Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.2783-19
Intern Med 58: 2809-2817, 2019
http://internmed.jp

【 CASE REPORT 】

A Large Carcinosarcoma of the Gallbladder Accompanied by Pancreaticobiliary Maljunction: A Case with a Six-year Survival

Hiroyuki Matsubayashi[1], Toru Matsui[1], Teichi Sugiura[2], Rie Makuuchi[3], Junichi Kaneko[1], Junya Satoh[1], Tatsunori Satoh[1], Shinya Fujie[1], Hirotoshi Ishiwatari[1], Keiko Sasaki[4] and Hiroyuki Ono[1]

Abstract:
Pancreatobiliary maljunction (PBM) is a rare congenital malformation, often associated with adenocarcinoma. However, PBM accompanying gallbladder carcinosarcoma has rarely been reported. A 72-year-old woman was referred to our hospital, complaining of abdominal pain. Computed tomography showed a polypoid mass in the gallbladder. Endoscopic retrograde cholangiopancreatography showed PBM, and aspirated bile demonstrated elevated levels of pancreatic-type amylase (26,780 U/L) and cancer cells. Extended cholecystectomy was performed. Histologically, the tumor had adenocarcinoma, squamous cell carcinoma and sarcoma components. Despite the large tumor size (84 mm) and intra-vessel cancer permeations, this patient has been healthy for 73 months since the surgery.

Key words: carcinosarcoma, gallbladder, pancreatobiliary maljunction, prognosis

(Intern Med 58: 2809-2817, 2019)
(DOI: 10.2169/internalmedicine.2783-19)

Introduction

Carcinosarcoma is a malignant tumor composed of both carcinomatous and sarcomatous elements (1). This histological type of tumor can develop in all types of organs (2-5), but its occurrence in the gallbladder is quite rare, accounting for less than 1% of all gallbladder malignancies (6).

Biliary cancer can occur in response to pancreatobiliary maljunction (PBM), a congenital malformation. In PBM, the pancreatobiliary duct union occurs outside the duodenal wall, and this anatomic anomaly causes continuous and chronic exposure of refluxed pancreatic juice to the biliary epithelium. The histology of these PBM-related biliary cancers is almost always adenocarcinoma, as most of these cancers (39-91%) develop in the background of biliary epithelial hyperplasia (7, 8). The anatomic pattern shows a correlation with the cancer location, as the incidence of bile duct cancer is greater in cases with congenital biliary dilatation (32%) than in those without this congenital anomaly (7%). By contrast, gallbladder cancer is less frequent in cases with congenital biliary dilatation (62%) than in those without it (88%) (9).

Gallbladder cancer accompanying PBM is now being increasingly frequently reported; however, carcinosarcoma of the gallbladder accompanying PBM has seldom been reported in the English literature (10, 11). We herein report a case with a six-year post-operative survival in a patient diagnosed with gallbladder carcinosarcoma accompanied by PBM.

Case Report

A 72-year-old woman visited her nearest hospital complaining of nausea and abdominal pain in her right upper quadrant. Abdominal ultrasonography (US) (Fig. 1a) showed

[1]Division of Endoscopy, Shizuoka Cancer Center, Japan, [2]Division of Hepato-Biliary-Pancreatic Surgery, Shizuoka Cancer Center, Japan, [3]Division of Gastric Surgery, Shizuoka Cancer Center, Japan and [4]Division of Pathology, Shizuoka Cancer Center, Japan
Received: February 3, 2019; Accepted: April 8, 2019; Advance Publication by J-STAGE: June 27, 2019
Correspondence to Dr. Hiroyuki Matsubayashi, h.matsubayashi@scchr.jp

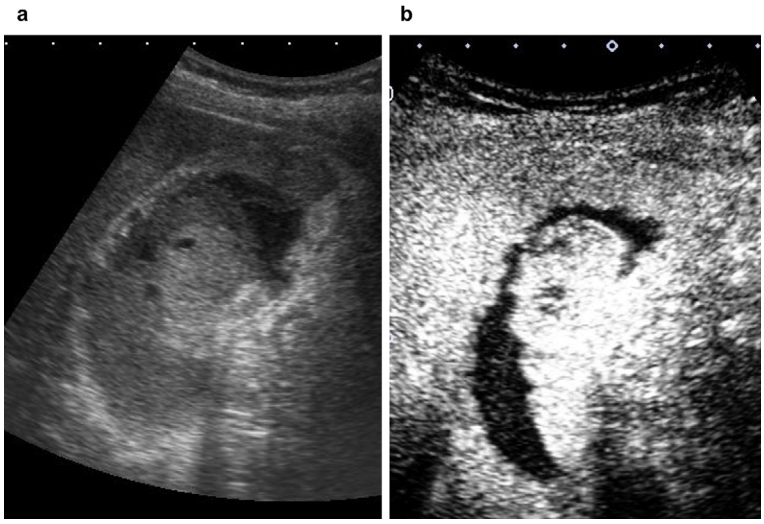

Figure 1. **Abdominal ultrasonography. A large polypoid lesion is recognized in the gallbladder (a). The tumor was diffusely and strongly enhanced by microbubble contrast (b).**

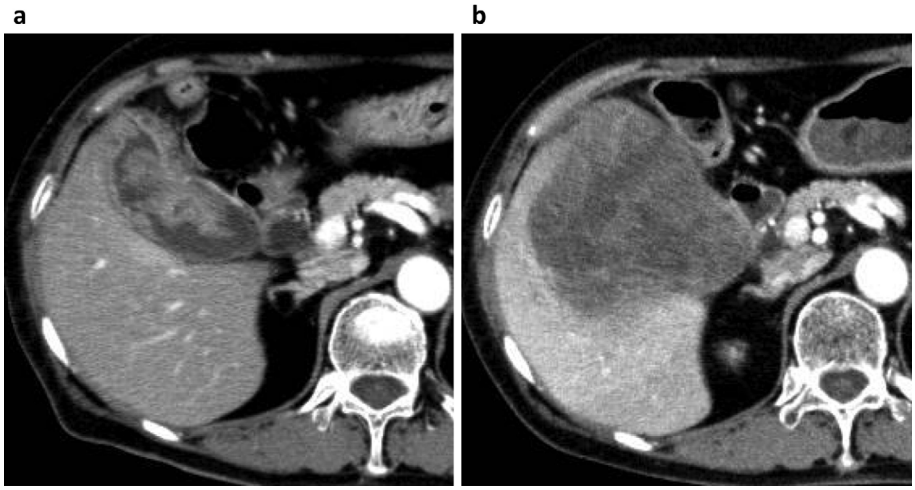

Figure 2. **Enhanced computed tomography (CT). A hypervascular polypoid lesion evident within the gallbladder (a) progressed and invaded the liver within six weeks (b).**

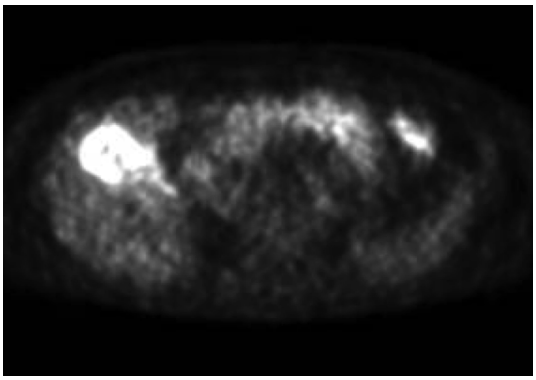

Figure 3. **^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET). A strong uptake is seen at the gallbladder.**

a bulky protruding mass in the gallbladder, and she was referred to our institution for a further investigation. Laboratory data showed elevated levels of serum alkaline phosphatase (ALP; 459 IU/L) and gamma-glutamyl transpeptidase (γ-GTP; 111 IU/L); other measurements, including those of tumor markers (carcinoembryonic antigen: 2.3 ng/mL, normal range: ≤5.0 ng/mL, and carbohydrate antigen 19-9: 15 U/mL, normal range: ≤37 U/mL), were normal.

Enhanced US revealed heterogeneous and strong contrast enhancement within the tumor from 10 seconds until 3 minutes after contrast injection (Fig. 1b), with diminished enhancement afterward. Multi-detector computed tomography (CT) (Fig. 2a) showed a large, irregularly shaped polypoid mass (48×16 mm) with heterogeneous wall thickness in the gallbladder. ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) showed a strong uptake at the gallbladder [Standard uptake value (SUV) max: 13.64] (Fig. 3). Magnetic resonance imaging (MRI) demonstrated heterogeneously low-intensity signals within the tumor on T1-weighted imaging, high-intensity signals on T2-weighted imaging, and reduced diffusing capacity on diffusion-weighted

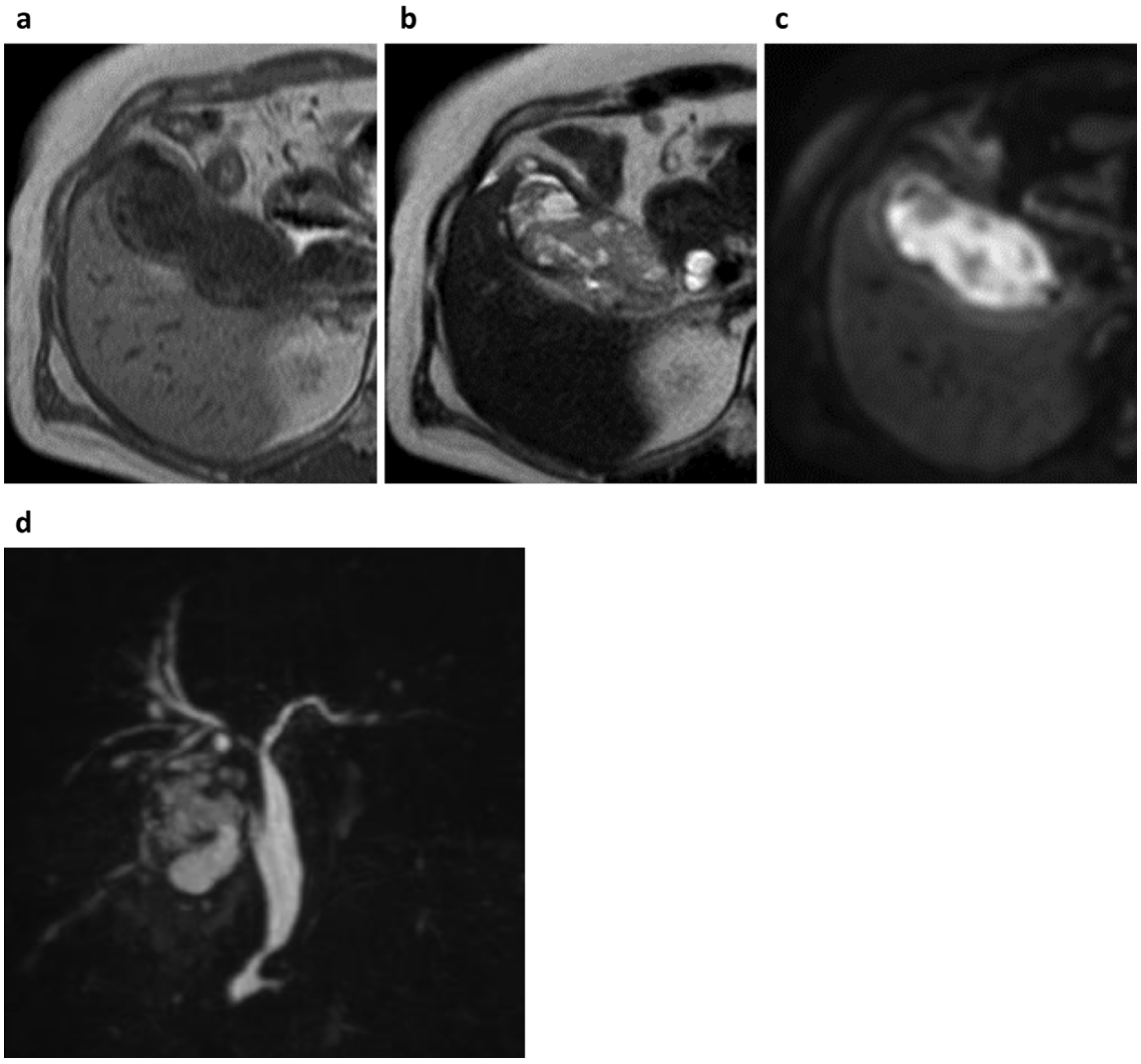

Figure 4. **Magnetic resonance imaging (MRI). The gallbladder tumor showed a low-intensity signal on T1-weighted imaging (a), heterogeneous high-intensity on T2-weighted imaging (b), and reduced diffusion capacity on diffusion-weighted imaging (c). Magnetic resonance cholangiopancreatography (MRCP) showed pancreatobiliary malformation (d).**

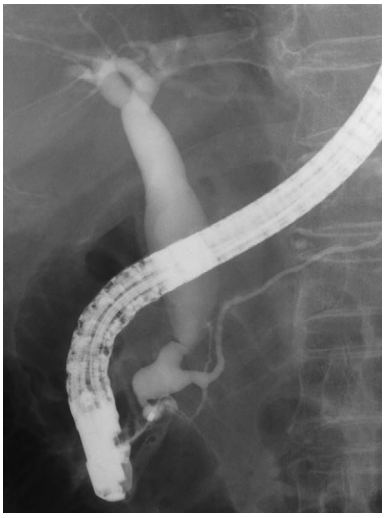

Figure 5. **Endoscopic retrograde cholangiopancreatography (ERCP). ERCP showed a complex-type pancreatobiliary malformation with mild biliary dilation.**

imaging (Fig. 4a-c). Magnetic resonance cholangiopancreatography (MRCP) was suggestive of PBM (Fig. 4d), and this diagnosis was confirmed by endoscopic retrograde cholangiopancreatography (ERCP) (Fig. 5).

Bile juice aspirated from the common bile duct demonstrated a high level of pancreatic-type amylase (26,780 U/L), and the presence of cancer cells was confirmed by cytology. Multiple stepwise forceps biopsies obtained from the hilar common duct and the superior, middle and inferior sites of the common bile duct all revealed non-neoplastic biliary epithelia. Extended cholecystectomy was scheduled based on the diagnosis of gallbladder cancer (GBC) associated with PBM; however, the patient refused surgery at that time.

Forty-five days after the initial diagnosis, she revisited our hospital with appetite loss. Repeat CT demonstrated considerable growth of the gallbladder tumor (90×85 mm) and apparent spread to the liver (Fig. 2b), so the surgery was performed 2 weeks later. On laparotomy, the hepatic invasion of the tumor was found to be less extensive than anticipated;

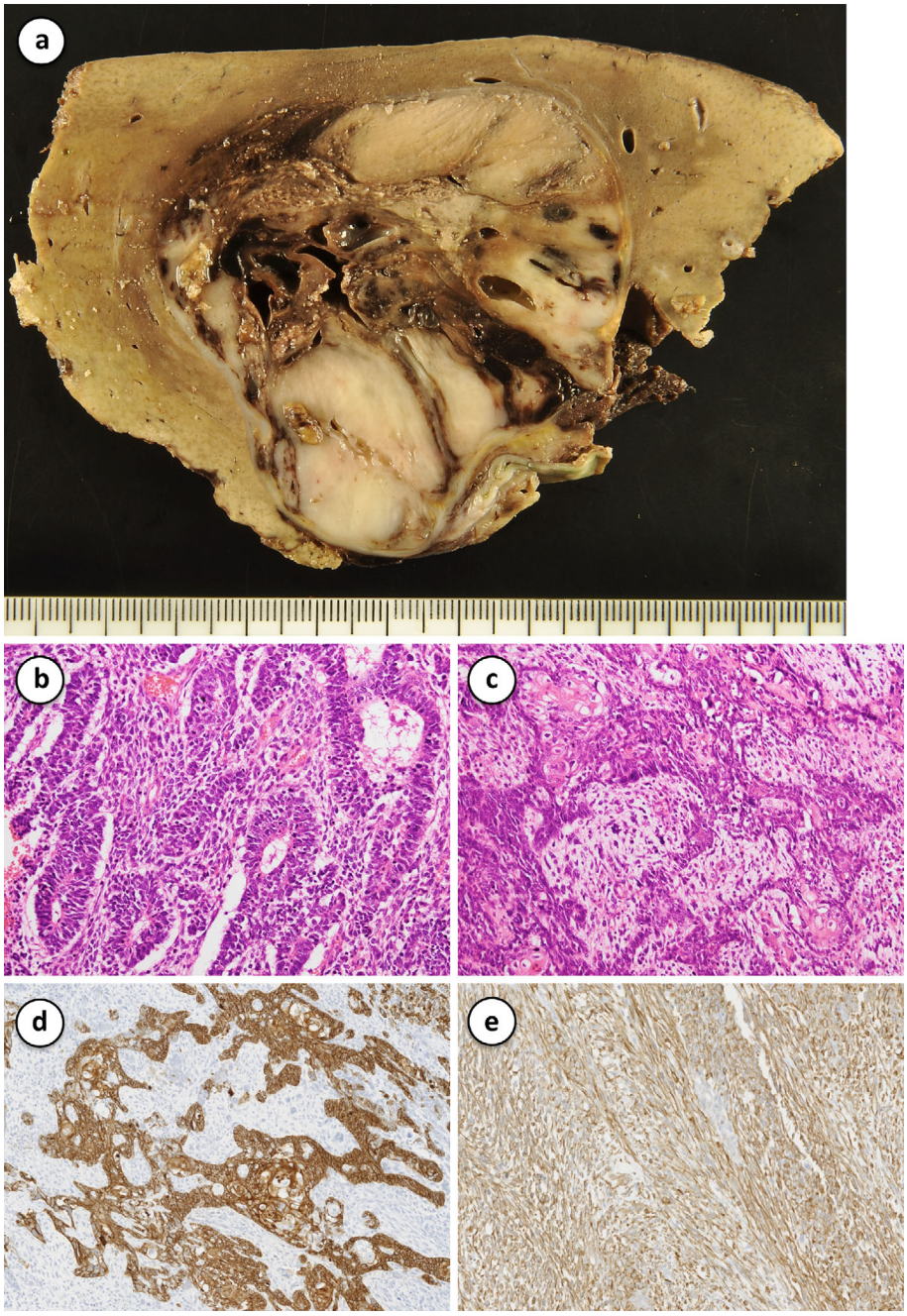

Figure 6. **Pathological findings. A macroscopic view of the resected gallbladder and adjacent liver (a). Transition of the histological components of sarcoma, adenocarcinoma (b), and squamous cell carcinoma (c) was seen (Hematoxylin and Eosin staining, ×100). Cytokeratin 5/6 was diffusely positive in the adenocarcinoma (d) and vimentin in the sarcoma (e) (×100).**

therefore, extended cholecystectomy was conducted without hepatic segmentectomy or lobectomy.

Regarding its gross appearance, the gallbladder tumor measured 84×72 mm in size, appeared rugged, and was attached to the liver bed. A cut section revealed that the entire cavity had been replaced by a yellowish solid tumor with bleeding necrosis (Fig. 6a). Histologically, the tumor consisted of three components (adenocarcinoma, squamous cell carcinoma and sarcoma) showing an intermediate growth pattern (INFb) with scanty stroma (medullary type) (12). The sarcoma component consisted largely of polymorphic cells and bundles of spindle cells, and this component occupied a large part of the tumor in the contiguous liver bed (pHinf1b) (12). Transition among the three histological components was recognized, and a diagnosis of so-called carcinosarcoma was made.

Immunohistochemical staining of the adenocarcinoma component was positive for cytokeratin but negative for vimentin, whereas the sarcoma component staining was positive for vimentin but negative for cytokeratin (Fig. 6b-e). Immunostaining of TP53 was diffusely over-expressed, and the Ki-67 labeling index was 60-80% in the tumor. Invasion

to the lymph vessel and peripheral vein was noted, but neural invasion was not seen. The surgical margin was negative for cancer, and lymph node metastasis was also negative (Stage IIIA by Japanese classification) (12). The patient's postoperative course was uneventful, and she was discharged 16 days after the operation. At 73 months after the surgery, she remained alive with no evidence of recurrence.

Discussion

Carcinosarcoma of the gallbladder (CSGB) is a rare neoplasm. However, according to our literature survey of PubMed and the Japan Medical Abstracts Society, more than 100 cases have been reported in the English and Japanese literature.

The findings of 35 of the Japanese cases reported in the last 15 years (2004-2018) are summarized in Table (13-44). Including our case, the mean age was 72 years old, showing a female predominance (13 men and 23 women). They were diagnosed mostly with a complaint of abdominal pain and showed a large tumor size (mean: 65 mm, range: 16-120 mm). Three CSGB cases accompanied by PBM were noted among these Japanese reports (Table), in addition to two cases reported in the English literature (10, 11).

Our patient also demonstrated a PBM. PBM is a well-known risk factor for gallbladder cancers (45), as the reflux of pancreatic juice into the biliary tract induces epithelial changes (hyperplasia) associated with long-term inflammation, which eventually lead to carcinogenesis (46). A Japanese nationwide survey reported that, among adult patients with congenital biliary dilation, 6.9% and 13.4% had cancers of the bile duct and gallbladder, respectively. In cases with PBM without biliary dilation, the rates of cancers of the bile duct and gallbladder were 3.1% and 37.4%, respectively (47). In our case, the common bile duct was slightly dilated (14 mm), but cancer of this area was clinically excluded by multiple stepwise biopsies before surgery. Nevertheless, the risk for developing cancer in the remnant biliary tract is still high, so careful follow-up is needed for this patient in the future.

CSGB is classified into two categories: true carcinosarcoma and so-called carcinosarcoma. True carcinosarcoma is diagnosed histologically, based on differentiation of the mesenchymal element into neoplastic bone and osteoid (26, 48, 49). The so-called carcinosarcoma is diagnosed when a spindle cell carcinoma (the sarcomatous component) originates from the dedifferentiated adenocarcinoma component; therefore, a histologically confirmed transitional finding is a key feature. The present case showed a transition of two elements, but no bone, osteoid or rhabdoid elements were observed. Immunohistochemistry showed cytokeratin staining mainly in the carcinomatous component, whereas vimentin staining was mainly confined to the sarcomatous area. Thus, the present case was diagnosed as a "so-called carcinosarcoma of the gallbladder" (11).

The preoperative diagnosis of CSGB is difficult because of the lack of radiological findings or serum markers specific for this entity (26). In the previous Japanese cases, serum CEA levels were within the normal limits or faintly elevated, and CA19-9 levels were markedly elevated only in a small fraction [>100 U/mL: 14.8% (4/27)] (Table). A typical CSGB tends to grow intraluminally with a polypoid form rather than by infiltration to adjacent organs (50) (Table). Nevertheless, 15-25% of adenocarcinomas of the gallbladder progress similarly to a macroscopic polypoid lesion. In the present case, the initial appearance was polypoid, and the tumor seemed to be noninvasive; however, it grew rapidly within a short period similar to the other reported cases (cases 18 and 25 in Table). Based on the tumor size, extended cholecystectomy was performed. Despite the aggressive behavior shown in the sequential images, the pathology of the tumor showed an expansive rather than invasive growth, and the liver invasion was limited to a few millimeters. This discrepancy may reflect the growth pattern typically shown by sarcoma cells, which is expansive rather than the invasive type common to ordinary gallbladder adenocarcinomas (26, 48, 49). Consequently, the tumor was removed en bloc, and R0 resection was achieved.

Most gallbladder cancer patients present with advanced-stage disease (51, 52). The prognosis of patients with serosal or liver invasion is especially poor, and the surgical outcomes are not always sufficient to confer any long-term survival benefit (1, 53). The survival of CSGB patients is also generally poor (54). A review by Zhang et al. of 68 cases of CSGB indicated a median survival time of 5 months, a 1-year survival rate of 19.5% and a 5-year survival rate of 16.5% (55). However, in cases where curative resection was performed for carcinosarcomas with invasion limited to the muscularis propria, the 5-year survival rate increased to 88.9% (56). Among Japanese cases (Table), a similar trend was recognized, and the post-operative prognosis was significantly longer in stage I-III cases than in stage IV cases (1-year survival rate: 86.7% vs. 37.5%, p=0.03, 5-year survival rate: 75.0% vs. 14.3%, p=0.04 by Fisher's test). The radical operation performed in the present case was considered to be one reason for the patient's favorable outcome (73 months of survival without recurrence). Therefore, for patients with gallbladder CSGB, surgical resection in the early stage is essential for a positive long-term prognosis.

Conclusion

Differentiating CSGB from ordinary GBC is difficult because of their overlapping imaging features. Some CSGBs demonstrate an intraluminal growth pattern, but these lesions may be able to be cured by radical surgery when the tumor invasion is limited. Careful surveillance is needed for biliary tract malignancies in patients with pancreatobiliary malformations.

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

Table. **Japanese Cases of Carcinosarcoma of the Gallbladder (Literature from 2004-2018).**

Case no.	Reference no.	Age (y.o)	Sex	Onset	Serum tumor marker		PBM	Tumor size (mm)	Depth of invasion	Density	Macroscopic type	Preopeative diagnosis	Type of carcinosarcoma	Stage	Treatment§	Dead (D)/ Alive (A)	Prognosis
					CEA (ng/mL)	CA19-9 (U/mL)											
1	13	63-77	M:1, F:3	abdominal pain: 2, tumor detection*: 1	normal	normal		ND	se	high	nodule	GBC	so-called	IVB	C	A	ND
2					normal	normal		ND	ss	high	nodule	GBC	so-called	I	EC	A	≥5y
3					normal	40		ND	ss	high	nodule	GBC	so-called	I	EC	A	≥5y
4				liver dysfunction	normal	normal		ND	se	marginal high	mass	GBC	so-called	III	EC, EHBDR	A	ND
5	14	77	F	right-hypochondralgia	normal	normal		60	ss	high	polypoid	GBC	so-called	III	C, R (40Gy) → UFT	A	8y
6	15	73	F	back pain	3.1	0		70	ss	high	mass	GBC	so-called	III	C, HSR, EHBDR	D	10m
7	16	57	F	tumor detection	normal	normal		45	ss	high	nodule	GBC	true	II	EC	A	8m
8	17	84	F	right-hypochondralgia	5.4	240.6		84	se	ND	polypoid	GBC	ND	ND	C, TC	D	2m
9	18	72	M	right-hypochondralgia	normal	normal		70	si (colon, liver)	high	polypoid	GBC	so-called	IVA	C, HSR, TC	D	8m
10	19	60	F	epigastralgia	5.4	42		30	ss	low	papillary mass	GBC	true	III	EC	A	54m
11	20	54	F	right-hypochondralgia	1.3	<2		100	si (colon, liver)	low	giant mass	colon cancer	so-called	IVA	EC, TC, PD	D	15m
12	21	72	M	abdominal pain, jaundice	ND	ND		10, 30, 40	si (liver)	ND	nodule	GBS	so-called	ND	EC, EHBDR	D	2m
13	22	84	M	right-hypochondralgia	ND	ND		70	se	low	mass	GBT+GBS	so-called	II	C	A	4y
14	23	69	M	right-hypochondralgia, fever	normal	normal		90	se	high	mass	GCSF·AFP producing GBC	so-called	II	EC	A	6m
15	24	79	F	abd pain	5.7	<0.6		90	ss	low	wall thickeness	GBT+GBS	so-called	IVA	C, HSR, EHBDR	D	4m
16	25	77	F	abd pain	3.9	4,829		60	ss	high	polypoid	GBT+GBS	true	II	C	A	9m
17	26	72	F	ND	ND	ND		25	mp	ND	ND	ND	ND	II	ND	A	5y
18	27	70	F	abdominal dystension	2.1	6		120→200 (2weeks)	si (omentum)	low	multilocular cyst	tumor#, GBS	true	IVB	C, HSR, OR	D	2m
19	28	72	F	abdminal pain	1.1	28		16	mp	low	polypoid	GBC+GBS	true	I	C	A	3y
20	29	70s	M	right-hypochondralgia, fever	0.9	4.8		80	si	high	mass	GBC	so-called	II	C, HSR	A	20m
21	30	70	M	melena	2.7	13.4	(+)	120	si (colon)	heterogeneous	mass	GBC	true	IVA	EC, RHC	D	2m
22	31	62	F	tumor detection	ND	ND		52	ND	ND	polypoid	GBT+GBS	ND	II	C	A	10m
23	32	80	M	fever, icterus	ND	ND		76	se	high	papillary tumor	GBC	ND	ND	C, HSR → UFT→ GEM	D	13m
24	33	71	F	right-hypochondralgia	1.3	1.1		38	ss	irregulary high	mass	GBC	so-called	II	EC, EHBDR →S-1	A	2y

Intern Med 58: 2809-2817, 2019 DOI: 10.2169/internalmedicine.2783-19

Table. **Japanese Cases of Carcinosarcoma of the Gallbladder (Literature from 2004-2018). (continued)**

Case no.	Reference no.	Age (y.o)	Sex	Onset	Serum tumor marker		PBM	Tumor size (mm)	Depth of invasion	Density	Macroscopic type	Preopeative diagnosis	Type of carcinosarcoma	Stage	Treatment[§]	Dead (D)/ Alive (A)	Prognosis
					CEA (ng/mL)	CA19-9 (U/mL)											
25	34	50s	F	right-hypochondralgia	2	26.2	(+)	60→90 (1m)	ss	irregulary high	polypoid	GBC	true	IVB	EC, EHBDR, PD	D	4m
26	35	68	F	vomitting, appetite loss	2.3	730		50	si (du)	low	wall thickness	GBC	so-called	IIIB	EC, PPPD	D	3m
27	36	82	M	weight loss	normal	normal		70	si (colon)	irregulary high	solid tumor	CSGB	true	IIIB	EC, RHC	A	18m
28	37	70s	F	ND	ND	ND		68	ss	heterogeneous	cauliflower-like tumor	GBC	ND	ND	C → PH, MR	A	2y
29	38	68	M	tumor detection	normal	normal		85	si (liver)	low	polypoid	GBT	so-called	IIIA	ERH, PVTTR →GEM	A	5y
30	39	60	M	right-hypochondralgia	1.7	14.6		45	si (liver)	heterogeneous	nodule	GBC	so-called	IVB	C, HSR, EHBDR → S-1	A	7m
31	40	87	M	abdominal pain	ND	ND		60	si (colon)	low	mass	GBC	so-called	ND	C, TC	D	**
32	41	64	M	hematemesis	ND	ND		100	si (du, colon)	irregulary high	nodule	GBC	so-called	IVA	HPD (S6) → S-1 → GEM-Cisplatin	A	17m (rec)
33	42	85	F	right-hypochondralgia	ND	95.5		50	si (liver)	high	polypoid	GBC	ND	IVA	C, TC	A	7y
34	43	69	F	nausea, fatigue	ND	ND		70	si (liver, du)	irregulary high	mass	GBT	so-called	IIIA	HPD → R	A	5m (rec)
35	44	70s	F	upper abdominal pain	2.4	255.8	(+)	50	ss	irregulary high	mass	GBC	so-called	II	C → S-1+GEM, PH → GEM	A	32m (rec)
36	Present case 2019	72	F	abdominal pain	2.4	15	(+)	48→90 (1.5m)	si (liver)	irregulary high	mass	GBC	so-called	IIIA	EC, EHBDR	A	73m

[#]a tumor originated from gallbladder, liver or omentum, *tumors were incidentally detected by image examinations, **died early post-operative days.

PBM: pancreatobiliary maljunction, ND: not described, du: duodenum, GB: gallbladder, GBC: gallbladder cancer, GBT: gallbladder tumor, GBS: gallbladder stone, CSGB: carcinosarcoma of the gallbladder.

[§]Treatment; C: cholecystectomy, EC: extended cholecystectomy, EHBDR: extrahepatic bile duct resection, TC: transverse colectomy, PD: partial duodenectomy, OR: omentum resection, RHC: right hemicolectomy, PD: pancreatoduodenectomy, PPPD: pylorus preserving pancreatoduodenectomy, PH: partial hepatectomy, MR: metastases resection, ERH: extended right hepatectomy, PVTTR: portal vein tumor thrombus resection, HPD: hepatopancreatoduodenectomy, R: radiation, UFT: tegafur/uracil, GEM: gemcitabine, S-1: tegafur/gimeracil/oteracil, rec: recurred

Intern Med 58: 2809-2817, 2019 DOI: 10.2169/internalmedicine.2783-19

Hiroyuki Matsubayashi and Toru Matsui contributed equally to this work.

References

1. Huguet KL, Hughes CB, Hewitt WR. Gallbladder carcinosarcoma: a case report and literature review. J Gastrointest Surg **9**: 818-821, 2005.
2. Cantrell LA, Blank SV, Duska LR. Uterine carcinosarcoma: a review of the literature. Gynecol Oncol **137**: 581-588, 2015.
3. Hennessy BT, Giordano S, Broglio K, et al. Biphasic metaplastic sarcomatoid carcinoma of the breast. Ann Oncol **17**: 605-613, 2006.
4. Madan AK, Long AE, Weldon CB, Jaffe BM. Esophageal carcinosarcoma. J Gastrointest Surg **5**: 414-417, 2001.
5. Baschinsky DY, Chen JH, Vadmal MS, Lucas JG, Bahnson RR, Niemann TH. Carcinosarcoma of the urinary bladder - an aggressive tumor with diverse histogenesis. A clinicopathologic study of 4 cases and review of the literature. Arch Pathol Lab Med **124**: 1172-1178, 2000.
6. Pu JJ, Wu W. Gallbladder carcinosarcoma. BMJ Case Rep **2011**: bcr0520103009, 2011.
7. Yamamoto M, Nakajo S, Tahara E, et al. Mucosal changes of the gallbladder in anomalous union with the pancreatico-biliary duct system. Pathol Res Pract **187**: 241-246, 1991.
8. Tanno S, Obara T, Fujii T, et al. Proliferative potential and K-ras mutation in epithelial hyperplasia of the gallbladder in patients with anomalous pancreaticobiliary ductal union. Cancer **83**: 267-275, 1998.
9. Morine Y, Shimada M, Takamatsu H, et al. Clinical features of pancreaticobiliary maljunction: update analysis of 2nd Japan-nationwide survey. J Hepatobiliary Pancreat Sci **20**: 472-480, 2013.
10. Coetzee K, Omoshoro-Jones J, Michelow P. Carcinosarcoma of the gallbladder arising in a patient with pancreaticobiliary maljunction: a case report and review of the literature. J Cytol Histol **2**: 115, 2011.
11. Eriguchi N, Aoyagi S, Hara M, et al. A so-called carcinosarcoma of the gallbladder in a patient with multiple anomalies--a case report. Kurume Med J **46**: 175-179, 1999.
12. Miyazaki M, Ohtsuka M, Miyakawa S, et al. Classification of biliary tract cancers established by the Japanese Society of Hepato-Biliary-Pancreatic Surgery: 3(rd) English edition. J Hepatobiliary Pancreat Sci **22**: 181-196, 2015.
13. Koshikawa H, Suyama M, Sai J, et al. Clinicopathological study of so-called carcinosarcoma of gallbladder. JJBA (Tando) **18**: 240-245, 2004 (in Japanese, Abstract in English).
14. Saito H, Tsuchida A, Kitamura K, et al. A case of carcinosarcoma of the gallbladder. J Jpn Col Surg **29**: 273-276, 2004 (in Japanese, Abstract in English).
15. Sugimoto K, Hayashi N, Furukawa K, Suzuki R, Miyazaki M. A case of so-called carcinosarcoma (Undifferentiated spindle cell carcinoma) of the gallbladder. J Jpn Surg Assoc **65**: 761-765, 2004 (in Japanese, Abstract in English).
16. Takenaka Y, Ishiyama J, Sakai S, Yamakawa T. A case of carcinosarcoma of the gallbladder. J Jpn Surg Assoc **65**: 195-199, 2004 (in Japanese, Abstract in English).
17. Takahashi Y, Fukushima J, Fukusato T, Shiga J. Sarcomatoid carcinoma with components of small cell carcinoma and undifferentiated carcinoma of the gallbladder. Pathol Int **54**: 866-871, 2004.
18. Kubota K, Kakuta Y, Kawamura S, et al. Undifferentiated spindle-cell carcinoma of the gallbladder: an immunohistochemical study. J Hepatobiliary Pancreat Surg **13**: 468-471, 2006.
19. Okamura Y, Ishigure K, Ishikawa K, et al. A long-term survival case of carcinosarcoma of the gallbladder with chondroid differentiation after surgical curative resection. Jpn J Gastroenterol Surg **39**: 1505-1510, 2006 (in Japanese, Abstract in English).
20. Sakurai N, Yamauchi J, Shibuma H, Ikeda E, Sasou S. A case of advanced carcinosarcoma of the gallbladder. Jpn J Gastroenterol Surg **39**: 677-682, 2006 (in Japanese, Abstract in English).
21. Katoh T, Ban S, Kinno M, et al. Cytology of sarcomatoid carcinoma (undifferentiated carcinoma, spindle and giant cell type) of the gallbladder - a case report -. J Jpn Soc Clin Cytol **46**: 222-226, 2007 (in Japanese, Abstract in English).
22. Kohtani T, Masuda J, Hisaki T, Shimase K, Mizuguchi K. Long-term survival of an elderly patient with carcinosarcoma of the gallbladder after cholecystectomy. Case Rep Gastroenterol **3**: 235-239, 2009.
23. Shimada K, Iwase K, Aono T, et al. Carcinosarcoma of the gallbladder producing alpha-fetoprotein and manifesting as leukocytosis with elevated serum granulocyte colony-stimulating factor: report of a case. Surg Today **39**: 241-246, 2009.
24. Matsukiyo H, Watanabe M, Asai K, et al. A case of "so-called carcinosarcoma of the gallbladder" associated with acute cholecystitis. J Jpn Surg Assoc **70**: 1491-1496, 2009 (in Japanese, Abstract in English).
25. Ishibashi Y, Ito Y, Wakabayashi K, Yamada K. A case of carcinosarcoma of the gallbladder. J Jpn Surg Assoc **70**: 520-523, 2009 (in Japanese, Abstract in English).
26. Okabayashi T, Sun ZL, Montgomey RA, Hanazaki K. Surgical outcome of carcinosarcoma of the gall bladder: a review. World J Gastroenterol **15**: 4877-4882, 2009.
27. Bando M, Sugita H, Murata Y, Hattori S, Machinami M, Sato Y. A case of of giant true carcinosarcoma of the gallbladder. Surgery (Geka) **72**: 1576-1580, 2010 (in Japanese, Abstract in English).
28. Araki M, Nanashima A, Tobinaga S, Sumida Y, Nakashima M, Nagayasu T. A case of pure carcinosarcoma of the gallbladder. JJBA (Tando) **25**: 214-219, 2011 (in Japanese, Abstract in English).
29. Takehara Y, Kasugai H, Hidaka E, et al. A disease-free survival case of hepatic recurrence with so-called carcinosarcoma of the gallbladder after surgical resection. J Jpn Surg Assoc **72**: 2611-2615, 2011 (in Japanese, Abstract in English).
30. Nagasaki K, Yamafuji K, Takeshima K, Asami A, Kubochi K, Akatsuka S. Rapid growth of a carcinosarcoma of the gallbladder. J Jpn Surg Assoc **72**: 2904-2908, 2011 (in Japanese, Abstract in English).
31. Ishida J, Ajiki T, Hara S, Ku Y. Gallbladder calcification leads to discovery of carcinosarcoma of the gallbladder. Surgery **152**: 934-935, 2012.
32. Sadamori H, Fujiwara H, Tanaka T, et al. Carcinosarcoma of the gallbladder manifesting as cholangitis due to hemobilia. J Gastrointest Surg **16**: 1278-1281, 2012.
33. Saeki T, Matsuno T, Miyamoto A, Ishii T, Inoguchi K, Fujisawa K. A case of carcinosarcoma of the gallbladder. J Jpn Surg Assoc **73**: 454-459, 2012 (in Japanese, Abstract in English).
34. Okaniwa S, Tamai M, Nakamura Y, Horigome N, Itoh N. Acase of pure carcinosarcoma of the gallbladder associated with anomalous arrangement of the pancreaticobiliary ductal system. JJBA (Tando) **27**: 732-738, 2013 (in Japanese, Abstract in English).
35. Natsume S, Hiramatsu K, Kato T, Shibata Y, Yoshihara M, Aoba T. A case of so-called carcinosarcoma of the gallbladder associated with squamous cell carcinoma. J Jpn Surg Assoc **74**: 1348-1353, 2013 (in Japanese, Abstract in English).
36. Noguchi T, Watanabe H, Ikeda T, Ojima E, Konishi N, Tonoguchi H. Coexistent carcinosarcoma and carcinoma of the gallbladder: A case report. J Jpn Col Surg **38**: 1101-1104, 2013 (in Japanese, Abstract in English).
37. Kishino T, Mori T, Kawai S, et al. Carcinosarcoma, an atypical subset of gallbladder malignancies. J Med Ultrason (2001) **41**: 487-490, 2014.

38. Wada Y, Takami Y, Tateishi M, et al. Carcinosarcoma of the gallbladder: report of a case. Clin J Gastroenterol **7**: 455-459, 2014.
39. Okada K, Sakashita Y, Nakai S, Fujimoto M, Miyamoto K, Shimamoto F. A case of adenosquamous cell carcinoma of the gallbladder with so-called carcinosarcoma. J Jpn Surg Assoc **75**: 1043-1049, 2014 (in Japanese, Abstract in English).
40. Tonouchi A, Yokoyama N, Hashidate H, Matsuzawa N, Katayanagi N, Otani T. Education and imaging. Gastroenterology: carcinosarcoma of the gallbladder presenting as a cholecysto-colic fistula. J Gastroenterol Hepatol **30**: 1112, 2015.
41. Karahashi T, Yoshimizu N, Seki M, et al. A resected case of carcinosarcoma of the gallbladder with liver metastasis effectively treated by gemcitabine-cisplatin therapy. J Jpn Surg Assoc **76**: 1169-1175, 2015 (in Japanese, Abstract in English).
42. Yoneyama T, Eguchi T. Long-term survival in a case of advanced carcinosarcoma with adenosquamous carcinomsa of the gallbladder. J Jpn Surg Assoc **76**: 3047-3052, 2015 (in Japanese, Abstract in English).
43. Nagatsu A, Maeda Y, Shinohara T, Futakawa N, Hamada T. A case of gallbladder carcinosarcoma with duodenal invasion that was treated by resection. J Jpn Surg Assoc **77**: 2053-2057, 2016 (in Japanese, Abstract in English).
44. Endo Y, Noda H, Watanabe F, Kaneda Y, Tanaka A, Rikiyama T. Resection of a hepatic metastasis of a primary carcinosarcoma of the gallbladder: a case report. JJBA (Tando) **31**: 831-837, 2017 (in Japanese, Abstract in English).
45. Kimura K, Ohto M, Saisho H, et al. Association of gallbladder carcinoma and anomalous pancreaticobiliary ductal union. Gastroenterology **89**: 1258-1265, 1985.
46. Tsuchiya R, Harada N, Ito T, Furukawa M, Yoshihiro I. Malignant tumors in choledochal cysts. Ann Surg **186**: 22-28, 1977.
47. Kamisawa T, Kuruma S, Chiba K, Tabata T, Koizumi S, Kikuyama M. Biliary carcinogenesis in pancreaticobiliary maljunction. J Gastroenterol **52**: 158-163, 2017.
48. Born MW, Ramey WG, Ryan SF, Gordon PE. Carcinosarcoma and carcinoma of the gallbladder. Cancer **53**: 2171-2177, 1984.
49. Kataria K, Yadav R, Seenu V. Sarcomatoid carcinoma of the gall bladder. J Surg Case Rep **2012**: 5, 2012.
50. Inoshita S, Iwashita A, Enjoji M. Carcinosarcoma of the gallbladder. Report of a case and review of the literature. Acta Pathol Jpn **36**: 913-920, 1986.
51. Goetze TO. Gallbladder carcinoma: prognostic factors and therapeutic options. World J Gastroenterol **21**: 12211-12217, 2015.
52. Hundal R, Shaffer EA. Gallbladder cancer: epidemiology and outcome. Clin Epidemiol **6**: 99-109, 2014.
53. Uzun MA, Koksal N, Gunerhan Y, Celik A, Gunes P. Carcinosarcoma of the gallbladder: report of a case. Surg Today **39**: 168-171, 2009.
54. Kim HH, Hur YH, Jeong EH, et al. Carcinosarcoma of the gallbladder: report of two cases. Surg Today **42**: 670-675, 2012.
55. Zhang L, Chen Z, Fukuma M, Lee LY, Wu M. Prognostic significance of race and tumor size in carcinosarcoma of gallbladder: a meta-analysis of 68 cases. Int J Clin Exp Pathol **1**: 75-83, 2008.
56. Park SB, Kim YH, Rho HL, Chae GB, Hong SK. Primary carcinosarcoma of the gallbladder. J Korean Surg Soc **82**: 54-58, 2012.