

CASE REPORT

Adenoendocrine cell carcinoma of the extrahepatic bile duct: Report of a case and review of the literature

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Abstract

Extrahepatic bile duct cancer with endocrine cell component has rarely been reported. Here, we experienced a case that had an adenoendocrine cell carcinoma in the middle bile duct. An 82 year old man admitted to the hospital for jaundice and anorexia. Computed tomography and magnetic resonance imaging examination showed papillary low density and intensity area in the middle bile duct. Endoscopic retrograde cholangiography showed obstruction of the bile duct and brushing cytology of the bile duct revealed adenocarcinoma. We resected the extrahepatic bile duct with regional lymph node dissection. The pathological examination revealed neuroendocrine component showing small cytoplasmic cells with hyperchromatic nuclei and rosette like structure in the middle of the tumor. In the peripheral mucosal region, there was a well differentiated adenocarcinoma composed of columnar to cuboidal epithelial cells with clear and slightly granular, eosinophilic cytoplasm. Immunohistochemical analysis showed positive staining for CD56, following the diagnosis of adenoendocrine cell carcinoma. The Ki-67 rate was more than 30% suggesting a small cell type of endocrine carcinoma. The adenocarcinoma component was infiltrated into the endocrine component, and some of the endocrine component was positive for cytokeratin, suggesting the transdifferentiation of the adenocarcinoma into the endocrine component rather than the originating from the common precursor cell. The patient experienced liver metastasis at 3 months and had died at 6 months after the operation. Adenoendocrine tumor of the bile duct is extremely rare and the adjuvant chemotherapy is necessary according to the malignant potential of the neuroendocrine

tumor rather than that of adenocarcinoma.

Introduction

Most of the tumors of the bile duct are adenocarcinoma that arises from bile duct epithelium.

Because the normal mucosa of the bile duct has a very small number of Kulchitsky cells

(somatostatin-containing D cells) ¹, endocrine cell tumors account for only 0.2% of the bile duct

tumors. The coexistence of endocrine component with adenocarcinoma is further rare, and no more

than 22 cases are reported so far. Here we present a rare adenoendocrine cell tumor of the bile

duct. Initially he was diagnosed as a bile duct cancer by cytology, and found to be the case of an

adenoendocrine cell tumor.

Case Report

An 82 years old man was initially admitted to the nearest hospital on September 2008 with a history of an anorexia, body weight loss and jaundice. An abdominal computed tomography (CT) at the hospital disclosed a dilatation of the intrahepatic bile duct as well as the papillary low density mass in the middle of the bile duct. Because of the high serum bilirubin concentration (5.3mg/dl), he received an endoscopic retrograde cholangiopancreatography (ERCP) and was found to have 2.6-cm irregular filling defect in the middle bile duct (Figure 1). The bile juice was drained through endoscopic nasal bile drainage (ENBD). The brushing cytology of the bile duct revealed adenocarcinoma (Figure 1, inset).

He admitted to our hospital for further investigation. Physical examination showed no specific tumor palpable on his abdomen. No lymph node swelling palpable on his body surface but slight tenderness was present on right upper abdomen. Magnetic resonance imaging (MRI) showed a papillary tumor protruding in the middle of the duct but no distant metastasis (Figure 2a). CT examination revealed less possibility of invasion to the neither common hepatic artery nor portal vein (Figure 2b). Positron emission tomography with ¹⁸F-fluorodeoxyglucose (FDG-PET) showed strong accumulation at the tumor in the middle common bile duct (Figure 2c). Laboratory tests including tumor markers such as CEA, CA19-9, CA125 and Elastase1 were in normal range. Under the diagnosis of middle bile duct cancer, we performed a bile duct resection with lymphnode dissection around the hepato-duodenal ligament two months after the initial symptom.

At surgery, macroscopic examination of the abdomen revealed no ascites or peritoneal dissemination. The bile duct adhered to the adjacent tissues because of inflammation but the tumor itself did not invade. An intraoperative frozen examination showed free of malignant cells in the resected margin of the resected bile duct, resulting in a curative resection. The macroscopic findings of the resected specimens revealed a fragile, yellowish 18 mm sized tumor surrounded by a hard, whitish 25 mm sized tumor, located in the middle of the common bile duct. (Figure 2d). The tumor obliterated the lumen of the common bile duct but did not extend to the lateral side.

Histopathologically, the tumor was composed of two cell patterns. The cells with columnar to cuboidal epithelial cells with clear and slightly granular, eosinophilic cytoplasm (adenocarcinoma component) was surrounded by the ones that have hyperchromatic nuclei and distributed in solid sheets with rosette-like features (endocrine component), just like the adenocarcinoma tree with endocrine cell leaves (Figure 3a). The adenocarcinoma component occupied nearly 60% of the tumor defining the adenoendocrine carcinoma. Immunohistochemically, the tumor cells negatively stained with chromogranin A, or synaptophysin but stained focally positive for CD56 (Figure 3b), indicating the origin of the endocrine tumor. Around 30 to 40% of the endocrine component was stained positive with Ki67 antibody and the adenocarcinoma component showed less (Figure 3c). The adenocarcinoma component was clearly stained positive for cytokeratin and there was a transitional area from adenocarcinoma to the endocrine component (Figure 3d), suggesting the transdifferentiation from the adenocarcinoma component. The tumors were categorized as

intermediate type, INFBeta, ly0,v0, pn3, T1N0M0 and stage I by UICC TNM classification.

The patient showed an uneventful postoperative course and was discharged 3 weeks after the surgery. Three months later, CT examination revealed multiple metastasized tumors in the liver and he died of cancer 6 months after the operation.

Discussion

Adenoendocrine tumor in the extrahepatic bile duct is extremely rare. Since Van Der Wal reported the adenoendocrine tumor in the extrahepatic bile duct in 1989 ², only 22 cases have been reported (Table 1). In reviewing these cases including our case, 16 cases were man and 7 cases were women. The mean age of the group was 65.8 years with the range of 25 to 82 years old. Kim et al reviewed a carcinoid tumor of the extrahepatic bile duct and reported 40% of the patients were man, and the mean age was 47 years old ³. Comparing to them, adenoendocrine tumor of the extrahepatic bile duct tends to be more in male and in older cases. Because the mean age of the pure cholangiocarcinoma patients is comparatively older age and the gender of them demonstrates no sexual predilection ⁴, these findings suggest the endocrine component in the adenoendocrine tumor is derived from the adenocarcinoma of the bile duct and its character is potentially different from the pure endocrine one in the bile duct.

Endocrine cell tumor in the gastrointestinal tract was originally defined as carcinoid tumor. Recently it has been separated into two groups according to its biological features; the classical carcinoid that shows less malignant, well-differentiated tumor, and the small cell carcinoma with more malignant, higher dysplastic tumor. Small cell carcinoma shows severer atypia, higher Ki-67 expression and angio- and perineural invasion in its early stage. It could co-exist with adenocarcinoma component ⁵. Our case showed high Ki-67 positivity and perineural invasion although the size of the tumor was comparatively small, and was defined as a small cell carcinoma.

The histopathogenesis of the adenoendocrine tumors has not been clearly described yet.

There are two hypothesis for the origin of the endocrine component; (1) bidirectional neoplastic change from the common precursor cells ⁶, and (2) differentiation from the initial adenocarcinoma ⁷. Although we could not prove the origin of the endocrine component of the current tumor, there are several circumstantial evidence suggesting the latter hypothesis. First, the background adenocarcinoma is more differentiated and less Ki-67 expression compared to endocrine component, suggesting the poorer differentiation in the endocrine component. Secondly, the endocrine component showed small area of CD56 expression and no synaptophysin expression, but slight cytokeratin expression. On the other hand, adenocarcinoma component did not show any endocrine marker, suggesting a transdifferentiating process from adenocarcinoma to the endocrine tumor. Lastly, there are infiltrating areas of the adenocarcinoma component into the endocrine component and grossly the endocrine component was surrounded by adenocarcinoma.

The presenting symptoms are mostly jaundice due to the obstruction of the common bile duct. Because of the rarity of this disease, a preoperative diagnosis of the adenoendocrine tumors is difficult. As in our case, preoperative cytology often represents adenocarcinoma.

The survival of the adenoendocrine tumor was determined by the biological characteristics of the endocrine component, since most of the metastatic tumor of the liver or lymph node show the endocrine component ^{8,9}. Albores-Saavedra et al. studied a large scale patient cohort about neuroendocrine and small cell carcinoma of extrahepatic bile duct¹⁰. According to them, small cell

carcinoma is highly malignant, and showed 0% of the 10 year survival. The adenoendocrine tumor seems to have also the similar malignant features. It is interesting to note that 15 out of 22 cases in the reported adenoendocrine tumors show early metastasis to the liver as well as the bone because the hematogenous spread suggests the metastasis from the plethoric endocrine component. Fifty six percent of the patients died within one year even after curative resection. Our case represents multiple liver metastases after 3 months of the operation and he died in 6 months.

The treatment to the adenoendocrine carcinoma should include chemotherapy for small cell carcinoma in addition to the surgical therapy because of the high incidence of the hematogenous dissemination as above. In small cell carcinoma of the lung, Levenson et al suggested chemotherapy rather than local resection because those patients potentially have a distant metastasis at the time of diagnosis¹¹. However, as mentioned above, the diagnosis of the adenoendocrine tumor before operation is extremely difficult. As a result, chemotherapies are applied after the diagnosis of small cell carcinoma by initial operation. Sabanathan et al and others applied cisplatin plus etoposide, and cyclophosphamide plus doxorubicin plus vincristin to the adenoendocrine carcinoma^{12, 13} according to the regimen of the lung small cell carcinoma, and found several good results. Our patients received no chemotherapies because of his old age, above 80 years.

In conclusion, we experienced a rare case of adenoendocrine tumor of the bile duct. Additional chemotherapy to the endocrine component as well as surgical resection is necessary to improve its survival.

Conflict of interest statement: Toshihiko Masui and other co-authors have no conflict of interest

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Figure legends

Figure 1

Endoscopic retrograde cholangiopancreatography showed a blunt narrowing of the middle common bile duct (arrow head). Inset: The brushing cytology from the bile duct contained cells with large nucleus and coarse chromatin, diagnosed as adenocarcinoma.

Figure 2

(a) A magnetic resonance cholangiopancreatography showed a papillary protrusion inside the middle common bile duct (arrowhead).

(b) An abdominal computed tomography scan revealed a 22 mm x 25 mm sized mass (arrowhead) and close to the gastroduodenal artery but apart from the common hepatic artery.

(c) The tumor revealed high intensity in the FDG-PET. The SUVmax was 7.9.

(d) Gross view of the specimen after a coronal section of tumor of the common bile duct. A fragile, yellowish 18 mm sized tumor (arrow head) was surrounded by a hard, whitish 25 mm sized tumor (arrow), which was located in the middle of the common bile duct. Both hepatic and ampullary edge of the bile duct was tumor free.

Figure 3.

Microscopic and immunohistochemical findings.

(a) The adenocarcinoma compartment (arrowhead) was surrounded by the endocrine tumor cells (arrow) (hematoxylin and eosin, x 200).

(b) The tumor was composed of sheets of uniform cells with granular cytoplasm, central, round nuclei and coarse, clustered chromatin. The cells were arranged into clumps or rosettes. The tumor cells were partly positive for CD56 (CD56 staining, x200).

(c) The positiveness of the Ki67 in endocrine component was 30 to 40% and that in the adenocarcinoma cells were less than 10% (Ki-67 staining, x200).

(d) The tumor cell of the endocrine component also partially positive for cytokeratin (arrowhead).

There was a clear transition area between adenocarcinoma and endocrine component (cytokeratin staining, x200).

Table 1. All reported patients with adenoendocrine cell carcinoma of the bile duct from 1989 to 2009.

Case #	Author	Year	Age	Gender	Location	Mode of operation	Survival time (months)	recurrence
1	Van Der Wal	1989	55	male	middle	bile duct resection	NR	NR
2	Motojima	1989	67	male	middle	PD	10	liver
3	Ashizawa	1992	71	male	middle	PD	30	liver, bone
4	Koide	1992	65	male	middle	PD	96 alive	liver
5	Miyoshi	1994	75	female	distal	PD	9	liver
6	Takimoto	1996	65	male	middle	PD	3	liver, bone
7	Tanaka	1999	62	male	middle	PD	80 alive	
8	Kim	2000	64	male	middle	PPPD	24 alive	
9	Nishie	2000	67	male	distal	PPPD	47 alive	
10	Koide	2000	25	female	distal	bile duct resection	12	liver
11	Ohta	2001	74	male	distal	PPPD	22 alive	
12	Umiwatari	2001	64	female	distal	PD	9	liver
13	Okimura	2003	53	male	distal	PPPD	3	liver
14	Nishimura	2004	62	male	hilar/middle	PPPD	7	liver
15	Shinchi	2005	73	male	hilar	bile duct resection	4	liver
16	Mikami	2005	75	female	distal	PD	24 alive	
17	Mori	2005	76	female	middle	bile duct resection	22	liver
18	Kaiho	2005	66	female	middle	PPPD	8	liver
19	Kurozumi	2006	59	male	distal	PPPD	14 alive	
20	Satoh	2006	68	male	distal	PPPD	3	liver
21	Yamada	2008	64	male	distal	PPPD	12	liver
22	Endoh	2008	72	female	distal	PPPD	34 alive	liver
23	our case	2009	82	male	middle	bile duct resection	6	liver

PD: pancreatoduodenectomy,

PPPD: pylorus-preserving pancreatoduodenectomy,

NR: not reported





