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CASE REPORT

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Primary mucoepidermoid carcinoma of the intrahepatic bile duct: A case report

Kenichi Kato[1] | **Yasuyuki Hara**[1] | **Akiko Nishida**[2] | **Shuhei Suzuki**[3] | **Hidenori Sato**[4] | **Masahiro Chin**[1] | **Eiji Hashizume**[1]

[1]Department of General Surgery, Nihonkai General Hospital, Yamagata, Japan

[2]Department of Pathology, Nihonkai General Hospital, Yamagata, Japan

[3]Department of Clinical Oncology, Yamagata University Faculty of Medicine, Yamagata, Japan

[4]Genomic Information Analysis Unit, Institute for Promotion of Medical Science Research, Yamagata University Faculty of Medicine, Yamagata, Japan

Correspondence
Yasuyuki Hara, Department of General Surgery, Nihonkai General Hospital, 30 Akiho-cho, Sakata, Yamagata 998-8501, Japan.
Email: yasuhara5150@gmail.com

Abstract

Mucoepidermoid carcinoma (MEC) is the most common salivary gland carcinoma; however, hepatobiliary MEC is extremely rare. A 74-year-old patient was diagnosed with hepatobiliary MEC after hepatectomy. We considered its origin could be the peribiliary glands. Its genome profile was similar to salivary MEC rather than standard biliary tract carcinoma.

KEYWORDS

cancer genome, companion diagnostic test, fusion gene analysis, hepatobiliary mucoepidermoid carcinoma, peribiliary gland

1 | BACKGROUND

Mucoepidermoid carcinoma (MEC) is a type of cancer, which is pathologically consisted of mucin-secreting cells, epithelioid cells, and intermittent cells.[1] It is the most common malignant tumor in the salivary gland.[2] It can arise from other structures such as the bronchi[3]; however, primary hepatobiliary MEC is rare.[1] Although salivary gland MEC usually has low malignancy,[4–7] hepatobiliary MEC tends to show poor prognosis.[1,3] In addition, its pathogenesis mechanism has not been elucidated, and there are still no established therapeutic strategies for hepatobiliary MEC. Its genomic features are also unknown. We report a case of MEC diagnosed after hepatectomy and provide a brief literature review.

2 | CASE PRESENTATION

The patient was a 74-year-old man previously treated for hepatitis C with interferon therapy 10 years before. He achieved a sustained virological response (SVR). He had also undergone laparoscopic cholecystectomy for adenomyomatosis and gallbladder polyp 2 years before. During his follow-up after the SVR, a B2 localized intrahepatic bile duct dilatation was found on abdominal ultrasonography (US) (Figure 1). Computed tomography (CT) and magnetic resonance cholangiopancreatography also showed a B2 dilatation and an S2 localized tumor, which appeared to obstruct B2 (Figure 1). During endoscopic retrograde cholangiopancreatography (ERCP), brush cytology was performed at the B2 narrow point, and nasobiliary drainage was placed at

the B2 dilated segment (Figure 2). Brush cytology revealed some atypical cells with an enlarged, deeply stained nucleus. Intrahepatic cholangiocarcinoma was suspected, but an exact diagnosis could not be made. Fluorodeoxyglucose-positron emission tomography (FDG-PET) showed no abnormal FDG uptake other than the S2 tumor (maximum standardized uptake value: 13.69) (Figure 2).

Left lobe hepatectomy was performed for diagnosis and treatment. A pathological evaluation of the left hepatic duct stump during surgery was negative. The surgical time was 285 min. Blood volume was 1065 ml. The patient was in the intensive care unit until postoperative day (POD) 1. Oral intake was started on POD 3, and he was discharged on POD 11 with no major postoperative complications.

The size of the tumor was 45 × 25 × 25 mm (Figure 3). It had unclear margins and included necrotic tissue. Densely arranged mucous, intermediate, and epidermoid cells were seen on pathological examination (Figure 4). The patient was diagnosed with MEC. The pathological staging was pT3N0M0 pStageIII, based on the General Rules for the Clinical Pathological Study of Primary Liver Cancer.[8] The mass existed under the B2 epithelium; no atypia was seen in the epithelium. This finding implied that the mass arose in the subepithelium of B2 (Figure 4). It invaded neural fibers, lymphatic vessels, and extrahepatic adipose tissue. Approximately 16 mitotic cells per 10 high-power fields were seen, and a cystic component was not included in the tumor tissue. Mucous cells were positive for periodic

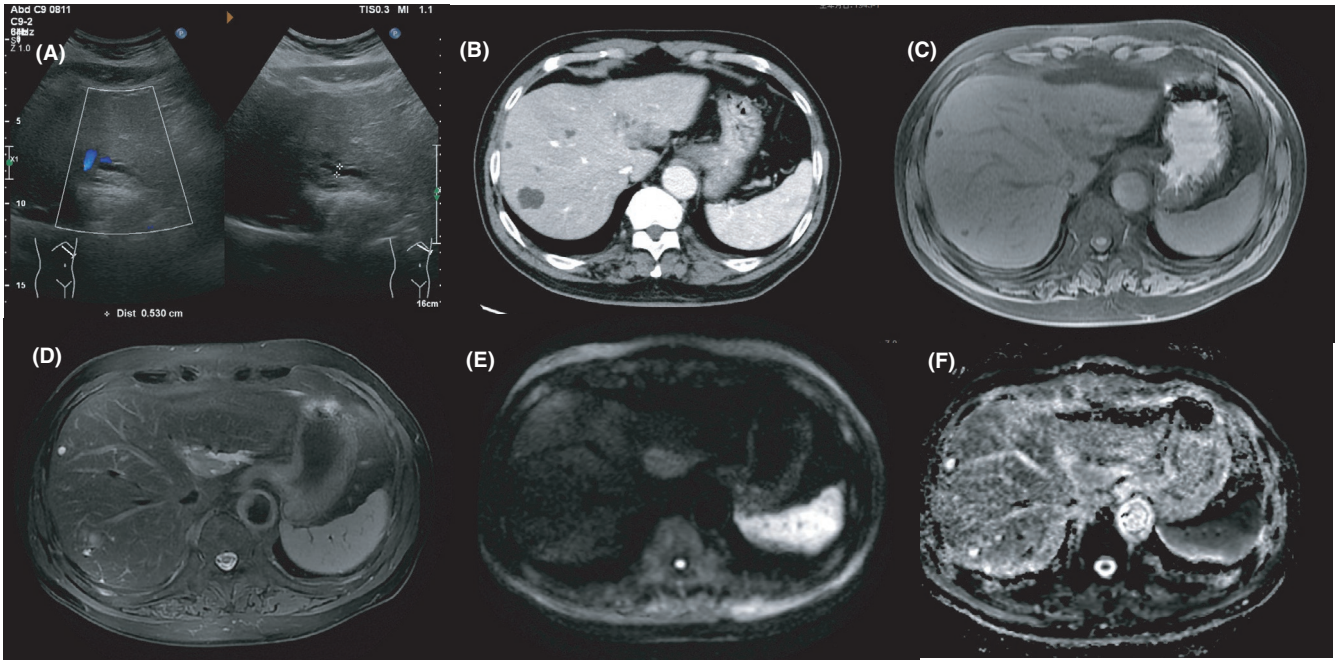

FIGURE 1 Preoperative US, CT, and MRI. (A) US showed B2 dilatation. (B) Enhanced CT revealed a low-density mass at S2. (C–F) MRI study. The mass is seen with (C) a low signal in the T1-weighted image, (D) a high signal in the T2-weighted image, (E) a high signal in the diffusion-weighted image, and (F) a low signal in the apparent diffusion coefficient. CT indicates computed tomography; MRI, magnetic resonance imaging; US, ultrasonography

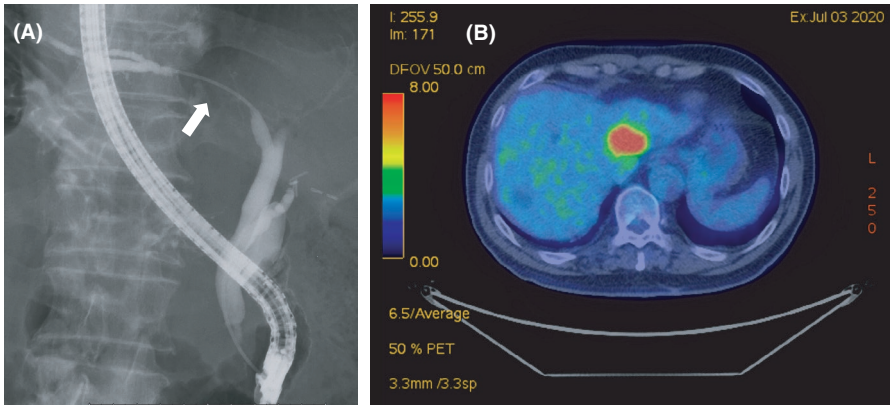

FIGURE 2 Preoperative ERCP and FDG-PET. (A) ERCP revealed B2 tumor obstruction (arrow); a nasobiliary drainage tube was placed in B2. (B) FDG-PET showed high FDG uptake at S2 tumor. ERCP, endoscopic retrograde cholangiopancreatography; FDG, fluorodeoxyglucose; PET, positron emission tomography

acid-Schiff (PAS) stain and Alcian blue stain (Figure 5). In addition, immunohistochemical staining was done (Figure 5). Mucous cells were positive for CK7; epidermoid cells were positive for CK5/6 and p40 and negative for CK7. This finding meant that these cells had traits of squamous cells. Intermittent cells were simultaneously positive for CK7 and p40, meaning that they had properties of both mucous and epidermoid cells. All cell types were negative for CK20 and CA19-9. The Ki-67 index was 40%.

After the pathological diagnosis was confirmed, an otorhinolaryngology examination was performed to search for another primary lesion, but no neoplasm was found. The patient was diagnosed with primary hepatobiliary MEC. Five months after surgical resection, CEA increased from 3.0 ng/ml 1 month after surgery to 6.0 ng/ml. A liver hilar lymph node recurrence was also detected on follow-up CT (Figure 6). Systemic chemotherapy (gemcitabine/cisplatin) was started. At the same time, a tissue-based companion diagnostic test (FoundationOne® CDx) was done. The result is shown in Table 1. He was eligible for BI 907828 (an MDM2–p53 antagonist) in a phase 1 trial (ClinicalTrials.gov ID: NCT03449381) since an MDM2 amplification was found. However, he could not participate because recruitment was temporarily terminated. There were no driver mutations, and no eligible clinical trials were available. Moreover, ribonucleic acid (RNA) sequencing was done for fusion gene analysis to search for CRTC1/3-MAML2 fusion. Multiple fusion genes including MDM2 were detected, which might reflect MDM2 amplification seen in the companion diagnostic test, but no significant findings including CRTC1/3-MAML2 fusion were found. The result is shown in Table 2. A follow-up CT revealed recurrent liver hilar lymph node enlargement and additional paraaortic lymph node metastasis 12 months after surgery. The chemotherapy regimen was changed to gemcitabine/S-1 therapy.

At this writing, 15 months after surgery, the patient is alive and continues gemcitabine/S-1 therapy.

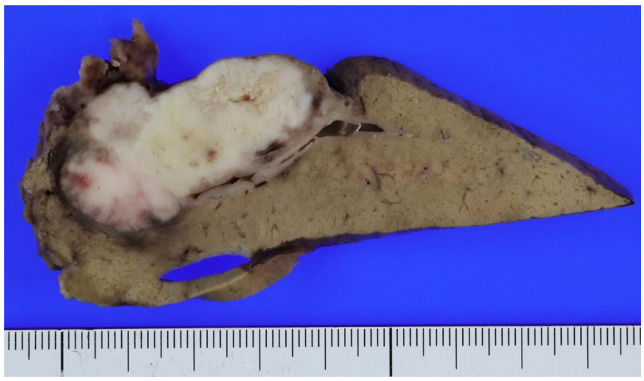

FIGURE 3 Gross resected specimen. The tumor size was 45 × 25 × 25 mm. Its cross-section looked white. It had unclear margins

3 | DISCUSSION

MEC is the most frequent histopathological type of salivary gland carcinoma.[2] It can arise from the lung, bronchus, esophagus, and thyroid gland,[3] but liver MEC is

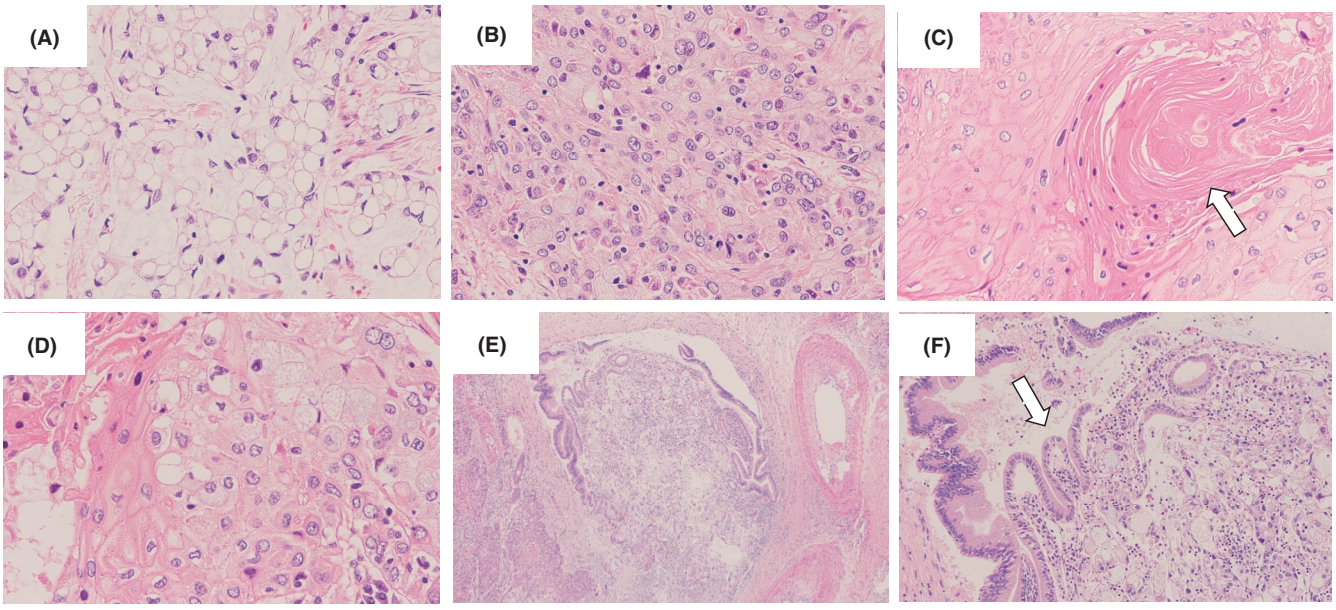

FIGURE 4 Microscopic findings of the tumor (hematoxylin and eosin stain). (A) Mucous cell dominant area. (B) Intermediate cell dominant area. (C) Epidermoid cell dominant area with keratinization (arrow). (D) Coexistence of mucous and epidermoid cells. (E,F) The tumor presented papillary growth in the intrahepatic bile duct (B2) lumen. The epithelium lining its surface had no atypia (arrow), meaning that it was generated from the subepithelium

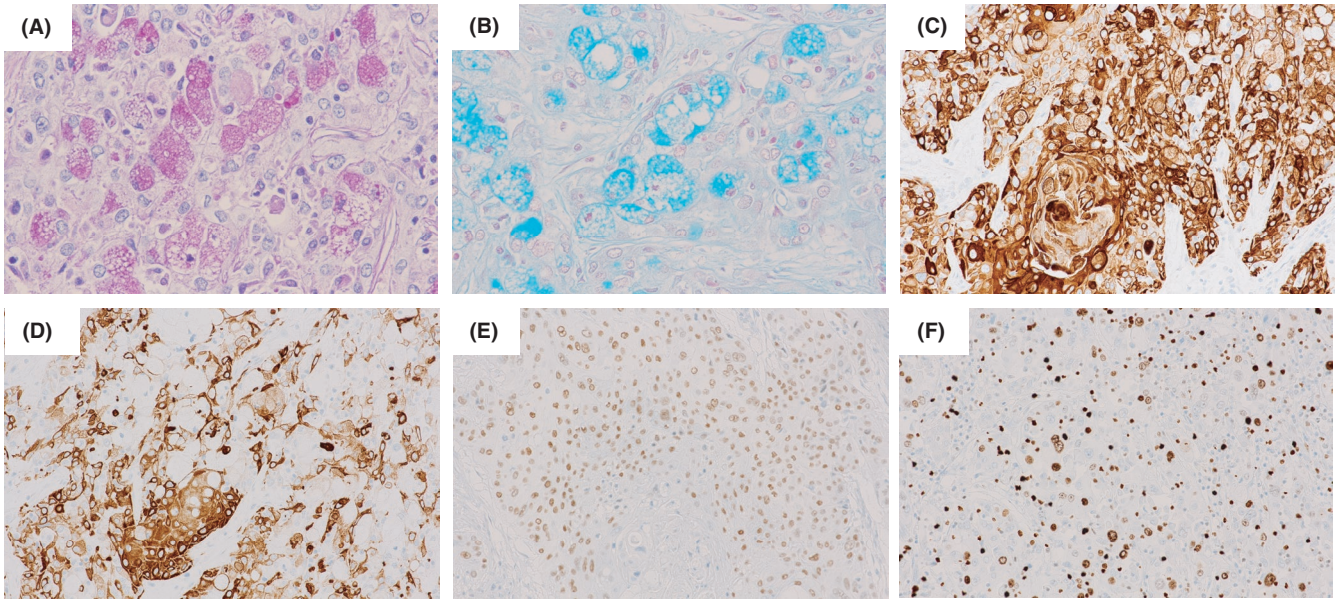

FIGURE 5 Other staining and immunohistochemical findings of the tumor. (A) PAS stain, (B) Alcian blue stain, (C) CK7, (D) CK5/6, (E) p40, and (F) Ki-67. Mucous cells were positive for (C) CK7; epidermoid cells were positive for (C) CK7, (D) CK5/6, and (E) p40; intermediate cells were positive for (C) CK7 and (E) p40. (F) Ki-67 index was 40%. PAS, periodic acid-Schiff

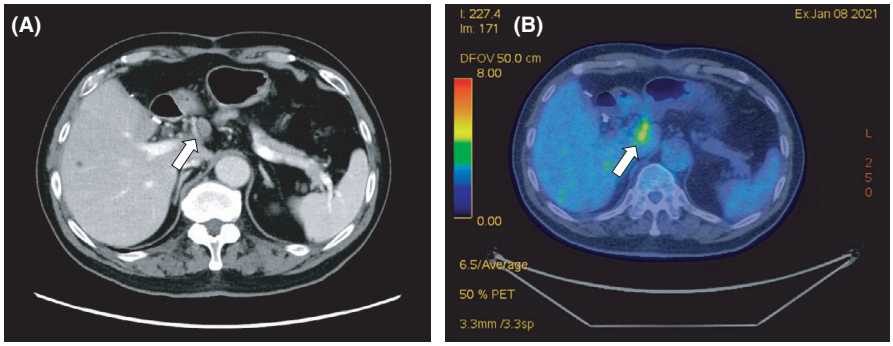

FIGURE 6 CT and FDG-PET at recurrence. (A) Hilar node metastasis was seen in CT 5 months after surgery (arrow). (B) High FDG uptake at metastatic node was seen in FDG-PET (arrow). CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography

TABLE 1 Present case result of FoundationOne® CDx

Nucleated tumor cell rate	20%
Purity	22.6
Depth	1086
TMB	0.0 Muts/Mb
MSI-H	Not detected
Quality	PASS
Single nucleotide variance	STK11 F354L 59.3% (VUS) STK11 E199fs*88 19.2%
Copy number variance	CDKN2A loss CDKN2B loss MDM2 amplification; copy number 16 MTAP loss PTEN loss FAS loss

TABLE 2 Fusion genes detected from RNA sequencing

Detected fusion genes from RNA sequencing		
RNU5B−1RNA28SN5	MDM2-SMPD3	MDM2-CDC40
MDM2-ADA2	MDM2-DPP10	MDM2-ZBTB7C
ARHGEF12-AGAP1		

Abbreviation: RNA, ribonucleic acid.

rare. Most salivary gland MECs have low malignancy, and their 5-year overall survival is 80%–90%.[4–7] In contrast, liver and esophageal MECs typically demonstrate high malignancy.[1,3] We reviewed previous case reports of hepatobiliary MEC and summarized them (Table 3).[9–24] In previous case reports, all but two cases died within 1 year after admission or surgery. In this case, the tumor also relapsed early after surgery, and the prognosis appears poor.

Regarding the origin of MEC, the salivary gland is an exocrine organ rich in secretory glands. Other structures where MEC can arise, such as the bronchi and esophagus, also have exocrine glands. MEC from the pancreas, colon, and breast, as rare as hepatobiliary MEC, has been reported.[25–27] They also have exocrine glands that can be the origin of MEC. MEC can also arise from the

TABLE 3 Reported cases of hepatobiliary MEC

Case	Year	Author	Age	Sex	Size (cm)	Location	Symptom	Metastasis	Treatment	Outcome
1	1971	Pianzola	44	Male	15	Right lobe	Abdominal pain	None	Surgical excision	Died 45 days after surgery
2	1980	Ho	65	Male	8		Jaundice	Lymph nodes	Conservation	Died 14 days after laparotomy
3	1980	Ho	63	Female	6		Abdominal pain Jaundice	Pancreas, portal vein, lymph nodes	Conservation	Died 16 days after admission
4	1982	Koo	44	Female	12	Left lobe	Epigastric pain	None	Surgical excision, Chemotherapy	Died 6 months after surgery
5	1982	Koo	66	Male	4	Common hepatic duct	Jaundice	Gall bladder, lymph nodes, right hepatic artery	Surgical excision	Died 7 days after surgery
6	1982	Koo	62	Male	1.5	Common hepatic duct	Jaundice	None	Surgical excision	Living 10 months after surgery
7	1984	Katsuda	78	Male	11	Left lobe	Abdominal discomfort	Lymph nodes, lung, kidney	Chemotherapy	Died 3 months after admission
8	1986	Lambrianides	59	Female	18	Right lobe	Abdominal pain	Right kidney	Conservation	Died 14 days after admission
9	1987	Hayashi	46	Female	3	Left lobe	Abdominal pain	None	Surgical excision	Died 11 months after surgery
10	1992	Di Palma	66	Female	9.5		Abdominal pain	Diaphragm, pericardium, portal vein	Surgical excision	Died 6 months after surgery
11	2000	Shuangshoti	64	Male	5		Jaundice	Lymph nodes, pancreas, portal vein Common bile duct	Conservation	Died 7 days after admission
12	2003	Kang	52	Male	9		Abdominal pain	Diaphragm	TAE, surgical excision	Died 6 months after surgery
13	2004	Choi	69	Female	16	Right lobe	Abdominal pain	Diaphragm	Surgical excision	Died 4 months after surgery
14	2008	Arakawa	81	Female	10	Right lobe	Fever	Lymph nodes, portal vein	Chemotherapy	Died 117 days after admission
15	2013	Moul	83	Female	2	Common bile duct	Jaundice	Liver	Surgical excision, Chemotherapy	Died 13 months after surgery
16	2014	Guo	60	Female	8.5		Jaundice, abdominal discomfort	Lymph nodes	Surgical excision, chemotherapy	Died 6 months after surgery
17	2019	Nallacheruvu	50	Male	8	Gall bladder		Liver	Surgical resection	Died 6 month after surgery
18	2019	Watanabe	79	Female	5.3	Left lobe	Abdominal pain	None	Surgical excision, chemotherapy	Living 10 years after surgery
19	2021	Hou	64	Male	10	Left lobe	Abdominal distention	None	Surgical resection	Died 3 months after surgery
20	2021	present case	74	Male	4.5	Left lobe (B2)	None	Lymph nodes	Surgical excision, chemotherapy	Living 15 months after surgery

Abbreviation: MEC, mucoepidermoid carcinoma

thyroid gland.[3] It does not have to be an exocrine gland, but it is reported that thyroid gland MECs originate in solid cell nests (SCNs).[28] SCNs are ultimobranchial body remnants that are found in the thyroid gland.[29] They sometimes include mucus cells that can be the origin of MEC.[29] In the hepatobiliary system, the extrahepatic bile duct, cystic duct, and intrahepatic large bile duct have secretory glands in the subepithelium called peribiliary glands.[30] According to Table 3, obstructive jaundice was seen in 7 cases (35%), and some extrahepatic bile duct MECs were also reported. Although obstructive jaundice was not seen, MEC occurred in the subepithelium of the intrahepatic large bile duct and obstructed B2 in this case. We suggest that the origin of hepatobiliary MEC may be the peribiliary gland. Although it is difficult to explain why MEC can arise from gallbladder which has no peribiliary glands,[22,31] that may be why the gallbladder MEC has ever been reported only one case in the world.

MEC is pathologically characterized by the coexistence of mucin-secreting, epithelioid, and intermediate cells.[1] Goode made a pathological grading system of salivary gland MEC that classifies them into three grades (low, intermediate, and high).[7] Their grading parameters consist of a cystic component, <20%, neural involvement, four or more mitotic figures per 10 high-power fields, necrosis, and anaplasia. This case meets these five criteria and is categorized as high-grade MEC. This result matches the unfavorable course of this case that relapsed early after surgery; however, it has been reported that the grading scheme for MEC of the salivary glands is not useful for hepatic MEC because those in the liver are always high grade.[1]

Some driver mutations of biliary tract cancers have been reported by analyzing their genome.[32,33] Reported driver mutations are shown in Table 4. On the contrary, frequently mutated genes in salivary gland MEC were also reported. Those that mutated in more than 10% of salivary gland MEC were CDKN2A (41.6%), TP53 (39.6%), CDKN2B (29.2%), BAP1 (20.8%), PIK3CA (20.8%), and HRAS (10.4%).[34] Of these, CDKN2A loss and CDKN2B loss were seen in this case. The CDKN2A mutation is listed in both but was seen in only 5 out of 412 biliary tract cancer cases.[32] It is a major driver mutation of salivary gland MEC than biliary tract cancer.

Furthermore, the CDKN2B mutation is listed in salivary MEC and biliary tract carcinoma. Its genome appears to be similar to salivary gland MEC rather than standard biliary tract cancer. In addition to that, MDM2 amplification was detected. MDM2 binds and inhibits p53, acting as an oncogene.[35] Andrews et al. have reported that MDM2 is highly expressed in salivary MEC tissue and MDM2-p53

TABLE 4 Reported driver mutations of biliary tract cancer

Nakamura et al.				
Common bile duct				
TP53	BRCA1	BRCA2	ERBB2	PIK3CA
Common to intra- and extrahepatic bile duct				
KRAS	SMAD4	ARID1A	GNAS	
Intrahepatic bile duct				
FGFR2 fusion	IDH1	IDH2	EPHA2[a]	BAP1
Extrahepatic bile duct				
PRKACA fusion[a]	PRKACB fusion[a]	ELF3[a]	ARID1B[a]	
Gallbladder				
EGFR	ERBB3	PTEN	ARID2[a]	MLL2
MLL3[a]	TERT promoter			
Wardell et al.				
TP53	KRAS	SMAD4	NF1	ARID1A
PBRM1	KMT2D	ATR	PIK3CA	ERBB3
KMT2C[a]	APC	BAP1	POLQ[a]	ARID2[a]
IDH1	TET1[a]	CTNNB1	BRAF	TGFBR2
PTEN	DNMT3A	FBXW7	ELF3[a]	CDKN2A
MSH6	STK11	RNF43	NRAS	MLH1
TGFBR1[a]				

[a]Not included in FoundationOne® CDx.

interaction inhibitor decreases MEC cancer stem cells.[36] MDM2 amplification may be an important finding of hepatobiliary MEC, and although we could not access the MDM2–p53 antagonist clinical trial, MDM2 inhibition may be effective for MEC. In addition, TMB was 0.0 Muts/Mb, so a genomic mutation, in this case, appeared very little.

CRTC1/3-MAML2 fusion is sometimes seen in MEC, and it is considered a favorable prognostic factor of salivary gland MEC.[37,38] A reported case of hepatobiliary MEC with CRTC1-MAML2 fusion presented a good prognosis without recurrence 10 years after surgery.[23] CRTC1/3-MAML2 fusion was not detected in this case, and early systemic chemotherapy was administered according to the treatment protocol for unresectable recurrent biliary tract carcinoma. More studies and discussions are needed to define the therapeutic strategy since there is no established treatment for hepatobiliary MEC because of its rarity.

4 | CONCLUSIONS

We report a primary hepatobiliary MEC with early recurrence after surgical resection. We believe that it originated from the peribiliary glands. Its genome profile was more similar to salivary MEC than biliary tract carcinoma.

ACKNOWLEDGEMENTS
None.

CONFLICT OF INTEREST
All authors report no conflicts of interest.

AUTHOR CONTRIBUTIONS
Author 1 performed surgery, managed the perioperative course, and wrote the manuscript. Author 2 performed surgery, managed the perioperative course, followed up the patient and did chemotherapy, and mainly supervised the manuscript. Author 3 diagnosed with hepatobiliary MEC pathologically, considered its origin, and supervised pathological part of the manuscript. Author 4 considered the result of companion diagnostic test and fusion gene analysis and supervised oncogenomical part of the manuscript. Author 5 did RNA sequencing for fusion gene analysis and considered the result. Author 6 supervised the patient surgical treatment and checked and approved the manuscript as a person responsible for the department of surgery. Author 7 supervised the patient surgical treatment and checked and approved the manuscript as a person responsible for the department of surgery.

ETHICAL APPROVAL
The present study was conducted in accordance with the ethical review board of our hospital.

CONSENT
Written informed consent for publication of this case report and any accompanying images was obtained from the patient.

DATA AVAILABILITY STATEMENT
The datasets used during the current report are available from the corresponding author on reasonable request.

ORCID
Kenichi Kato https://orcid.org/0000-0002-6977-8289

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