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Case report

Small-cell carcinoma manifesting systemic lymphadenopathy combined with adenocarcinoma in the gallbladder: aggressiveness and sensitivity to chemotherapy

Hirotaka Okamoto[1,2], Kazuo Miura[1], Tadahiko Ogawara[2], Hideki Fujii[1], and Yoshiro Matsumoto[1]

[1] First Department of Surgery, Yamanashi Medical University, Yamanashi, 1110 Tamaho, Nakakoma, Yamanashi 409-3898, Japan
[2] Department of Gastroenterology and Surgery, Kanoiwa General Hospital, Yamanashi, Japan

Small-cell carcinoma of the gallbladder is a very rare tumor. In this report, we describe a patient with small-cell carcinoma combined with adenocarcinoma in the gallbladder. The patient was a 70-year-old man, who clinically manifested systemic lymphadenopathy. An incisional biopsy of Virchow's lymph node revealed small-cell carcinoma. Abdominal computed tomography (CT) showed massive multiple paraaortic lymph node swelling and a round mass in the gallbladder, although chest CT did not show any abnormal masses in the lung. After two courses of chemotherapy (PVP therapy; cisplatin [CDDP], 80 mg/m^2, day 1, intravenous injection; and etoposide [VP-16], 50 mg/m^2, every day, per oral intake; given every 3 weeks) were performed, the systemic lymphadenopathy had completely diminished and only the gallbladder tumor remained on clinical examinations. Endoscopic retrograde cholangiopancreatography (ERCP) revealed nodular tumors in the gallbladder fundus. Cholecystectomy with partial resection of the liver was performed. Pathological examination revealed small-cell carcinoma combined with adenocarcinoma of the gallbladder. We discuss the characteristics and the treatment of this rare tumor.

Key words: small-cell carcinoma, adenocarcinoma, gallbladder, systemic lymphadenopathy, preoperative chemotherapy

Introduction

Malignant tumors of the gallbladder are uncommon, with approximately 90% being adenocarcinoma.[1–3] The other less frequent type of tumors include carcinoid tumors, large-cell anaplastic carcinomas, lymphomas, sarcomas, and small-cell carcinomas. Small-cell carcinomas occurring in the gallbladder are extremely rare. These tumors combined with adenocarcinoma in the gallbladder are even rarer. Only several cases have been reported in the literature.[4,5]

We present a case of small-cell carcinoma of the gallbladder that occurred in a 70-year-old man. Clinical aggressiveness and response to chemotherapy in small-cell carcinoma of the gallbladder are reported.

Case report

A 70-year-old Japanese man who presented with epigastralgia was admitted to our hospital on April 17, 2000. Abdominal ultrasonography (US) revealed massive multiple abdominal masses with a gallbladder mass (Fig. 1ab). Abdominal computed tomography (CT) also demonstrated multiple masses between the pancreas head and abdominal arota, and a mass with similar characteristics in the gallbladder fundus (Fig. 2a), although chest CT did not show any abnormal masses in the lung. On physical examination, the Virchow's lymph node was found to be swollen, with a hard, stony consistency. Laboratory data on admission revealed a high serum glucose level and a high lactate dehydrogenase level. C-Reactive protein (CRP) was slightly elevated. Tumor marker levels were as follows: carcinoembryonic antigen (CEA), 2.0 ng/ml (normal range, less than 5.0 ng/ml); carbohydrate antigen 19-9 (CA19-9), 15.1 U/ml (normal range, less than 37.0 U/ml); neuron-specific enolase (NSE), 320 ng/ml (normal range, less than 10 ng/ml); and NCC-ST439, 32 U/ml (normal range, less than 7.0 U/ml). On April 20, an incisional biopsy of the Virchow's lymph node was performed. The resected specimen was histopathologically diagnosed as a metastatic small-cell carcinoma (Fig. 3a).

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Reprint requests to: H. Okamoto

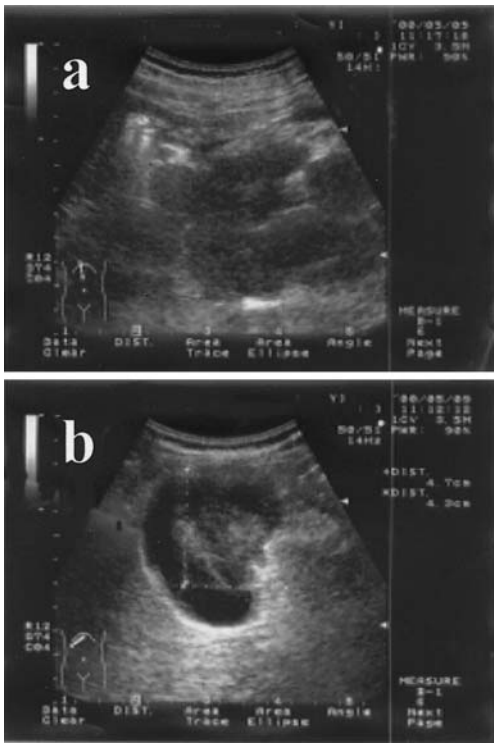

Fig. 1a,b. Abdominal ultrasonography (US), showing **a** multiple homogeneous round tumors in the upper abdomen; **b** a heterogeneous tumor 4.7 × 4.3 cm in size in the gallbladder fundus

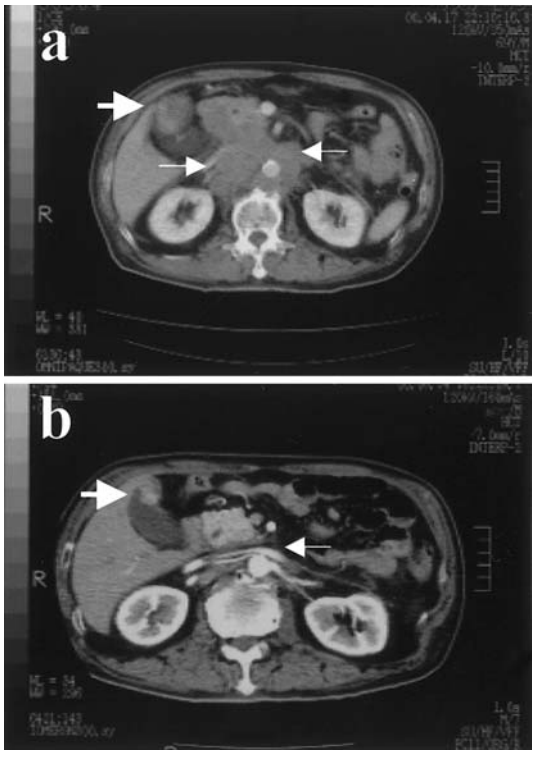

Fig. 2a,b. Abdominal computed tomography (CT), showing **a** severe paraaortic lymphadenopathy (indicated by *small arrows*) and gallbladder tumor (indicated by the *large arrow*). Note the shifting of the pancreas head to the ventral side. **b** CT shows remarkable shrinking of the paraaortic lymphadenopathy after chemotherapy (indicated by the *small arrow*) and decreased gallbladder tumor size (indicated by the *large arrow*)

Because the tumor was considered to be extensive (Fig. 4), systemic chemotherapy was chosen at first. On May 11, PVP therapy (cisplatin [CDDP], 80 mg/m^2, day 1, intravenous injection; and etoposide [VP-16], 50 mg/m^2, every day, per oral intake; given every 3 weeks) was started. After two courses of the chemotherapy, remarkable shrinkage of the abdominal tumors and Virchow's lymph node was noted (Fig. 2b). Levels of the tumor markers NSE and NCC-ST439 had decreased markedly, to 6.4 ng/ml and 8.7 U/ml, respectively. However, the tumor in the gallbladder remained. Endoscopic retrograde cholangiopancreatography (ERCP) was carried out on July 6, and showed an irregular tumor in the gallbladder fundus (Fig. 5). On July 13, cholecystectomy, with partial resection of the liver, was performed. The resected specimen showed a white nodular mass close to a papillary tumor (Fig. 6). There were no stones in the gallbladder. Pathological examination revealed papillary adenocarcinoma and small-cell carcinoma, 3.7 cm × 2.2 cm in size (Fig. 3b). The papillary adenocarcinoma had invaded the subserosa of the gallbladder, whereas the small-cell carcinoma had directly invaded the liver parenchyma. There were no communications between the tumors. On July 25, the patient was discharged from our hospital.

Discussion

Small-cell carcinoma of the gallbladder is an uncommon type of gallbladder tumor. Among these, tumors, small-cell carcinoma combined with adenocarcinoma is very rare,[4–6] and few combined cases have been reported. The present case was an unusual case of combined tumors in the gallbladder. In our patient, the adenocarcinoma in the gallbladder was incidentally identified on pathological examination of the resected specimen. Transitional areas between these two tumor types have been reported.[7,8] These reports suggested that the endocrine-cell carcinoma was of metaplastic epithelial cell origin. In our patient, however, microscopic examination did not show a transitional area between the small-cell carcinoma and adenocarcinoma, and metaplastic epithelial cells. On the other hand, gastrointestinal neuroendocrine tumor is speculated to be of endodermal-cell origin.[9] It also remains a possibility that these tumors may be derived from a multipotential stem cell.[10–13] This hypothesis is supported by the findings of small-cell carcinoma combined with certain

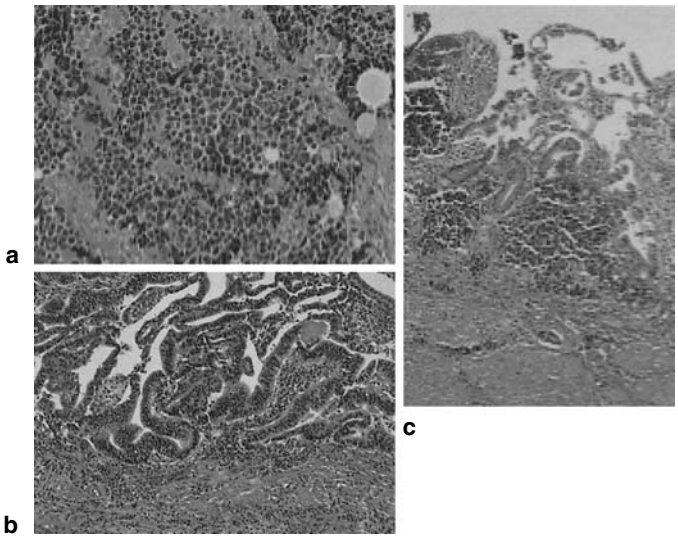

Fig. 3a–c. Histopathological findings. **a** Biopsy specimen of Virchow's lymph node. The tumor consisted of small atypical cells and was diagnosed as small-cell carcinoma. **b** Resected specimen of the gallbladder showing papillary adenocarcinoma. **c** There are no communications between the small-cell carcinoma and papillary carcinoma. **a** H&E, ×60; **b** H&E, ×30; **c** H&E, ×30

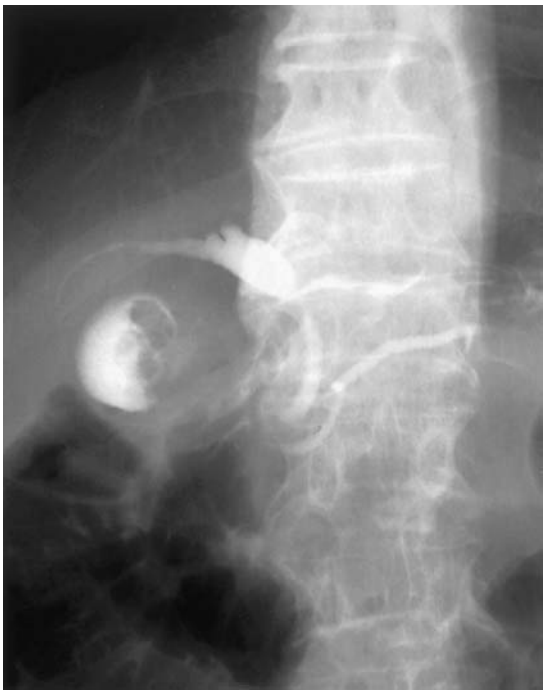

Fig. 5. Endoscopic retrograde cholangiopancreatography (ERCP) revealed an irregular nodular tumor in the gallbladder fundus

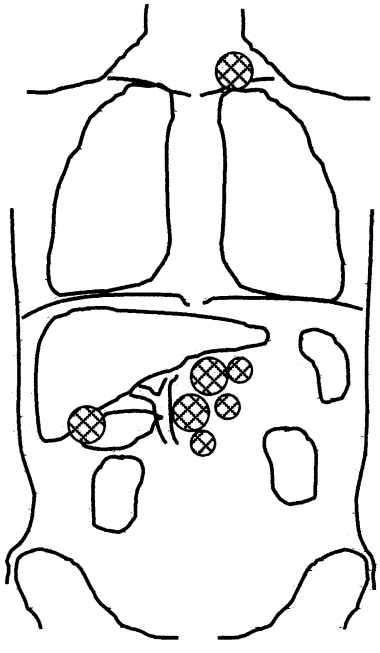

Fig. 4. Schema showing the extent of small-cell carcinoma of the gallbladder. *Checkered circles* indicate the extent of the small-cell carcinoma

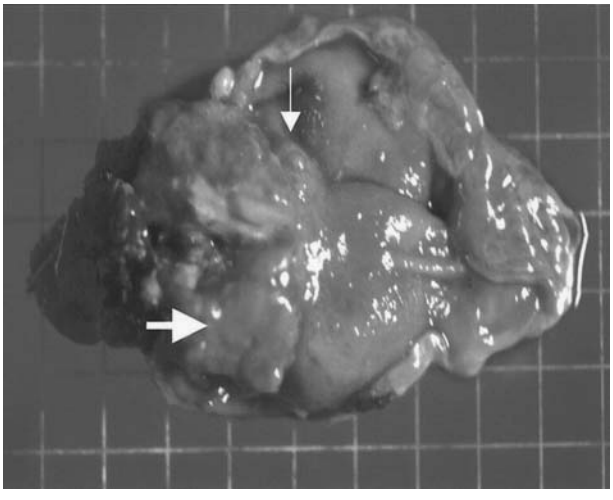

Fig. 6. Surgically resected specimens shows gallbladder tumor in the fundus. The *large arrow* indicates small-cell carcinoma in the proper muscular layer, with papillary elements in the mucosal layer (*small arrow*)

kinds of malignancy in various organs, such as squamous cell carcinoma or adenocarcinoma in the esophagus,[14,15] transitional cell carcinoma or adenocarcinoma in the urinary bladder,[12,16] adenocarcinoma in the colon and rectum,[17] and lobular carcinoma in the breast.[18] Although the origin of these types of malignant cells is obscure, the findings in our patient do not directly support the idea that small-cell carcinoma may arise from metaplastic epithelial cells, because the two types of tumors did not communicate with each other, and meta-

plastic epithelial cells were not revealed in the microscopic findings. Endodermal multipotent stem cells are attractive candidates to elucidate the origin of gastrointestinal neuroendocrine tumors.[19]

Undifferentiated carcinoma of the gallbladder has been classified into three types: small-cell type, pleomorphic type, and spindle-cell type.[20] Although immunocytochemical and ultrastructural studies were not performed in the present patient, the pathological study indicated the features of small-cell carcinoma; first, nuclear chromatin in the tumor cells was found to be rough and homogeneous; second, the nucleolus was not clear; and third, there was palisading of the nucleoli in a short spindle shape, and fourth, apoptotic bodies of the tumor cells were seen. Additionally, the serum NSE and NCC-ST 439 levels were in parallel with the clinical manifestation of the tumors, suggesting the characteristics of small-cell carcinoma.

Small-cell carcinoma is common in the lung (accounting for approximately 20% of all lung cancers), because the normal lung contains neuroendocrine cells.[21] There is a possibility that gallbladder small-cell carcinoma is a metastatic tumor. However, in the present patient, chest CT did not reveal an abnormal mass in the lung. Furthermore, the upper and lower gastrointestinal tract and urinary tract did not show any abnormal lesions. In addition, there have been no reports of metastatic gallbladder small-cell carcinoma. After the systemic chemotherapy, only the tumor in the gallbladder remained on clinical examinations. Therefore, the small-cell carcinoma was clinically considered to be derived from the gallbladder.

Standard chemotherapy treatment regimens for pulmonary small-cell carcinoma include CDDP, VP-16, cyclophosphamide, doxorubicin, methotrexate, and vincristine.[22–24] Of these, treatment of pulmonary small-cell carcinoma was reported to show good responses with such regimens as CDDP and VP-16.[22–24] Although a typical treatment of gallbladder small-cell carcinoma has not been recommended, treatment patterns for extrapulmonary small-cell carcinoma have tended to follow the treatment patterns for pulmonary small-cell carcinoma.[25] In our patient, we chose a neoadjuvant chemotherapy of CDDP and VP-16, resulting in a good response to chemotherapy. Subsequently, cholecystectomy with partial liver resection was performed, after which the patient survived for 6 months. He died of respiratory failure with much pleural effusion. Cytological diagnosis of the pleural effusion revealed small-cell carcinoma cells. The pleuritis carcinomatosa may have been due to lymphatic spread to the pleural cavity.

In the literature, the longest survival time for patients with small-cell carcinoma of the gallbladder was 181 months, in stage III disease, with cholecystectomy and chemotherapy. The median survival was 31 months in stage III or IV disease.[5] In the longest surviving patient, the disease was stage III, T2N1M0. In the shortest surviving patient, the initial treatment was laparoscopic cholecystectomy for gallstones. After the initial treatment, port-site recurrence was found, and the disease was restaged as stage IVB, T2N2M1. In the present patient, the disease was stage IV, T2N2M1 before treatment. His short survival time is considered to be due to the presence of extensive disease pretreatment. However, the neoadjuvant chemotherapy in our patient seemed to be effective, because the systemic lymphadenopathy diminished. However, the chemotherapy with CDDP and VP-16 after surgery had no effect on disease progression. Therefore, the present patient seemed to have become tolerant to chemotherapy with CDDP and VP-16 after the adjuvant chemotherapy. It is unclear why the patient became tolerant to the first chemotherapy. The development of multidrug resistance has posed major obstacles to the efficacy of chemotherapy.[26] In our patient, multidrug resistance may have been involved in this phenomenon. Genetic analysis is needed to elucidate the development of tolerance to chemotherapy. To obtain longer survival, drug resistance should be investigated, and alternative chemotherapy regimens appear to be required.

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