Surg Today
Jpn J Surg (2000) 30:89–93

SURGERY TODAY

Small-Cell Carcinoma of the Gallbladder: Report of a Case

SHIGETOSHI MATSUO[1], TAKUO SHINOZAKI[1], SATOSHI YAMAGUCHI[1], SUMIHIRO MATSUZAKI[1], YUKO TAKAMI[1], TOMAYOSHI HAYASHI[2], and TAKASHI KANEMATSU[3]

Departments of [1] Surgery and [2] Pathology, Nagasaki Prefectural Shimabara Onsen Hospital, 7895 Shimokawajiri, Shimabara, Nagasaki 855-0861, Japan
[3] Department of Surgery II, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan

Abstract: We report herein the case of an 81-year-old woman in whom a mass in the gallbladder was revealed by an ultrasound examination conducted as part of a follow-up study for a silent gallstone. The mass showed evidence of invasion into the adjacent liver parenchyma. Under the tentative diagnosis of malignant neoplastic disease originating in the gallbladder, a cholecystectomy with partial hepatectomy was performed. Histological examination of the tumor confirmed a diagnosis of small-cell carcinoma of the gallbladder, which is considered to be a rare type of neoplasm.

Key Words: gallbladder, small-cell carcinoma

Introduction

Small-cell carcinoma, otherwise known as oat-cell carcinoma, is a new entity for gallbladder and extrahepatic bile duct tumors,[1,2] that was recently included as a variant of malignant epithelial tumors in the second edition of the WHO Histological Classification of Tumors of the Gallbladder and Extrahepatic Bile Ducts.[3,4] This type of tumor has many common histologic, immunohistochemical, and electron-microscopic features, in contrast to small-cell carcinoma of the lung. It characteristically demonstrates a proliferation of round to oval small cells with chromatin-rich nuclei and scanty cytoplasm, histochemically; positive staining for such neuroendocrine markers as cytokeratin and neuron-specific enolase (NSE), immunohistochemically; and the presence of neurosecretary granules in the cytoplasm, electron-microscopically. We recently treated a patient found to have a gallbladder tumor which was subsequently proven to be small-cell carcinoma. The present study reports this case and reviews the English literature on this unusual disease entity.

Reprint requests to: S. Matsuo
(Received for publication on Dec. 16, 1998; accepted on July 13, 1999)

Case Report

An 81-year-old woman was admitted to Nagasaki Prefectural Shimabara Onsen Hospital on February 10, 1998 for investigation of an ultrasonographic mass shadow of the gallbladder, found during a follow-up examination after treatment for gallstones. She had no abnormal laboratory findings, including levels of the tumor markers such as carcinoembryonic antigen (CEA) and 19-9 carbohydrate antigenic determinant (CA19-9) which were all within normal limits. Ultrasonography showed a broad-necked mass, 17×10 mm in size, with evidence of invasion into the liver. Stones were also detected in the gallbladder. Endoscopic retrograde cholangio-pancreatography did not reveal any evidence of pancreaticobiliary maljunction. Magnetic resonance imaging (MRI) showed a mass with a low signal intensity on the T_1-weighted images (WI) and a slightly high signal intensity on the T_2-WI. Under the provisional diagnosis of a malignant tumor of the gallbladder with stones, surgery was performed on February 18, 1998. No evidence of metastases in the liver, peritoneum, or regional lymph nodes in the hepatoduodenal ligament was observed; however, the levels of CA19-9 in the bile of the gallbladder were very high, at 17×10^4 U/ml. A cholecystectomy with partial hepatectomy and sampling of the lg. cystica was performed. A tumor with a dome-like appearance, $27 \times 40 \times 13$ mm (height) in size, was found in the gallbladder with some cholesterol stones. On cut section, the solid tumor was white, and hard in consistency. Histologically, the proliferation of small round to oval cells with scanty cytoplasm and a large amount of mitoses was seen in all layers of the gallbladder and adjacent liver. There were two different proliferative areas, one of which demon-

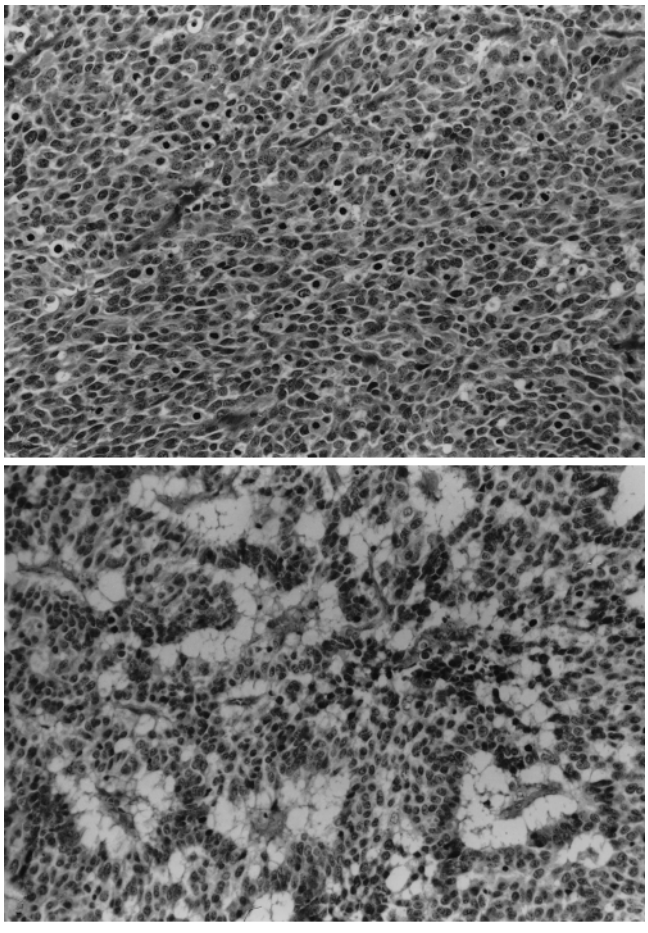

Fig. 1. Histological findings showed a sheet or nest-like proliferation (**a**) and a rosette or ribbon-like proliferation (**b**) (H & E, ×100)

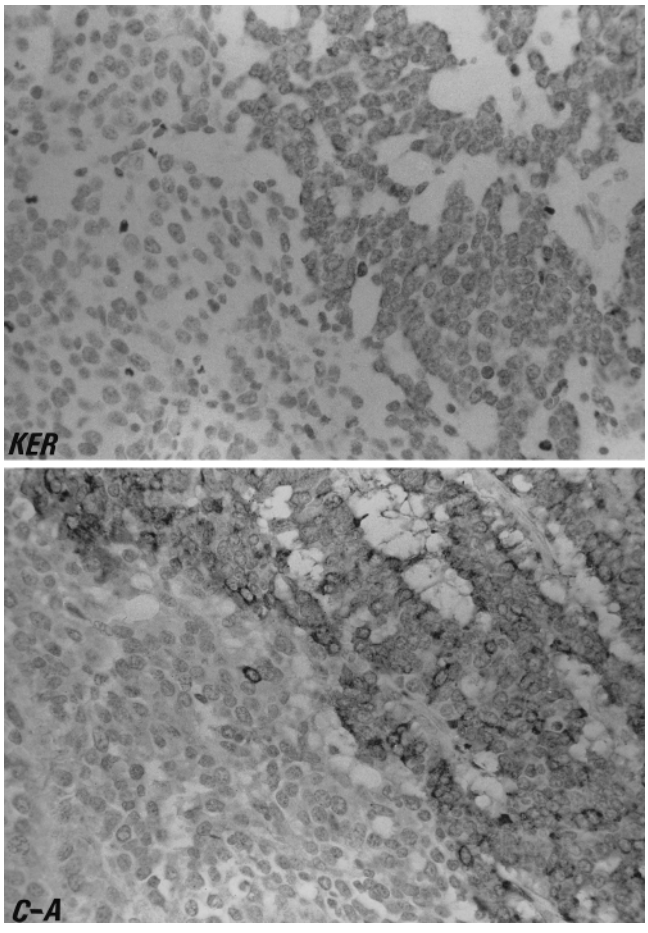

Fig. 2. Immunohistochemical staining for cytokeratin (*KER*) and chromogranin A (*C-A*). Note the differences in staining between the area of sheet or nest-like proliferation (*left*) and that of rosette or ribbon-like proliferation (*right*) (×100)

strated a sheet or nest-like appearance and the other, a rosette or ribbon-like appearance (Fig. 1). Goblet-cell metaplasia was present in the normal mucosa. Immunohistochemically, the tumor cells showed strongly positive staining for epithelial membrane antigen (EMA), cytokeratin (KER), synaptophysin (Sph), NSE, and chromogranin A (C-A) in the areas of rosette or ribbon-like proliferation, and weakly positive staining in the areas of sheet or nest-like proliferation (Fig. 2). Both areas were negative for CEA, CA19-9, and Leu-7. CA19-9 was positively observed only on the normal mucosal surface of the gallbladder. Destructive dense-core secretary granules were found in the cytoplasm, as a result of the reverse ultrastructural study of the formalin-fixed and paraffin-embedded specimens. Thus, the tumor was histologically diagnosed as small-cell carcinoma of the gallbladder. The patient was not given postoperative chemotherapy, and has been doing well without any evidence of recurrence for 5 months since her operation.

Discussion

To the best of our knowledge, only 32 cases of small- or oat-cell carcinoma of the gallbladder, including ours, have been reported to date. These 32 cases are summarized in Table 1.[1,5–15] The small-cell type of undifferentiated carcinoma[16] was excluded from this series, because no immunohistochemical staining for neuroendocrine markers had been performed. Small-cell carcinoma of the gallbladder tends to occur most frequently in women (78%), in association with cholecystolithiasis (78%), and is highly lethal when demonstrating liver, lymph node, or lung metastases. The average age of the patients reported was 61 years old, with a range of 37 to 82 years, and the mean size of the tumor at the time of diagnosis was 6.0 cm in diameter. Surgical resection was performed in 50% of the patients. Of the 32 cases, 9 were diagnosed as small-cell carcinoma associated with adenocarcinoma, and 1 was diagnosed as small-cell carcinoma associated with adenocarcinoma and squamous

Table 1. Documented cases of small-cell carcinoma of the gallbladder

No.	Year[Ref.]	Age (years)	Sex	St.	Re.	Pr.	Meta. Site	Size	Pat. Dx.	NSG	IHC
1	1984[1]	75	F	+	nd		L. Lu. LN.	2.5 (1)			
2		67	F	+	nd		L. Lu. LN.	>7 (18)			
3		66	F	+	nd		LN.				
4		67	F	+	nd		L. Pe. LN.				
5		60	F	+	nd		L. Lu. LN.		SCC + AD (4)		
6		60	F	+	nd		L. Pe. Ov. LN.		SCC (15)		
7		72	F	+	nd		L. LN.				
8		48	F	+	nd		L. Lu. LN.				
9		79	F	+	C	<4 m	L. LN.			+ (3)	
10		58	F	+	C	<4 m	L. LN.			/ (16)	
11		55	F	+	C	11 m	L. LN.				
12		74	F	+	nd		L. PI. Pa. Dp. LN.				
13		72	F	+	nd		L. LN.				
14		55	F	+	nd		L. Om. LN.				
15			F	+	C	<4 m	L. LN.				
16		50	F	+	nd		L. LN.				
17		55	M	+	nd		L. LN.				
18		65	M	+	nd		L. Pe. PI. LN.				
19		52	F	−	C	13 m	L.				
20	1984[5]	49	M	−	PD	5 m	Local	7	SCC + AD		
21	1990[6]	72	F	+	C	12 m		8	SCC		NSE+
22	1990[7]	58	F	+	C	28 m	B.	3	SCC + AD		EMA+ CEA+ AAT+ CA19-9+
23	1991[8]	71	F	−	C	4 m	L. Pe.	5	SCC + AD	+	NSE+ CEA+ Sph+ C-A−
24	1991[9]	70	M	−	nd	2 m	L. LN. Rec. Pa. Ad.	1	SCC + AD	+	KER+ EMA+ NSE+ L-7− NF−
25	1992[10]	62	F	−	C	5 m	L.	6.5	SCC + AD + SQ	+	NSE+ L-7+
26	1992[11]	60	M	+	nd	18 m	L. LN.		SCC		NSE+
27	1993[12]	61	M	+	C	2 m	L. Pe.		SCC	+	KER+ NSE+ EMA− CEA−
28	1994[13]	71	F	−	C	20 m		5	SCC + AD		NSE+ CEA− C-A− L-7−
29	1996[14]	37	F	−	C	13 m	L. Pe. LN.	3.8	SCC	+	
30	1996[14]	82	M	+	C		L. LN.		SCC		
31	1998[15]	76	F	+	C		L	4	SCC		NSE+ C-A+ Sph+
32	1998*	81	F	+	C	4 m		4	SCC	+−	EMA+ KER+ Sph+ C-A+ NSE+ L-7− CA19-9−

Year, reported year; St, gallstone (−, without; +, with); Re, resection (nd, not done; C, cholecystectomy; PD, pancreaticoduodenectomy; HPD, hepatectomy and PD); Pr, prognosis (m, months); Meta. Site, metastatic site (L, liver; Lu, lung; LN, lymph node; Pe, peritoneum; Ov,ovary; Pa, pancreas; Dp, diaphragma; Om, omentum; PL, pleura; Rec, rectum; Ad, adrenal gland; SK, skin; B, bone); Pat. Dx., pathological diagnosis (SCC, small-cell carcinoma; AD, adenocarcinoma; SQ, squamous cell carcinoma); NSG, ultrastructural neurosecretary granules; IHC, immunohistochemistry (EMA, epithelial membrane antigen; CEA, carcinoembryonic antigen; AAT, alpha-1-antitrypsin; NSE, neuron-specific enolase; KER, cytokeratin; Sph, synaptophysin; C-A, chromogranin-A; CA19-9, 19-9 cancer antigen; NF, neurofilament)
*Our case

cell carcinoma. Neurosecretary granules were ultrastructurally detected in 9 of the patients who were examined. Immunohistochemical examination was performed in only 10 patients, the results of which showed immunoreactive NSE to be the most reliable marker for neuroendocrine differentiation, although this marker was not specific.[2]

Histogenetically, the origin of small-cell carcinoma of the gallbladder remains controversial, although an undifferentiated endodermal or neuroendocrine origin has been proposed,[17,18] which was supported by the coexpression of CEA, KER, NSE, bombesin, and C-A in human neuroendocrine tumors, and the presence of ultrastructural neurosecretary granules.[19,20] On the other hand, a common neuroectodermal origin of all cells belonging to the amine precursor uptake and decarboxylation system has also been proposed.[21]

It remains unelucidated why neuroendocrine tumors arise from the gallbladder, considering that neuroendocrine cells are absent in the normal cholecystic mucosa,[22] although they may be found in the metaplastic mucosa, which is known to occur in chronic cholecystitis with gallstones. In fact, metaplastic neuroendocrine change in nonneoplastic mucosa has been described in carcinoid tumors of the gallbladder.[23] Some authors in the present series[10,13,15] described the presence of metaplasia in nonneoplastic mucosa of the gallbladder, but one[8] did not. Goblet-cell metaplasia was also recognized in our patient.

Interestingly, ten of the reported cases of small cell carcinoma were found to be associated with adenocarcinoma and/or squamous cell carcinoma of the gallbladder, 2 of which showed transitional areas between the small-cell carcinoma and adenocarcinoma. This finding suggests that small-cell carcinoma originates from an ordinary type of adenocarcinoma of the gallbladder. In an ultrastructural study of oat-cell carcinoma, it was reported that, in addition to neurosecretary granules, a few tumor cells contained microvilli and intracytoplasmic lumina, indicating both endocrine and glandular differentiation.[24]

The prognosis of this disease appears to be very poor, as shown in Table 1, although one patient who was given chemotherapy was still alive more than 28 months after surgery, this patient being the longest survivor. Postoperative chemotherapy with adriamycin, vincristine, cyclophosphamide, and nitrosourea has been reported to prolong the survival.[1]

In conclusion, a definitive diagnosis of small-cell carcinoma of the gallbladder is considered to be important for investigating the nature and treatment of the disease. Albores-Saavedra et al.[1] originally reported that the diagnosis of oat-cell carcinomas should be based on cell morphology and histologic patterns; however, depending on the findings of various immunohistochemical studies, we can now postulate that the combined immunohistochemical activity for neuroendocrine markers, as well as the detection of ultrastructural neurosecretary granules, are essential, in addition to the light-microscopic findings.

References

1. Albores-Saavedra J, Soriano J, Larraza-Hernandez O, Aguirre J, Henson DE (1984) Oat cell carcinoma of the gallbladder. Hum Pathol 15:639–646
2. Zamboni G, Franzia G, Bonetti F, Scarpa A, Chilosi M, Colombari R, Menestrina F, Pea M, Iacano C, Serio G, Fiore-Donati L (1990) Small cell neuroendocrine carcinoma of the ampullary region. A clinicopathologic, immunohistochemical and ultrastructural study of three cases. Am J Surg Pathol 14:703–713
3. Albores-Saavedra J, Henson DE, Sobin LH (1991) WHO histological typing of tumors of the gallbladder and extrahepatic bile ducts. Springer, Berlin
4. Albores-Saavedra J, Henson DE, Sobin LH (1992) The WHO histological classification of tumors of the gallbladder and extrahepatic bile ducts. A commentary on the second edition. Cancer 70:410–414
5. Muto Y, Yamada M, Okamoto K, Uchimura M (1984) Small cell carcinoma of the gallbladder associated with an ordinary adenocarcinoma: a mixed type tumor. Ryukyu Med J 7:90–96
6. Friedman MDJ, Wheeler WE (1990) Cancer of the gallbladder. South Med J 83:485–486
7. Motojima K, Furui J, Terada M, Shiogama T, Kohara N, Tsunoda T, Tsuchiya R (1990) Small cell carcinoma of the pancreas and biliary tract. J Surg Oncol 45:164–168
8. Cavazzana AO, Fassina AS, Tollot M, Ninfo V (1991) Small-cell carcinoma of gallbladder. An immunocytochemical and ultrastructural study. Pathol Res Prac 187:472–476
9. Duan H-J, Ishigame H, Ishii Z, Itoh N (1991) Small cell carcinoma of the gallbladder combined with adenocarcinoma. Acta Pathol Jpn 41:841–846
10. Iida Y, Tsutsumi Y (1992) Small cell (endocrine cell) carcinoma of the gallbladder with squamous and adenocarcinomatous components. Acta Pathol Jpn 42:119–125
11. Ron I-G, Wigler N, Ilie B, Chaitchik S (1992) Small cell carcinoma of the gallbladder: clinical course and response to chemotherapy. Tumori 78:207–210
12. Johnstone AK, Zuch RH, Anders KH (1993) Oat cell carcinoma of the gallbladder. A rare and highly lethal neoplasm. Arch Pathol Lab Med 28:106–112
13. Nishihara K, Nagai E, Tsuneyoshi M, Nagashima M (1994) Small-cell carcinoma combined with adenocarcinoma of the gallbladder. A case report with immunohistochemical and flow cytometric studies. Acta Pathol Lab Med 118:177–181
14. Muraina OI, Tank R, Dhingra C, Vuletin JC, Colella F, Abdelsayed G, Pachter BR, Honikman L (1996) Small cell carcinoma of gallbladder: report of two cases. Am J Gastroenterol 91:792–794
15. Kuwabara H, Uda H (1998) Small cell carcinoma of the gallbladder with intestinal metaplastic epithelium. Pathol Int 48:303–306
16. Guo K-J, Yamaguchi K, Enjoji M (1988) Undifferentiated carcinoma of the gallbladder. A clinicopathologic, histochemical, and immunohistochemical study of 21 patients with a poor prognosis. Cancer 61:1872–1879
17. Banks-Schlegel SP, Gadzar AF, Harris CC (1985) Intermediate filaments and cross-linked envelope expression in human lung tumor cell lines. Cancer Res 45:1187–1197

18. Pearse AG (1969) The cytochemistry and ultrastructure of polypeptide hormone producing cells of the APUD series and the embryonic, physiologic and pathologic implications of the concept. J Histochem Cytochem 17:303–313
19. Godwin JD II (1975) Carcinoid tumors: an analysis of 2837 cases. Cancer 36:560–569
20. Gould VE, Chejfec G (1978) Neuroendocrine carcinomas of the colon. Am J Surg Pathol 7:31–38
21. Pearse AG, Polak JM (1971) Neural crest origin of the endocrine polypeptide (APUD) cells of the gastrointestinal tract and pancreas. Gut 12:783–788
22. Albores-Saavedra J, Henson DE, Angeles-Angeles A (1989) Entero endocrine cell differentiation in carcinoma of the gallbladder and mucinous cystoadenocarcinoma of the pancreas. Pathol Res Pract 183:169–175
23. Wada A, Ishiguro S, Tateishi R, Ishikawa O (1983) Carcinoid tumor of the gallbladder associated with adenocarcinoma. Cancer 51:1911–1917
24. Larraza-Hernandez O, Henson DE, Albores-Saavedra J (1984) The ultrastructure of gallbladder carcinoma. Acta Morphol Hung 32:279–293