CASE REPORT – OPEN ACCESS

International Journal of Surgery Case Reports 39 (2017) 43–50

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.casereports.com

A long-term recurrence-free survival of a patient with the mixed adeno-neuroendocrine bile duct carcinoma: A case report and review of the literature

Wataru Izumo[a,*], Ryota Higuchi[a], Takehisa Yazawa[a], Shuichiro Uemura[a], Yutaro Matsunaga[a], Masahiro Shiihara[a], Toru Furukawa[b], Masakazu Yamamoto[a]

[a] Department of Surgery, Institute of Gastroenterology, Tokyo Women's Medical University, Japan
[b] Institute for Integrated Medical Sciences, Tokyo Women's Medical University, Japan

ARTICLE INFO

Article history:
Received 3 March 2017
Received in revised form 26 July 2017
Accepted 26 July 2017
Available online 4 August 2017

Keywords:
Mixed adeno-neuroendocrine carcinoma
MANEC
Bile duct
Long term survival
Case report

ABSTRACT

INTRODUCTION: Neuroendocrine tumors arising primarily in the bile duct are rare. And among these tumors, mixed adeno-neuroendocrine carcinoma (MANEC) is quite uncommon. We report a patient with MANEC who achieved long-term recurrence-free survival. And our case report includes analysis previous case reports.

PRESENTATION OF CASE: A 66-year-old man underwent investigation for persistent anorexia and fatigue. Laboratory tests showed that the values of hepatobiliary enzymes were increased. On CT, a 10 mm × 8 mm hypervascular tumor was observed in the distal bile duct and the proximal bile duct was markedly dilated. Endoscopic retrograde cholangiography (ERC) also showed a stenosis with a long diameter of 10 mm. Examination of a biopsy specimen obtained from the narrow site of the bile duct at the time of ERC revealed tubular adenocarcinoma. Therefore, pylorus-preserving pancreaticoduodenectomy was performed under a preoperative diagnosis of distal bile duct carcinoma. Postoperative pathologic examination revealed alveolar structures and a mixture of moderately differentiated adenocarcinoma with synaptophysin-positive and chromogranin-A-positive neuroendocrine carcinoma. Therefore, the final diagnosis was MANEC, pT3, pN1, M0, pStage II B (TNM classification of the UICC). Curative resection was achieved and there has been no recurrence after 30 months.

DISCUSSION: In the previous reports, only five patients (14.7%) survived for 24 months or longer. Median survival was longer (14 months) in the curative resection group and shorter (6 months) in the non-curative resection group.

CONCLUSION: Curative resection is essential to achieve long-term survival in patients with bile duct MANEC, even if these patients have lymph node metastasis.

1. Introduction

Neuroendocrine tumors arising primarily in the bile duct are rare. Among these tumors, mixed adeno-neuroendocrine carcinoma (MANEC) is quite uncommon and its prognosis is thought to be poor. We report a patient with MANEC arising primarily in the bile duct who achieved long-term recurrence-free survival.

2. Presentation of case

A 66-year-old man underwent investigation for persistent anorexia and fatigue which had persisted for one month. On his past history and family history, there was nothing noteworthy, including no evidence of multiple endocrine neoplasia type1or von Hippel-Lindau disease. And he was not a smoker or a drinker. On his occupational history, he had not worked in printing industry where incidence of the bile duct carcinoma is known to be high. On his physical examination, the bulbar conjunctiva was yellow. Laboratory tests showed that the values of hepatobiliary enzymes were increased (T-Bil was 8.9 mg/dl, D-Bil was 5.6 mg/dl, AST was 377 U/L, ALT was 653 U/L, ALP was 1105 U/l, and γ-GTP was 2291 U/l). CEA and CA19-9 were within normal limits. On abdominopelvic contrast-enhanced CT, an enhancing 10 mm × 8 mm hypervascular tumor was observed in the distal bile duct and the proximal bile duct was markedly dilated (Fig. 1).

Abbreviations: CT, computed tomography; ERC, endoscopic retrograde cholangiography; MANEC, mixed adeno-neuroendocrine carcinoma; MRI, magnetic resonance imaging; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NETs, neuroendocrine tumors.

* Corresponding author. Present address: Department of Surgery, Institute of Gastroenterology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan.
E-mail address: izumo@ige.twmu.ac.jp (W. Izumo).

http://dx.doi.org/10.1016/j.ijscr.2017.07.052

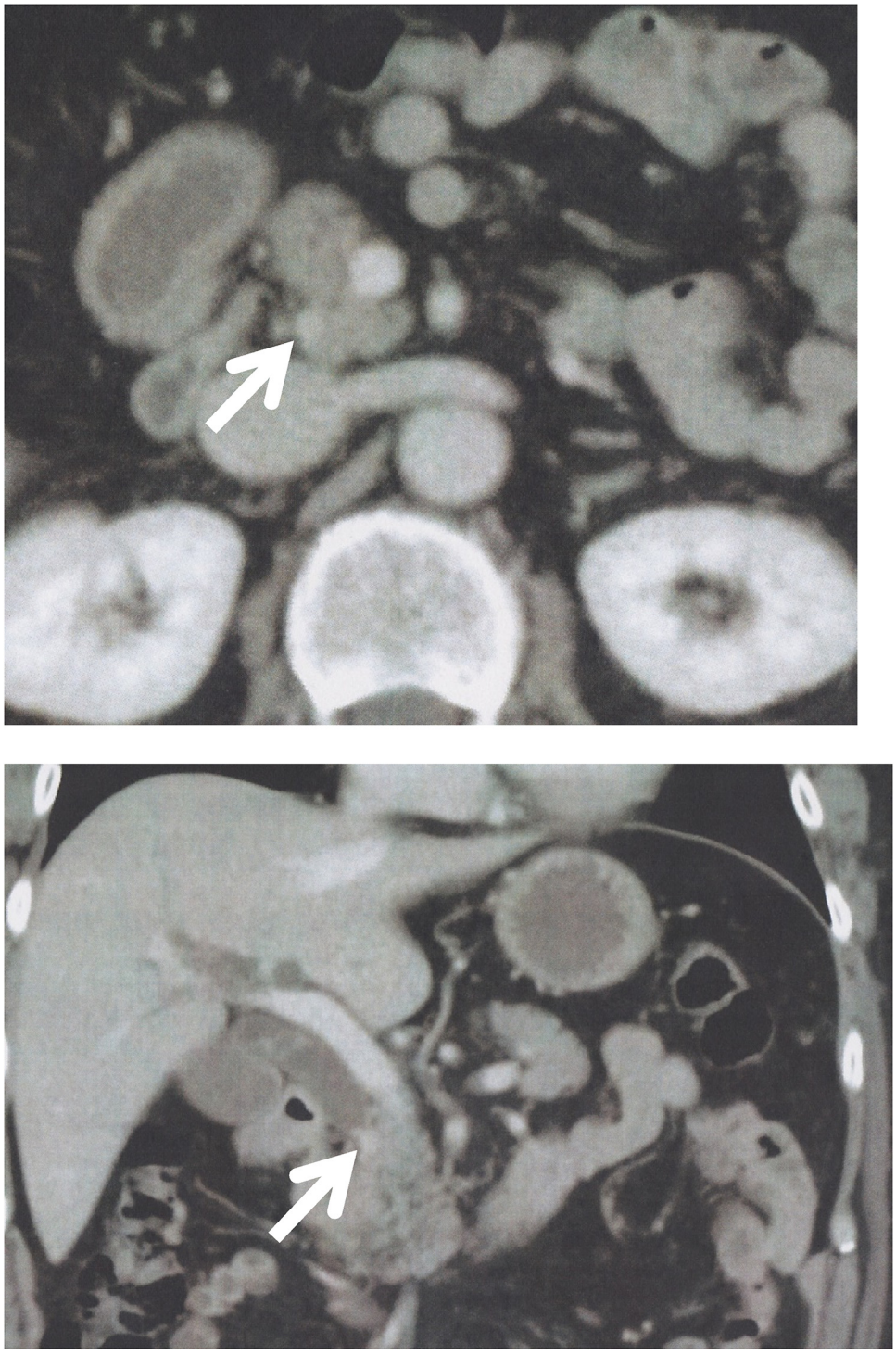

Fig. 1. Abdominal contrast-enhanced CT scan: an enhancing tumor of 10 mm × 8 mm in size was seen in the distal bile duct.

MRCP demonstrated a filling defect spanning 10 mm in the maximal diameter in the distal bile duct with markedly dilatation of the proximal bile duct. There was no evidence of pancreatobiliary maljunction (Fig. 2). Endoscopic retrograde cholangiography (ERC) also showed a stenosis of 10 mm in the maximal diameter was observed in the distal bile duct (Fig. 3). Examination of a biopsy specimen obtained from the narrow site of the bile duct at the time of ERC revealed moderately differentiated tubular adenocarcinoma. With a preoperative diagnosis of distal bile duct cancer, pylorus-preserving pancreaticoduodenectomy was performed. On surgical findings, a median incision was made in the upper abdomen and observation of the abdominal cavity did not reveal tumor dissemination or liver metastasis. The tumor was palpable as an induration in the distal bile duct. Pylorus-preserving pancreaticoduodenectomy (Child II-A) was performed. The operating time was 343 min and blood loss was 533 mlMacroscopic findings (Fig. 4) shows a white nodular infiltrating tumor of 10 mm in the maximal diameter was observed in the distal bile duct. Histopathological findings (Fig. 5) shows the tumor composed of cells in solid clusters and cells forming tubular structures with abundant fibrous

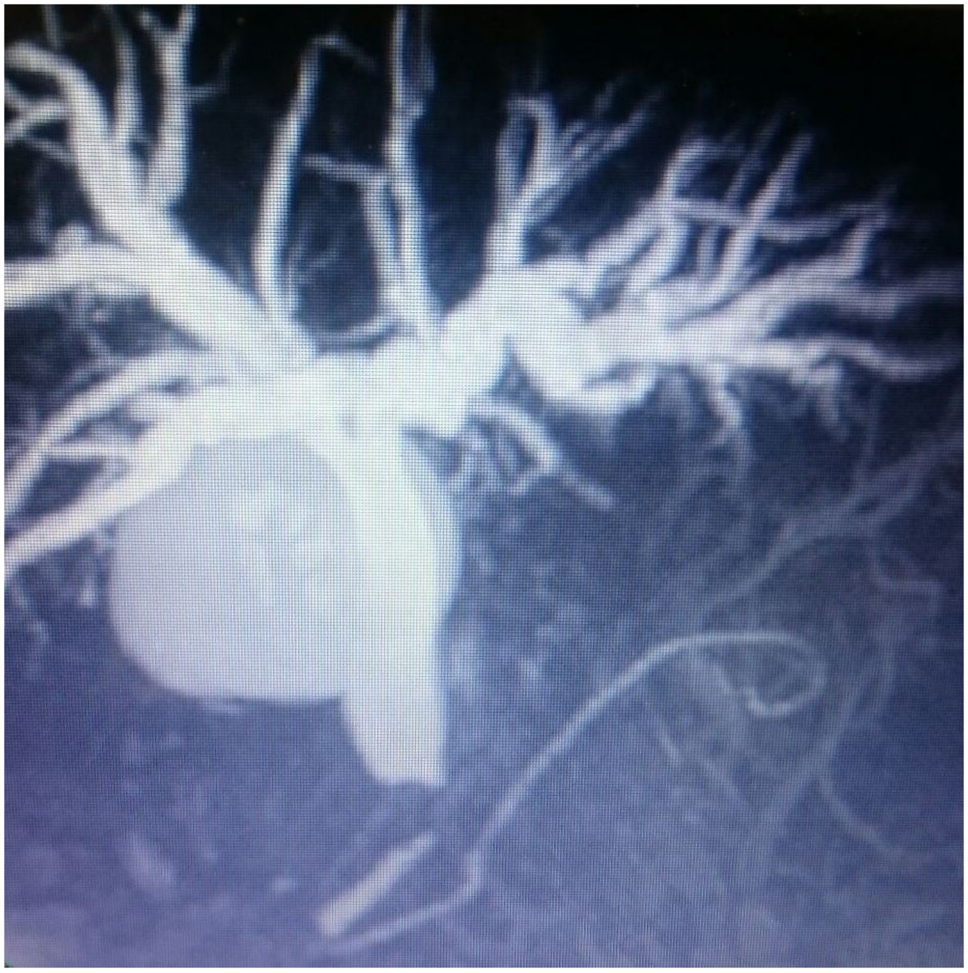

Fig. 2. MRCP: a filling defect of 10 mm in the maximal diameter was observed in the distal bile duct. The proximal bile duct was markedly dilated. There is no evidence of pancreatobiliary maljunction.

stroma. The solid clustered cells were positive for synaptophysin and chromogranin −A in immunohistochemistry, which indicated neuroendocrine differentiation. The cells also showed numerous mitoses and high-Ki-67 labeling index (25 mitotic figures/10 HPF; 30% Ki-67-positive). The proportion of each component was at least 30%. The final diagnosis was the mixed adeno-neuroendocrine carcinoma (MANEC), large cell type. The pathological stage was pT3, pN1, M0, and pStage II B according to the TNM classification of the UICC. Curative resection was achieved.

2.1. Postoperative course

A pancreatic fistula (Grade B) occurred postoperatively, but it resolved with drainage. The patient was discharged from our hospital at 39 days after the operation. No adjuvant treatment has been performed since discharge, and his recurrence-free survival time is 30 months.

3. Discussion

In 1907, a neuroendocrine tumor was reported as a gastrointestinal carcinoid by Oberndorfer [1]. Since then, although the definition of neuroendocrine tumors has been vague, the term neuroendocrine neoplasm (NEN) was coined with a grading based on mitotic figures and the Ki-67 index into G1, G2, and G3 in 2010 in WHO classification [2], NENs are classified into neuroendocrine tumors (NETs), neuroendocrine carcinomas (NECs), and MANECs. This classification defines MANEC as a tumor mixed with components of adenocarcinoma and NEC, in which each component comprises at least 30% of total.

Three hypotheses have been proposed regarding the developmental mechanism of MANEC, which are 1) that it arises from adenocarcinoma, 2) it arises from endocrine tumor, or 3) it develops from pluripotent cells or juvenile cells. Kijima et al. [3] examined samples of endocrine cell carcinoma and demonstrated continuity from an adenocarcinoma component in all samples. Therefore, the hypothesis of MANEC originating from adenocarcinoma is thought to be most likely. In our patient's tumor, the neuroendocrine cancer component was contiguous with a moderately differentiated adenocarcinoma component, which supports the hypothesis of the origin of MANEC from adenocarcinoma.

Neuroendocrine tumors arising primarily in the bile duct are rare. It has been reported that biliary neuroendocrine tumors account for only 0.19% of all malignant biliary tumors [4]. It also has been reported that biliary MANEC are even rarer and the prognosis is poor.

The Pub med and Japan Medical Abstracts Society databases were searched using each of the following search terms: "bile duct", "biliary tract", "MANEC", "mixed adenoneuroendocrine carcinoma", "neuroendocrine carcinoma", "small cell carcinoma", "large cell carcinoma", "adenoneuroendocrine carcinoma", or "adenocarcinoid". These searches identified 34 patients who had undergone surgical resection of MANEC, including our patient [5–37] (Table 1).

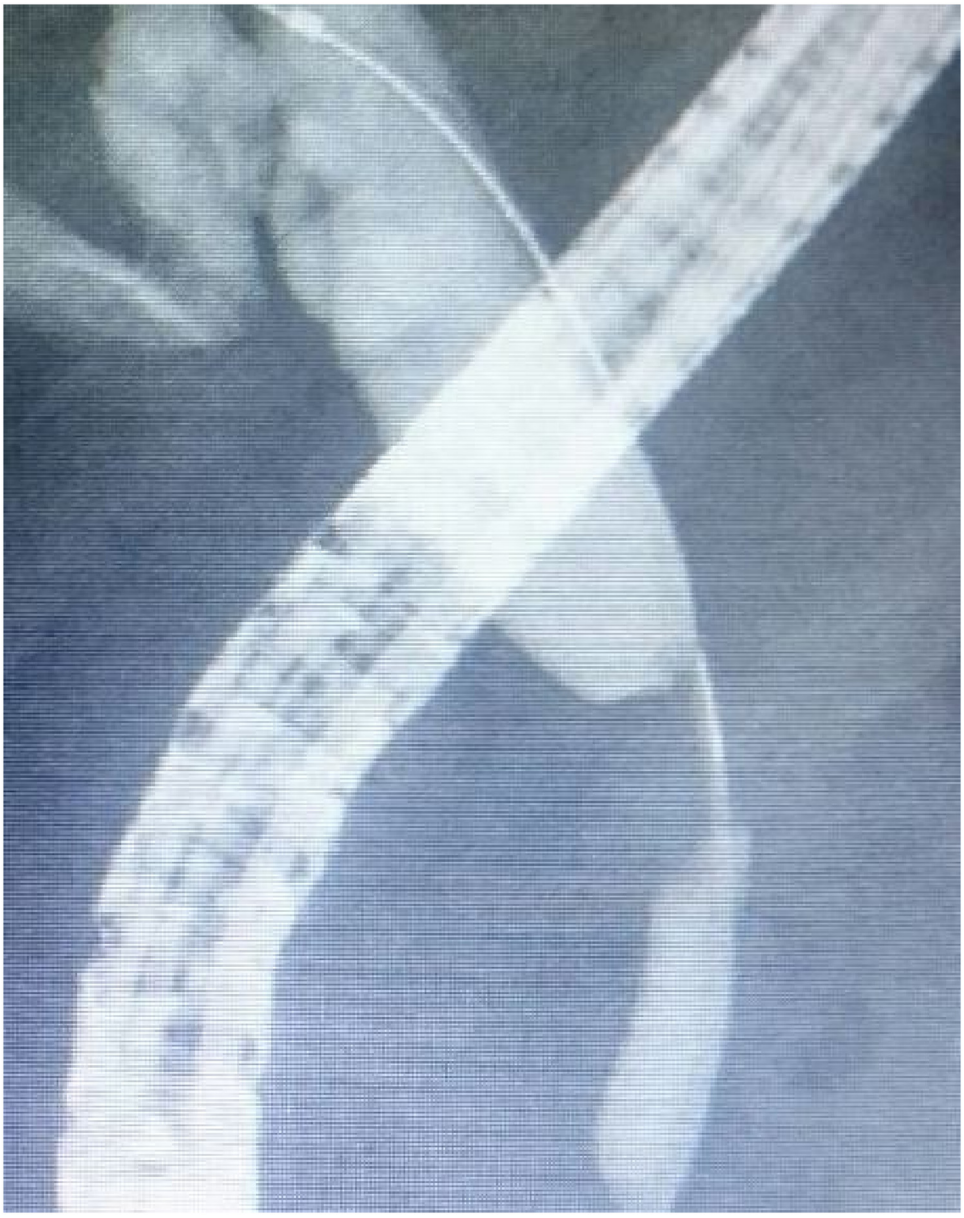

Fig. 3. ERC: A stenosis of 10 mm in the maximal diameter was observed in the distal bile duct.

The mean age of the patients was 68 (53–85) years and they included 23 men and 11 women. The mean tumor diameter was 27 (10–60) mm. Tumors occurred in the distal bile duct in 26 patients, in the hepatic ducts in six patients, and in both the distal bile duct and hepatic duct in one patient. The tumor location was unknown in one patient. Surgery (some patients had more than one operation) was pancreaticoduodenectomy in 25 patients, hepatopancreatoduodenectomy in one patient, resection and reconstruction of the extrahepatic bile duct in four patients, segmental or more extensive hepatic resection in three patients, hepatic tumor resection in two patients, and combined vascular resection in two patients. The operative method was not reported for one patient. Preoperative chemotherapy was performed in one patient. Curative resection was achieved in 12 patients and was not achieved in nine patients, while the curability of surgery was not reported in 13 patients. The tumor histological type was large cell in three patients, small cell in 22 patients, and unknown in nine patients. The stage (TNM classification of the UICC) of tumors in the distal bile duct was IA in one patient, IB in three patients, IIA in five patients, IIB in 11 patients, IV in one patient, and unknown in seven patients. In addition, the stage of tumors in the hepatic ducts was II in one patient, IVB in two patients, and unknown in three patients. Median survival time was 8 (3–48) months. Twelve patients (35.3%) survived for 12 months or longer, but only five patients (14.7%) survived for 24 months or longer. Median survival was longer (14 months) in the curative resection group and shorter (6 months) in the non-curative resection group. Median survival was very short (5 months) in patients with liver metastasis at diagnosis.

Median survival was longer in patients with lymph node metastasis than in patients without lymph node metastasis (14 months vs.6 months). This was probably because curative resection was achieved in 7/11 patients with lymph node metastasis, but was only achieved in 4/21 patients without lymph node metastasis. Thus, achieving curative resection may have influence the outcome rather than the presence or absence of lymph node metastasis.

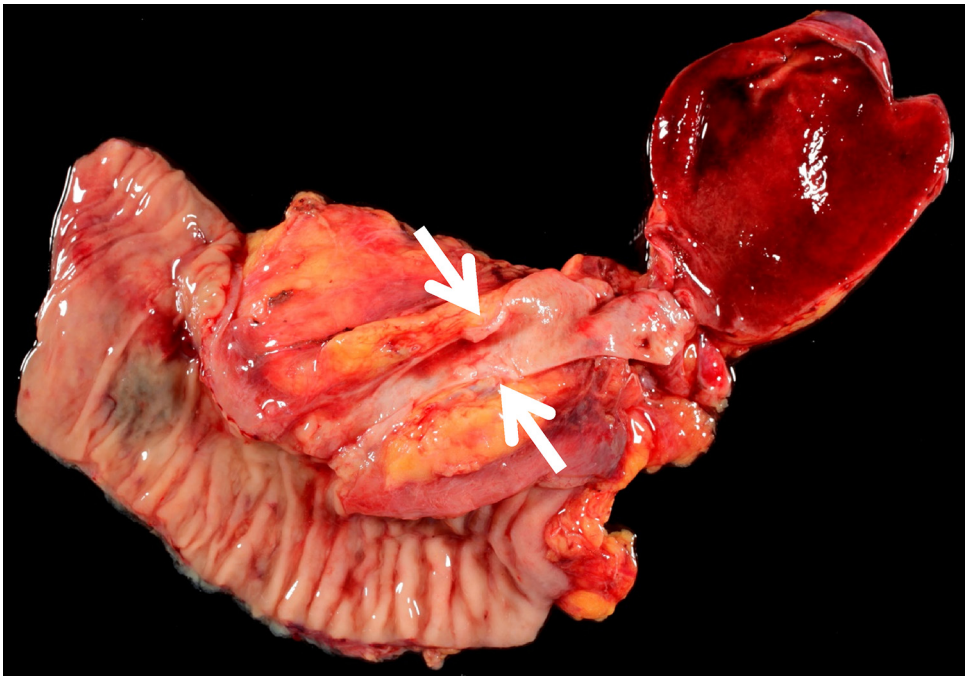

Fig. 4. A white nodular infiltrating tumor of 10 mm in the maximal diameter was shown in the distal bile duct.

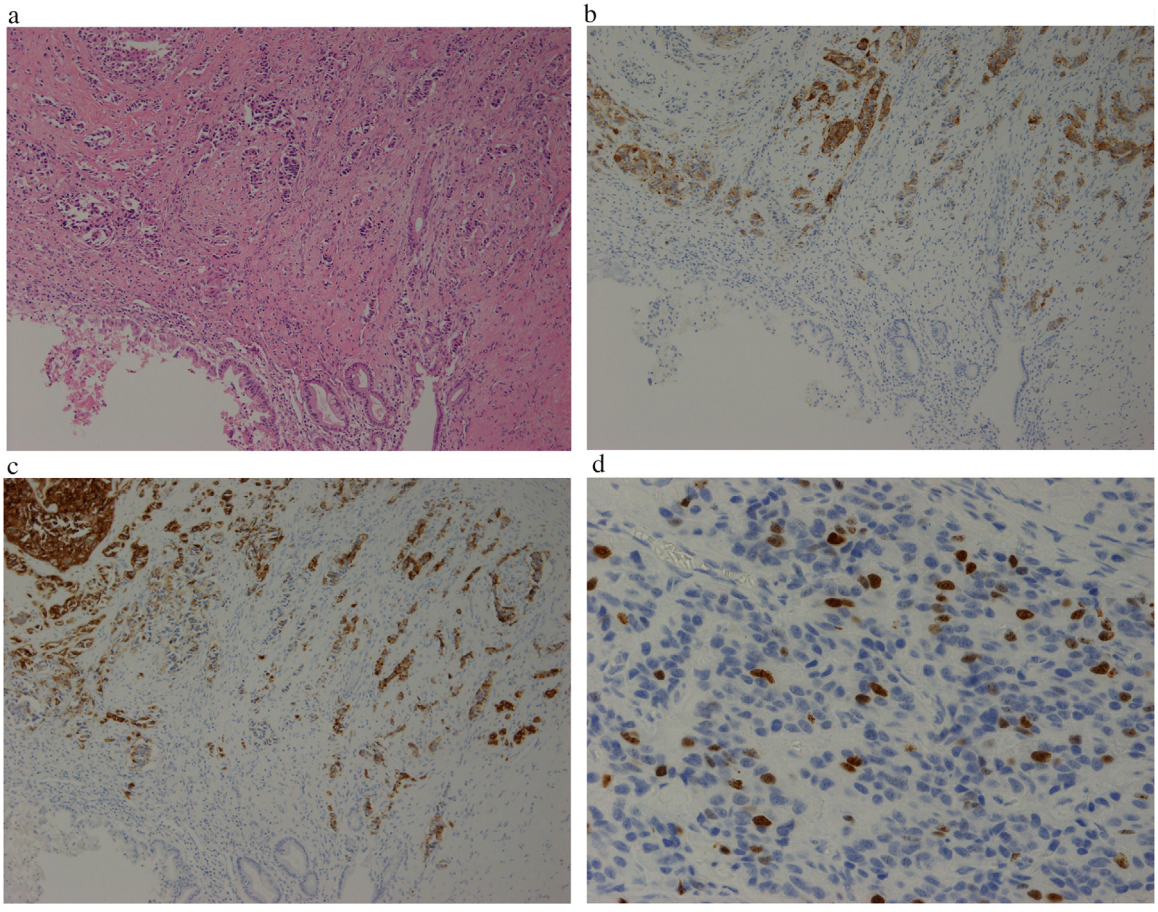

Fig. 5. Histopathological findings: There were solid clustered cells (NEC components) (upper part of the figure) and tubular structured cells (adenocarcinoma components) (lower part of the figure) with transition between the 2 components in abundant fibrous stroma (a). The NEC cells were labeled with antibodies for synaptophysin (b) and chromogranin A (c). Ki-67 labeling index was 30% (d). Original magnificent: a–c, ×100, d, ×200.

Table 1
Reported cases of Mixed adenoneuroendocrine carcinomas

Age	Sex	Location	Size (mm)	Treatment	Pathology	Curative resection	Type	Outcome	Author
66	Man	Bd	10	PpPD	T3,N1,Stage II B	Yes	Large	Recurrence free survive (30months)	Our case
65	Man	Bdp	36	Extrahepatic bile duct resection	T2,N0,Stage I B	Yes	Large	Dead(5months)	2014 Jojn Wysocki
74	Woman	Bd	20	PpPD	Tx,N0	ND	Small	ND	2014 Onishi
82	Man	Bd	19	PD	T2,N1,Stage II B	Yes	ND	Recurrence free survive (6months)	2013 Revital Linder
85	Man	Bd	10	PD	T3,N1,Stage II B	No	ND	Recurrence free survive (3months)	2012 Arakawa
82	Man	Bd	18	Extrahepatic bile duct resection	T1,N0,Stage I A	Yes	Small	Dead(6months)	2011 Masui
62	Man	Bd	30	NAC → PD	ND	Yes	Small	Dead(23months)	2009 Okamura
55	Woman	Bpd	ND	Right trisegmentectomy and extended main bile duct resection	ND	ND	ND	Recurrence free survive (6months)	2008 Matteo Costantini
82	Woman	Bd	ND	PpPD	T3,N1,Stage II B	Yes	ND	Recurrence free survive (45months)	2001 Edakuni
64	Man	Bd	30	PpPD	T2,N1,Stage II B	ND	Small	ND	2000 Se Hoon Kim
68	Man	Bd	60	Operation	ND	ND	Small	Alive with disease(8months)	1999 Tanaka
71	Woman	Bp	60	Liver segmentectomy(S4 + S5) + Extrahepatic bile duct resection	ND	ND	Small	Alive with disease	1998 Yamamoto

BP: perihilar extrahepatic bile duct.
Bd: distal extrahepatic bile duct.
ND: Not described.
NAC: Neoadjuvant chemotherapy.
PD: pancreatoduodenectomy.
PpPD: pylorus preserving pancreatoduodenectomy.
HPD: hepatopancreatoduoedenctomy.
SSPPD: sub stomach preserving pancreatoduodenectomy.
PV: portal vein resection and reconstruction.

It has been reported that the prognosis of bile duct carcinoma is influenced by the presence or absence of lymph node metastasis [38]. However, these findings suggest that if patients with MANEC have lymph node metastasis, their survival can be extended by curative resection.

Thus, our patient has shown long-term recurrence-free survival because the primary operation successfully achieved curative resection with no residual tumor and no distant metastasis including liver metastasis was detected.

NEN is a plethoric tumor that is characterized by hypervascular enhancement in the arterial phase of CT scans [39], while bile duct carcinoma is often visualized as a tumor with a poor enhancement. The tumor showed enhancement in our patient and MANEC should be taken into consideration under such circumstances.

It was reported that the accuracy of preoperative EUS-FNA was 83.3% for diagnosis of pancreatic NET [40]. There are several problems to make a diagnosis of NET by EUS-FNA. First, the grade of NET varies depending on biopsy sites due to the heterogeneity of tumor [41]. In addition, it may be difficult to make a definitive diagnosis of mixed tumors like MANEC through examining a small specimen obtained by EUS-FNA. In our patient, adenocarcinoma was diagnosed by EUS-FNA, but MANEC should have been taken into consideration because of the imaging findings.

In patients with surgically non-resectable pancreatic and gastrointestinal neuroendocrine carcinomas, high response rates have been achieved by platinum-based combination therapy (etoposide and cisplatin or irinotecan and cisplatin) [42,43]. As chemotherapy for non-resectable bile duct carcinoma, based on the results of studies performed in Britain and Japan [44,45], gemcitabine + cisplatin has been recommended (grade 1 recommendation) [46]. However, no standard chemotherapy has been reported for MANEC. It is possible that chemotherapy targeting the more dominant component (adenocarcinoma or NEC) could be effective, but evidence-based chemotherapy has not been established and standard adjuvant chemotherapy has not been reported either.

In our patient, periodic follow-up has been performed without adjuvant chemotherapy. However, if recurrence is detected in the future, chemotherapy targeting the dominant component will be performed after histological confirmation.

In conclusion, we experienced a rare case of bile duct MANEC diagnosed by postoperative pathologic examination, in which recurrence-free survival for 30 months has been achieved. We think that curative resection is essential to achieve long-term survival in patients with bile duct MANEC. Even if these patients have lymph node metastasis, survival can be extended if curative resection is achieved.

Conflicts of interest

All authors have no conflicts of interest.

Funding

This study had no funding.

Ethical approval

This study had not applicable for ethical approval.

Consent

We had a consent.

Author contribution

All authors revised the manuscript for important intellectual content, approved the final version, and agree to be accountable for all aspects of the work.

Registration of research studies

This study had a registration in our institute.

Guarantor

All authors had the guarantor for this study.

Acknowledgment

None.

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