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## [症例報告] Carcinosarcoma (sarcomatoid carcinoma) of the Gallbladder Presenting with a Cholecystocolic Fistula and a Marked Leukocytosis : A Case Report

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## Carcinosarcoma (sarcomatoid carcinoma) of the Gallbladder Presenting with a Cholecystocolic Fistula and a Marked Leukocytosis: A Case Report

Naoji Hanashiro<sup>1)</sup>, Satoshi Tamaki<sup>1)</sup>, Tsunemori Naka<sup>1)</sup>, and Yoshihiro Muto<sup>2)</sup>

<sup>1)</sup> Division of Surgery, Naka Hospital, Kadena, Okinawa 904-0203 and

<sup>2)</sup> The First Department of Surgery, Faculty of Medicine, University of the Ryukyus, Nishihara, Okinawa 903-0215, Japan

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### ABSTRACT

We herein report a case of carcinosarcoma (sarcomatoid carcinoma) of the gallbladder with a cholecystocolic fistula and evidence of marked leukocytosis in a 77-year-old Japanese man. The patient presented with episodes of right upper quadrant pain and fever in April 2000. The physical examination revealed a painful, palpable mass in the right upper quadrant. Routine laboratory findings showed leukocytosis ( $18,000/\text{mm}^3$ ). Abdominal sonography showed an echogenic mass occupying the entire gallbladder lumen. Abdominal CT demonstrated a solid mass lesion measuring  $8 \times 7$  cm in size with a clear, hypodense asterisk configuration, suggesting a communication between the gallbladder and the gastrointestinal tract. At exploratory laparotomy, a large solid gallbladder tumor showed direct invasion into the transverse colon and regional lymph node metastasis. The tumor was evaluated to be Stage IV. With the intention of performing cytoreductive surgery, a cholecystectomy together with a partial transverse colectomy was thus performed. The gallbladder tumor showed penetration into the transverse colon, forming a cholecystocolic fistula. On a cut section analysis, the tumor occupied the entire gallbladder lumen and measured  $7 \times 5$  cm in size. No gallstones were observed. The tumor was composed of two different histologic features: an adenocarcinomatous feature that was composed of moderately differentiated adenocarcinoma and a sarcomatous feature that consisted primarily of pleomorphic, spindle cells. Immunohistochemically, the adenocarcinoma cells were positive for keratin, EMA and CEA whereas the sarcomatous spindle cells were positive for vimentin and CEA. However, both the carcinoma cells and sarcomatous cells were negative for G-CSF. Postoperatively, the patient's WBC counts increased from  $26.9 \times 10^3/\text{mm}^3$  to  $103.0 \times 10^3/\text{mm}^3$ . Finally, the patient died with clinical manifestations of peritonitis carcinomatosa one month after surgery. *Ryukyu Med. J., 20(2)77~80, 2001*

Key words: carcinosarcoma, gallbladder, cholecystocolic fistula, leukocytosis

### INTRODUCTION

Carcinosarcomas are a rare variant of the gallbladder cancer<sup>1-5)</sup>. It is characterized by invasive growth, a propensity of infiltrating into the neighboring organs and a worse prognosis compared to common adenocarcinoma. To our knowledge, this type of gallbladder cancer associated with malignant cholecystocolic fistula is extremely rare<sup>6-7)</sup>. This rarity has prompted us to report the present case. We herein report a case of carcinosarcoma (sarcomatoid carcinoma) of the gallbladder with associated cholecystocolic fistula and marked leukocytosis.

### CASE REPORT

A 77-year-old man presented with episodes of right upper quadrant pain and fever in April 2000. The patient was immediately admitted to our hospital. His medical history revealed that he had previously undergone an operation for a compression fracture of the lumbar vertebrae in 1997 and had also been treated with H<sub>2</sub> receptor antagonists for a gastric ulcer in 1998. On admission, the patient appeared moderately ill. The physical examination revealed muscle guarding and tenderness over the entire abdomen and a palpable mass in the right upper quadrant. Routine laboratory findings showed leukocytosis (WBC  $18,800/\text{mm}^3$ ) and CRP of 3.4mg/dl (normal,  $0.27 < \text{mg/dl}$ ). The serum

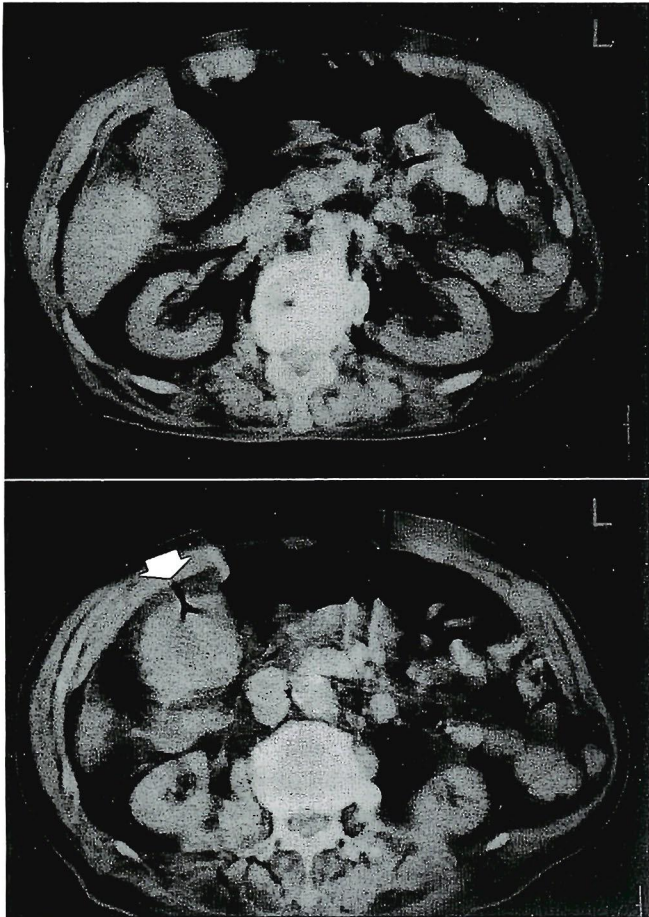


Fig. 1 Abdominal CT demonstrating a large solid mass lesion with air (arrow) measuring 8 cm in greatest dimension of the gallbladder.

carcinoembryonic antigen (CEA) and carbohydrate antigen (CA 19-9) levels were not examined.

Abdominal ultrasonograms showed a heterogeneously echogenic mass occupying the entire gallbladder lumen. Computed tomograms demonstrated a solid mass lesion measuring  $8 \times 7$  cm in size with a clear, hypodense asterisk configuration similar to Benz sign which is occasionally seen in gallstones, suggesting communication between the gallbladder and the gastrointestinal tract (Fig. 1).

Based on these findings, the patient was diagnosed to have advanced gallbladder carcinoma associated with an internal biliary fistula. During an exploratory laparotomy, a large solid gallbladder mass lesion showed direct invasion mainly to the transverse colon and the adjacent organs, resulting in the form of a large conglomerated mass lesion. The patient was determined to have Stage IV-gallbladder carcinoma. With the intention of performing cytoreductive surgery, a cholecystectomy together with a partial transverse colectomy was thus performed.

After surgery, the WBC counts were  $26.9 \times 10^3$  on May 6,  $53.1 \times 10^3$  on May 12,  $69.0 \times 10^3$  on May 15 and  $103.0 \times 10^3$  on May 16, respectively. About 60 to 70 percent of the WBCs



Fig. 2 The resected gallbladder revealing a large tumor lesion occupying the entire gallbladder lumen with a thickened wall (top) and the transverse colon showing the tumor invading into the colonic lumen, thus forming a cholecystocolic fistula (bottom).

were composed of segmented neutrophils. During this period, ATL-like cells (adult T-cell lymphoma) were observed in the peripheral blood smears, but human T-cell lymphotropic virus type 1 (HTLV-1) (ELISA) was negative. Unfortunately, the serum G-CSF was not examined. Postoperatively his disease was extensively aggressive and he died while demonstrating clinical manifestations of peritonitis carcinomatosa one month after surgery.

Grossly, the gallbladder was entirely occupied with carcinoma which had penetrated into the transverse colon, forming a cholecystocolic fistula measuring 2 cm in diameter. On bisection, the gallbladder tumor was solid, partially necrotic and measured  $7 \times 5$  cm in size. The gallbladder wall was diffusely thickened and extensively adhered to the transverse colon. The cystic duct of the gallbladder was occluded by the carcinoma and no gallstones were found in the gallbladder (Fig. 2). Histologically, the tumor was composed of two different histologic features: an adenocarcinomatous feature that showed moderately to poorly differentiated carcinoma in the superficial portion of the tumor (approximately 10% of the tumor) and a sarcomatous feature that consisted of pleomorphic, spindle cells with nuclear pleomorphism (Fig. 3). Morphologically, a gradual trans-

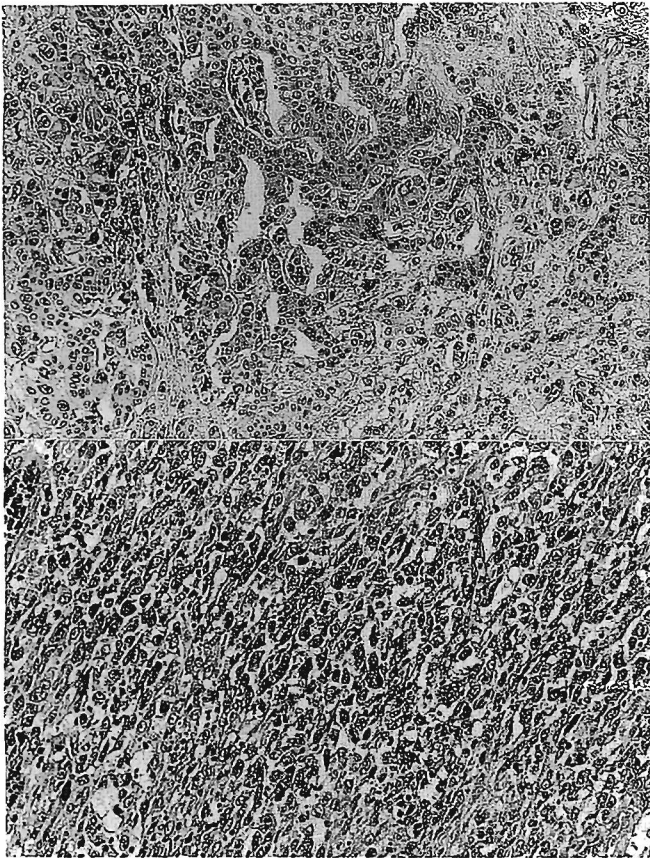


Fig. 3 Histology of the tumor showing nests with glandular structures of round to oval tumor cells (top; HE  $\times 50$ ) and spindle-shaped cells (bottom; HE $\times 50$ ).

ition was observed between these two components. According to an immunohistochemical examination, adenocarcinoma cells were positive for keratin, EMA and CEA, but were negative for vimentin. Sarcomatous spindle cells were positive for vimentin and CEA, but were negative for keratin. Staining with anti-G-CSF monoclonal antibody did not demonstrate G-CSF in both the carcinoma and sarcomatous cells.

## DISCUSSION

Internal biliary fistula (IBF) is an abnormal communication between the biliary tract and adjacent organs, including the duodenum or colon<sup>9-11</sup>. The most frequent cause of IBF is cholelithiasis representing up to 90% of all cases while the second is a chronic duodenal ulcer, accounting for up to 6%. The cause of gallbladder carcinoma comprises approximately 4% of all cases. The frequency of IBF has been reported to be from 1.2 to 5.0% in biliary surgical cases<sup>10</sup>. Therefore, the frequency of IBF associated with gallbladder carcinoma may account for less than 0.2% in biliary surgery<sup>12</sup>.

On the other hand, approximately 40 gallbladder carcinosarcoma cases have been reported in the English

literature<sup>3-4</sup>. Furthermore, of more than 50 cases of G-CSF-producing tumors, only two cases of carcinosarcoma of the maxillary sinus and the esophagus have been reported<sup>13</sup>. Based on these data reviewed in the literature, this case has attracted great interest because of the rare type of gallbladder tumor, the formation of a malignant cholecystocolic fistula and a marked leukocytosis.

Carcinosarcoma is an unusual tumor which is characterized by a close admixture of carcinomatous and sarcomatous components<sup>2</sup>. Although there has been much confusion regarding the term, diagnosis and histogenesis of carcinosarcoma, it is now generally accepted that all of these various terms indicate the same tumor entity both clinically and morphologically<sup>14-16</sup>. Regarding the treatment and prognosis of this tumor, the treatment of carcinosarcoma of the gallbladder is closely similar to that for adenocarcinoma of the gallbladder. Both tumors usually demonstrate advanced disease and thus have an extremely poor clinical outcome<sup>3</sup>. In general, the extent of tumor spread greatly influences the prognosis. In our experience, 3 cases of carcinosarcoma of the gallbladder including this case were clinically detected at a rather advanced stage and the patient died within 1 to 7 months after surgery<sup>4, 5</sup>.

As mentioned previously, a malignant cholecystocolic fistula represents an uncommon complication of gallbladder carcinoma. Gallbladder tumors progressively grow, extend completely through the bowel wall and involve contiguous structures such as the duodenum or colon. Occasionally, central necrosis and ulceration of an intramural tumor causes a perforation or penetration into the adjacent organs. Histologically, this gallbladder tumor showed necrosis of a tumor around the fistula. In this case, it is possible that the aggressive growth of the gallbladder tumor to the transverse colon could have caused the necrosis and ulceration of an intramurally invaded tumor, thus leading to a cholecystocolic fistula.

Finally, a marked leukocytosis in this case was a unique feature. To our knowledge, there has been no previous clinical report of a marked leukocytosis of carcinosarcoma of the gallbladder in the literature. Although the mechanism of producing G-CSF by tumor cells is still unclear, leukocytosis is occasionally associated with a malignant tumor as a result of the production of growth factors that regulate proliferation, differentiation of myeloid cells and synergistic interactions among multiple cytokines, including granulocyte-colony stimulating factor (G-CSF), tumor necrosis factor  $\alpha$  (TNF  $\alpha$ ), and interleukin-1 (IL-1)<sup>16, 17</sup>. In our case, we did not extract and cultured the tumor tissues and examined serum G-CSF concentration for demonstration of G-CSF activity. The immunohistochemical examinations of G-CSF in tumor cells were performed using the avidin-biotin complex method on paraffin-embedded sections. A reaction for G-CSF was negative in both carcinoma and spindle cells. Unfortunately, the clinical implications of leukocytosis in tumors remains unresolved. If we encoun-

ter a cancer patient with a marked leukocytosis in future, increased serum G-CSF activity, demonstration of G-CSF activity in the tumor extract solution or tumor tissue culture solution or immunostaining of the tumor tissues with anti-G-CSF antibody should be examined.

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