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CASE REPORT

Primary biliary cholangitis metachronously complicated with combined hepatocellular carcinoma-cholangiocellular carcinoma and hepatocellular carcinoma

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Author contributions: Ide R and Oshita A made conception and design of this case report; authors other than Ide R and Oshita A, Nishisaka T, Nakahara H, Aimitsu S and Itamoto T contributed to collection and interpretation of data; Ide R and Oshita A wrote the draft manuscript, and other authors performed critical revision of the manuscript; all authors gave final approval of the version to be published; Oshita A has overall responsibility and guarantees the scientific integrity.

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Abstract

Primary biliary cholangitis (PBC) is a progressive cholestatic liver disease characterized by the presence of highly specific antimitochondrial antibodies, portal inflammation and lymphocyte-dominated destruction of the intrahepatic bile ducts, which leads to cirrhosis. While its pathogenesis remains unclear, PBC that shows histological progression to fibrosis carries a high risk of carcinogenesis; the same is true of viral liver diseases. In patients with PBC, the development of hepatocellular carcinoma (HCC) is rare; the development of combined hepatocellular carcinoma and cholangiocellular carcinoma (cHCC-CCC) is extraordinary. Herein, we report a rare case of PBC metachronously complicated by cHCC-

CCC and HCC, which, to the best of our knowledge, has never been reported. We present a case report of a 74-year-old Japanese woman who was diagnosed as PBC in her 40's by using blood tests and was admitted to our department for further management of an asymptomatic liver mass. She had a tumor of 15 mm in size in segment 8 of the liver and underwent a partial resection of the liver. Subsequent pathological findings resulted in the diagnosis of cHCC-CCC, arising from stage 3 PBC. One year after the initial hepatectomy, a second tumor of 10 mm in diameter was found in segment 5 of the liver; a partial resection of the liver was performed. Subsequent pathological findings led to HCC diagnosis. The component of HCC in the initial tumor displayed a trabecular growth pattern while the second HCC showed a pseudoglandular growth pattern, suggesting that metachronous tumors that arise from PBC are multicentric.

Key words: Primary biliary cholangitis; Combined hepatocellular carcinoma and cholangiocellular carcinoma; Hepatocellular carcinoma

Core tip: Primary biliary cholangitis (PBC) is a progressive cholestatic liver disease characterized by the presence of highly specific antimitochondrial antibodies, portal inflammation and lymphocyte-dominated destruction of the intrahepatic bile ducts, which leads to cirrhosis. While its pathogenesis remains unclear, PBC that shows histological progression to fibrosis carries a high risk of carcinogenesis; the same is true of viral liver diseases. In patients with PBC, the development of hepatocellular carcinoma is rare; the development of combined hepatocellular carcinoma and cholangiocellular carcinoma (cHCC-CCC) is extraordinary. Herein, we report a rare case of PBC metachronously complicated by cHCC-CCC and HCC, which, to the best of our knowledge, has never been reported.

Ide R, Oshita A, Nishisaka T, Nakahara H, Aimitsu S, Itamoto T. Primary biliary cholangitis metachronously complicated with combined hepatocellular carcinoma-cholangiocellular carcinoma and hepatocellular carcinoma. *World J Hepatol* 2017; 9(36): 1378-1384 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i36/1378.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i36.1378

INTRODUCTION

Primary biliary cholangitis (PBC)[1] is a progressive cholestatic liver disease characterized by the presence of a highly specific antimitochondrial antibody, portal inflammation, and lymphocyte-dominated destruction of the intralobular bile ducts, which lead to cirrhosis. According to recent and relatively large cohort studies conducted in European countries, the United States and Japan, the development of hepatocellular carcinoma (HCC) is estimated to be 0.7%-3.6%; this frequency increases as histological stages progress[2]. While its pathogenesis remains unclear, PBC cases that display histological progression to fibrosis are at a high risk of carcinogenesis; the same is true of viral liver diseases[3,4]. Although some cases of PBC complicated by HCC have been reported[5-8], to our knowledge, a case of PBC with cholangiocellular carcinoma (CCC) has never been described. In patients with PBC, the development of combined hepatocellular carcinoma and cholangio cellular carcinoma (cHCC-CCC) is extremely rare[9]. Herein, we report a case of PBC metachronously complicated by cHCC-CCC and HCC.

CASE REPORT

A 74-year-old Japanese woman was diagnosed as PBC in her 40's by using blood tests. Imaging studies, including abdominal ultrasonography (US) and computed tomography (CT), and tumor markers consisting of alpha fetoprotein (AFP) and protein induced by vitamin K absence (PIVKA-II) were checked up every 6 mo to 12 mo[4]. She was admitted to our department for further management of an asymptomatic liver mass. The patient denied alcohol consumption. Hepatitis B virus antigen and anti-hepatitis C virus antibody tests were negative. Liver function test results, with daily intake of 600 mg of ursodeoxycholic acid, were stable. Serum levels of AFP, PIVKA-II, carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9 and the L3 fraction of AFP were all within normal limits (Table 1).

Abdominal US, dynamic CT, and magnetic resonance imaging (MRI) showed a liver tumor of 15 mm in size in segment 8 of the liver. Since the tumor was located in the peripheral lesion and was in contact with the middle hepatic vein (MHV), we performed partial resection of the liver in segment 8 including partial resection of MHV. Hematoxylin-eosin (HE) staining revealed two components consisting of the trabecular type of HCC and CCC, resulting in the definitive diagnosis of cHCC-CCC. According to the classification for the severity of PBC[10,11], the hepatic parenchyma, excluding carcinomatous tissue, showed stage 3 PBC (Figure 1). In the immunohistochemistry, the component of HCC was negative for AFP but positive for cytokeratin (CK) 18 and hepatocyte, while that of CCC was positive for CK7 and CK19. The components of both HCC and CCC are positive for the epithelial cell adhesion molecule (EpCAM) (Figure 2).

One year after the initial hepatectomy, tumor marker levels for AFP, PIVKA-II, CEA and CA 19-9 were within normal limits; only AFP-L3 isoform level was elevated (Table 2). Dynamic CT and MRI showed a peripheral tumor of 10 mm in diameter in segment

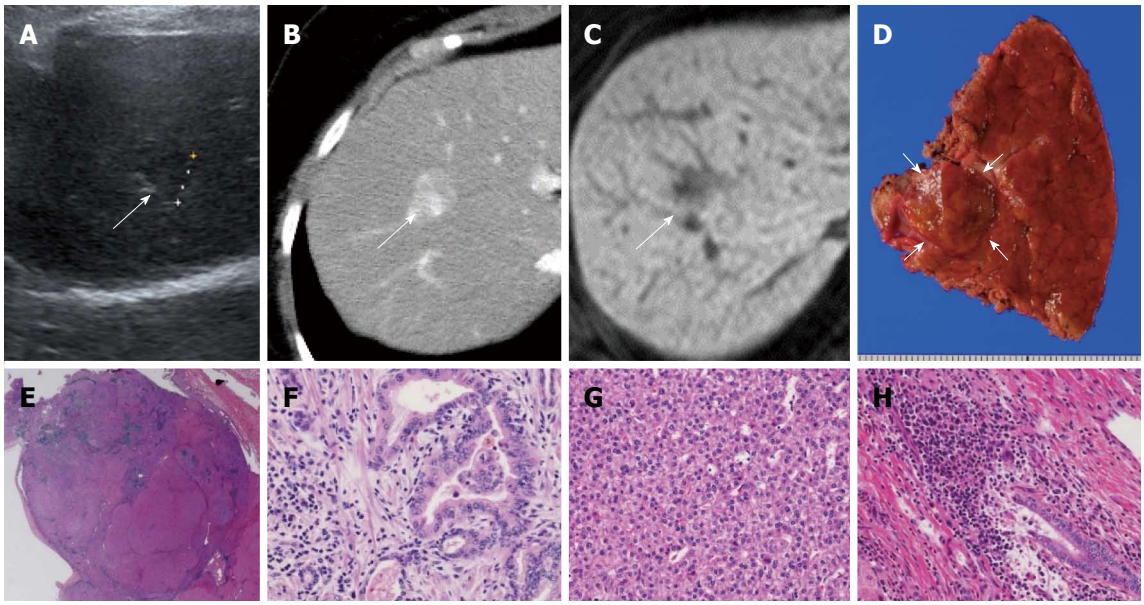

Figure 1 The initial tumor. A: Low-echoic tumor of 15 mm in size in segment 8 in US; B: The enhanced tumor on the early phase in dynamic CT; C: Low-intensity tumor on the hepatocyte phase in MRI; D: Cut surface of the 15-mm solid mass in segment 8; E: HE staining of the resected specimen; F: Adenocarcinoma in the component of CCC; G: HCC with a trabecular pattern; H: Dense fibrous tissue was formed and intrahepatic biliary ducts were showing destruction, while a loose lymphoid aggregate indicated stage 3 of primary biliary cirrhosis. CCC: Cholangiocellular carcinoma; CT: Computed tomography; HCC: Hepatocellular carcinoma; HE: Hematoxylin-eosin; MRI: Magnetic resonance imaging; US: Ultrasonography.

Table 1 Laboratory data on the initial hepatectomy

WBC	5800/μL	ALP	228 U/L	PIVKA-II	18 mAU/mL
RBC	432 × 10^4/μL	γ-GTP	65 U/L	AFP	3 ng/mL
Hb	13.0 g/dL	ChE	280 IU/L	AFP-L3	0.5%
Ht	38%	BUN	14.5 mg/dL	CEA	1.2 ng/mL
Plt	22.6 × 10^4/μL	Cr	0.54 mg/dL	CA 19-9	7 U/mL
PT	77.3%	T-Chol	203 mg/dL	ANA	× 40
PT-INR	1.04	TG	77 mg/dL	AMA	× 640
TP	7.9 g/dL	ICG-R15	8.3%	AMA-M2	158 Index
Alb	4.2 g/dL	Glucose	109 mg/dL	HBs Ag	(-)
TBil	0.5 mg/dL	CRP	0.2 mg/dL	HBs Ab	(-)
AST	19 U/L	IgG	1760 mg/dL	HBc Ab	(-)
ALT	14 U/L	IgM	305 mg/dL	HCV Ab	(-)
LDH	183 U/L				

AFP: Alpha-fetoprotein; AFP-L3: A Lens culinaris agglutinin-reactive fraction of alpha-fetoprotein; Alb: Albumin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AMA: Antimitochondrial antibody; AMA-M2: Anti-mitochondrial M2 antibody; ANA: Antinuclear antibodies; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CA 19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; ChE: Cholinesterase; Cr: Creatinine; CRP: C-reactive protein; γ-GTP: Gamma-glutamyltransferase; Hb: Hemoglobin; HBcAb: Hepatitis B core antibody; HBsAb: Hepatitis B surface antibody; HBsAg: Hepatitis B virus antigen; HCVAb: Hepatitis C virus antibody; Ht: Hematocrit; ICG-R15: 15-min retention rates of indocyanine green test; IgG: Immune globulin G; IgM: Immune globulin M; LDH: Lactate dehydrogenase; PIVKA-II: Prothrombin-induced vitamin K absence II; Plt: Platelet; PT: Prothrombin time; PT-INR: Prothrombin time international normalized ratio; RBC: Red blood cell count; TBil: Total bilirubin; T-Chol: Total cholesterol; TG: Triglyceride; TP: Total protein; WBC: White blood cell count.

5 of the liver. Since it was not possible to detect the tumor with intraoperative US, partial resection of the liver on the basis of the anatomical structure, including the Glissonean sheath and the hepatic vein, was performed. HE staining revealed a pseudoglandular pattern of HCC (Figure 3). In the immunohistochemistry, recurrent HCC was negative for AFP and EpCAM but positive for CK18 and hepatocyte (data not shown). There was no recurrence and/or metastasis 10 mo after re-hepatectomy.

DISCUSSION

While some cases of PBC complicated by HCC have been reported[5-8], only 1 case of PBC with cHCC-CCC has been reported[9]. The present case of PBC was metachronously complicated by both cHCC-CCC and HCC; to the best of our knowledge, such a case has never been reported.

While the etiology of PBC remains unknown, it is well known that the intrahepatic bile ducts are to be destructed slowly and progressively, leading to cirrhosis[12]. PBC

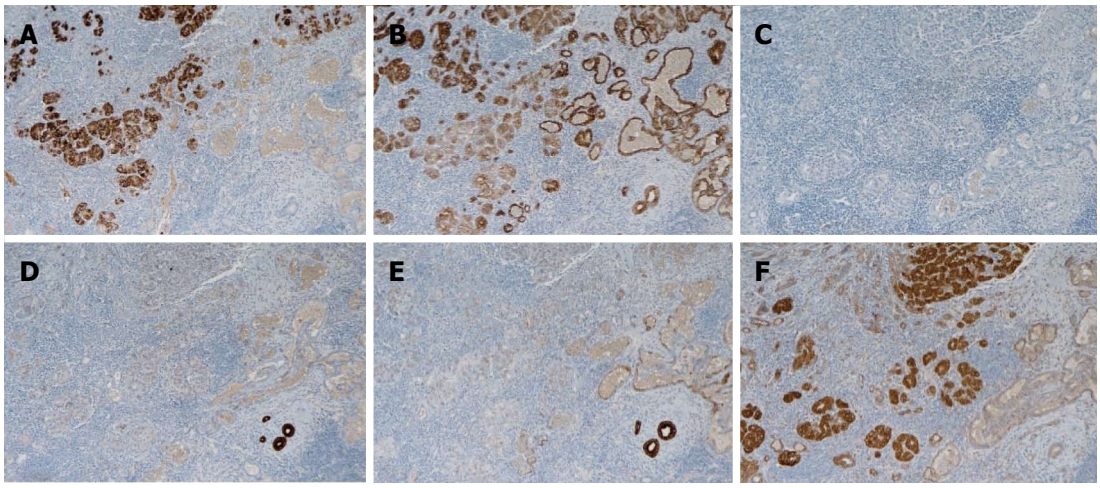

Figure 2 Immunohistochemistry findings for the initial tumor. A: HCC component stained positive for hepatocyte; B: HCC component stained positive for CK18; C: Both HCC and CCC components stained negative for alpha fetoprotein; D: CCC component stained positive for CK7; E: CCC component stained positive for CK19; F: Epithelial cell adhesion molecule stained positive for the HCC component and weakly positive for the CCC component. CCC: Cholangiocellular carcinoma; CK: Cytokeratin; HCC: Hepatocellular carcinoma.

Table 2 Laboratory data on the re-hepatectomy

WBC	3600/μL	AST	29 U/L	PIVKA-II	28 mAU/mL
RBC	397 × 10^4/μL	ALT	18 U/L	AFP	5 ng/mL
Hb	12.0 g/dL	LDH	186 U/L	AFP-L3	11.7%
Ht	35.9%	ALP	300 U/L	CEA	1.0 ng/mL
Plt	22.3 × 10^4/μL	γ-GTP	79 U/L	CA 19-9	29 U/mL
PT	77.3%	ChE	211 IU/L	ICG-R15	7.4%
PT-INR	1.12	BUN	16.1 mg/dL	Glucose	138 mg/dL
TP	7.3 g/dL	Cr	0.6 mg/dL	CRP	0.2 mg/dL
Alb	3.8 g/dL	T-Bil	0.4 mg/dL		

AFP: Alpha-fetoprotein; AFP-L3: A Lens culinaris agglutinin-reactive fraction of alpha-fetoprotein; Alb: Albumin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; ChE: Cholinesterase; Cr: Creatinine; CRP: C-reactive protein; γ-GTP: Gamma-glutamyltransferase; Hb: Hemoglobin; Ht: Hematocrit; ICG-R15: 15-min retention rates of indocyanine green test; LDH: Lactate dehydrogenase; PIVKA-II: Prothrombin-induced vitamin K absence II; Plt: Platelet; PT: Prothrombin time; PT-INR: Prothrombin time international normalized ratio; RBC: Red blood cell count; T.Bil: Total bilirubin; TP: Total protein; WBC: White blood cell count.

occurs more often in middle-aged women and is often asymptomatic in its early stage[13,14]. The frequency of HCC development in patients with PBC is estimated to be 0.7%-3.6%. While this frequency increases as the histological stages progress[2,5,6,9,11,15-20], the carcinogenic mechanism of primary liver cancer in PBC remains unclear. Although our patient's PBC progressed to stage 3 of 4, when primary liver cancer was found, she had no liver cirrhosis symptoms.

Few studies have evaluated the imaging characteristics of cHCC-CCC, and no studies have evaluated the ability of preoperative imaging to determine diagnosis. The appearance of HCC and CCC is well known on contrast-enhanced MRI and CT. The histological composition and relative ratio of CCC and HCC components within cHCC-CCC appear to dictate the imaging appearance. Tumors may show features typical of HCC, such as arterial enhancement, washout and pseudocapsule, whereas other regions within the tumor show progressive or delayed enhancement, necrosis and possible ductal dilation more akin to CCC[21]. The cHCC-CCC display enhancement patterns resembling CCC or HCC in comparable proportion on both contrast-enhanced US and CT[22]. Some suggest that the combination of imaging features and tumor markers may be helpful in preoperative diagnosis of cHCC-CCC[23]. In our case, since dynamic CT showed arterial enhancement and washout imaging, we performed initial hepatectomy expected for HCC.

Allen *et al*[24] classified cHCC-CCC into three subtypes: type A, "double cancer" representing cases in which HCC and CCC exist separately; type B, "combined" type, HCC and CCC components existing contiguously, but independently; and type C, "mixed" type, consisting of truly combined HCC and CCC components originating from the same tumor. Based on the morphological findings from HE staining, the present case was classified as mixed type cHCC-CCC.

In recent years, the ability of hepatic precursor cells to differentiate into hepatocytes and bile duct cells,

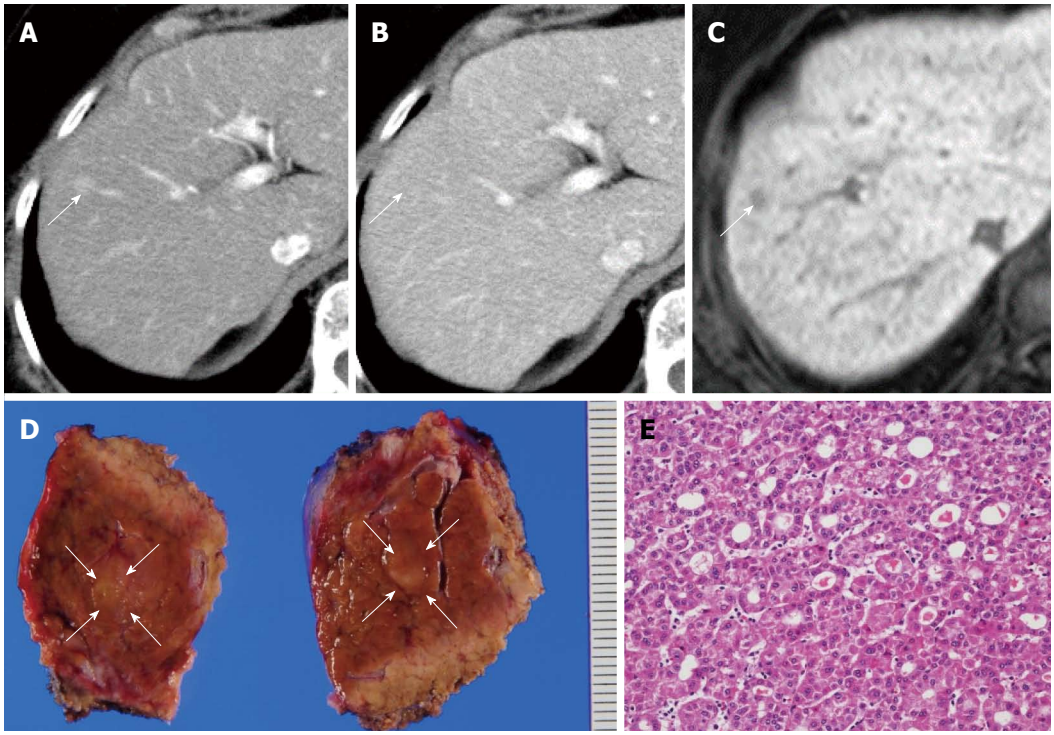

Figure 3 The second tumor. A: The enhanced tumor of 10 mm in diameter in segment 5 on the early phase in dynamic CT; B: The iso-density tumor on the delayed phase; C: Low intensity tumor on the hepatocyte phase in MRI; D: Cut surface of the 10-mm solid mass in segment 5; E: HE staining showing a pseudoglandular pattern of HCC. CT: Computed tomography; HCC: Hepatocellular carcinoma; HE: Hematoxylin-eosin; MRI: Magnetic resonance imaging.

and of hepatic stem cells to proliferate and differentiate have been proposed. As candidate stem cells, cells derived from the Herring duct or small oval cells may be able to differentiate into hepatocytes and bile duct cells[25-27]. Carcinogenesis of the precursor cells has been suggested as a developmental mechanism for cHCC-CCC with tissue components of HCC and CCC. In the present case, as Theise *et al*[28] indicated, the result of EpCAM immunohistochemistry (a stem cell marker), might be consistent with that of mixed type cHCC-CCC.

The pathological results of the initial tumor showed the trabecular pattern in the component of HCC, while that of the second tumor showed the pseudoglandular pattern in HCC. Immunohistochemistry also revealed the different pattern, which led the authors to speculate that the second tumor did not recur from the HCC component of cHCC-CCC, but the multicentric development of PBC-derived metachronous tumors.

In conclusion, we herein report a rare case of PBC metachronously complicated by both cHCC-CCC and HCC. In patients with PBC, it is necessary to check up not only liver function but also carcinogeneses, including HCC, CCC and cHCC-CCC.

ARTICLE HIGHLIGHTS

Case characteristics

A 74-year-old Japanese woman was diagnosed as primary biliary cholangitis (PBC) in her 40's by using blood tests. Imaging studies, including abdominal ultrasonography (US) and computed tomography (CT), and tumor markers consisting of alpha fetoprotein (AFP) and protein induced by vitamin K absence (PIVKA-II) were checked up every 6-12 mo. She was admitted to the authors' department for further management of an asymptomatic liver mass.

Differential diagnosis

Combined hepatocellular carcinoma and cholangiocellular carcinoma (cHCC-CCC), hepatocellular carcinoma (HCC) and cholangiocellular carcinoma (CCC) were considered from imaging tests.

Laboratory diagnosis

In the initial surgery, serum levels of AFP, PIVKA-II, carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9, and the L3 fraction of AFP were all within normal limits. One year after the initial hepatectomy, tumor marker levels for AFP, PIVKA-II, CEA, and CA 19-9 were within normal limits; only AFP-L3 isoform level was elevated.

Imaging diagnosis

The authors diagnosed both the first and second tumors as HCC from the imaging findings.

Pathological diagnosis

First, hematoxylin-eosin (HE) staining revealed two components, consisting of the trabecular type of HCC and CCC, resulting in the definitive diagnosis of cHCC-CCC. Second, HE staining revealed a pseudoglandular pattern of HCC.

Treatment

The first one was that the tumor was involved in middle hepatic vein (MHV). If radiofrequency ablation was performed, the cooling effect around the MHV would have occurred, leading to the insufficient ablation. The second one was that the tumor was not detected using US preoperatively. Moreover, the tumor was not detected even with intraoperative contrast-enhanced US. Therefore,

the authors performed partial resection on the basis of the anatomical structure, including the Glissonean sheath and the hepatic vein.

Related reports

This report relates to this reference: Kobayashi M, Furuta K, Kitamura H, Oguchi K, Arai M, Koike S, Nakazawa K. A case of primary biliary cirrhosis that complicated with combined hepatocellular and cholangiocellular carcinoma. *Clin J Gastroenterol* 2011; 4: 236-241.

Term explanation

PBC: Primary biliary cholangitis, is marked by slow progressive destruction of the intrahepatic bile ducts, which leads to cirrhosis.

Experiences and lessons

In patients with PBC, it is necessary to check up not only liver function but also carcinogenesis including HCC, CCC and cHCC-CCC.

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