Rapidly Growing Mucinous Cholangiocarcinoma

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A 65-year-old man was hospitalized due to an abdominal tumor. Several imaging studies showed multilocular tumors in the right hepatic lobe and in the pancreatic head, 4 and 7 cm in size, respectively. The hepatic tumor rapidly grew to 9 cm in 4 weeks, associated with a rapid increase in the serum carcinoembryonic antigen level from 125 ng/ml to 1,000 ng/ml. The pathologic diagnosis of the resected liver tumor was mucinous cholangiocarcinoma. This hepatic tumor produced a large amount of mucin, but did not secrete mucin into the bile ducts. Therefore, there was no obstructive jaundice. The incidentally accompanied pancreatic tumor was a typical serous cystadenoma. The present case suggested that mucinous cholangiocarcinoma could present rapid growth of the tumor. The clinicopathological features of mucinous cholangiocarcinoma are demonstrated for the first time, and the differences between mucinous cholangiocarcinoma and mucin-producing papillary adenocarcinoma of duct-spreading type are discussed.

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Key words: mucin, liver tumor, pancreatic tumor, tumor growth, tumor marker, imaging diagnosis

Introduction

Mucin production is one of the characteristics of cholangiocarcinoma, but usually only small amounts are produced. There are, however, some cases of cholangiocarcinoma producing large amounts of mucin. Mucin-producing cholangiocarcinoma showing intraductal spreading has been reported previously (1–4), and this type of cholangiocarcinoma causes obstructive jaundice due to mucinous compaction in the common bile duct. Usually the growth of mucin-producing cholangiocarcinoma is slow, and pathologically it is well-differentiated papillary adenocarcinoma, containing mucin in the bile duct lumen (1–4).

On the other hand, according to the histological classification of cholangiocarcinoma of Sugihara and Kojiro (5), there is a type called mucinous carcinoma, but its clinical features have not yet been reported. Pathologically, in mucinous carcinoma, large amounts of mucin is present within the cells and also extracellularly (5, 6). By contrast, in mucin-producing papillary adeno-

carcinoma, mucin is present mainly extracellularly.

Here, we report a patient with cholangiocarcinoma of the mucinous carcinoma type. The patient also had a serous cystadenoma of the pancreas making the clinical diagnosis difficult but interesting.

Case Report

A 65-year-old man was hospitalized for closer examination of abdominal tumor. His medical history included acute encephalomyelitis at the age of 2, but no parasitic infection or exposure to Thorotrast. His mother died of uterine cancer. He had complained of slight nausea for 6 months. Physical examination revealed a firm mass approximately 7 cm in size in the right upper abdominal quadrant. Laboratory data on admission (Table 1) were within normal limits except for a slight decrease in serum total protein (6.1 g/dl). However, serum levels of carcinoembryonic antigen (CEA) and carbohydrate antigen 72–4 (CA72–4), or tumor associated glycoprotein (TAG)-72 (7), were markedly elevated (Table 2). No

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Mucinous Cholangiocarcinoma

Table 1. Laboratory Data on Admission (1)

RBC	445 × 10 ⁴ /μl	ALP	7.7 KAU
Hb	14.0 g/dl	γ-GTP	29 mu/ml
WBC	5,400/μl	ChE	198 IU/l
Plts	23 × 10 ⁴ /μl	S-Amyl	66 somogyiU
ESR	17 mm/h	U-Amyl	249 U/dl
Urinalysis	n.p	lipase	75 IU/l
stool	OB (—)	T-chol	179 mg/dl
FBS	86 mg/dl	TG	65 mg/dl
PT	11.2 sec	BUN	16.8 mg/dl
HPT	92%	Cr	1.0 mg/dl
TP	6.1 g/dl	UA	5.3 mg/dl
T-bil	0.61 mg/dl	Na	142 mEq/l
TTT	0.9 U	K	3.7 mEq/l
ZTT	6.0 U	Cl	107 mEq/l
GOT	21 U	CRP	(—)
GPT	21 U		
LDH	387 U		

Table 2. Laboratory Data on Admission (2)

Tumor marker		Cut off value
CEA	125 ng/ml	(2.5 ng/ml)
CA 72-4	71 U/ml	(4.0 U/ml)
CA 19-9	35 U/ml	(37 U/ml)
SLX	47 U/ml	(38 U/ml)
CA 125	20 U/ml	(50 U/ml)
DU-PAN-2	72 U/ml	(150 U/ml)
NCC-ST 439	6.8 U/ml	(7.0 U/ml)

antibodies against various parasitic antigens including *Clonorchis sinensis* were detected by enzyme-linked immunosorbent assay. Ultrasonography (US) (Fig. 1A), especially endoscopic ultrasonography (EUS) (Fig. 2), disclosed a high-echoic tumor with less echogenic portions in the right anterior inferior segment of the liver. The tumor resembled a cavernous hemangioma. US also showed a large high-echoic tumor in the pancreatic head (Fig. 1B). Computed tomography (CT) (Fig. 3) showed multilocular low density areas in the liver and the pancreas. Magnetic resonance imaging also depicted two tumors, which showed low intensity on T1-weighted images and high intensity on T2-weighted images. Celiac angiography disclosed that the hepatic tumor was marginally hypervascular whereas the pancreatic tumor was diffusely hypervascular (Fig. 4). The hepatic tumor

Fig. 2. Endoscopic ultrasonographic findings of the hepatic tumor. The hyperechoic tumor resembled a cavernous hemangioma.

Fig. 1. Ultrasonographic findings of the hepatic tumor (A) and the pancreatic tumor (B).

grew from 4 cm to 9 cm, associated with an increase in the serum CEA level from 125 ng/ml to 1,000 ng/ml in

4 weeks (Fig. 5). Endoscopic examination disclosed no abnormalities in the upper or lower gastrointestinal tract. There were non-neoplastic cysts in the liver and right kidney, but no cystic lesions in the brain. Operative findings were as follows: the hepatic tumor was exposed to the liver surface, and was soft and spongy. There were no obvious cysts in the tumor. There was no intrahepatic

Fig. 4. Angiographic findings of the tumors in the liver (A) and the pancreas (B). The hepatic tumor (arrows) showed less vascularity than the pancreatic tumor.

Fig. 3. Computed tomographic findings of the tumors in the liver (A, B) and the pancreas (C). Both tumors were depicted as multilocular low density areas. The hepatic tumor grew rapidly from 4 cm (A, on admission) to 9 cm (B, after 4 weeks). There was an independent cyst in the vicinity of the hepatic tumor.

Fig. 5. Serial changes of CEA and CA72-4 in this case. Both tumor markers increased rapidly and decreased after the operation.

metastasis. The pancreatic tumor was slightly firm. Frozen section diagnosis of the tumors in the liver and pancreas was adenocarcinoma and cystadenoma, respectively. A small amount of gelatinous fluid, resembling egg white, was seen in the peritoneal cavity. Radical resection of the hepatic tumor was performed, combined with cholecystectomy. In addition, a tissue specimen was obtained from the pancreatic tumor to make the histologic diagnosis. Because of ischemic heart disease and mild respiratory dysfunction, and because of the benignity of the pancreatic tumor, pancreaticoduodenectomy was not performed. The hepatic tumor grossly appeared multicystic, but there were no apparent cysts. Histologically, it consisted of adenocarcinoma cell nests floating in a mucinous lake (Fig. 6). Mucin was accumulated in the cytoplasm of the carcinoma cells. Mucin production was confirmed by staining with periodic acid Schiff (PAS), alcian blue and mucicarmin (Muto Pure Chemicals, Tokyo). Electron microscopic examination of the hepatic tumor showed mucin-containing vacuoles in the cytoplasm of the columnar carcinoma cells (Fig. 7). At the tumor front, cholangiocarcinoma invaded the hepatic parenchyma. Thin fibrous septa were present between the mucin of the tumor and the surrounding liver tissues. There was no tumor invasion in the bile ducts grossly or histologically. On the other hand, the pancreatic tumor was a serous cystadenoma (Fig. 8). The tumor consisted of small cysts lined with low cuboidal

Fig. 6. Histologic findings of the hepatic tumor. Proportion of mucin in the tumor greatly exceeded that of tumor cells (HE stain, A: $\times 120$, B: $\times 350$).

epithelia with little atypia. The cytoplasm of the tumor cells contained glycogen vacuoles, as was confirmed by PAS staining with diastase digestion and electron microscopy. There were no carcinoma cells in the gelatinous fluids obtained from the peritoneal cavity, but peritoneal dissemination of cholangiocarcinoma was strongly suspected. The patient was discharged 1.5 months after the operation in fair condition, and was followed up by his family doctor. But he died of hepatic failure due to the recurrence of mucinous cholangiocarcinoma 4 months after the operation. An autopsy was not performed.

Discussion

Mucinous cholangiocarcinoma (mucinous carcinoma) is a very rare primary liver cancer (5, 6). The entity of mucinous carcinoma has been described in the histologic classification of Sugihara and Kojiro (5). In a series of cases reported by Nakajima et al (6), there was only one mucinous carcinoma among 102 consecutively examined cases of intrahepatic cholangiocarcinoma. This type is

Fig. 7. Electron microscopic findings of the hepatic tumor. Mucin-producing vacuoles were seen in the cytoplasm of the columnar carcinoma cells ($\times 6,000$).

Fig. 8. Histologic findings of the pancreatic tumor. It consisted of multiple cysts lined by cuboidal epithelia without atypia (HE stain, $\times 140$).

different from mucinous cystadenocarcinoma. On the other hand, there is a different type of mucin-producing cholangiocarcinoma with intraductal spreading, with most affected patients showing obstructive jaundice caused by mucinous compaction in the common bile duct (1–4).

Here, we describe a patient with mucinous cholangiocarcinoma, which did not secrete mucin into the bile ducts. Since the proportion of mucin volume in the tumor exceeded that of tumor cells, the rapid growth

observed was probably due to the large amounts of mucin secreted by the tumor cells. But the tumor markers such as CEA and CA72-4 also increased rapidly as shown in Fig. 5. Therefore, the tumor cells themselves might have had a potential of rapid growth.

Clinical features of mucinous carcinoma have not yet been described in detail. Among all of the findings of imaging studies, biochemical data including tumor markers and pathological findings of mucinous carcinoma, the most striking was the clinical characteristic of the tumor in its very rapid growth as mentioned above.

It is difficult to distinguish mucinous carcinoma from mucin-producing papillary adenocarcinoma of the duct-spreading type. However, there are definite differences between the two tumors. Mucin-producing cholangiocarcinoma is usually a slow-growing tumor and shows a good prognosis. It spreads intraductally and causes obstructive jaundice. Pathologically, mucin-producing cholangiocarcinoma is well-differentiated papillary adenocarcinoma (1–4). Therefore, this type of cholangiocarcinoma can be called intraductal papillary adenocarcinoma.

By contrast, here, mucinous carcinoma grew rapidly toward hepatic parenchyma, did not cause obstructive jaundice, and showed a very poor prognosis. Pathological findings of mucinous carcinoma showed that large amounts of mucin existed both intra- and extracellularly. It is unknown whether mucinous carcinoma secretes mucin into bile ducts or not. If the mucinous carcinoma in this report secreted mucin into the bile duct system,

the clinical picture might be similar to intraductal papillary adenocarcinoma with regard to the development of obstructive jaundice. But the feature of the rapid growth of the tumor would not change even in that case.

Factors etiologically related to cholangiocarcinoma include (5): exposure to thorium dioxide (Thorotrast), hepatolithiasis, hepatic infestation by *Clonorchis sinensis*, hepatic cysts, and anabolic steroids, although these factors did not seem to play a role in the present case. Moreover, the factors responsible for the copious production of mucin by the tumor are unknown.

Serous cystadenoma of the pancreas (SCAP) is also a rare pancreatic tumor (8, 9) and usually shows a benign biologic behavior. However, there has been a report of a patient with SCAP showing invasion and metastasis (10). The preoperative differential diagnosis of the present case, therefore, included SCAP with liver metastasis.

Several imaging studies such as US, CT and magnetic resonance imaging (MRI) showed similar patterns of multilocular tumors in the liver and the pancreas, although the hepatic tumor resembled a cavernous hemangioma on EUS examination. Celiac angiography revealed a difference in vascularity between the two tumors. The hepatic tumor was hypervascular only in the periphery, whereas the entire pancreatic tumor showed marked hypervascularity. The large amount of mucin seems to account for the avascular or hypovascular areas in the hepatic tumor.

There has been no report on the simultaneous development of mucinous cholangiocarcinoma and SCAP in a single patient. This very rare combination may be an incidental occurrence. SCAP is known to be associated with cystic lesions in other organs such as the liver, kidney, retina and brain, especially in von Hippel-Lindau disease (11). Although our patient had non-neoplastic cysts in the liver and right kidney, brain CT and ophthalmologic examinations showed no evidence of von Hippel-Lindau disease. The mucinous cholangiocarcinoma was probably derived from bile duct epithelium, or possibly from intrahepatic peribiliary glands (12). On the other hand, centroacinar cells are considered to be the origin of SCAP. Therefore, the two tumors do not seem to have a direct relationship, and they have no etiological influence on each other. From the clinical viewpoint, however, the combination in the present case made the

preoperative diagnosis very difficult but interesting. The difference in vascularity between the intrahepatic cholangiocarcinoma and SCAP was most striking in this patient. Although the initial signs and symptoms of the patient were caused by the pancreatic tumor, the rapidly growing hepatic tumor determined his prognosis.

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References

- 1) Chou ST, Chan CW. Mucin-producing cholangiocarcinoma: an autopsy study in Hong Kong. *Pathology* **8**: 321, 1976.
- 2) Ohta T, Konishi K, Higashino Y, et al. A case of mucinous biliary obstruction associated with multiple cholangiocarcinoma. *J Biliary Tract Pancreas* **4**: 687, 1983 (in Japanese).
- 3) Homma S, Nagamori S, Fujise K, et al. Human bile duct carcinoma cell line producing abundant mucin *in vitro*. *Gastroenterol Jpn* **22**: 474, 1987.
- 4) Kokubo T, Itai Y, Ohtomo K, Itoh K, Kawauchi N, Minami M. Mucin-hypersecreting intrahepatic biliary neoplasms. *Radiology* **168**: 609, 1988.
- 5) Sugihara S, Kojiro M. Pathology of cholangiocarcinoma. in: *Neoplasms of the Liver*, Okuda K, Ishak KG, Eds. Springer-Verlag, Tokyo, 1987, p143.
- 6) Nakajima T, Kondo Y, Miyazaki M, Okui K. A histopathologic study of 102 cases of intrahepatic cholangiocarcinoma: histologic classification and modes of spreading. *Hum Pathol* **19**: 1228, 1988.
- 7) Motoo Y, Satomura Y, Kawakami H, et al: Serum levels of tumor-associated glycoprotein (TAG-72) in digestive cancers. *Oncology* **47**: 456, 1990.
- 8) Alpert LC, Truong LD, Bossart MI, Spjut HJ. Microcystic adenoma (serous cystadenoma) of the pancreas: a study of 14 cases with immunohistochemical and electron-microscopic correlation. *Am J Surg Pathol* **12**: 251, 1988.
- 9) Warshaw AL, Compton CC, Lewandrowski K, Cardenosa G, Mueller PR. Cystic tumor of the pancreas: new clinical, radiologic and pathologic observations in 67 patients. *Ann Surg* **212**: 432, 1991.
- 10) George DH, Murphy F, Michalski R, Ulmer BG. Serous cystadenocarcinoma of the pancreas: a new entity? *Am J Surg Pathol* **13**: 61, 1989.
- 11) Horton WA, Wong V, Eldridge R. Von Hippel-Lindau disease. Clinical and pathological manifestations in nine families with 50 affected members. *Arch Intern Med* **136**: 769, 1976.
- 12) Terada T, Nakanuma Y. Pathological observations of intrahepatic peribiliary glands in 1,000 consecutive autopsy livers. II. A possible source of cholangiocarcinoma. *Hepatology* **12**: 92, 1990.