Huge Pancreatic Acinar Cell Carcinoma with High Levels of AFP and Fucosylated AFP (AFP-L3)

Atsushi Hiraoka¹, Hiromasa Nakahara^{1,2}, Hideki Kawasaki³, Yuko Shimizu¹, Satoshi Hidaka¹, Yusuke Imai¹, Hiroki Utsunomiya¹, Haruka Tatsukawa¹, Nayu Tazuya¹, Hiroka Yamago¹, Nobukazu Yorimitsu¹, Tetsuya Tanihira¹, Aki Hasebe¹, Yasunao Miyamoto¹, Tomoyuki Ninomiya¹, Masanori Abe⁴, Yoichi Hiasa⁴, Bunzo Matsuura⁴, Morikazu Onji⁴ and Kojiro Michitaka¹

Abstract

A 25-year-old Japanese woman with a large abdominal tumor (10 cm in diameter) and high level of serum alpha-fetoprotein (AFP, 1,222.4 ng/mL) was introduced and admitted to our hospital in January 2011. Pre-operative imaging modalities could not identify the tumor origin. There was no chronic hepatic viral disease, however, the elevated level of fucosylated AFP (87.8%) and connection with the left hepatic lobe led us to diagnose the tumor as a hepatocellular carcinoma. Surgical resection was performed in February. Histological findings revealed a pancreatic acinar cell carcinoma (ACC). Herein, we provide details of this difficulty to diagnose a case of ACC.

Key words: pancreatic neoplasm, acinar cell carcinoma, AFP, AFP-L3

(Intern Med 51: 1341-1349, 2012)

(DOI: 10.2169/internalmedicine.51.6536)

Introduction

Serum alpha-fetoprotein (AFP) and fucosylated AFP (AFP-L3) are known as tumor markers of hepatocellular carcinoma (HCC) (1, 2). Only a small number of pancreatic acinar cell carcinoma (ACC) cases with elevation of AFP have been reported in literature (Table 1) (3-28). Moreover, only a small number of reports have documented lectin fractionation of AFP in ACC (8, 17, 21). We present a case of large pancreatic ACC accompanied by high levels of AFP and AFP-L3, which was difficult to diagnose prior to surgery.

Case Report

A 25-year-old Japanese woman with a large abdominal tumor and high level of serum AFP (1,222.4 ng/mL) was introduced to our hospital in January 2011 for further exami-

nations. When she bruised her abdomen in skiing and abdominal computed tomography (CT) was performed for the pain. A large abdominal tumor was found incidentally. Dynamic CT revealed a huge hypervascular abdominal tumor with central necrosis without other tumors or metastasis (Fig. 1). Abdominal ultrasonography (US) showed a hypoechoic tumor 10 cm in diameter with connection to the left hepatic lobe, stomach, and pancreas (Fig. 2a). We considered that the mass originated from the left hepatic lobe. Laboratory data on admission are presented in Table 2.

The serum levels of AFP and AFP-L3 were 2,550.8 ng/mL and 87.8%, respectively. Neither markers of viral hepatitis nor elevated serum levels of carcinoembryonic antigen (CEA, 2.0 ng/mL) or carbohydrate antigen 19-9 (CA19-9, 17.7 U/mL), DUPAN-2 (66 U/mL), or Span-1 (10.8 U/mL) were detected (Table 2). ¹⁸F-fluorodeoxy glucose positron emission tomography (FDG-PET)/CT showed a high uptake of ¹⁸F-fluorodeoxy glucose (max-standardized uptake value,

¹Gastroenterology Center, Ehime Prefectural Central Hospital, Japan, ²Department of Internal Medicine, Matsuyama Shimon Hospital, Japan, ³Department of Surgery, Ehime Prefectural Central Hospital, Japan and ⁴Department of Gastroenterology and Metabology, Ehime University Graduate School of Medicine, Japan

Received for publication September 10, 2011; Accepted for publication January 6, 2012

Correspondence to Dr. Atsushi Hiraoka, hirage@m.ehime-u.ac.jp

Table 1. Reported Cases of Alpha-fetoprotein Producing Pancreatic Acinar Cell Carcinoma

Author	year	Age (years)	sex	Size (cm)	Symptoms	Pre-operative (pre-autopsy) diagnosis	Therapy (anticancer drug)	Location of tumor (metastasis)	AFP (ng/mL)	AFP-L3 (%)	Prognosis (observation period)
Ono	1984	69	M	6.5	Right upper quadrant pain and discomfort	Duodenal tumor	Resection	Pancreas head (with dissemination to the peritoneum)	65,000	NA	Died (3M)
Inui	1984	30	F	NA	Epigastralgia and cough	Pancreas tumor	Chemotherapy (5-FU, MMC and OK432)	Pancreas head (with pulmonary and lymph node metastases)	1,700	NA	Died (7M)
Kikuchi	1985	38	M	NA	Lumbago and diarrhea	Pancreatic cancer	Chemotherapy (NA)	Pancreas body and head (with peritoneal metastasis)	26,800	NA	Died (1.5M)
Kikuchi	1985	60	M	NA	Melena	NA	NA	NA (with hepatic metastasis)	200	NA	Died (16M)
Yajima	1987	38	M	NA	Epigastralgia, back pain, diarrhea and body weight loss	Pancreatic cancer	Chemotherapy (5-FU, MMC and urokinase)	Pancreas body and tail (lymph node metastasis)	800	NA	Died (15M)
Takezaki	1988	77	M	14.0	Appetite loss and general fatigue	Pancreas tumor	UFT	Pancreas body (with hepatic metastasis)	7,756	NA	Died (2M)
Nojima	1992	57	M	6.5	Epigastric pain and vomiting	Pancreas tumor	Resection and chemotherapy (NA)	Pancreas tail (with hepatic metastasis)	1,500	58	Alive (32M)
Kawamoto	1992	77	F	6.0	Epigastric pain	Pancreas tumor	Resection	Pancreas body	5,790	NA	Alive (2M)
Itoh	1992	60	M	NA	None (pointed out by a routine health check)	Pancreatic cancer	Resection	Pancreas body and tail	415	NA	Alive (24M)
Ishizaki	1995	57	M	3.6	Epigastralgia with vomiting	Pancreatic cystadenocarcinoma	Resection	Pancreas tail (with hepatic metastasis)	1,500	NA	Died (37M)
Okamoto	1995	18	M	8.0	Icterus	Pancreas tumor or malignant lymphoma	Resection	Pancreas head	11,900	NA	Alive (8M)
Fujiki	1996	41	F	4.8	Epigastralgia and icterus	Pancreatic cancer	Chemotherapy (5-FU, epirubicin and MMC)	Pancreas body	23,003	NA	Died (8M)
Sakon	1996	56	M	9.5	Epigastralgia and back pain	Pancreas tumor	Resection	Pancreas tail	253	NA	Alive (16M)
Morii	1998	47	M	NA	Abdominal fullness and appetite loss	Pancreatic cancer	Resection and chemotherapy (5-FU, adriamycin, MMC)	Pancreas tail (with hepatic and splenic metastases)	11,550	NA	Died (10M)
Shinagawa	1999	30	F	4.0	Epigastric discomfort	Pancreatic tumor	Resection	Pancreas head	350	NA	NA
Eriguchi	2000	67	M	12.0	Severe epigastralgia	Rupture of HCC	Resection	Upper abdominal cavity (=pancreas body)	125.5	1.4	Alive (6M)
Chen	2001	78	F	12.0	Anorexia, nausea, vomiting, epigastralgia and body weight loss	Pancreatic acinar cell carcinoma (by a sono-guided biopsy)	Chemotherapy (Gemcitabine)	Pancreas head	8,164	NA	Alive (2M)

Author	year	Age (years)	sex	Size (cm)	Symptoms	Pre-operative (pre-autopsy) diagnosis	Therapy (anticancer drug)	Location of tumor (metastasis)	AFP (ng/mL)	AFP-L3 (%)	Prognosis (observation period)
Akashi	2001	50	M	10.0	Appetite loss and back pain	Pancreatic cancer	Chemotherapy (5-FU and CDDP)	Pancreas body (with pulmonary and lymph node metastases)	62	NA	Died (13M)
Yamauchi	2001	63	F	5.0	Epigastralgia, icterus	Pancreatic acinar cell carcinoma (biopsy against hepatic metastasis)	Chemotherapy (5-FU and Carboplatin)	Pancreas head (with hepatic metastasis)	2,490	NA	Died (8M)
Mori	2004	33	M	8.0	Epigastralgia and back pain	Pancreatic acinar cell carcinoma (by EUS-FNA)	Chemotherapy (5-FU and CDDP)	Pancreas head and body (with invasion to portal vein and hepatic artery)	12,886	38.1	Alive (11M)
Mishima	2005	49	M	3.0	Epigastralgia and back pain	Pancreatic cancer	Chemotherapy (Gemcitabine)	Pancreas head	823	NA	Died (10M)
Oka mura	2005	60	M	3.0	Epigastralgia and suffered left backache	Pancreatic islet cell tumor	Chemotherapy (NA)	Pancreas tail (with hepatic and lymph nodes metastasis)	899	NA	Died (10M)
Lin	2007	47	M	2.0	None (routine health check-up)	Pancreatic adenocarcinoma or endocrine tumor	resection	Pancreas tail	463.69 (HBV carrier)	NA	Alive (36M)
Kolb-van Harten	2007	77	M	NA	Increasing fatigue and impaired appetite	Pancreatic acinar cell carcinoma (by EUS-FNA)	Chemotherapy (Gemcitabine and MMC)	Pancreas body	>32,000	NA	Died (7M)
Kawaguchi	2009	63	M	10.0	Epigastralgia	Abdominal tumor	Resection	Left upper abdomen	871.1	NA	Alive (6M)
Fujii	2010	59	M	4.5	Anemia	Pancreas tumor	Resection [Chemotherapy (CDDP and S1) against recurrence with hepatic metastasis]	Pancreas head	8,228 (Data at recurrence)	NA	Died (36M)
Lee	2010	48	F	1.2	Chest tightness	Pancreatic cancer	Resection	Pancreas head	89.95 (U/L) (HBV carrier)	NA	Alive (71M)
Present case	2011	25	F	10.0	None (pain for a bruise on the abdomen on skiing)	Suspected for HCC	Resection and chemotherapy (Gemcitabine)	Upper abdominal cavity (=pancreas head) (with hepatic metastasis)	2,550.8	87.8	Died (10M)

HCC, hepatocellular carcinoma; NA, not available; AFP, alpha-fetoprotein; AFP-L3, fucosylated AFP; EUS-FNA, endoscopic ultrasound with fine needle aspiration; CDDP, cisplatin; 5-FU, 5-fluorouracil; OK432, Picibanil; MMC, mitomycin C; UFT, tegafur - uracil; HBV, hepatitis B virus

8.4) in the tumor and no metastasis (Fig. 2b). A contrast-enhanced US (CEUS) examination with Sonazoid (Perflubutane; Daiichi Sankyo, Tokyo, Japan) showed a suspected necrotic area in the center of the tumor and the description was non-vascular. Furthermore, B-mode US did not detect another hepatic tumor other than the main large abdominal mass. In the Kupffer phase of CEUS, a small defect (0.9 cm in diameter) was detected in the 5th segment of the liver (Fig. 2c), which was enhanced by re-injection of Sonazoid

(Fig. 2d). Though, pancreas became atrophic and the main pancreatic duct (MPD) appeared to be suspended due to oppression of the tumor, the dilatations of MPD and common bile duct were not revealed by magnetic resonance cholangiopancreatography (MRCP). However, occlusion of the splenic vein was suspected by late phase of dynamic CT. Angiography showed the occlusion of the splenic vein by compression with the tumor and formation of collateral vessels. In spite of the compression with the tumor, the portal

Figure 1. Dynamic computed tomography (CT) image showing a large hypervascular abdominal tumor with central necrosis. There was no hepatic lesion detected by dynamic CT.

vein was intact by portography, and gastroduodenal artery was found to be the main feeder of the tumor (Fig. 3). We made a diagnosis of HCC and intrahepatic metastasis of HCC based on serological examination results (AFP, AFP-L3), as well as hypervascular findings in dynamic CT and CEUS images.

Surgical resection of the main tumor and small lesion in the 5th segment of the liver was performed in February 2011 (pancreaticoduodenectomy-II A-2, Hr0). The main tumor was located in the pancreas head. Portal vein and common bile duct were oppressed by the tumor. Adhesion between the tumor and splenic vein was observed in macroscopic finding (Fig. 4a-c). The atypical cells with eosinophilic cytoplasm formed microglandular structures as seen by Hematoxylin and Eosin (HE) staining. The large tumor and hepatic tumor were diagnosed as a pancreatic acinar cell carcinoma. Chromogranin was negative by immune staining (Fig. 4f-h). Pathological examinations of the tumors revealed ACC and hepatic metastasis (medullary type, INF α , ly1, v1, ne0, mpd-, pCH-, pDU, pS-, pRP-, pPVsp+, pA-, pPLX, pOO-, n(-0/4). pT4N0M1(HEP), pStage IV) (29). Tumor invasion to the splenic vein was proven histologically. Immunostaining for AFP was positive (Fig. 4i). Multiple hepatic metastases and peritoneal dissemination were diagnosed 8 months after resection and she was treated by chemotherapy with Gemcitabine (Gemzar®). Two months after

diagnosis of recurrence, she was died.

Discussion

Pre-operative diagnosis is difficult in many cases of ACC (30). One case was diagnosed as rupture of HCC (17). In the present case, both AFP and AFP-L3, which is known as a specific tumor marker for HCC (1, 2), were elevated, and elevation of the latter made it difficult to diagnose the huge tumor originating from the pancreas before the operation. Although the positivity rate for AFP is reported to be under 10% in cases of fibrolamellar carcinoma (31), it must be considered in the differential diagnosis (32) along with ectopic HCC (33) in cases with an abdominal tumor in another organ other than the liver, as in the present case. In 4 cases of past reports, AFP-L3 was examined, and 3 of them showed elevation of AFP-L3. Elevation of AFP-L3 in AFP-producing ACC might not be rare. There were only 4 cases (14.3%), which were diagnosed as ACC pre-operative or pre-autopsy, in past reports (Table 1).

An ACC is a rare tumor that comprises approximately 1% of exocrine pancreatic tumors (34, 35). Klimstra et al. reported no significant gender differences for affected patients and a poor prognosis, and also estimated that AFP producing ACC tumors were found in 6% of these cases, with pancreatic ACC found in the head of the pancreas in slightly

Figure 2. a. The tumor was revealed as a hypoechoic lesion (10 cm in diameter) by abdominal B-mode ultrasonography (US). There was no detection of hepatic tumor by B-mode US. The head of the pancreas and common bile duct could not be revealed because of oppression. The tumor was adjacent to the left hepatic lobe and the body of stomach. b. ^{18}F -fluorodeoxy glucose positron emission tomography (FDG-PET)/CT revealed a high level of uptake of ^{18}F -fluorodeoxy glucose (max-standardized uptake value, 8.4) in the tumor and no detection of metastasis. c. In the Kupffer phase of contrast-enhanced US, a small defect (0.9 cm in diameter) was detected in the 5th segment of the liver (black arrowhead). d. The defect was enhanced by re-injection of Sonazoid (white arrow).

Table 2. Laboratory Data on Admission

White blood cells	2,710/uL	TP	7.1 g/dL	AFP	2,550.8 ng/mL
Red blood cells	$424 \times 10^4/\mu\text{L}$	Alb	4.3 g/dL	AFP-L3	87.8%
Hemoglobin	12.4g/dL	T-Bil	0.5 mg/dL	PIVKA-II	24 mAU/L
Hematocrit	37.4%	AST	14 IU/L	CEA	2.0 ng/mL
Platelets	$16.6 \times 10^4/\mu\text{L}$	ALT	15 IU/L	CA19-9	17.7 U/mL
Prothrombin time	86.0%	ALP	147 IU/L	DUPAN-2	66 U/mL
		ChE	241 IU/L	Span-1	10.8 U/mL
HbA1c	5.9%	TTT	3.6 U	S-IL-2 R	238 U/mL
FBG	108 mg/dL	ZTT	7.5 U		
ESR	20 mm (1hr.)	Amy	35 IU/L	HBsAg	(-)
	55 mm (2hr.)	BUN	8.6 mg/dL	HBcAb	(-)
		Cre	0.61 mg/dL	Anti-HCV	(-)
		Na	140 mEq/L	ANA	<40
		K	4.5 mEq/L	AMA(M2)	<5.0
		Cl	103 mEq/L	IgG	1,331 mg/dL
				Ferritin	25.4 ng/mL

HbA1c, hemoglobin A1c; FBG, fasting blood glucose; ESR, erythrocyte sedimentation rate; PT, prothrombin time; TP, total protein; Alb, albumin; T-Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline Phosphatase; ChE, cholinesterase; TTT, thymol turbidity test; ZTT, zinc turbidity test; Amy, amylase; BUN, blood urea nitrogen; Cre, creatinine; Na, sodium; K, potassium; Cl, chlorine; AFP, alpha-fetoprotein; AFP-L3, fucosylated AFP; PIVKA-II, protein induced by vitamin K absence-II; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; S-IL-2 R, soluble interleukin-2 receptor; HBsAg, hepatitis B surface antigen; HBcAb, hepatitis B core antibody; anti-HCV, hepatitis C virus antibody; ANA, antinuclear antibody; AMA (M2), antimitochondrial antibody (M2); IgG, immunoglobulin G

more than half (56%) (36). On the other hand, the 5-year survival rate after resection was described to be favorable (43.9%) in the resectable cases (30).

AFP is a tumor marker for HCC. Ishizaki et al. reported that cases of pancreatic ACC with elevated serum AFP are very rare (11), whereas the frequency of pancreatic neo-

Figure 3. a. In late phase of dynamic CT, occlusion of the splenic vein due to oppression of the tumor was suspected. The portal vein was intact. b. Though, the pancreas became atrophic and the main pancreatic duct (MPD) appeared to be suspended due to oppression of the tumor, the dilatation of MPD was not detected by magnetic resonance cholangiopancreatography (MRCP) (black arrowhead). c. The portal vein was intact by portography. d. Angiography showed gastroduodenal artery was the main feeder of the tumor. e. Occlusion of the splenic vein was caused by compression with the tumor and formation of collateral vessels was seen.

plasms in patients with elevated serum AFP levels is higher in previous reports (37). Other studies also noted that ACCs comprised 27% of pancreatic neoplasms in cases with elevated serum AFP levels (38). The mechanism of production of AFP without HCC has not been elucidated, though production of AFP by hepatoid differentiation of cancer cells (39-41) and production of AFP by entero-blastic differentiation (42) have been proposed. The reasons for the elevation of AFP-L3 could not be clearly elucidated. It is important to bear in mind that elevation of AFP-L3 could be observed in AFP producing ACC.

Metastasis was not detected by FDG-PET/CT in the present case. Although it is a powerful modality for screening of metastasis, FDG-PET/CT has a limitation for the detection of small metastatic hepatic tumors (<1 cm) in the liver because of resolution limits (43). CEUS with Sonazoid has been reported as a useful modality for the detection for hepatic malignant tumors (44) and screening of hepatic metastasis (43). Using CEUS with Sonazoid, a small tumor was detected as a defect in the 5th segment of the liver in the Kupffer phase in the present case and enhanced uniformly by re-injection (45). We diagnosed the small tumor as intra-hepatic metastasis of HCC prior to resection. Although, distal MPD was revealed without dilatation by MRCP, multi-

planar reconstruction images of enhanced CT (MPR-CT) provided more information than magnetic resonance imaging (MRI) and MRCP regarding portal and splenic veins in pre-operative studies of the present case. Though, the enhancement pattern of the tumor was similar to HCC, and serum levels of AFP and AFP-L3 were elevated, we should suspect that the origin of the tumor was the pancreas head, because displacement of the bilateral lobes of the liver was observed and the main feeder of the tumor was the gastroduodenal artery. Further examination endoscopic ultrasonography (EUS) should be considered to perform in order to discriminate whether the origin of the tumor was the pancreas or not. Recently, EUS fine needle aspiration (EUS-FNA) has been reported to be an effective modality for the diagnosis of AFP producing ACC (21, 25). The elevation of the levels of AFP and AFP-L3 mislead us in the present case. And we suspected an ectopic or fibrolamellar HCC at first, and did not plan to perform EUS-FNA. Following surgical resection, HE staining showed that the atypical cells with eosinophilic cytoplasm formed microglandular structures. It is difficult to obtain stability of immune staining of trypsin, chymotrypsin, lipase, and/or elastase. Though, these immune stainings of trypsin and chymotrypsin were negative in the present pathological findings, pancreatic ductal cancer and neuroen-

Figure 4. a. Huge tumor was located at the pancreas head. Portal vein and common bile duct were oppressed by the tumor. b. Adhesion between the tumor and splenic vein was observed in macroscopic findings. c. Simultaneously, the splenic vein was resected and portal vein repaired in pancreaticoduodenectomy. d. The maximum diameter was enlarged rapidly to 14 cm in diameter. e. The hepatic tumor (enlarged to 1.5 cm in diameter) was resected simultaneously. f, g. The atypical cells with eosinophilic cytoplasm formed microglandular structures as seen by Hematoxylin and Eosin staining. The large tumor and hepatic tumor were diagnosed as a pancreatic acinar cell carcinoma. h. Chromogranin was negative by immune staining. i. Alpha-fetoprotein was positive following immune staining.

doocrine tumor were denied, and histological findings led to a final diagnosis of AFP producing ACC.

In the past reports, 1- and 3-year survival rates of the cases that could be treated with resection were approximately 70 and 50%, respectively. However, the prognoses of the cases which were not indicated for surgical resection and treated only with chemotherapy were very poor. One-year survival rate of such cases was approximately 20%. Establishment of effective methods for preoperative diagnosis and a therapeutic strategy for ACC is needed. No therapeutic strategy except for resection has been established. Accumulation of additional cases is needed to establish strategies for the diagnosis and therapy for ACC, especially those producing AFP.

The authors state that they have no Conflict of Interest (COI).

References

- Aoyagi Y, Isemura M, Suzuki Y, et al. Fucosylated alpha-fetoprotein as marker of early hepatocellular carcinoma. *Lancet* ii 1353-1354, 1985.
- Kumada T, Nakano S, Takeda I, et al. Clinical utility of Lens culinaris agglutinin-reactive alpha-fetoprotein in small hepatocellular carcinoma: special reference to imaging diagnosis. *J Hepatol* 30: 125-130, 1999.
- Ono J, Sakamoto H, Sakoda K, et al. Acinar cell carcinoma of the pancreas with elevated serum alpha-fetoprotein. *Int Surg* 69: 361-364, 1984.
- Inui K, Nakae Y, Watanabe K, et al. An autopsy case of acinar cell carcinoma of the pancreas with elevated serum AFP levels. *Tan to Sui* 5: 783-789, 1984 (in Japanese).
- Kikuchi Y, Moroboshi T, Kanda M, et al. Acinar cell carcinoma of the pancreas. Report of three cases with immunocytochemical and electronmicroscopical studies. *Kan Tan Sui* 10: 305-310, 1985 (in Japanese).
- Yajima T, Hino K, Hunatomi H, et al. A case of alpha-fetoprotein producing acinar cell carcinoma of the pancreas. *Shoukakika* 6: 318-324, 1987 (in Japanese, abstract in English).
- Takezaki E, Takaishi K, Kagawa K, et al. An autopsy case of pancreatic cancer with a tentative diagnosis of hepatocellular carcinoma due to metastatic tumor of the liver and elevated levels of serum AFP. *Tan to Sui* 9: 1271-1276, 1988 (in Japanese).
- Nojima T, Kojima T, Kato H, Sato T, Koito K, Nagashima K. Alpha-fetoprotein-producing acinar cell carcinoma of the pancreas. *Human Pathol* 23: 828-830, 1992.
- Kawamoto S, Hiraoka T, Kanemitsu K, et al. Alpha-fetoprotein-producing pancreatic cancer-a case report and review of 28 cases. *Hepatogastroenterol* 39: 1271-1276, 1992.
- Itoh T, Kishi K, Tojo M, et al. Acinar cell carcinoma of the pancreas with elevated serum alpha-fetoprotein levels: a case report and a review of 28 cases reported in Japan. *Gastroenterol Jpn* 27: 785-791, 1992.
- Ishizaki K, Koito T, Namieno T, et al. Acinar cell carcinoma of the pancreas: a rare case of an alpha-fetoprotein-producing cystic tumor. *Eur J Radiol* 21: 468-476, 1995.
- Okamoto K, Maesiro K, Ikeda S, et al. AFP producing acinar cell carcinoma of the pancreas in a 18-year-old man: a case report. *Fukubu Gazou Shindan* 15: 468-476, 1995 (in Japanese).
- Fujiki T, Fuchino Y, Maki T, et al. A case of alpha-fetoprotein-positive advanced acinar cell carcinoma of the pancreas markedly improved by intra-arterial infusion chemotherapy. *J Jpn Surg Assoc* 57: 2793-2797, 1996 (in Japanese, Abstract in English).
- Sakon M, Osato H, Kishimoto S, et al. A patient with pancreatic acinar cell carcinoma, effectively treated by the infusion chemotherapy through hepatic artery using 5-FU, CDDP and MMC. *Jpn J Cancer Chemother* 23: 1614-1616, 1996 (in Japanese, Abstract in English).
- Morii K, Okushin H, Yuasa S, et al. A case of alpha-fetoprotein-producing acinar cell carcinoma of the pancreas. *Jpn J Cancer Clin* 44: 915-920, 1998 (in Japanese, Abstract in English).
- Shinagawa T, Tadokoro M, Yamagushi S. Cytomorphology of alpha fetoprotein-producing acinar cell carcinoma of the pancreas. *St. Marianna Med J* 27: 63-69, 1999.
- Eriguchi N, Aoyagi S, Hara M, et al. Large acinar cell carcinoma of the pancreas in patient with elevated serum AFP level. *J Hepatobiliary Pancreat Surg* 7: 222-225, 2000.
- Chen CP, Chao Y, Li CP, et al. Concurrent chemoradiation is effective in the treatment of alpha-fetoprotein-producing acinar cell carcinoma of the pancreas: report of a case. *Pancreas* 22: 326-329, 2001.
- Akashi T, Funakoshi A, Sumii T, Iguchi H, Yonemasu H, Hattanda Y. Efficacy of chemotherapy in acinar cell carcinoma of the pancreas with elevated serum AFP level: case report. *Suizo* 16: 10-17, 2001 (in Japanese, abstract in English).
- Yamauchi N, Ozeki Y, Sumi Y, et al. A case of alpha-fetoprotein-producing acinar cell carcinoma of the pancreas with portal vein obstruction. *Tan to Sui* 22: 1011-1016, 2001 (Abstract in Japanese).
- Mori S, Kondoh S, Ryozaawa S, et al. A case of AFP producing pancreatic acinar cell carcinoma diagnosed by EUS FNA and treated by intraarterial injection chemotherapy. *Nisshoshi* 101: 177-182, 2004 (in Japanese).
- Mishima Y, Kobayashi J, Yamada M, et al. A case of AFP-producing pancreatic acinar cell carcinoma revealed by autopsy: usefulness of 5-FU/cisplatin chemotherapy to improve QOL. *Matsue Shiritsu Byouin Igaku Zasshi* 9: 47-53, 2005 (in Japanese, Abstract in English).
- Okamura N, Kida M, Yanagisawa N, Ohbu M, Okayasu I. Pancreatic alpha fetoprotein-producing acinar cell carcinoma: an autopsy case report. *Kitasato Med J* 35: 27-29, 2005.
- Lin YC, Lee PH, Yao YT, Hsiao JK, Sheu JC, Chen CH. Alpha-fetoprotein-producing pancreatic acinar cell carcinoma. *J Formos Med Assoc* 106: 669-672, 2007.
- Kolb-van Harten P, Rosien U, Klöppel G, Layer P. Pancreatic acinar cell carcinoma with excessive alpha-fetoprotein expression. *Pancreatol* 7: 370-372, 2007.
- Kawaguchi Y, Kono K, Mizukami Y, Hirai Y, Fujii H. A case of alpha-fetoprotein-producing acinar cell pancreatic carcinoma of which was indistinguishable from gastric cancer. *J Jpn Surg Assoc* 70: 2816-2822, 2009 (in Japanese, Abstract in English).
- Fujii M, Sato H, Ogasawara T, et al. A case of liver metastasis of pancreatic acinar cell carcinoma treated with S-1 and intra-arterial CDDP combination therapy. *Jpn J Cancer Chemother* 37: 1987-1990, 2010 (in Japanese, Abstract in English).
- Lee JH, Lee KG, Oh YH, et al. Acinar cell carcinoma of the pancreas: a report of two cases with long-term follow-up and a review of the literature. *J Korean Surg Soc* 79: 310-315, 2010.
- Japan Pancreas Society. General Rules for the Study of Pancreatic Cancer. 5th ed. 2002.
- Kitagami H, Kond S, Hirano S, Kawakami H, Egawa S, Tanaka M. Acinar cell carcinoma of the pancreas: clinical analysis of 115 patients from pancreatic cancer registry of Japan Pancreas Society. *Pancreas* 35: 42-46, 2007.
- Craig JR, Peters RL, Edmonson HA, et al. Fibrolamellar carcinoma of the liver: a tumor of adolescents and young adults with distinctive clinic-pathologic features. *Cancer* 46: 372-379, 1980.
- Edmondson HA. Differential diagnosis of tumors and tumor-like lesions of liver in infancy and childhood. *Am J Dis Child* 91: 168-

- 186, 1956.
33. Collan Y, Hakkilouto A, Hastbacka J, et al. Ectopic liver. *Ann Chir Gynaecol* **67**: 27-29, 1978.
34. Cubilla AL, Fitzgerald PJ. Morphological patterns of primary nonendocrine human pancreas carcinoma. *Cancer Res* **35**: 2234-2248, 1975.
35. Morohoshi T, Held G, Kloppel G. Exocrine pancreatic tumor and their histological classification. A study based on 167 autopsy and 97 surgical cases. *Histopathology* **7**: 645-661, 1983.
36. Klimstra DS, Heffess CS, Oertel JE, Rosai J. Acinar cell carcinoma of the pancreas. A clinicopathologic study of 28 cases. *Am J Surg Pathol* **16**: 815-837, 1992.
37. Patrick JF, Joseph GF, Robin CW, et al. The value of diagnostic aids in detecting pancreas cancer. *Cancer* **41**: 868-879, 1978.
38. Shimizu E, Kikuyama M, Hashimoto M, et al. A case of alpha-fetoprotein-producing pancreatic carcinoma. Review of 41 cases reported in Japan. *Nisshoshi* **93**: 921-926, 1996 (in Japanese).
39. Ishikura H, Kirimoto K, Shamoto M, et al. Hepatoid adenocarcinoma of the stomach. An analysis of seven cases. *Cancer* **58**: 119-126, 1986.
40. Kudo M, Takamine Y, Nakamura K, et al. Des-gamma-carboxy prothrombin (PIVKA-II) and alpha-fetoprotein-producing II c-type early gastric cancer. *Am J Gastroenterol* **87**: 1859-1862, 1992.
41. Reddy JK, Rao MS, Qureshi SA, et al. Induction and origin of hepatocytes in rat pancreas. *J Cell Biol* **98**: 2082-2090, 1984.
42. Ooi A, Nakanishi I, Sakamoto N, et al. Alpha-fetoprotein (AFP)-producing gastric carcinoma. Is it hepatoid differentiation? *Cancer* **65**: 1741-1747, 1990.
43. Hiraoka A, Kume M, Miyagawa M, et al. Diagnostic value of Sonazoid for hepatic metastasis: comparison with FDG PET/CT. *Hepatogastroenterol* **57**: 1237-1240, 2010.
44. Hatanaka K, Kudo M, Minami Y, Maekawa K. Sonazoid-enhanced ultrasonography for diagnosis of hepatic malignancies: comparison with contrast-enhanced CT. *Oncology* **75**: 42-47, 2008.
45. Kudo M, Hatanaka K, Chung H, Minami Y. A proposal of novel treatment-assist technique for hepatocellular carcinoma in the Sonazoid-enhanced ultrasonography: value of defect re-perfusion imaging. *Kanzo* **48**: 299-301, 2007 (in Japanese, Abstract in English).