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Mixed adenoneuroendocrine carcinoma of the distal bile duct: A case report

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ABSTRACT

INTRODUCTION: Mixed adenoneuroendocrine carcinomas (MANECs) of the distal bile duct are extremely rare, and only a few cases have been reported in the English literature.
PRESENTATION OF CASE: An 82-year-old man was referred to our hospital for increasing biliary enzymes. Abdominal computed tomography (CT) showed enlargement of the intrahepatic bile ducts and stenosis of the distal bile duct. Endoscopic retrograde cholangiopancreatography showed stenosis of the distal bile duct and a high-density signal at the same site on diffusion weighted imaging. PET-CT showed increased FDG accumulation (SUVmax: 4.5) at the distal bile duct stenosis. Biopsy specimens obtained by endoscopic ultrasonography-guided fine-needle aspiration revealed adenocarcinoma. The patient was diagnosed with adenocarcinoma of the distal bile duct and underwent subtotal stomach-preserving pancreaticoduodenectomy with regional lymph node dissection. The resected distal bile duct tumor was $18 \times 14 \times 12$ mm in diameter. Hematoxylin and eosin staining revealed a composite carcinoma with adenocarcinoma and non-adenocarcinoma elements. The non-adenocarcinoma component stained positive for synaptophysin and chromogranin A. The Ki-67 labeling index was 37%. The non-adenocarcinoma component was therefore diagnosed as a neuroendocrine carcinoma. The two composite carcinoma was diagnosed as MANEC of the distal bile duct. The patient was treated with surgery alone and he remained disease-free for 7 months after the surgery.
DISCUSSION: The treatment of MANECs of the bile duct remains controversial and the prognosis is poor.
CONCLUSIONS: There is no standard treatment for MANECs of the bile duct. Larger studies are required to establish standard treatment regimens.

1. Introduction

The present work has been reported in line with the SCAREcriteria [1].

Mixed adenoneuroendocrine carcinomas (MANECs) are defined as composite carcinomas that consist of adenocarcinoma and neuroendocrine carcinoma elements, with each element occupying at least 30% of the tumor (World Heath Organization (WHO) classification 2010, neuroendocrine neoplasms in the digestive system) [2]. MANECs of the distal bile duct are extremely rare, and only a few cases have been reported. These tumors are seldom diagnosed preoperatively, and patients tend to have a poor prognosis. We report herein a case of MANEC of the distal bile duct.

2. Presentation of case

An asymptomatic 82-year-old man with a history of multiple myeloma treated with bortezomib and dexamethasone was referred to our hospital for evaluation of abnormal biliary enzymes. Laboratory analysis revealed hemoglobin, 10.2 g/dL; white blood cell count, $2.65 \times 10^3/\mu L$; platelets, $11.8 \times 10^4/\mu L$; serum total protein, 8.1 g/dL; serum albumin, 3.4 g/dL; total bilirubin, 0.9 mg/dL; aspartate aminotransferase, 261 IU/L; alanine aminotransferase, 256 IU/L; alkaline phosphatase, 838 IU/L; and serum amylase, 84 IU/L. The serum levels of various tumor markers were normal, including carcinoembryonic antigen, 1.4 ng/ml; carbohydrate antigen 19–9, 28.3 U/ mL; DUPAN-2, 25 U/ml; and SPAN-1, 6 U/ml.

Computed tomography (CT) demonstrated enlargement of the intra- and extrahepatic bile ducts and stenosis of the distal bile

Abbreviations: MANEC, mixed adenoneuroendocrine carcinoma; WHO, World Heath Organization; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; IDUS, intraductal ultrasonography.

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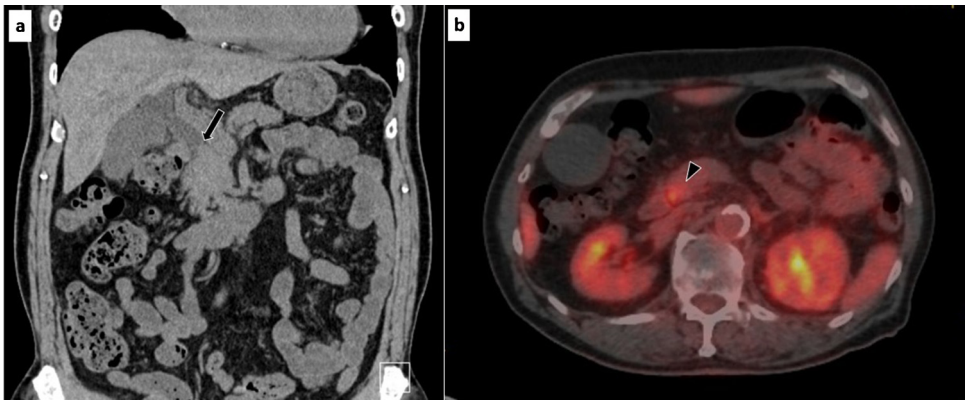

Fig. 1. Computed tomography (CT) showed diffuse enlargement of the common bile duct and a mass in the distal bile duct (black arrow) (Fig1a). PET-CT showed increased FDG accumulation (SUVmax: 4.5) in the distal bile duct mass (black arrowhead) (Fig. 1b).

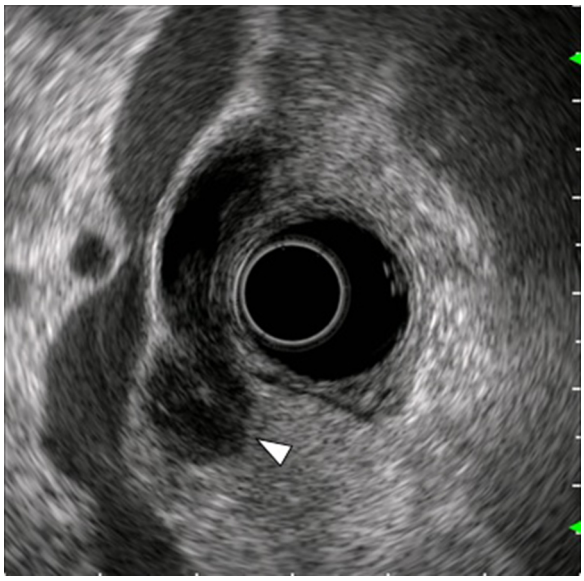

Fig. 2. Endoscopic ultrasonography showed a 10 mm hypoechoic mass in the stenotic region of the distal bile duct (white arrowhead).

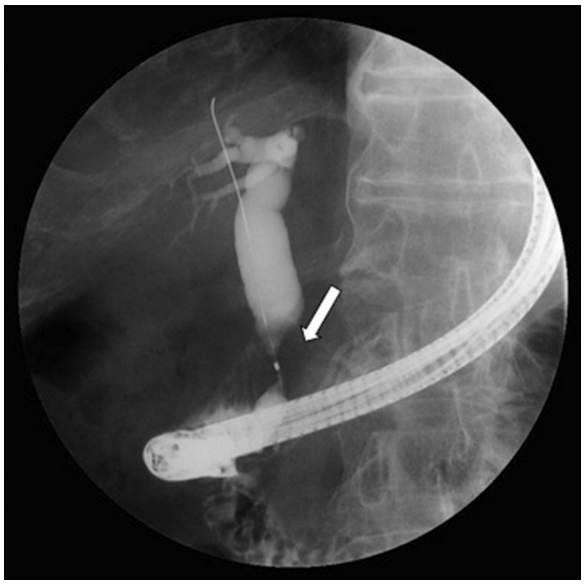

Fig. 3. Endoscopic retrograde cholangiopancreatography showed stenosis of the distal bile duct (white arrow).

duct (Fig. 1a). The para-aortic lymph nodes were enlarged to 10 mm due to multiple myeloma. Contrast enhanced CT revealed a replaced right hepatic artery. PET-CT showed increased FDG accumulation (SUVmax: 4.5) in the distal bile duct mass (Fig. 1b). Endoscopic ultrasonography showed a hypoechoic mass, 10 mm in diameter, at the distal bile duct (Fig. 2). Endoscopic retrograde cholangiopancreatography (ERCP) showed stenosis of the distal bile duct (Fig. 3). Intraductal ultrasonography (IDUS) showed thickening of the distal bile duct wall. The bile duct was drained with a 7Fr, 5 cm stent to prevent obstructive jaundice. A sample of the distal bile duct tumor was obtained using endoscopic ultrasonography-guided fine-needle aspiration and cytology revealed adenocarcinoma. The patient was diagnosed with distal bile duct carcinoma and underwent subtotal stomach-preserving pancreaticoduodenectomy with resection of the replaced right hepatic artery (non-revascularization) and regional lymph node dissection.

The cut surface of the surgical specimen demonstrated a nodular invasive tumor, measuring 18 × 14 × 12 mm, located in the distal bile duct (Fig. 4). Hematoxylin and eosin staining revealed a carcinoma composed of adenocarcinoma and non-adenocarcinoma elements, with each element occupying more than 30% of the tumor (Fig. 5a). The non-adenocarcinoma component stained positive for synaptophysin and chromogranin A (Fig. 5b,c). In addition, 37% of cells stained positive for Ki-67 (Fig. 5d). Based on these findings, the non-adenocarcinoma component was diagnosed as a neuroendocrine carcinoma. The patient was thus diagnosed with MANEC of the distal bile duct, Stage IIA (pT3N0M0) based on the 7th edition of the International Union Against Cancer tumor-node-metastasis classification.

The patient's postoperative course was complicated by a pancreatic fistula (ISGPF grade B) and delayed gastric emptying, but he was discharged on postoperative day 33. He remained disease-free for 7 months after surgery (Table 1).

3. Discussion

According to the WHO classification (2010), neuroendocrine neoplasms in the digestive system, including the gallbladder and extrahepatic bile ducts, are classed as NET G1 (carcinoid, mitotic count of <2 per 10 high powder fields (HPF) and/or ≤2% Ki67 index), NET G2 (mitotic count 2–20 per 10 HPF and/or 3–20% Ki67 index), or NET G3 (neuroendocrine carcinoma, mitotic count of >20 per 10 HPF and/or >20% Ki67 index). Moreover, composite carcinomas consisting of adenocarcinoma and neuroendocrine carcinoma elements, with each element composing at least 30% of the tumor, are

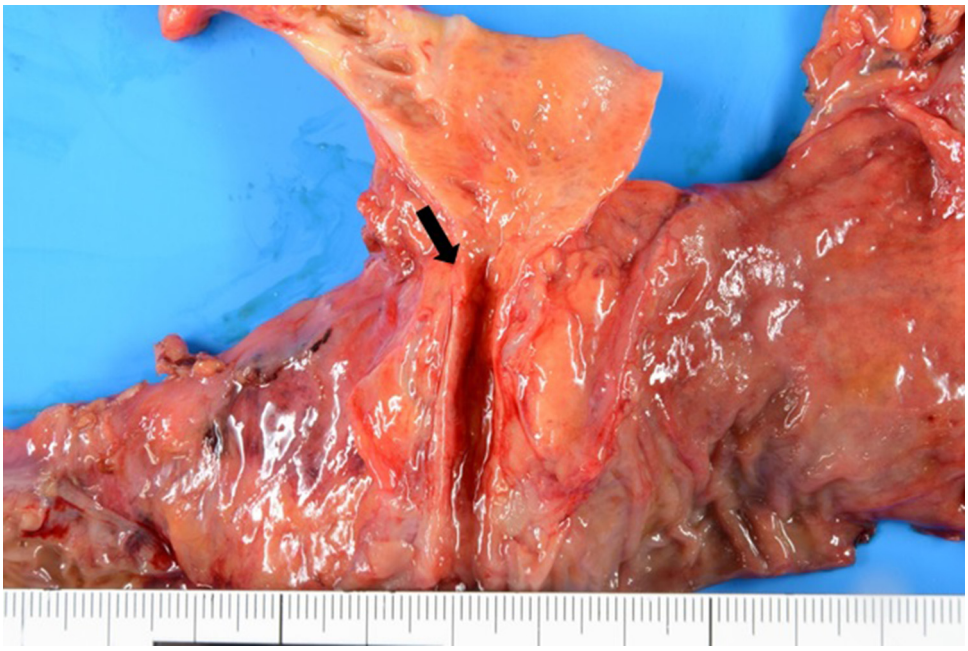

Fig. 4. Histopathology of the 18 × 14 × 12 mm distal bile duct mass (black arrow).

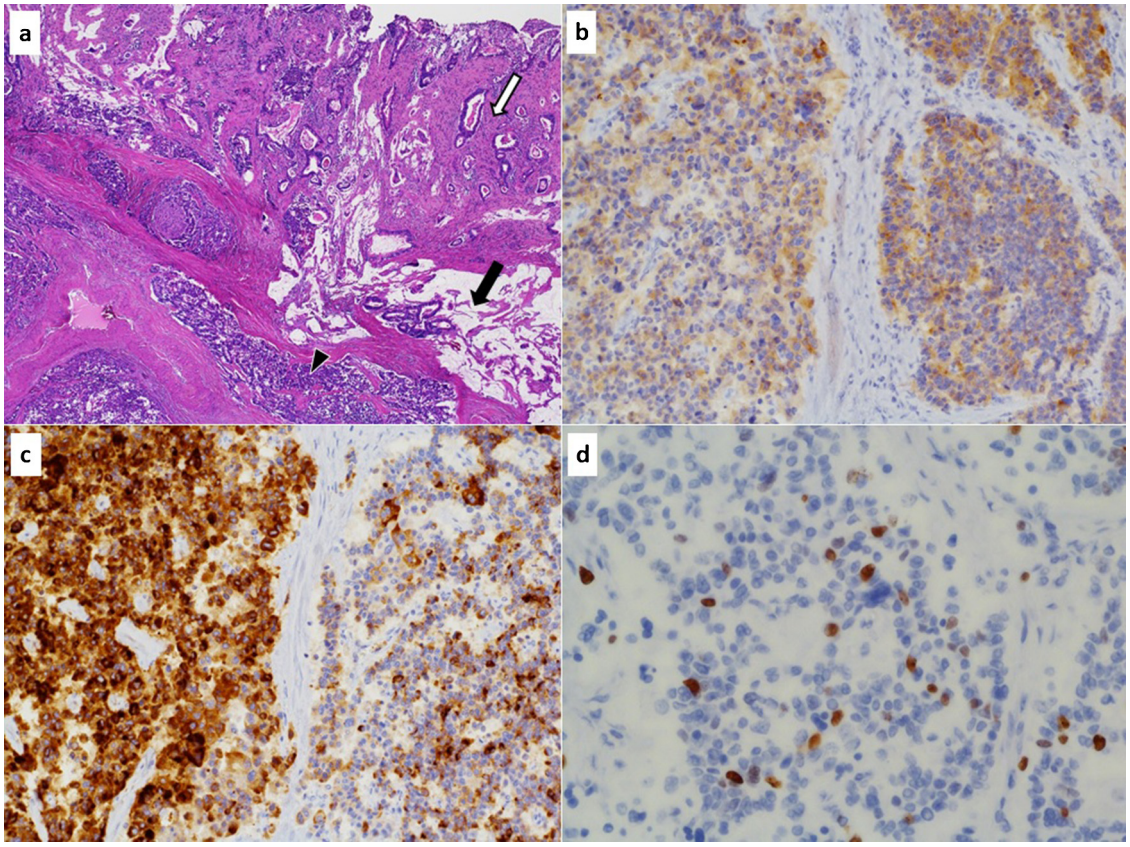

Fig. 5. Hematoxylin and eosin staining revealed a composit carcinoma consisting of adenocarcinoma and non-adenocarcinoma elements (a, white arrow: tub2. b, black arrow: muc. c, black arrowhead: NEC) (Fig. 5a). The non-adenocarcinoma component stained positive for synaptophysin (Fig. 5b) and chromogranin A (Fig. 5c). The Ki-67 index was 37% (Fig. 5d).

defined as MANECs [2]. MANECs of the distal bile duct are extremely rare and only a few cases have been reported; only 8 cases [3–7] have been reported in the English literature.

MANECs of the bile duct are seldom diagnosed preoperatively. Generally, the MANEC surface is composed of an ordinary adenocarcinoma and the neuroendocrine component is located deep within an area of vascular or perineural invasion [8]. Thus, preoperative pathological examination using ERCP brush cytology usually identifies the adenocarcinoma component and misses the neuroendocrine component [7]. Resectable biliary tumors detected by

Table 1
Reported cases of MANECs of the Bile Duct

Author	Year	Age	Gender	Location	Surgical procedure	Ki-67 index of NET (%)	Adjuvant chemotherapy	OS (months)	Recurrence
Kim[3]	2011	ND	ND	ND	PD	ND	ND	ND	Yes
		ND	ND	ND	PD	ND	ND	ND	Yes
Onishi[4]	2013	74	F	Bd	PPPD	ND	No	ND	ND
Lee[5]	2014	75	M	CBD	BDR	More than 30	No	11	No
Hong[6]	2015	59	M	CBD	BDR	ND	ND	ND	ND
	2015	41	F	CBD	PD	ND	ND	ND	ND
	2015	57	M	CBD	BDR	ND	ND	ND	ND
Akhilesh[7]	2016	76	M	CHD	BDR	90	No	ND	ND
Our case	2017	82	M	Bpd	SSPPD	37	No	7	No

PD pancreatoduodenectomy, *PPPD* pylorus preserving pancreatoduodenectomy, *SSPPD* subtotal stomach preserving pancreatocoduodenectomy, *BDR* bile duct resection, *CBD* common bile duct, *CHD* common hepatic duct, *ND* not described.

imaging studies are seldom biopsied, so MANECs are usually diagnosed on the surgical specimen [9].

In general, MANECs are highly aggressive and have a high risk of distant metastasis. Thus, patients with these tumors have a poor prognosis [10]. Harada et al. [8] reported that the majority of lymph node metastases involved neuroendocrine components, with features of G2 neuroendocrine tumors or neuroendocrine carcinomas. This suggests that the behavior of the neuroendocrine components, particularly NEC, in MANECs of the bile duct may determine prognosis. Previous investigators [5,10] have reported that the prognosis of MANECs of the bile duct is very poor, with an overall survival of only 11–12.2 months. Therefore, treatment of MANECs of the bile duct remains controversial. Acosta et al. [9] reported on 20 patients with biliary MANECs, 14 of whom (70%) were treated with surgery alone and 6 of whom (30%) were treated with radical resection plus adjuvant chemotherapy or chemoradiotherapy. Surgical resections have included bile duct resection only [5–7], pancreaticoduodenectomy [3,6], and pylorus-preserving pancreaticoduodenectomy [4]. According to the National Comprehensive Cancer Network guideline, the protocol for adjuvant treatment for NEC is the same as that for small cell lung cancer with or without radiation therapy [6]. Noda et al. [11] reported that irinotecan in combination with cisplatin is an effective treatment for metastatic small-cell lung cancer. Therefore, most patients with MANECs receive irinotecan and cisplatin as postoperative chemotherapy in Japan [12]. Alternatively, most cases of MANECs of the bile duct reported in the English literature were treated with surgery alone [4,5,7]. Bailey et al. [13] identified integrated genomic analysis of pancreatic ductal adenocarcinomas, defined the expression analysis in 4 subtypes. Aberrantly differentiated endocrine exocrine (ADEX) tumors of the 4 subtypes displayed upregulation of genes that regulate networks involved in KRAS activation, exocrine (NR5A2 and RBPJL), and endocrine differentiation (NEUROD1 and NKX2-2). Treatment outcomes are improved by targeting drugs to tumor subtypes in which they are selectively effective, with breast and lung cancers providing recent examples [14]. Knowledge of these subtypes may provide decision support in a clinical setting where the choice and timing of therapies is critical [15]. There is no studys about subtypes of MANECs of the bile duct. Further larger number of patients with MANECs of the bile duct are required to establish surgical procedure and adjuvant chemotherapy for the MANECs of the bile duct.

4. Conclusions

We have reported a case of MANEC of the distal bile duct. The treatment of MANECs of the bile duct remains controversial and the prognosis is poor. Additional case reports and long-term follow up data will help to define optimal treatment regimens.

Conflicts of interest

The authors declare that they have no Conflicts of interest.

Funding

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Ethical approval

Not applicable.

Consent for publication

When obtaining informed consent for surgical procedures, general consent for publication and presentation was obtained from the patients.

Authors' contributions

TK drafted the manuscript. TK, AN, IO and TK participated in the care of the patients. AN, IO and JH performed the literature search. MK provided the histopathological examination and diagnosis. TK, HM and NH participated in critical revision of the manuscript. All authors read and approved the final manuscript.

Guarantor

Toshihiko Kohashi.

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