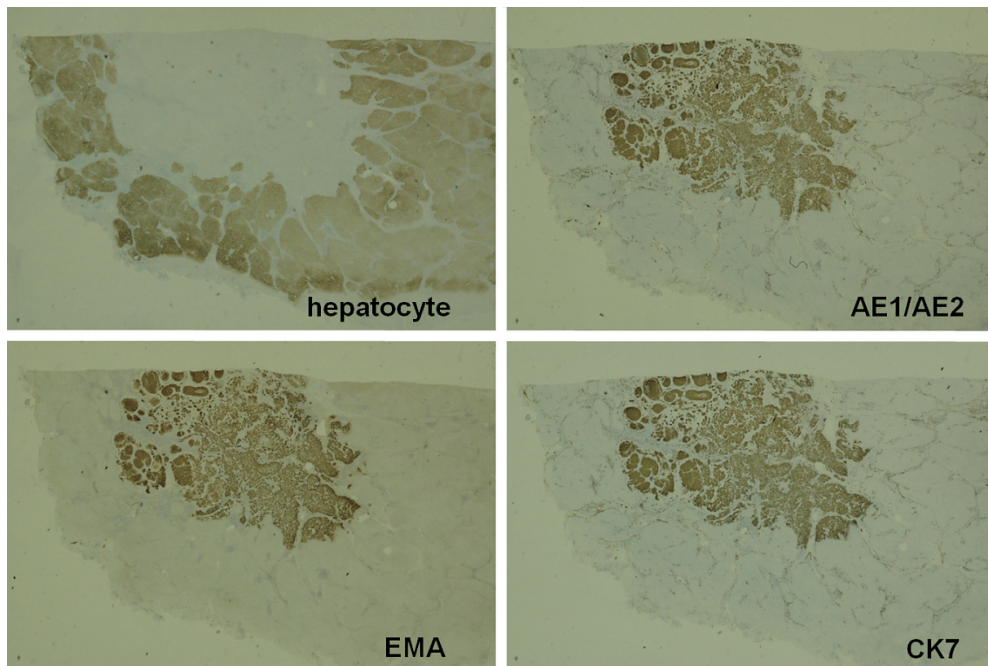


Fig. 6. Immunostaining of Resected Specimen of Lateral Lesion in S8

of growth (Figs. 5a and 5b). Another nodule was macroscopically showed as mass-forming-type white tumor without capsule nor biligenesis (Figs. 4c and 4d). It is histologically diagnosed as well-differentiated adenocarcinoma with a clear glandular structure or moderately differentiated adenocarcinoma including fused-glandular carcinoma (Figs. 5c and 5d). In immunostaining of the latter nodule, only the tumor part presents hepatocyte-negative results, and AE1/AE3, EMA, CK7 are positive. Thus, we diagnosed the latter nodule as a cholangiocellular carcinoma (Fig. 6).

#### **Clinical Course**

Although no evidence indicates recurrence of ICC during the last one year and eight months, recurrence of HCC was detected and therefore TACE and RFA were undergone.

#### **DISCUSSION**

Allen *et al.* classified the tumor into three types when development of HCC and ICC in a single liver were showed. Separate neoplastic masses may be comprised entirely of the liver cell type on the one hand, and of the bile duct type on the other

(double cancer). Contiguous masses, each of different character, may mingle as they grow (combined type). Individual masses may display both features so intimately associated that they can be interpreted only as arising from the same site (mixed type) [2]. In the fourth edition of The General Rules for the Clinical and Pathological Study of Primary Liver Cancer, combined type is defined as combined and mixed types in Allen's classification [3].

According to Report of the 18th Nationwide Follow-up Survey of Primary Liver Cancer in Japan, 94.0% of the newly registered cases are HCC, with 4.4% of ICC and 0.8% of combined hepatocellular and cholangiocarcinoma [4]. Since this report contains no information on cases of double cancer, the frequency of double cancer itself is not known. Kameyama *et al.* reported cases of double cancer of HCC and ICC which involve surgical resections in Japan [1], but the number of the cases they examined is only 21 from 1983 to 2008 and therefore it can be concluded that cases of double cancer are very rare.

Let us note here that the patients with ICC are associated with HCV or HBV infections and liver damages induced by these hepatitis virus. Furthermore, many patients with ICC are preoperatively



diagnosed as multiple HCC because most nodules of ICC strongly hypervascularised in the arterial phase enhancement. They are hypovascular for mass-forming type of ICC and some of them show a peripheral enhancement in the arterial phase. It is also recognized that they are hypovascular in both the venous and the equilibrium phases and show a delayed enhancement [5]. Yamamoto *et al.* examined resection case for mass-forming type of ICC [6]. ICC often co-occurs with hepatitis when the whole tumor is strongly hypervascularized in the arterial phase, and diameter of the hypervascular tumor is smaller than that of hypovascular one. They also point out that the possibility of lymph node metastasis is also significantly low and result of the resection are significantly good, and in the another report, most ICC patients who had been diagnosed as HCC preoperatively did not undergo lymph node dissection and none of them underwent extrahepatic bile duct resection, however, the surgical outcomes were better than patients who had been diagnosed as ICC [7]. In our case as well, the whole ICC tumor becomes hypervascular in the arterial phase and no recurrence of ICC is detected in the subsequent follow-up. In addition, since pathological examination showed that there was the potential to contain cholangiolocellular carcinoma in hypervascular ICC [5], we should pay special attention when making pathological diagnosis.

Differentiation between HCC and ICC crucially relates to the subsequent treatment strategies. Actually, Isaka *et al.* reported that TACE effects on double cancer which was preoperatively diagnosed as multiple HCC were evaluated as being insufficient and some part were left viable even after surgery [8]. For the treatment of ICC, surgical resection including a lymph node dissection is necessary. Therefore, even in cases which are diagnosed multiple HCC with imaging study, we should consider whether these lesions contain ICC or not and undergo biopsy when typical enhancement pattern of HCC is not revealed in dynamic study of CT, MRI or US.

## CONCLUSION

We reported here a case of double cancer of HCC and ICC. Since an apparent case of multiple HCC could actually be a case of double cancer which was developed with ICC or any other special types of tumors, special care should be taken when diagnosing and deciding subsequent treatment strategies.

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