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Case Report

Long-term surveillance of intrahepatic cholangiocarcinoma diagnosed after 20 years follow-up for hepatic hemangioma: a case report and literature review

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Abstract: Intrahepatic cholangiocarcinoma is the second most common primary malignancy of liver with poor prognosis. Four patients of intrahepatic cholangiocarcinoma were diagnosed after several years' observation with hepatic hemangioma in recent reports. Herein, we present a rare case of much longer surveillance of intrahepatic cholangiocarcinoma diagnosed after 20 years follow up for hepatic hemangioma. An asymptomatic 74-year old Chinese man was admitted to our hospital for a recent enlarged liver mass lesion, after 20 years follow-up for hepatic hemangioma. He was first diagnosed with a hemangioma in segment 8 of liver by abdominal ultrasound in February 1994, on basis of slightly hyperechoic feature with 1.6 × 1.1 cm in size. The mass lesion has enlarged markedly since 2013, which was confirmed by ultrasonography, computed tomography, magnetic resonance imaging, and positron emission tomography. Thus, hepatectomy was performed and histological characteristic revealed that the mass lesion was intrahepatic cholangiocarcinoma. This is the longest disease course of intrahepatic cholangiocarcinoma ever reported, which may change the former understanding of the biological behavior of intrahepatic cholangiocarcinoma and is worthy of further study.

Keywords: Intrahepatic cholangiocarcinoma, long-term surveillance, hepatic hemangioma, hepatectomy

Introduction

Intrahepatic cholangiocarcinoma (iCCA) is the second most common primary malignancy of liver in humans, after hepatocellular carcinoma (HCC) [1, 2]. A recent meta-analysis provided evidence of risk factors such as cirrhosis, chronic hepatitis B and C, alcohol, diabetes, and obesity [3, 4]. Although the incidence of iCCA worldwide is considerably less than HCC, several recent studies from around the world revealed rapidly rising incidence of iCCA over the past three decades [5, 6] and dismal prognosis with a median survival of less than 24 months [7], accompanying with notable global increase in mortality [8]. Even though the patients with iCCA undergo hepatectomy followed by curative intent, the 5-year survival is only 30~40% [9], due to difficulty in diagnosis and treatment. The prognosis of iCCA is much poorer for patients without surgical resection, resulting in nearly no survivors at 3 years [6]. However, four patients of iCCA were diagnosed after long-term surveillance for hepatic hemangioma, with range from 3 to 5 years follow-up [10-12]. To our knowledge, there has been no report of iCCA diagnosed after a much longer observation period with hepatic hemangioma. Herein, we present the case of a man who underwent hepatic resection with a diagnosis of iCCA after 20 years follow-up for hepatic hemangioma.

Case report

An asymptomatic 74-year-old Chinese man was admitted to Department of Hepatobiliary Surgery in our hospital for a liver mass lesion in

Table 1. Laboratory data on admission

Blood Count		*Biochemistry*		*Virology*	
WBC	5.68 G/L	T-Bil	5.7 μmol/L	HBsAg	(-)
NE	57.27%	D-Bil	2.8 μmol/L	HBsAb	(-)
RBC	4.03 T/L	AST	20 U/L	HBeAg	(-)
Hb	128 g/L	ALT	20 U/L	HBeAb	(+)
PLT	277 G/L	ALP	52 U/L	HBcAb	(+)
		γ-GT	30 U/L	Anti-HCV Ab	(-)
		TP	66 g/L	HEV IgM	(-)
Tumor marker		ALB	40.7 g/L	HEV IgG	(+)
CA19-9	7.3 U/mL	BUN	4.54 mmol/L	HEV RNA	(-)
CA125	8.7 U/mL	Cr	84.6 μmol/L		
AFP	3.0 μg/L	GLU	5.4 mmol/L	*Coagulation*	
CEA	3.8 μg/L	Na^+	139.0 mmol/L	PT	12.5 s
		K^+	3.87 mmol/L	APTT	39.7 s
		Ca^{2+}	2.2 mmol/L	INR	0.95

Abbreviations: WBC: white blood cells; *NE*: neutrophile granulocyte; *RBC*: red blood cells; *Hb*: hemoglobin; *PLT*: platelet; *CA19-9*: carbohydrate antigen 19-9; *CA125*: carbohydrate antigen 125; *AFP*: alpha fetoprotein; *CEA*: carcinoembryonie antigen; *T-Bil*: total bilirubin; *D-Bil*: direct bilirubin; *AST*: aspartate transaminase; *ALT*: alanine transaminase; *ALP*: alkaline phosphatase; *γ-GT*: gamma-carboxy prothrombin; *TP*: total protein; *ALB*: albumin; *BUN*: blood urea nitrogen; *Cr*: creatinine; *GLU*: blood glucose; *HB*: hepatitis B; *HCV*: hepatitis C virus; *HEV*: hepatitis E virus; *PT*: prothrombin time; *APTT*: activated partial thromboplastin time; *INR*: international normalized ratio.

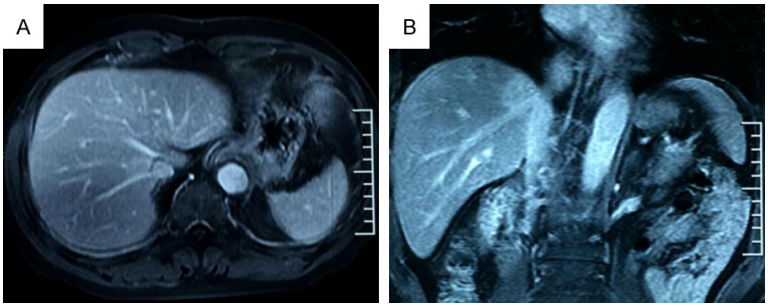

Figure 1. Contrast-enhanced T1-weighted MRI of liver mass lesion in June 2011. (A) Transected T1-weighted and (B) coronal T1-weighted image in delayed phase.

March 2014. Physical examination disclosed no significant abnormalities. The patient had a history of hepatitis B for more than 10 years and previous history of hypertension and type two diabetes. He also had a history of smoking for 59 years (one pack each day) and a history of drinking for 20 years (150 mL each day). The patient's laboratory data upon admission to our hospital were within normal limits except HBV and HEV (**Table 1**).

In February 1994, he was first diagnosed with hemangioma in liver segment 8 (S8) by abdominal ultrasound. On ultrasonography, the tumor appeared as a slightly hyperechoic mass with 1.6 × 1.1 cm in size. Ultrasound assessments were taken on eight occasions from June 1996 to July 2010, and the mass lesion was confirmed as a 2.2 × 1.7 cm hyperechoic tumor. In May 2008, the plain computed tomography (CT) showed the tumor as an approximately 1.2 × 1.0 cm size low-density area in the right lobe (Figure not shown). In June 2011, plain magnetic resonance imaging (MRI) showed the tumor as an irregularly shaped 2.4 × 2.0 cm mass in S8 adjacent to inferior vena cava (Figure not shown). Contrast-enhanced MRI demonstrated that the tumor was peripherally enhanced in the early phase and homogeneously median enhanced in the delayed phase (**Figure 1**). Anatomically, the mass lesion was located between the middle hepatic vein and the right hepatic vein, and attached tightly to the trunk of the middle hepatic vein. All the results indicated the liver mass lesion had remained almost the same size without malignancy.

However, the mass lesion had enlarged in recent years, which was confirmed by an ultrasonography as a slightly hyperechoic mass with 4.3 × 2.9 cm in August 2013. This change was proved by further MRI test. On March 7, 2014, plain and enhanced MRI showed that the tumor, which had been diagnosed as hepatic hemangioma, was suspected to be malignant due to enlargement. The tumor appeared as a nearly circular shaped mass adjacent to the second porta of liver in the right lobe, which appear hyperintense on T2-weighted images with central isointensity and hypointense on T1-weighted image (**Figure 2A-C**). The tumor has been increasing to 4.6 × 4.6 × 4.0 cm from 2.4 × 2.0 cm since 2011.

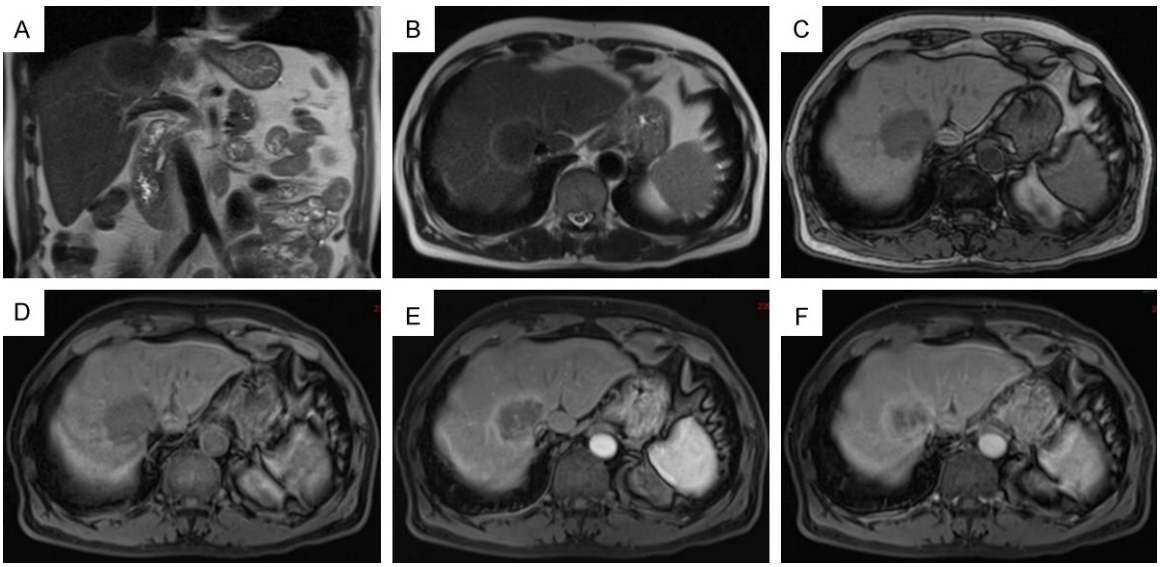

Figure 2. MRI of liver mass lesion in March 2014. (A-C) Plain scanning of liver: (A) coronal T2-weighted image, (B) transected T2-weighted image and (C) T1-weighted image. (D-F) Dynamic contrast-enhanced images: (D) early phase, (E) arterial phase and (F) delayed phase.

Figure 3. PET/CT images of liver mass lesion. (A) CT image, (B) PET image and (C) fused transaxial image.

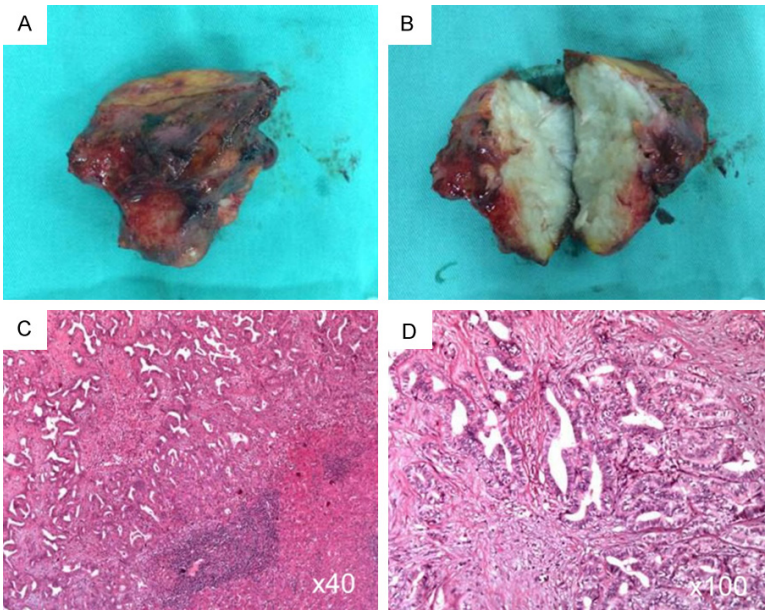

Figure 4. Macroscopic findings of the tumor (A and B) and hematoxylin & eosin staining of the mass lesion tissue (C and D).

Contrast-enhanced MRI showed peripheral enhancement in the arterial phase and followed by progressive and concentric enhancement in the venous phase (**Figure 2D-F**).

Therefore, this patient went to positron emission tomography (PET) center of our hospital for further examination. PET/CT images showed that the tumor as a well-demarcated area with slightly low-density was

Table 2. Detail of iCCA diagnosed after long-term surveillance for hepatic hemangioma in four cases

	Sasaki *et al.* [10]	Orii *et al.* [11]	Cheng *et al.* [12]	Xiao *et al.* [13]
Age (years)	69	68	59	60
Gender	Male	Female	Female	Male
Nationality	Japan	Japan	China	China
Publication	2012	2013	2013	2013
Symptoms	No	No	No	No
HBV markers				
HBsAg	(+)	(+)	(+)	(+)
HBeAb	(+)	N/A	(+)	(+)
HBcAb	N/A	N/A	(+)	(+)
Level of CA19-9	11.5 ng/mL	N/A	50 U/mL	323.18 U/mL
Follow-up (years)	4	3	5	5
Tumor characteristics				
Location	S5	S8	S4, 5, 8	Right lober
Size (cm)	4.1 × 2.5	4.0 × 3.5	7 × 3.5 × 2.5	6.5 × 5.5
Grain	Whitish, solid	Whitish/light yellowish, solid	Grey, solid	N/A
Ultrasonography	Hypoechoic	N/A	N/A	Slightly hyperechoic
Contrast-enhanced CT/MRI#	Typical appearance	Typical appearance	N/A	Typical appearance
Treatment	Hepatectomy	Hepatectomy	Hepatectomy	Biopsy and local ablation
Pathology	iCCA and CoCC	iCCA and CoCC	Moderately differentiated iCCA and hemangioma	Moderately differentiated iCCA

#The typical appearance on CT/MRI is hypodense/hypointense hepatic mass in the unenhanced phase, and peripheral enhancement in the arterial phase followed by progressive central enhancement in venous and delayed phases [2].

4.7 × 4.8 cm in size and located in the right lobe adhering to the second porta of liver (**Figure 3**). Distribution of radioactivity revealed that the tumor had a slightly abnormal uptake (SUVmax 3.8) in early stage and more uptake (SUVmax 4.5) in delayed stage. Thus, the tumor was suspected to be malignant.

On March 19, 2014, he underwent resection of S8 of the liver. Pathological morphology showed that a rigid mass with approximately 4.5 cm in diameter could be touched in S8 of the liver with mild cirrhosis, which was well demarcated, and had invaded tributaries of middle hepatic vein. No satellite lesions or swelling lymph nodes were found.

The gross findings for the tumor were: 6.0 × 4.5 cm in size, incanous, solid, and nonencapsulated (**Figure 4A** and **4B**). Microscopically, the tumor cells formed tubular and papillary structures with abundant fibrous stroma, indicating that it is highly differentiated iCCA, with partial necrosis and invasion to the envelope of the liver (**Figure 4C** and **4D**). The patient's postoperative course was uneventful except for massive ascites and he was discharged 26 days after surgery. The patient hads been followed-up without local recurrence or distant metastases of cholangiocarcinoma after resection.

Discussion

iCCA is the second most common primary liver cancer after HCC, accounting for 10% to 15% of primary liver cancers [13]. Although the incidence of iCCA worldwide is considerably less than HCC, it has increased from 0.32 per 100,000 to 0.85 per 100,000 over the recent three decades (an increase of 165%) [14]. The increased incidence of iCCA is believed due to a true increase in the disease, rather than improvements in diagnostic accuracy or changes in pathologic reporting [6], and this rapidly rising incidence has been noticed by physicians around the world. Compared with some other liver malignancies, iCCA has a shorter survival, lower resectability and curability rate [15]. Given the increasing incidence and high fatality rate of this disease, the epidemiology, risk factor, pathogenesis, along with diagnosis, and treatment methods of iCCA should be further studied.

To our knowledge, four papers have reported cases of iCCA diagnosed after long-term surveillance for hemangioma with follow-up period range from 3 to 5 years (**Table 2**) [10-12]. All four patients were asymptomatic, with chronic HBV infection and were misdiagnosed as hepatic hemangioma. The tumor marker carbo-

hydrate antigen 19-9 (CA19-9) has low sensitivity to iCCA in the early stage. After several years' of follow-up, three patients were suspected to be malignant due to an enlargement and a change in the contrast pattern of the tumor mass, except the Cheng's case. The tumor masses were diagnosed as iCCA by histological examination, coexisting with cholangiolocellular carcinoma (CoCC) or hepatic hemangioma. Our case presents the longest disease course of iCCA so far. In our case, the tumor had remained almost the same size in the past 19 years' follow-up for hemangioma and was found enlarged in the last periodic test of CT scanning. This case may change the former understanding of the biological behavior of iCCA and is worthy of further studies.

Imaging features of iCCA similar to those of hemangioma and iCCA may be misdiagnosed and followed up as hemangioma. On CT or MRI scanning, they both appear as peripheral enhancement in the arterial phase followed by progressive and concentric enhancement in the venous and delayed phases [2, 16]. Given that the prognosis of these two diseases are quite different and the key of treatment for iCCA is discovering and resecting the tumor in the early stage, more imaging features of these two diseases should be studied in order that differential diagnosis could be made in these early stages.

One interesting point about this case is that, usually, iCCA could not possibly have this long-term disease course. Could this transformed tumor form other relatively benign liver masses? Orii's case informed us of the transformation process from CoCC to iCCA and that CoCC seems to be less malignant than iCCA in aspects of enlargement and metastasis [11]. CoCC is considered to have potential to differentiate into either iCCA or HCC [17, 18]. Thus, is it possible that the tumor in our case is differentiated from CoCC? However, we can find no proof either in imaging study or postoperative pathology.

This case presents us with the longest disease course of iCCA ever reported. iCCA may be followed up as hemangioma. More differences of imaging features between iCCA and hemangioma should be studied for differential diagnosis. More cases about iCCA and CoCC should be reported so that we can learn more about these malignancies and their relationship and establish better treatment of them.

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Disclosure of conflict of interest

None.

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