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Case Report

A Case of Dual-pathology Hepatocellular Carcinoma (HCC) and Cholangiolocellular Carcinoma (CoCC) after Eradication of Hepatitis C Virus (HCV) Infection

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A 75-year-old Japanese man visited our hospital for further examination of liver tumors. He had a history of successful hepatitis C virus (HCV) eradication and therapy for hepatocellular carcinoma (HCC) at another hospital. Magnetic resonance imaging (MRI) revealed two tumors in the liver. He underwent anterior inferior (S5) and posterior inferior (S6) subsegmentectomy of the liver. Microscopic examination found that one tumor was HCC while the other was cholangiolocellular carcinoma (CoCC).
We experienced a rare case of liver cancer with two synchronous pathologies, HCC and CoCC.

Key words: hepatocellular carcinoma (HCC), cholangiolocellular carcinoma (CoCC), hepatitis C virus (HCV)

Eradication of HCV has generally been shown to prevent the occurrence of HCC [1,2]. On the other hand, some reports have shown that HCC develops in some patients who achieve sustained viral response (SVR) with interferon-ribavirin combination therapy and/or direct-acting antiviral agents (DAAs) [3,4]. The frequency of primary liver cancer manifesting synchronously with different pathologies is very low [5]. Moreover, cholangiolocellular carcinoma (CoCC) is rare among primary malignant liver tumors [6].

Case Report

The patient was a 75-year-old man who was referred to our hospital for further examination of liver tumors. He had a history of successful HCV eradication 3 years prior, and transcatheter arterial chemoembolization (TACE) therapy and radiofrequency ablation (RFA) 2 years prior, at a different hospital. He also had a history of cerebral infarction and diabetes, but no history of blood transfusion or excessive alcohol intake. His physical examination showed no abnormality.

Blood studies upon admission showed that he had normal liver function, with aspartate aminotransferase (AST) of 28 U/l (normal range: 13-30), alanine aminotransferase (ALT) 16 U/l (10-42), and gamma-glutamyl transpeptidase (γGTP) 23 U/l (13-64). He did have mild anemia with hemoglobin 11.6 g/dl (14.0-17.5) and a slightly elevated HbA1c of 6.7% (4.3-5.8). Other labs were normal: total bilirubin, 0.6 mg/dl (0.30-1.20); total protein, 8.1 g/dl (6.7-8.3); albumin, 4.4 g/dl (3.8-5.3); prothrombin time, 70.0% (70-130) and 1.10 (international normalized ratio) (0.90-1.10); alpha-fetoprotein (AFP), 3.2 ng/ml (0-8.8); and protein-induced vitamin K absence or antagonist (PIVKA-II), 32 mAU/ml (0-40). His indocyanine green retention rate at 15 minutes (ICG-R15) of 17.5 meant slight dam-

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age to his hepatic reserve. Hepatitis B virus (HBV) surface antigen (HBsAg) was negative, and HCV antibody (HCVAb) was positive but not detected on HCV-RNA by nested reverse transcription polymerase chain reaction (RT-PCR) (Table 1).

Abdominal ultrasonography (US) showed a low- and high-echoic lesion 14 mm in diameter, in the inferior subsegment of anterior sector (Couinaud's segment 5: S5) (Fig. 1). In the non-contrast computed tomography (CT) study, the lesion was unclear, but contrast CT depicted a homogeneously enhanced tumor in the early phase with a low-density area compared to the adjacent parenchyma on the late phase. Both CT and US suggested that liver had only a single lesion (Fig. 2).

However, MRI revealed that there were two heterogeneous tumors in S5. The larger one (as described lesion) which was unclear on T1-weighted images and high-intensity on T2-weighted images, was the tumor identified by US and CT (Fig. 3). But another tumor 6 mm in diameter coexisted near the gallbladder in S5. This smaller tumor showed slightly low intensity on T1-weighted images and high intensity on T2-weighted images. This smaller tumor was only detected by MRI (Fig. 4).

Angiographic imaging showed only one hypervascular tumor stain in S5 (Fig. 5).

Table 1 Laboratory findings on admission

WBC	4400	/μl	BUN	19.2	mg/dl
RBC	395×10^4	/μl	CRTN	0.9	mg/dl
Hb	11.6	g/dl	Uric acid	5.9	mg/dl
Ht	34.6	%	Na	144	mEq/l
PLT	16.5×10^4	/μl	K	4.7	mEq/l
PT	83.8	%	Cl	106	mEq/l
CRP	0.04	mg/dl	Ca	9.8	mg/dl
			HDL-cho	46	mg/dl
T.Bil	0.61	mg/dl	LDL-cho	138	mg/dl
D.Bil	0.07	mg/dl	Triglyceride	87	mg/dl
T.P	7.5	g/dl	Blood sugar	108	mg/dl
Alb	3.9	g/dl	HbA1c	6.7	%
AST	28	U/l	HBsAg	(−)	
ALT	16	U/l	HCVAb	(+)	
ALP	420	U/l	HCV-RNA	n.d	
γGTP	23	U/l	AFP	3.2	ng/ml
LDH	220	U/l	PIVKA-II	32	mAU/ml
ChE	211	U/l	ICG-R15	17.5	

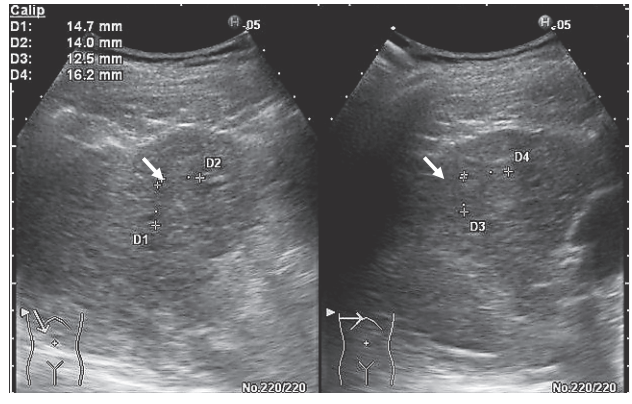

Fig. 1 Abdominal ultrasonography (US) showed a poorly demarcated lesion with low-echoic peripheral area and high-echoic central area in the anterior inferior portion of the liver.

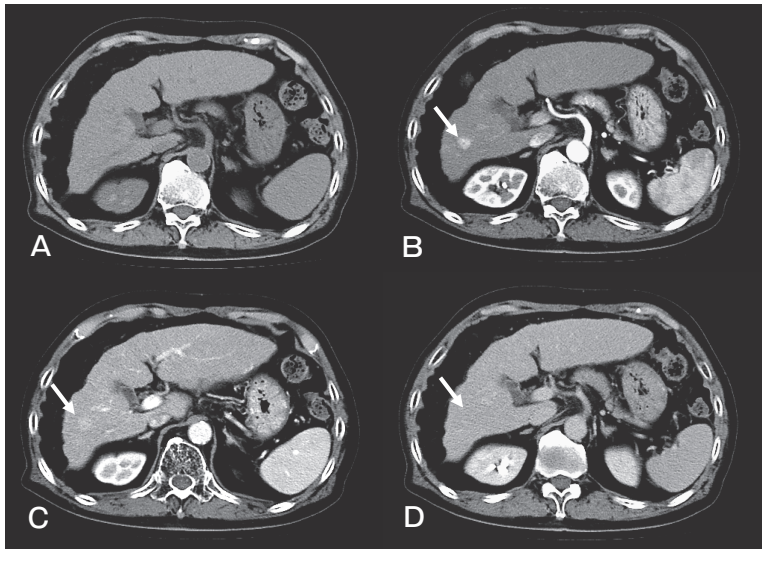

Fig. 2 Abdominal computed tomography (CT) without contrast study (**A**) and with contrast study (**B–D**); The non-contrast CT study showed an unclear lesion (**A**). However, contrast CT depicted a homogeneously enhanced tumor in the early phase (**B**), and a tumor with lower density than the adjacent hepatic parenchyma in the delayed phase (**D**). The liver itself looked cirrhotic.

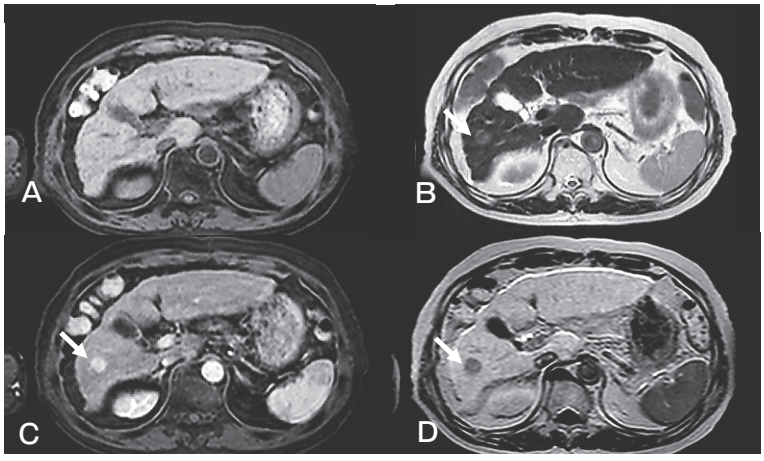

Fig. 3 On abdominal magnetic resonance imaging (MRI), the large lesion was not observed with T1-weighted imaging (**A**) but was observed as a hyperintense mass on T2-weighted imaging (**B**) in the anterior inferior portion (S5) of the liver. The same lesion was observed as a hyperintense mass in the artery phase (**C**) and as a hypointense mass in the hepatobiliary phase after the administration of Gd-EOB-DTPA.

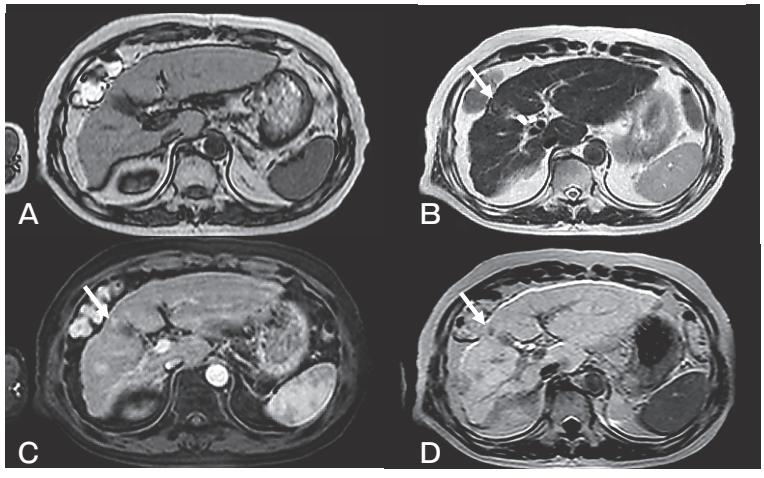

Fig. 4 On abdominal magnetic resonance imaging (MRI), the smaller lesion near the gallbladder that was undetected by US and CT was also not observed on T1-weighted imaging (**A**), but was observed as a hyperintense mass on T2-weighted imaging (**B**). The same lesion was observed as a hyperintense mass in the artery phase (**C**) and as a hypointense mass in the hepatobiliary phase after the administration of Gd-EOB-DTPA.

We thought that the larger tumor was HCC and considered the smaller tumor a satellite nodule. In June 2010 the patient underwent anterior inferior (S5) and posterior inferior (S6) subsegmentectomy of the liver, together with cholecystectomy.

Macroscopically, the resected section of the liver was observed to contain the larger tumor as a well-encapsulated whitish mass, 11 mm in diameter. The smaller tumor near the gallbladder was unclear upon gross inspection (Fig. 6).

On microscopic examination, the larger tumor in S5 was found to be well-differentiated HCC (Fig. 7A), while the smaller tumor near the gallbladder was CoCC (Fig. 7B-D). The cells of the smaller tumor had ovoid nuclei with few atypia and had proliferated in the anastomosing pattern of small glands, mimicking a ductular reaction — similar to cholangioles with a background of abundant fibrous stroma and hyaline tissue (Fig. 7B). These cells were immunohistologically positive for poly-

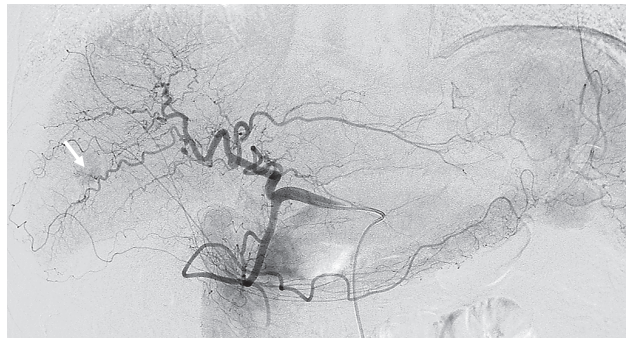

Fig. 5 Angiographic imaging showed only one hypervascular tumor stain in S5 but did not stain the nearby gallbladder. Hepatic arteries had a corkscrew appearance.

clonal CEA and CD56 (N-CAM) (Fig. 7C, D). The liver parenchyma surrounding the 2 tumors showed cirrhotic and chronic active inflammation. The patient's postoperative course was uneventful, and he was discharged on postoperative day 20. Unfortunately, he died of pneumonia 2 years later, but with no recurrence of HCC or CoCC.

Discussion

Cells of CoCC resemble cholangioles in structure, and mimic a ductular reaction with abundant fibrous stroma [7]. CoCC is composed of small, regular glandular structures that are enlarged to border sheets of cuboidal cells with oval nuclei [7].

It is typically very difficult to diagnose CoCC. Not only is the frequency of CoCC extremely rare, but also the malignancy of the tumor is extremely difficult to identify pathologically [8]. The features that may help to differentiate CoCC from benign ductular reactions are the presence of more than one cell layer linking the tumoral ductular structures, the location of tumoral ductules in the middle of the lobules and at the margin of the portal tract, and an infiltrative pattern at the border of the lesion as well as the invasion of portal tracts within the tumor itself [8]. CD56 (N-CAM) is expressed in benign bile ductules as well as ductular structures of CoCC [9]. Differential diagnosis from intrahepatic cholangiocarcinoma (ICC) or cholangiocellular carcinoma (CCC) is easier because ICC/CCC has a more malignant appearance with architectural and cytologic abnormalities, and ICC/CCC is commonly negative for CD56 (N-CAM) [9]. In our patient, the cells of the smaller tumor had ovoid nuclei with few atypia, and had proliferated in the anastomosing pattern of small glands, mimicking a ductular reaction with a background of abundant fibrous stroma and hyaline tissue. These cells were immunohistologically positive for polyclonal CEA [7]and CD56 (N-CAM) [9]. Hence, we could diagnose CoCC but not ICC/CCC.

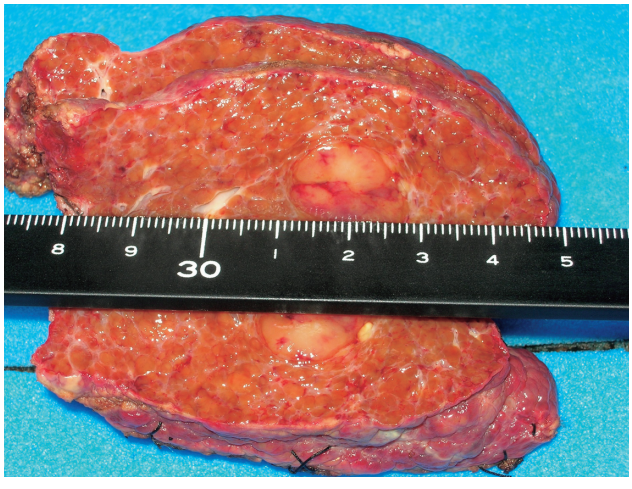

Fig. 6 Macroscopically, the large resected tumor specimen appeared as a well-encapsulated whitish mass, 11 mm in diameter. The smaller tumor near the gallbladder was not easily visualized.

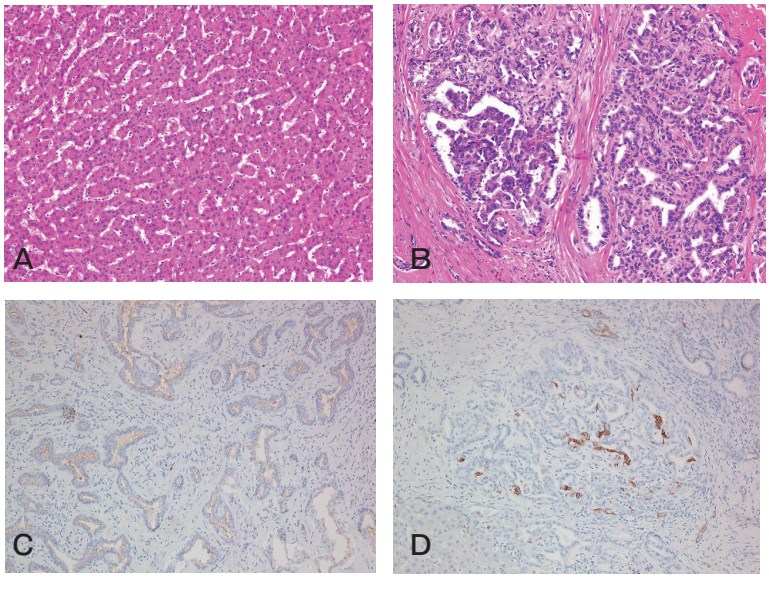

Fig. 7 Microscopically, the large lesion was well differentiated hepatocellular carcinoma (HCC) (**A**: Hematoxylin and eosin (H-E) stain). The smaller lesion appeared as cells with ovoid nuclei, which proliferated in an anastomosing pattern of small glands, mimicking ductular reactions with a background of abundant fibrous stroma and hyaline tissue (**B**: H-E stain). These cells were immunohistologically positive for polyclonal CEA (**C**) and CD56 (N-CAM) (**D**); thus, the histological diagnosis was cholangiolocellular carcinoma (CoCC).

Recently, eradication of HCV has been shown to prevent the occurrence of HCC [1]. Singal *et al.* reported that achieving SVR was associated with lower liver-related morbidity and mortality [10]. But other studies showed that HCC developed in some patients although they achieved SVR with therapy of interferon and ribavirin [3]. In a study by Sanefuji *et al.* comparing 6 SVR with 20 non-SVR patients, the intervals between the achievement of SVR and the detection of the initial HCC ranged from 13 to 152 months with a mean interval of 74 months (6.2 years) [11]. Nojiri *et al.* reported in their study that potential risk factors for HCC after SVR ware male gender, advanced fibrosis, older age at treatment and sustained elevated ALT [12]. Huang *et al.* reported a lack of strong evidence for increased risk of HCC occurrence or recurrence in HCV-infected patients treated with DAAs, but significant evidence for a decline in the incidence of HCC occurrence after SVR [4].

The frequency of synchronous dual-pathology primary cancers in the liver is very low, and most cases reported with this phenomenon had HCC and ICC/CCC [5]. In our search of the English literature, we found 6 case reports of synchronous dual-pathology liver cancers with HCC and CoCC [13-18]. The first case of CoCC was reported by Steiner and Higginson [6]. Recently, several studies have postulated that CoCC originates with hepatic stem cells [7,8,19]. CoCC is a very rare malignant primary hepatic tumor, accounting for 0.56% of primary hepatic tumors in Japan [19]. In an assessment of the 6 CoCC cases by Shiota *et al.*, 3 of the 6 (50%) cases were positive for HCVAb, one case (16.7%) was positive for HBsAg, and 2 cases (33.3%) were negative for both HBsAg and HCVAb [19]. In a report of 24 CoCC cases checked for serum virus markers, 6 of 24 (25%) were positive for HCVAb, one case (4.2%) was positive for HBsAg only, and 2 cases (8.3%) were negative for both HBsAg and HCVAb [7]. These findings may suggest that occurrence of CoCC is mainly associated with HCV infection. Our patient was also positive for HCVAb, but was not detected as such on HCV-RNA by RT-PCR. The reason why MRI was the only diagnostic tool that could differentiate CoCC might be the slow-growing nature of this smaller tumor.

Unfortunately, histopathological study of the primary liver tumor was not done before our patient received TACE and RFA. Therefore, we cannot determine the clinical details of how his synchronous dual-pathology hepatic cancer occurred. We speculate that the primary liver tumor would be CoCC or combined HCC/CoCC, and that different component cancers recurred synchronously in the different liver areas.

Further research is needed to clarify the frequency of synchronous dual-pathology HCC and CoCC cancer, and to investigate the frequency of CoCC occurrence after eradication of HCV.

References

1. DiMartino V, Crouzet J, Hillon P, Thevenot T, Minello A and Monnet E: Long-term outcome of chronic hepatitis C in a population-base cohort and impact of antiviral therapy: a propensity-adjusted analysis. J Viral Hepat (2011) 18: 493–505.
2. Ioannou GN, Green PK and Berry K: HCV eradication induced by direct- acting antiviral agents reduced the risk of hepatocellular carcinoma. J Hepatol (2018) 68: 25–32.
3. Kurokawa M, Hiramatsu N, Oze T, Mochizuki K, Yakushijin T, Kurashige N, Inoue Y, Igura T, Imanaka K, Yamada A, Oshita M, Hagiwara H, Mita E, Ito T, Inui Y, Hijioka T, Yoshihara H, Inoue A, Imai Y, Kato M Kiso S, Kanto T, Takehara T, Kasahara A and Hayashi N: Effect of interferon α-2b plus ribavirin therapy on incidence of hepatocellular carcinoma in patients with chronic hepatitis. Hepatol Res (2009) 39: 432–438.
4. Huang P, Liu M, Zang F, Yao Y, Yue M, Wang J, Fan H, Zhuo L, Wu J and Xia X: The development of hepatocellular carcinoma in HCV-infected patients treated with DAA: A comprehensive analysis. Carcinogenesis (2018) 39: 1497–1505.
5. Allen RA and Lisa JR: Combined liver and bile duct carcinoma. Am J Pathol (1949) 25: 647–655.
6. Steiner PE and Higginson J: Cholangiolocellular carcinoma of the liver. Cancer (1959) 12: 753–750.
7. Komuta M, Spee B, Borght SV, DeVos R, Verslype C, Aerts R, Yano H, Suzuki T, Matsuda M, Fujii H, Desmet VJ, Kojiro M and Roskams T: Clinicopathological study on cholangiolocellular carcinoma suggesting hepatic progenitor cell origin. Hepatology (2008) 47: 1544–1556.
8. Sempoux C, Fan C, Singh P, Obeidat K, Roayaie S, Schwartz M, Fiel MI and Thung SN: Cholangiolocellular carcinoma: An innocent-looking malignant liver tumor mimicking ductular reaction. Semin Liver dis (2011) 31: 104–110.
9. Guetgemann I, Haas S, Berg JP, Zhou H, Buettner R and Fischer HP: CD56 expression aids in the differential diagnosis of cholangiocarcinomas and benign cholangiocellular lesions. Virchows Arch (2006) 448: 407–411.
10. Singal AG, Volk ML, Jensen D, DiBisceglie AM and Schoenfeld PS: A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. Clin Gastroenterol Hepatol (2010) 8: 280–288.
11. Sanefuji K, Kayashima H, Iguchi T, Sugimachi K, Yamashita Y, Yoshizumi T, Soejima Y, Nishizaki T, Taketomi A and Maehara Y: Characterization of hepatocellular carcinoma developed after achieving sustained virological response to interferon therapy for hepatitis C. J Surg Oncol (2009) 99: 32–37.
12. Nojiri K, Sugimoto K, Shiraki K, Kusagawa S, Tanaka J, Beppu T, Yamamoto N, Takei Y, Hashimoto A, Shimizu A, Omori S,

Tameda M and Takase K: Development of hepatocellular carcinoma in patients with chronic hepatitis C more than 10 years after sustained virological response to interferon therapy. Oncol Letters (2010) 1: 427–430.
13. Matsuda M, Hara M, Suzuki T, Kono H and Fujii H: Synchronously resected double cancers—hepatocellular carcinoma and cholangiolocellular carcinoma. J Hepatobiliary Pancreat Surg (2006) 13: 571–576.
14. Ikeda M, Morise Z, Takeura C, Kagawa T, Tanahashi Y, Okabe Y, Tokoro T, Mizoguchi Y and Sugioka A: A resected case of double primary hepatic carcinomas-hepatocellular carcinoma and cholangiolocellular carcinoma. Jpn J Gastroenterol Surg (2010) 43: 1141–1145.
15. Kawano Y, Kikuchi S, Miyanishi K, Nagashima H, Hirakawa M, Tamura F, Yoshida M, Takahashi S, Takada K, Hayashi T, Sato T, Sato Y, Takimoto R, Kobune M, Kawamoto M, Mizoguchi T, Hirata K, Hasegawa T and Kato J: A case of double cholangiolocellular carcinoma and hepatocellular carcinoma complicated with non-alcoholic steatohepatitis. Kanzo (2012) 53: 615–623.
16. Sunahara M, Kurauchi N, Tsunetoshi Y, Suzuki S, Kimura J, Kudo K and Shimoyama N: A case of synchronous double cancer of the liver consisting of cholangiocellular and hepatocellular carcinomas in the background of chronic hepatitis C. J Jpn Soc Clin Surg (2013) 74: 2572–2576.
17. Suzumura K, Asano Y, Hirano T, Okada T, Uyama N, Aizawa N, Iijima H, Nakasho K, Nishiguchi S and Fujimoto J: Synchronous double cancers of primary hepatocellular carcinoma and cholangiolocellular carcinoma: a case report. Surg Case Rep (2016) 2: 139.
18. Yamamoto M, Oshita A, Nishisaka T, Nakahara T, Nakahara H and Itamoto T: Synchronous double primary hepatic cancer consisting of hepatocellular carcinoma and cholangiolocellular carcinoma: a case report. J Med Case Rep (2018) 12: 224–229.
19. Shiota K, Taguchi J, Nakashima O, Nakashima M and Kojiro M: Clinicopathologic study on cholangiolocellular carcinoma. Oncol Rep (2001) 8: 263–268.