J Gastroenterol 2005; 40:993–998
DOI 10.1007/s00535-005-1684-y

Journal of Gastroenterology

Case report

Primary undifferentiated spindle-cell carcinoma of the gallbladder presenting as a liver tumor

Tomotaka Akatsu[1], Masakazu Ueda[1], Motohide Shimazu[1], Go Wakabayashi[1], Koichi Aiura[1], Minoru Tanabe[1], Shigeyuki Kawachi[1], Kaori Kameyama[2], and Masaki Kitajima[1]

[1]Department of Surgery, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
[2]Division of Diagnostic Pathology, Keio University School of Medicine, Tokyo, Japan

Undifferentiated spindle-cell carcinoma (SpCC) of the gallbladder is extremely rare. There is very little information available regarding the characteristics and treatment of this disease. We herein report the unique case of a 76-year-old female patient with a primary SpCC of the gallbladder that presented as a liver tumor. Preoperative radiologic examinations showed a 5-cm liver tumor around the gallbladder bed, and irregular thickening of the gallbladder wall. The patient underwent en-bloc resection of the gallbladder and segments 4b and 5 of the liver (including the liver tumor). Microscopic findings revealed that both lesions consisted mainly of a sarcomatous spindle-shaped component. Small foci of well-differentiated adenocarcinoma cells were identified in the gallbladder mucosa. There was a gradual transition between the two different components, thereby implying that these two cell types had a common origin. Immunohistochemical studies showed that the spindle-shaped cells were epithelial in nature. The patient's postoperative course was uneventful. However, she died of recurrent liver disease 6 months after the surgery. In conclusion, we surmised that the sarcomatous spindle cells originated from a carcinomatous component in the gallbladder mucosa through dedifferentiation. Further studies are needed to better understand the characteristics of this deadly tumor, and to establish an effective therapy for it.

Key words: spindle-cell carcinoma, gallbladder, liver tumor

Received: April 6, 2005 / Accepted: June 27, 2005
Reprint requests to: M. Ueda

Introduction

Undifferentiated spindle-cell carcinoma (SpCC) is usually found in organs where squamous cell carcinoma commonly occurs (such as lung, female genital tract, esophagus, larynx, upper aerodigestive tract, and skin).[1–5] This disease sometimes originates in the digestive system, breast, and urinary tract.[6–8] SpCC of the gallbladder is extremely uncommon. There have been only six reports in the English-language literature so far.[9–14] There is a paucity of information available regarding its characteristics and effective treatment. We herein report the unique case of a 76-year-old female patient with a primary SpCC of the gallbladder that presented as a liver tumor.

Case report

A 76-year-old woman was admitted to our hospital for the evaluation and treatment of suspected liver and gallbladder disease. She had been diagnosed with cholelithiasis 9 years previously, and had been followed up periodically. On physical examination, no mass was palpable in the abdomen. There was no abdominal tenderness. The patient had no prior history of other gastrointestinal disease. Pertinent laboratory data on admission were normal. Tumor markers, including carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9, were within normal ranges. Serological tests for hepatitis B and C were negative. Abdominal ultrasonography (US) showed a 14-mm gallstone, and a heterogeneously hypoechoic mass around the gallbladder bed (Fig. 1). Abdominal computed tomography (CT) showed a 5-cm hypodense liver tumor around the gallbladder bed (Fig. 2) and irregular thickening of the gallbladder wall.

Surgery was performed with the preoperative diagnosis of liver and gallbladder tumors. Surgical exploration

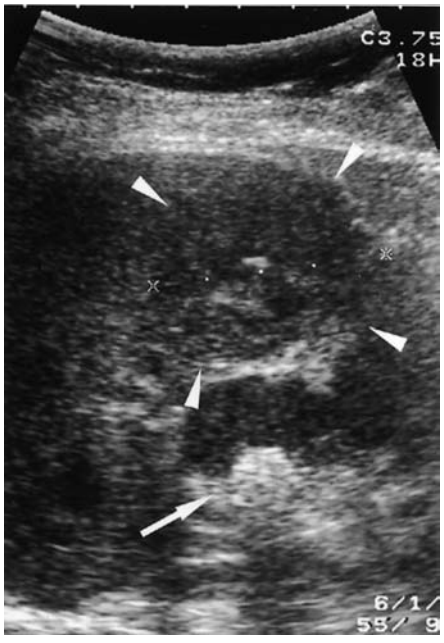

Fig. 1. Abdominal ultrasonography (US), showing a 14-mm gallstone (*arrow*), and a heterogeneously hypoechoic mass around the gallbladder bed (*arrowheads*)

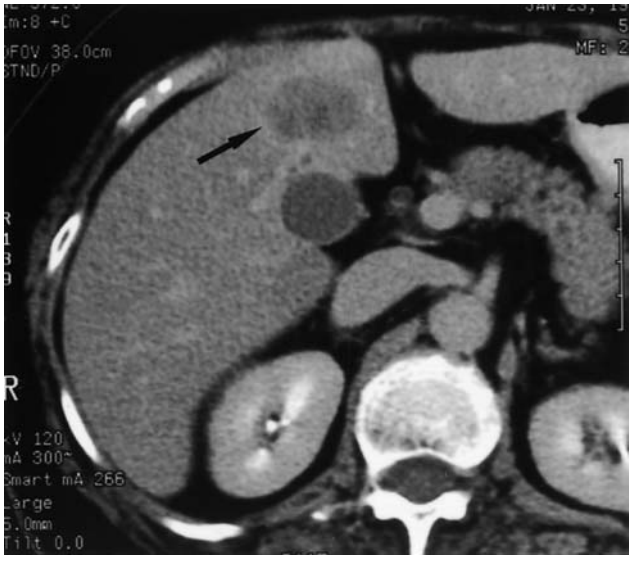

Fig. 2. Abdominal computed tomography (CT), demonstrating a hypodense liver tumor around the gallbladder bed (*arrow*)

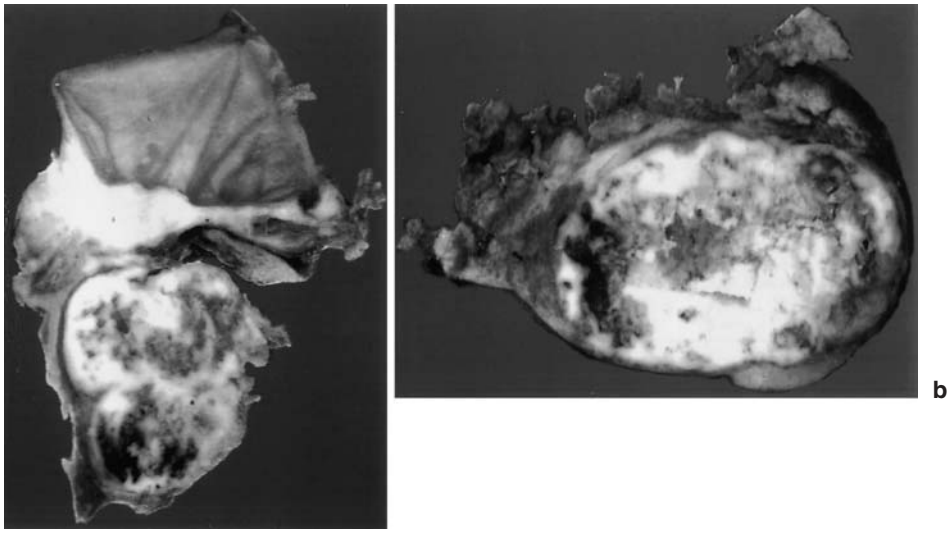

Fig. 3a,b. Cut sections of the resected specimen. The liver mass is connected to the thickened, fibrous gallbladder wall

Table 1. Immunohistochemical studies in spindle cells and adenocarcinomatous cells

	Spindle cells	Adenocarcinoma cells
Cytokeratin CAM 5.2 (low-molecular-weight cytokeratin)	(+)	(+)
Cytokeratin 34βE12 (high-molecular-weight cytokeratin)	(–)	(–)
Cytokeratin AE1/AE3 (wide-spectrum cytokeratin)	(–)	(+)
CEA	(–)	(+)
CA 19-9	(–)	(+)
S-100	(–)	(–)
p53	(+)	(+)
Ki-67 index	51 ± 9%	9 ± 5%*

* $P < 0.05$ vs spindle cells
Values are means ± SD

showed that the gallbladder strongly adhered to the liver mass. No regional lymph node metastasis was identified. The patient underwent en-bloc resection of the gallbladder and segment 4b and 5 of the liver (including the liver tumor). The cut sections of the resected specimen revealed that the liver mass was connected to the thickened, fibrous gallbladder wall (Fig. 3a,b). Microscopically, both lesions mainly consisted of a sarcomatous spindle-shaped component (Fig. 4a). Small foci of well-differentiated adenocarcinoma cells were identified in the gallbladder mucosa. There was a gradual transition between the adenocarcinomatous and spindle-cell components (Fig. 4b).

Immunohistochemical studies, including studies with cytokeratin CAM 5.2 (low-molecular-weight cytokeratin), cytokeratin 34βE12 (high-molecular-weight cytokeratin), and cytokeratin AE1/AE3 (wide-spectrum cytokeratin) are summarized in Table 1. The spindle cells were positive for cytokeratin CAM 5.2 (Fig. 4c). The adenocarcinoma cells were immunoreactive for cytokeratin CAM 5.2, cytokeratin AE1/AE3, CEA, and CA 19-9. Both cell types were positive for p53 protein. The Ki-67 labeling index for the spindle cells (51% ± 9%; $n = 5$) was significantly higher than that of the adenocarcinoma cells in the gallbladder (9% ± 5%; $n = 5$; $P < 0.05$). Statistical analysis was performed using the unpaired *t*-test.

The patient's postoperative course was uneventful. However, she died of recurrent liver disease 6 months after the surgery.

Discussion

Primary carcinoma of the gallbladder includes various histologic variants: adenocarcinoma, adenosquamous carcinoma, squamous carcinoma, and oat-cell carcinoma, in decreasing order of frequency.[15] SpCC of the gallbladder is extremely uncommon. We reported the unique case of a patient with this rare disease that presented as a liver tumor.

We summarized the clinicopathological findings of the 18 reported patients (including the present patient) with SpCC arising in the gallbladder (Table 2). The median age was 66 years (range, 53 to 91 years), and there were 2.6 times more females ($n = 13$) than males ($n = 5$). Ten patients presented with abdominal pain, 2 noticed an abdominal mass, and 1 had fever due to cholangitis. Although there was little information available concerning the imaging features, because most of the reports focused mainly on pathologic aspects, two tumors were demonstrated as hypoechoic on US and hypodense on CT. Gallstones were present in 9 of the 18 patients. Fifteen patients underwent surgery, while 2 received chemotherapy. Macroscopically, the tumors

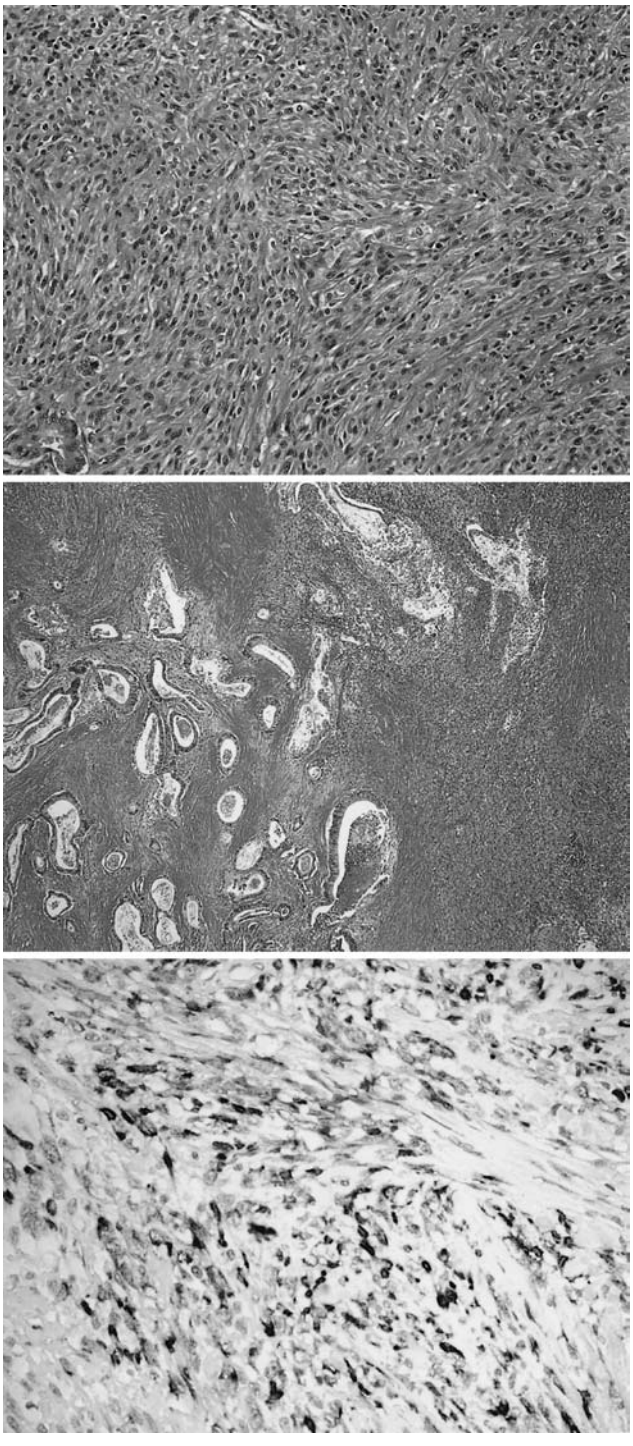

Fig. 4a–c. Microscopic findings of the tumor. **a** Dense proliferation of sarcomatous spindle-shaped cells. **b** Transition between carcinomatous component (*left side*) and spindle-cell component (*right side*). **c** The sarcomatous spindle-shaped cells are positive for cytokeratin CAM 5.2. **a** H&E, ×75; **b** H&E, ×30; **c** ×150

Table 2. Clinicopathological findings of the reported patients with spindle-cell carcinoma (SpCC) of the gallbladder

Patient no.	Age (years)	Sex	Presentation	US	CT	Gallstone	Treatment	Macroscopic findings	Size (cm)	Prognosis	Reference no.
1	91	M	Abdominal pain	ND	ND	Yes	None	ND	ND	DOD (0.5 month)	[9]
2	75	F	Abdominal pain	ND	ND	Yes	Cholecystectomy, hepatectomy	ND	5	DOD (1 month)	[9]
3	54	F	Abdominal pain	ND	ND	Yes	Cholecystectomy	ND	3	ND	[10]
4	61	M	Yes[a]	ND	ND	No	Surgery[b]	Nodular	7.1	DOD (3 months)	[11,12]
5	63	F	Yes[a]	ND	ND	No	Surgery[b]	Infiltrating	9.5	AW (39 months)	[12]
6	66	M	Yes[a]	ND	ND	No	Surgery[b]	Nodular	7.2	DOD (19 months)	[11,12]
7	66	F	Yes[a]	ND	ND	Yes	Surgery[b]	Nodular	5	DOD (1 month)	[12]
8	69	M	Yes[a]	ND	ND	No	Surgery[b]	Nodular	6.5	DOD (3 months)	[11,12]
9	70	F	Yes[a]	ND	ND	No	Surgery[b]	Nodular	4.2	DOD (7 months)	[12]
10	75	F	Yes[a]	ND	ND	No	Surgery[b]	Infiltrating	16	DOD (6 months)	[12]
11	80	F	Yes[a]	ND	ND	No	Surgery[b]	Infiltrating	5	DOD (1.5 months)	[12]
12	61	F	No	ND	ND	Yes	Chemotherapy	Nodular	3	DOD (6 months)	[11,12]
13	62	F	No	ND	ND	Yes	Chemotherapy	Infiltrating	3.8	DOD (2 months)	[11,12]
14	59	F	Yes[a]	ND	ND	Yes	Surgery[b]	Nodular	ND	DOD (1.5 months)	[12]
15	53	M	Abdominal mass	Hypoechoic	Hypodense	Yes	Cholecystectomy	Nodular	11	DOD (7 months)	[13]
16	63	F	ND	ND	ND	ND	Surgery	Nodular	4	ND	[14]
17	71	F	ND	ND	ND	ND	Surgery	Nodular	3	ND	[14]
18	76	F	No	Hypoechoic	Hypodense	Yes	Cholecystectomy, hepatectomy	Nodular	5	DOD (6 months)	Present patient

ND, not described; CT, computed tomography; US, ultrasonography; DOD, died of disease; AW, alive and well

[a] Of these nine patients, seven presented with abdominal pain, one noticed an abdominal mass, and one had fever due to cholangitis

[b] Of these nine patients with surgery, two underwent cholecystectomy, while seven underwent cholecystectomy with partial hepatectomy

were nodular in 11 patients, and infiltrating in 4 patients. The median tumor size was 5 cm (range, 3 to 16 cm). Fourteen patients died of the disease within 2 years (median, 3 months; range, 0.5 to 19 months). Only one patient was alive and well 39 months after the surgery.

SpCC is composed of an admixture of carcinomatous and sarcomatoid components. Therefore, this tumor has also been called by other names, including "sarcomatoid carcinoma," "so-called carcinosarcoma", and "carcinoma with sarcomatous transformation".[13,16,17] The diagnosis of SpCC is sometimes confused with that of other types of tumors. When a neoplasm consists of carcinomatous cells and nonspindle sarcomatous cells, it is diagnosed as true carcinosarcoma. Differentiation between these two tumor types (SpCC and true carcinosarcoma) is usually made based on the morphology of the sarcomatous components.[18,19]

Although the histogenesis of SpCC has long been a matter of speculation, the following hypothesis has been proposed.[20–22] True carcinosarcoma is derived from totipotent stem cells, which separately differentiate into epithelial and sarcomatous cells. In contrast, SpCC is a morphologic variant of carcinoma which is transformed to sarcomatous features.

We speculated that the spindle cells in our patient originated from a carcinomatous component in the gallbladder mucosa through dedifferentiation; this idea was based on several reasons. First, the cells in the sarcomatous area were spindle-shaped. Second, immunohistochemical studies revealed that the spindle cells were positive for several epithelial markers, thereby suggesting that the sarcomatoid spindle cells were epithelial in nature. Third, the gradual transition between adenocarcinoma cells and spindle cells implie that the two components had a common origin.

Although it is also possible that the two different tumors developed separately at the same time, this seems unlikely.

The etiology underlying the transformation of carcinoma cells to spindle cells remains unclear, although several hypotheses have been proposed. One study reported that the frequency of sarcomatous appearance was significantly higher in carcinoma patients who received anticancer therapy.[23] That study also reported that the overall incidence of sarcomatous transformation increased as anticancer therapy became more common. In addition, sarcomatous change of the carcinoma may be associated with radiation therapy, alteration of the *p53* gene, and bone morphologic protein (BMP).[24–26]

In the present patient, the Ki-67 labeling index of the spindle cells (51%) was significantly higher than that of the adenocarcinoma cells in the gallbladder (9%), suggesting that the spindle cells had a greater proliferative capacity than did the carcinomatous cells.

The current patient died of recurrent disease 6 months after the surgery. Although the advantages of radical resection for patients with adenocarcinoma of the gallbladder have been demonstrated,[27–29] there are minimal data available regarding the postresectional survival of patients with SpCC of the gallbladder. Nishihara and Tsuneyoshi[12] reported that the majority (78%) of surgical patients died of the disease within 1 year postoperatively. Moreover, the survival time of the SpCC patients (9 months) was significantly shorter than that of the patients with adenocarcinoma of the gallbladder (81 months). These unfavorable results for SpCC of the gallbladder could be explained by the advanced TNM stage and/or highly aggressive clinical behavior (such as rapid spread). Further studies are needed to better understand the characteristics of this deadly tumor, and to establish an effective therapy for it.

References

1. Matsui K, Kitagawa M. Spindle cell carcinoma of the lung. A clinicopathologic study of three cases. Cancer 1991;67:2361–7.
2. Hirose T, Sano T, Abe J, Hizawa K, Mori T. Spindle cell carcinoma of the uterus. Acta Pathol Jpn 1987;37:997–1002.
3. Battifora H. Spindle cell carcinoma: ultrastructural evidence of squamous origin and collagen production by the tumor cells. Cancer 1976;37:2275–82.
4. Goellner JR, Devine KD, Weiland LH. Pseudosarcoma of the larynx. Am J Clin Pathol 1973;59:312–26.
5. Zarbo RJ, Crissman JD, Venkat H, Weiss MA. Spindle-cell carcinoma of the upper aerodigestive tract mucosa. An immunohistologic and ultrastructural study of 18 biphasic tumors and comparison with seven monophasic spindle-cell tumors. Am J Surg Pathol 1986;10:741–53.
6. Robey-Cafferty SS, Grignon DJ, Ro JY, Cleary KR, Ayala AG, Ordonez NG, et al. Sarcomatoid carcinoma of the stomach. A report of three cases with immunohistochemical and ultrastructural observations. Cancer 1990;65:1601–6.
7. Ellis IO, Bell J, Ronan JE, Elston CW, Blamey RW. Immunocytochemical investigation of intermediate filament proteins and epithelial membrane antigen in spindle cell tumours of the breast. J Pathol 1988;154:157–65.
8. Wick MR, Brown BA, Young RH, Mills SE. Spindle-cell proliferations of the urinary tract. An immunohistochemical study. Am J Surg Pathol 1988;12:379–89.
9. Appelman HD, Coopersmith N. Pleomorphic spindle-cell carcinoma of the gallbladder. Relation to sarcoma of the gallbladder. Cancer 1970;25:535–41.
10. Suster S, Huszar M, Herczeg E, Bubis JJ. Adenosquamous carcinoma of the gallbladder with spindle cell features. A light microscopic and immunocytochemical study of a case. Histopathology 1987;11:209–14.
11. Guo KJ, Yamaguchi K, Enjoji M. Undifferentiated carcinoma of the gallbladder. A clinicopathologic, histochemical, and immunohistochemical study of 21 patients with a poor prognosis. Cancer 1988;61:1872–9.
12. Nishihara K, Tsuneyoshi M. Undifferentiated spindle cell carcinoma of the gallbladder: a clinicopathologic, immunohistochemical, and flow cytometric study of 11 cases. Hum Pathol 1993;24:1298–305.

13. Hotta T, Tanimura H, Yokoyama S, Ura K, Yamaue H. So-called carcinosarcoma of the gallbladder; spindle cell carcinoma of the gallbladder: report of a case. Surg Today 2002;32:462–7.
14. Arakawa A, Fujii H, Matsumoto T, Hirai S, Suda K. Loss of heterozygosity in clonal evolution with genetic progression and divergence in spindle cell carcinoma of the gallbladder. Hum Pathol 2004;35:418–23.
15. Henson DE, Albores-Saavedra J, Corle D. Carcinoma of the gallbladder. Histologic types, stage of disease, grade, and survival rates. Cancer 1992;70:1493–7.
16. Haratake J, Horie A. An immunohistochemical study of sarcomatoid liver carcinomas. Cancer 1991;68:93–7.
17. Sasaki M, Nakanuma Y, Nagai Y, Nonomura A. Intrahepatic cholangiocarcinoma with sarcomatous transformation: an autopsy case. J Clin Gastroenterol 1991;13:220–5.
18. Bertram P, Treutner KH, Tietze L, Schumpelick V. True carcinosarcoma of the colon. Case report. Langenbecks Arch Chir 1997;382:173–4.
19. Nakakubo Y, Okushiba S, Ohno K, Ito K, Sato K, Morikawa T, et al. True carcinosarcoma of the esophagus with osteosarcoma. Hepatogastroenterology 2001;48:137–9.
20. Fayyazi A, Nolte W, Oestmann JW, Sattler B, Ramadori G, Radzun HJ. Carcinosarcoma of the liver. Histopathology 1998;32:385–7.
21. Kubosawa H, Ishige H, Kondo Y, Konno A, Yamamoto T, Nagao K. Hepatocellular carcinoma with rhabdomyoblastic differentiation. Cancer 1988;62:781–6.
22. Nomura K, Aizawa S, Ushigome S. Carcinosarcoma of the liver. Arch Pathol Lab Med 2000;124:888–90.
23. Kojiro M, Sugihara S, Kakizoe S, Nakashima O, Kiyomatsu K. Hepatocellular carcinoma with sarcomatous change: a special reference to the relationship with anticancer therapy. Cancer Chemother Pharmacol 1989;23:S4–8.
24. Kawano R, Takeshima Y, Inai K. Alteration of the *p53* gene of lung carcinomas with sarcomatous transformation (spindle cell carcinoma): analysis of four cases. Pathol Int 1996;46:38–45.
25. Goldman RL, Weidner N. Pure squamous cell carcinoma of the larynx with cervical nodal metastasis showing rhabdomyosarcomatous differentiation. Clinical, pathologic, and immunohistochemical study of a unique example of divergent differentiation. Am J Surg Pathol 1993;17:415–21.
26. Hatakeyama S, Satoh M, Yoshimura N, Otsu T. Immunocytochemical localization of bone morphogenetic proteins (BMPs) in salivary gland pleomorphic adenoma. J Oral Pathol Med 1994;23:232–6.
27. Shirai Y, Ohtani T, Tsukada K, Hatakeyama K. Combined pancreaticoduodenectomy and hepatectomy for patients with locally advanced gallbladder carcinoma: long term results. Cancer 1997;80:1904–9.
28. Miyazaki M, Itoh H, Ambiru S, Shimizu H, Togawa A, Gohchi E, et al. Radical surgery for advanced gallbladder carcinoma. Br J Surg 1996;83:478–81.
29. Shirai Y, Yoshida K, Tsukada K, Muto T, Watanabe H. Radical surgery for gallbladder carcinoma. Long-term results. Ann Surg 1992;216:565–8.