Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

Mixed adenoneuroendocrine carcinoma derived from the cystic duct: A case report

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ARTICLE INFO

ABSTRACT

INTRODUCTION: Mixed adenoneuroendocrine carcinomas (MANECs) derived from cystic duct are extremely rare.

PRESENTATION OF CASE: An 80-year-old woman was admitted to the department of surgery, Onomichi general hospital with abnormal liver function and jaundice. Enhanced abdominal computed tomography (CT) detected a well-enhanced papillary tumor in the cystic duct, which protruded into the common bile duct. The intrahepatic bile duct was dilated due to tumor obstruction. The entire tumor showed high intensity in T2-weighted magnetic resonance imaging (MRI) imaging. Endoscopic retrograde cholangiopancreatography (ERCP) showed that the tumor ranged from part of communication of three ducts (cystic, common hepatic and common bile duct), to the middle of common bile duct. Biliary cytology determined a class V malignancy (adenocarcinoma). Endoscopic ultrasound determined that the tumor was primarily at the cystic duct with heterogeneous echoic pattern, which extended into the common bile duct. The preoperative diagnosis was cystic duct carcinoma (T3N0M0, StageIIIA). An extended cholecystectomy with regional lymph nodes dissection was performed. Histologically, the tumor had components of both well-differentiated tubular adenocarcinoma and neuroendocrine carcinoma, which is classified as MANECs according to the 2010 WHO classification of endocrine tumors. Eight months after surgery, multiple liver metastases were discovered, and treatment with adjuvant chemotherapy was initiated.

DISSCUSION: We present a rare case of MANECs derived from cystic duct. Until now, an established adjuvant systemic chemotherapy has not emerged, and curative resection, with poor long-term prognosis, remains the only treatment option.

CONCLUSION: Though standards of treatment for MANECs have not been established, multidisciplinary theraphy is necessary to improve outcome.

1. Background

This work has been reported in line with the SCARE criteria. R.A. Agha, A.J. Fowler, A. Saeta, I. Barai, S. Rajmohan, D.P. Orgill, The SCARE Statement: Consensus-based surgical case report guidelines, Int. J. Surg. (2016).

According to the 2010 World Health Organization (WHO) classification of endocrine tumors, at least 30% of neoplasms are defined as mixed adenoneuroendocrine carcinomas (MANECs) [1]. These tumors include: composite carcinoid, mucin-producing carcinoid, Argentaffin cell adenocarcinoma, goblet cell carcinoid, adenocarcinoid, and small cell undifferentiated carcinoma. Neuroendocrine tumors (NETs) commonly occur in the gastrointestinal tract, pancreas, and lung, but bile duct origin of NETs is uncommon [2]. Some cases of MANEC derived from the bile duct have been reported [3–6]. Although NECs of the bile duct are frequently associated with liver or lymph node metastases in the preoperative state, aggressive radical operative therapy and adjuvant chemotherapy contributes to long-term outcomes [7]. Herein, we report a rare case of MANEC that originated from the cystic duct following curative intent surgery.

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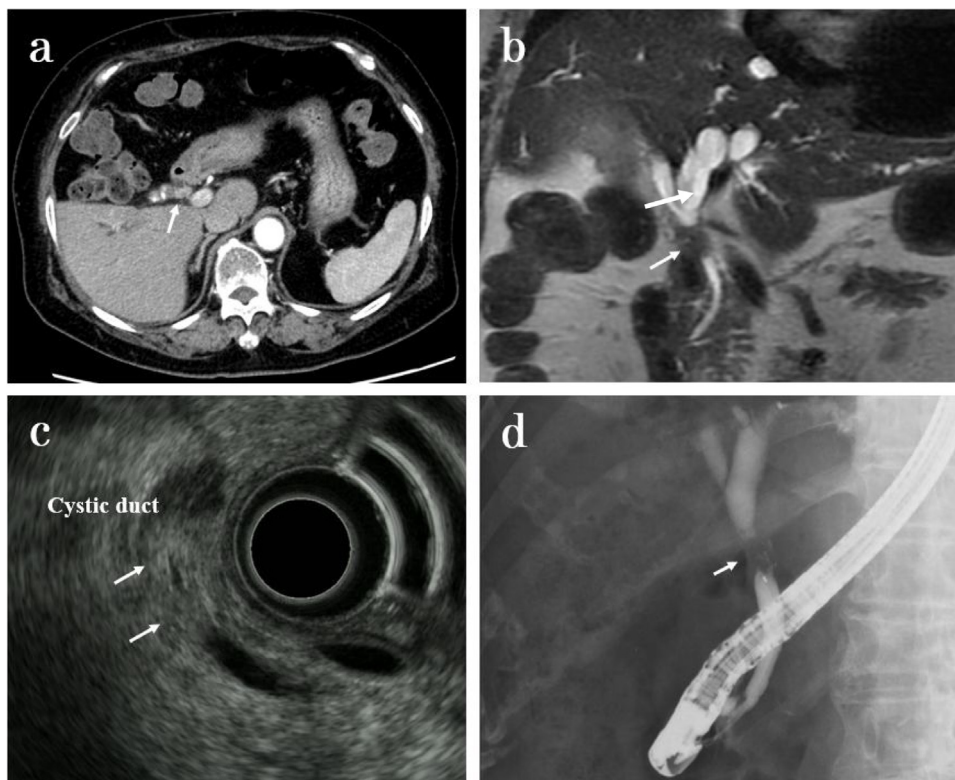E-mail address: t.abe.hiroshima@gmail.com (T. Abe).

Fig. 1. a: Abdominal computed tomography (CT) indicates mass formation at the part of communication of cystic, common hepatic and common bile duct (white arrow).
b: Magnetic resonance cholangiopancreatography (MRCP) reveals dilation of the common bile duct and signal defects. (white arrow).
c: Endoscopic ultrasonography (EUS) reveals a mass in the cystic duct extending to common bile duct (white arrow).
d: Endoscopic retrograde cholangiopancreatography (ERCP) shows a filling defects in the communication of cystic, common hepatic and common bile duct (white arrow).

2. Case presentation

An 80-year-old woman was admitted at the department of surgery, Onomichi general hospital, with liver function abnormalities and jaundice. The patient had a medical history of hypertension treated with calcium blocker and angiotensin receptor blocker.

Laboratory data revealed an elevation of total bilirubin (11.18 mg/dL), aspartate aminotransferase (162 U/L), alanine amino transferase (269 U/L), alkaline phosphatase (1482 U/L), and γ-glutamyltransferase (1156 U/L). There was no elevation in serum tumor markers (carcinoembryonic antigen, carbohydrate antigen 19-9). The patient's Child-Pugh score grade was B, and neither hepatitis virus B nor hepatitis virus C infection were detected. Abdominal contrast enhanced computed tomography (CT) imaging revealed a tumor located in the communication of three ducts (the cystic, common hepatic, and common bile ducts), as well as dilation of the common hepatic and intrahepatic bile ducts (Fig. 1-a). On magnetic resonance imaging (MRI), the entire tumor showed low signal in T1-weighted images and enhanced signal in T2-weighted images (Fig. 1-b). The tumor was 1.0×0.8 cm in size. The CT showed that the tumor was highly enhanced in the arterial phase, and this enhancement pattern was prolonged in the delay phase. An endoscopic ultrasound showed that the tumor had a heterogeneous echoic pattern, which was mainly located in the cystic duct. Endoscopic retrograde cholangiopancreatography showed that the dilation of the common hepatic and the intrahepatic bile ducts was due to tumor obstruction. In addition, the cystic and common bile ducts' communication showed severe stenosis. No portal vein or right hepatic artery invasion was observed. The range of horizontal extension of the tumor was considered to be from the part of communication of the main hepatic duct to the middle bile duct (Fig. 1-c

and d). Biliary cytology was determined to be class V (adenocarcinoma). The preoperative diagnosis was a cystic duct carcinoma, T3N0M0 Stage IIIA, according to 7th edition Union for International Cancer Control (UICC) TNM system. An extended cholecystectomy, extrahepatic bile duct resection, regional lymph nodes dissection, and choledochojejunostomy were performed; with a blood loss of 240 mL and an operative time of 304 min. Post operation, an intraabdominal abscess at the hepatic bed presented 8 days after surgery. This was treated by percutaneous drainage, which was graded as IIIA in according to the Clavien-Dindo classification [8].

Macroscopically, the tumor was mainly located from the cystic duct to the common biliary duct (Fig. 2-a). On microscopic examination, tumor cells extended from the cystic duct to the common bile duct. In the mucosal lesion, well-differentiated tubular adenocarcinoma was observed. In the invasive area, the tumor cells with hyperchromatic nuclei and scant cytoplasm were spread (Fig. 2-b and c). Immunohistochemically, the tumor cells were diffusely positive for chromogranin A, synaptophysin, and CD56. The Ki-67 labeling index was 80.0%. These findings were consistent with neuroendocrine carcinoma according to the WHO criteria for the clinicopathologic classification of neuroendocrine tumors (Fig. 3). Massive venous invasion of neuroendocrine carcinoma cells was detected. Neuroendocrine tumor cells extended into the subserosal layer (SS). The final pathological diagnosis was mixed adenoneuroendocrine carcinoma (MANEC) of cystic duct, with tumor dimensions of $13 \times 13 \times 7$ mm, Neuroendocrine carcinoma ≫ Well differentiated tubular adenocarcinoma, pT3, N0, M0, pStage IIIA according to 7th edition UICC TNM system. Eight months after surgery, multiple liver metastases were discovered, and treatment with adjuvant chemotherapy was initiated.
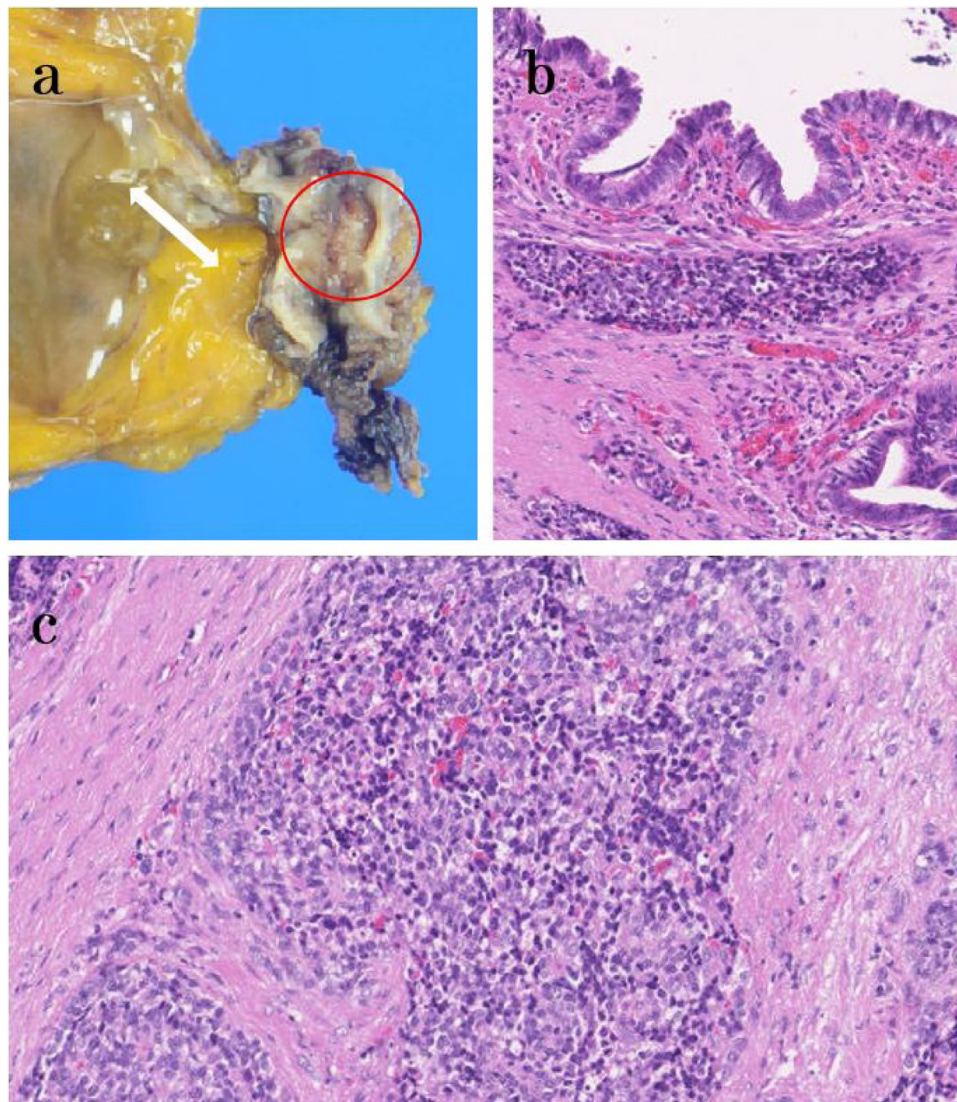
Fig. 2. Histological findings.
a: A tumor was located in the cystic duct (white arrow) and common biliary duct (red cicle).
b, c: On the surface of the tumor, cells represent well-differentiated adenocarcinoma. The infiltrative tumor comprises neuroendocrine carcinoma (H.E. staining).

3. Discussion

According to the WHO classification of treatment of the digestive system 4th edition, NETs are categorized by mitotic count and Ki-67 proliferation index: G1 (well-differentiated, low-grade), G2 (well differentiated, intermediate-grade), and neuroendocrine carcinoma (poorly differentiated, high-grade) [1]. MANECs are defined as neoplasms having both neuroendocrine carcinoma cells and adenocarcinoma cells, with each component representing at least 30% [1]. According to the report of Cho et al., NETs of the digestive system were mainly distributed in the rectum (48.0%) and stomach (14.6%), with biliary tract origin being rare (1.8%) [2]. Other initial reports showed that biliary tract NETs are only 0.2–2.0% of bile duct neoplasm [9,10], with reports of MANECs of the bile duct being scarce. There were reports of some bile duct MANECs since 2010, with their origins subdivided into the gallbladder [3,4,6,11,12]. This study is the first reported case of cystic duct MANEC.

Commonly, the mucosal surface in MANECs is replaced by well-to-moderate differentiated tubular adenocarcinoma, and the deep layer is invaded by neuroendocrine carcinoma cells [5]; these characteristics were observed in our case. The location of these tumor cells makes it difficult to detect neuroendocrine components by biopsy or cytology. Our preoperative diagnosis was cystic duct carcinoma, because the biliary cytology was class V (adenocarcinoma). Due to the rarity of this disease, the characteristic radiological findings were not confirmed. Typically, preoperative diagnosis of this disease is extremely difficult. However, the tumor showed relatively high-enhancement from the arterial to the delay phase on dynamic CT scan, which are findings similar to those of NEC. To obtain a precise diagnosis, dynamic CT findings may be helpful.

NECs of the bile duct commonly occur in liver and lymph node metastases in the preoperative state, with aggressive radical operative therapy and adjuvant chemotherapy contributing to positive long-term outcomes [7]. Until now, the standard adjuvant regimen for NEC has not been established; in many initial cases, the regimens for the treatment of small cell lung cancer, including cisplatin, CPT-11, and etoposide, were employed [13–16]. Sorbye et al. reported the predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma [17]. In our case, R0 resection was established, but the risk of recurrence in liver was estimated to be significantly
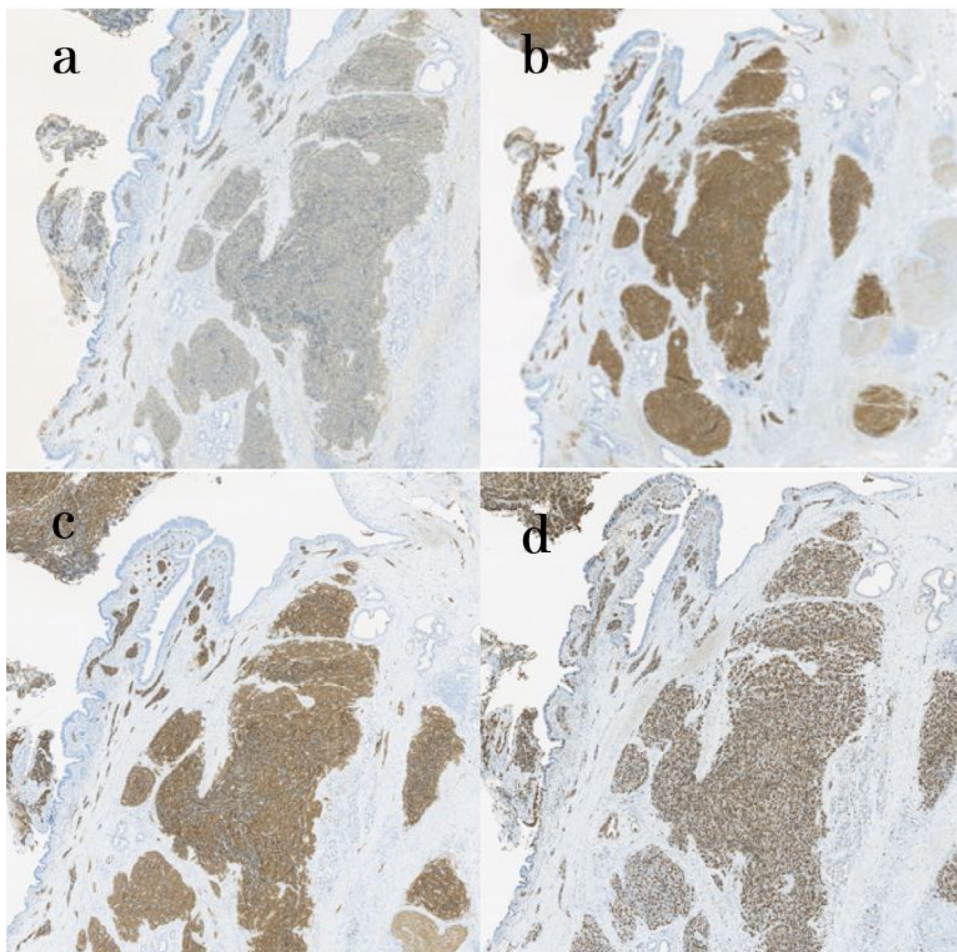
Fig. 3. Immunohistochemically findings.
The tumor cells were diffusely positive for chromogranin A (a), synaptophysin (b), CD56 (c). The Ki-67 positive cells were around 80.0% (d).

high, due to the detected venous invasion of the neuroendocrine carcinoma in the resection margin of the hepatic duct. Moreover, the Ki-67 index was high (approximately 80% of total tumor), with initial reports showing that gastrointestinal NEC patients with Ki-67 >55% had a significantly shorter survival than patients with Ki-67 levels <55% [17,18]. Tumors of neuroendocrine carcinoma have been effectively treated with cisplatin, CPT-11, and etoposide. Yamaguchi and Iwasa et al. showed the effectiveness of cisplatin, CPT-11, and etoposide as the chemotherapy regimen for advanced NEC of the digestive system [12,13]. In our case, platinum-based adjuvant therapy was administered but not completed due to renal dysfunction and poor performance.

4. Conclusions

In conclusion, since MANECs of the bile duct are rare, with cystic duct origin MANECs being extremely rare, further case studies are needed. Though standards of diagnosis and treatment have not been established, multidisciplinary therapy including primary tumor and lymph node resection, chemotherapy, and radiotherapy, is necessary to improve outcomes.

Conflicts of interest

None of the authors have any commercial or financial involvement in connection with this study that represents or appears to represent any conflicts of interest.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

Onomichi general hospital.

Consent

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

Authors contribution

All authors in this manuscript contributed to the interpretation of data, and drafting and writing of this manuscript. Yu-ki Takemoto is first author of this paper. Tomoyuki Abe is corresponding author of this paper. Yu-ki Takemoto, Tomoyuki Abe and Hironobu Amano conceived and designed the study and drafted the manuscript. Tomoyuki Abe first diagnosed. Yu-ki Takemoto, Tomoyuki Abe, Hironobu Amano and Masahiro Nakahara were engaged in patient's care in our hospital including surgery. Tsuyoshi Kobayashi contributed to study concept, and review of the final manuscript and submission of the paper. All the authors read and approved the final manuscript.

Guarantor

Tomoyuki Abe.

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