True Carcinosarcoma of the Gallbladder: A Case Report and Brief Review of the Literature

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Introduction: Carcinosarcoma of the gallbladder (CSGB) is very rare, accounting for less than 1% of gallbladder malignancies. Therefore, the biological behavior is not well known. We report the case of a patient with CSGB who showed long-term survival after treatment with surgery and postoperative adjuvant chemotherapy.

Case presentation: A 79-year-old man was referred to our department with suspected gallbladder cancer after undergoing positron emission tomography-computed tomography (PET-CT) scan for preoperative examination of lung cancer, which showed strong accumulation in the gallbladder. Abdominal contrast-enhanced computed tomography (CT) demonstrated a heterogeneous enhanced, 25-mm mass in the anterior wall of the gallbladder fundus. Cholecystectomy and hepatoduodenal mesenteric lymph node sampling revealed a polypoid tumor. Histopathological findings showed a mixture of adenocarcinoma and sarcoma with spindle-shaped cells. Immunohistochemical staining of the sarcoma showed negative results for the epithelial markers and positive results for the mesenchymal markers, leading to a diagnosis of true CSGB. We administered S-1 as postoperative adjuvant chemotherapy and was reported to be alive 45 months after surgery without recurrence.

Conclusion: CSGB has a poor prognosis, but if radical resection can be performed, there is a possibility of long-term survival. Further case studies and treatment options are needed to help understand this disease.

Key words: carcinosarcoma, gallbladder cancer, surgical outcome, chemotherapy

INTRODUCTION

Carcinosarcoma of the gallbladder (CSGB) is very rare, accounting for less than 1% of gallbladder malignancies [1, 2]. Therefore, its biological behavior and clinicopathological features are not well known. CSGB is difficult to diagnose in preoperative imaging studies and is often diagnosed on resection specimens [2, 3]. CSGB is classified as so-called carcinosarcoma or true carcinosarcoma [4, 5]. Herein, we report the case of a patient with true CSGB who showed long-term survival after undergoing surgery and postoperative adjuvant chemotherapy.

CASE REPORT

Positron emission tomography-computed tomography for preoperative examination of lung cancer showed strong ^{18}F-fluorodeoxyglucose accumulation in the gallbladder of a 79-year-old man. Gallbladder cancer was therefore suspected, and he was referred to our hospital. He had a history of endoscopic submucosal dissection for early-stage gastric cancer and diabetes. He had no family history of gallbladder cancer. He had consumed a glass of shochu every day and had smoked 30 cigarettes a day for 40 years. He had quit smoking 20 years ago.

No abnormalities were found on physical examination. Blood biochemistry showed no abnormal findings except for an elevated C-reactive protein level (1.06 mg/dL). Other tumors marker levels were within normal limits (carcinoembryonic antigen: 3.8 U/mL, cancer antigen 19−9: 14.3 mg/mL). Abdominal ultrasonography showed a hypoechoic mass of 31 × 24 × 25 mm extending internally from the fundus to the body of the gallbladder (Fig. 1). Abdominal contrast-enhanced computed tomography showed a heterogeneous enhanced mass, 25 mm in diameter, in the anterior wall of the gallbladder fundus with progressive enhancement in the later phase (Fig 2). Additional findings suggested caving in the gallbladder wall, perhaps due to muscular involvement. There were no findings indicative of hepatic involvement (Fig. 2) or regional or distant lymph node metastasis. T2-weighted magnetic resonance imaging (MRI) revealed a lobular, low-signal mass in the fundus of the gallbladder (Fig. 3). Endoscopic retrograde cholangiopancreatography showed a shade defect due to the presence of the mass in the gallbladder; bile cytology revealed class 1. No abnormalities of pancreaticobiliary ductal confluence were observed (Fig. 4). Therefore, the patient was di-

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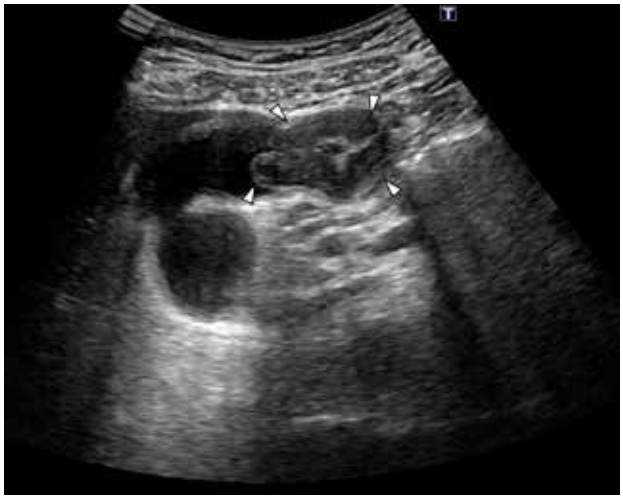


Fig. 1 Abdominal ultrasonography: A 31 × 24 × 25mm hypoechoic mass extending internally from the fundus to the body of the gallbladder is seen.

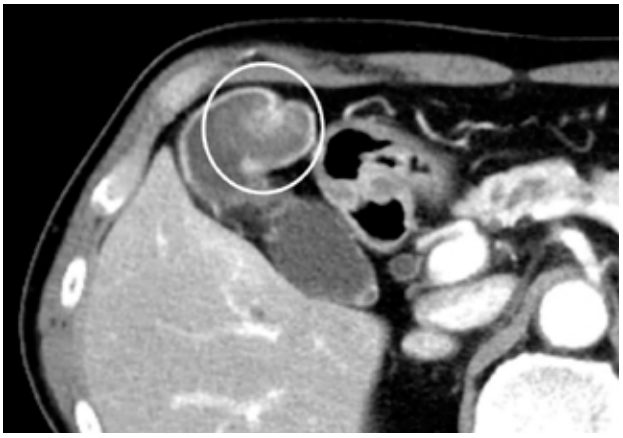


Fig. 2 Abdominal contrast-enhanced computed tomography in the arterial phase: A faintly contrasted mass, 25 mm in diameter, is seen. The serosa at the tumor site is retracted (white circle).

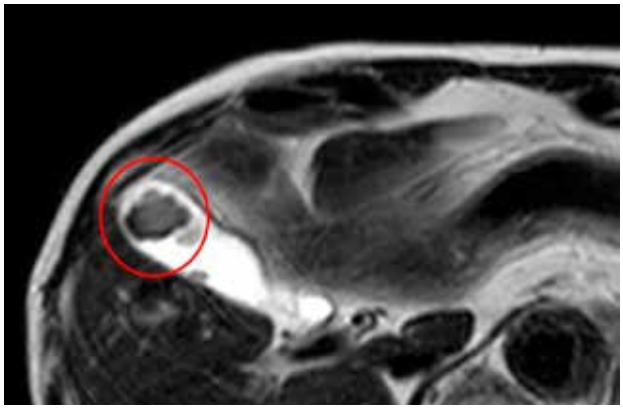


Fig. 3 T2-weighted magnetic resonance imaging: A lobulated low-signal mass is seen in the gallbladder lumen (red circle).

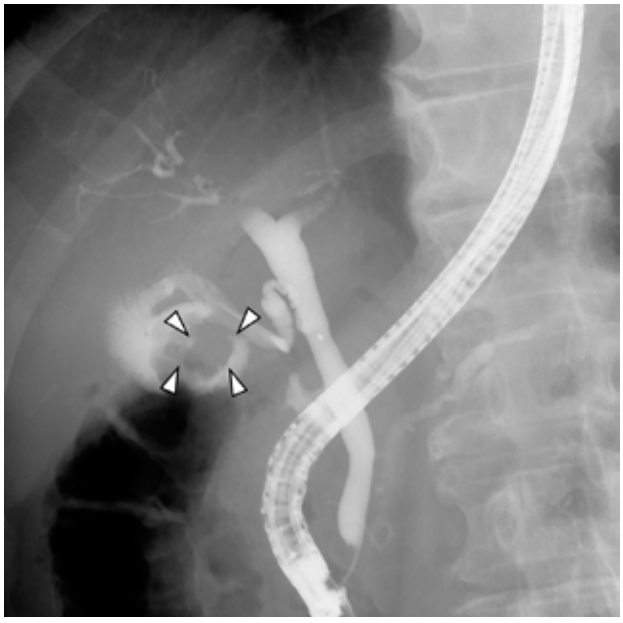


Fig. 4 Endoscopic retrograde cholangiopancreatography showed a shade defect due to a mass in the gallbladder.

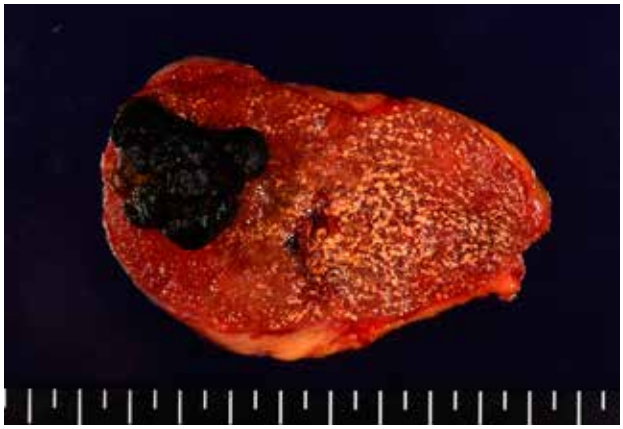
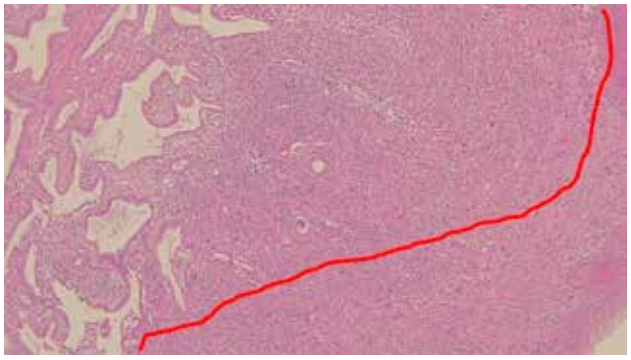


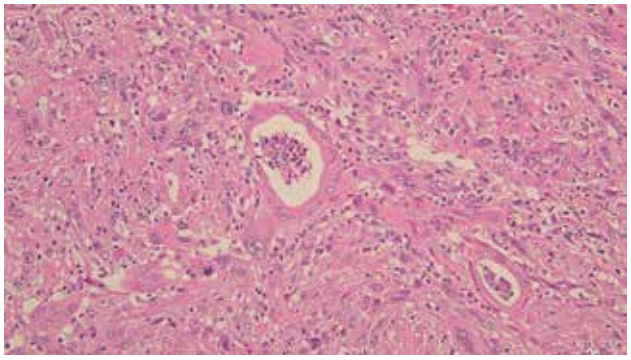
Fig. 5 Surgical specimen: A blackish polypoid tumor is observed in the gallbladder lumen. There is no tumor exposure on the serosal surface.

agnosed with clinical T2aN0M0 stage 2A gallbladder cancer (UICC TNM classification, 8th edition).

We opted for open surgery because advanced cancer was suspected and to prepare for the transition to extended surgery. Radical cholecystectomy and sampling of the hepatoduodenal mesenteric lymph nodes were performed. The surgical specimen showed a blackish polypoid tumor, measuring 30 × 25 mm and protruding into the gallbladder lumen (Fig. 5). Hematoxylin-eosin staining showed a mixture of carcinoma with adenoductal structures and sarcoma with spindle-shaped cells. There was no indication of a transition zone between the carcinoma and sarcoma (Fig. 6a–c). Immunohistochemical staining of the sarcoma



(a)



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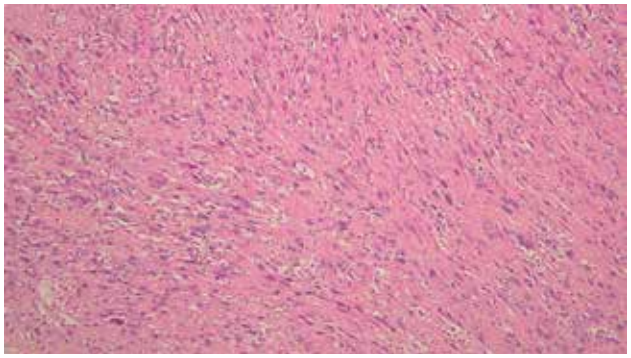
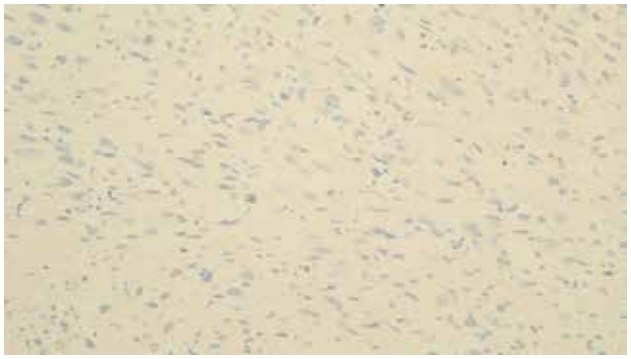
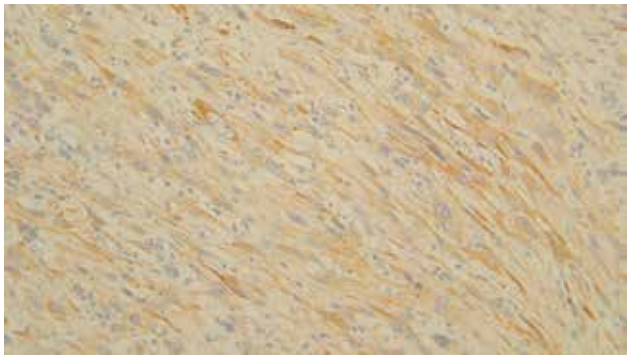


(C)

Fig. 6 Pathological findings: (a)The tumor consists of two tissue types: adenocarcinoma (left of the red line) and sarcoma (right of the red line). No transitional zone is observed between the adenocarcinoma and sarcoma. (Hematoxylin and eosin; magnification, × 12.5). (b) Adenocarcinoma (Hematoxylin and eosin; magnification, × 100). (C) Sarcoma (Hematoxylin and eosin; magnification, × 100)



(a)



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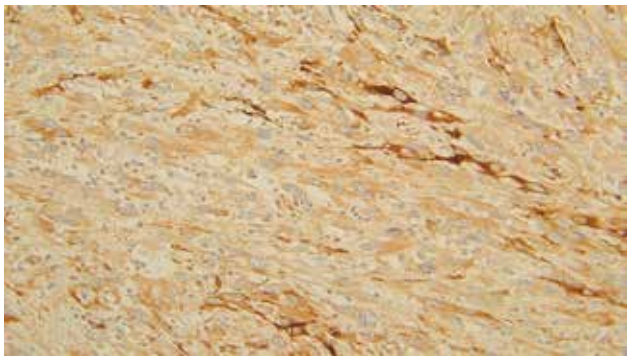

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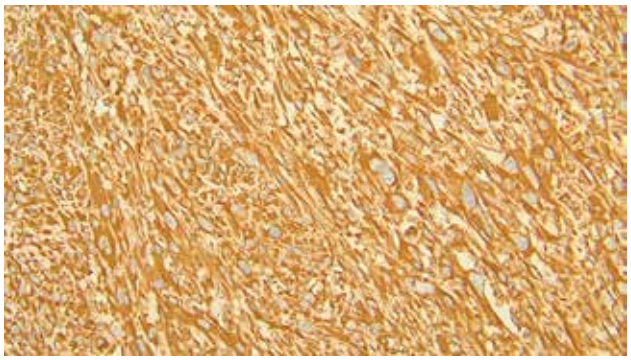

(d)

Fig. 7 Immunohistochemistry: The sarcoma cells are negative for AE1/3 (a), but positive for calponin (b), smooth muscle actin (c), and vimentin (d).

showed negative results for the epithelial marker AE1/AE3 and positive results for the mesenchymal markers calponin, smooth muscle actin, and vimentin (Fig. 7a–d). The final pathological diagnosis was true CSGB, T2aN0M0 Stage 2A. There were no postoperative complications, and the patient was discharged on the 9th postoperative day. The patient received 6 cycles of S-1 postoperative adjuvant chemotherapy and was alive 45 months postoperatively without recurrence.

DISCUSSION

A carcinosarcoma, first described by Virchow, is a malignant tumor characterized by the presence of both epithelial and mesenchymal components [6]. CSGBs

are relatively rare; the first report of a CSGB was published by Landsteiner in 1907 [7]. Carcinosarcoma is classified as either so-called or true. So-called carcinosarcoma is diagnosed when a spindle cell carcinoma originates from a dedifferentiated adenocarcinoma. The presence of a transition zone between the carcinoma and sarcoma in the pathology is an important diagnostic determinant of so-called carcinosarcoma [8–10]. True carcinosarcoma is diagnosed histologically, based on the differentiation of the mesenchymal element into neoplastic bone and osteoid. In true carcinosarcoma, no transition zone between the carcinoma and sarcoma is seen on histopathological examination [3–5]. In the present case, the absence of a transition zone and epithelial markers and the presence of mesenchymal markers led to a diagnosis of true carcinosarcoma.

A review of 68 CSGB cases reported a male to female ratio of 3.25:1 and a median age of 68 years (45–91 years). The median tumor diameter was 5 cm (124 cm) [11]. There are no specific serum tumor markers, and marker levels are often not elevated [12]. There are no characteristic findings on imaging, and preoperative diagnosis has been reported to be difficult [3, 12]. T2-weighted MRI can provide quantitative information about CSGB and aid its differentiation from gallbladder adenocarcinoma [13]; however, in the present case, the MRI signal of the tumor was low and relatively uniform as a whole. The diagnosis of rare cancers such as CSGB is challenging and may require consideration of a variety of imaging features.

CSGB has a papillary growth pattern that projects into the gallbladder lumen [10, 14]. This growth pattern is similar to that seen in the present case and is thought to occur because sarcoma cells, unlike adenocarcinoma cells, grow expansively rather than invasively. Therefore, direct invasion of other organs is considered unlikely, even if the tumor diameter is large [12, 15].

The prognosis for CSGB is poor, similar to that of adenocarcinoma of the gallbladder. About 30% of CSGB patients had either metastasis or locally advanced disease at the time of diagnosis [16]. Ajiki *et al.* divided CSGBs into two groups. One group exhibits sarcomatous differentiation such as chondroid or osteoid differentiation and corresponds to current true carcinosarcoma [17]. The other is called sarcomatoid carcinoma or spindle cell carcinoma and corresponds to current so-called carcinosarcoma. In their examination of 36 CSGB cases, Ajika *et al.* found no significant difference in the median postoperative survival times for chondrosarcoma, osteosarcoma, and spindle-cell carcinoma (4, 4, and 6 months, respectively). In other words, prognosis is equally poor for both true and so-called CSGB.

A CSGB review by Zhang *et al.* reported a median survival time of 5 months with a 1-year survival rate of 19.5% and a 5-year survival rate of 16.5% [11]. It also found that prognosis was significantly better for Japanese vs. non-Japanese patients (mean = 19.9 months vs. 11.5 months, median = 6 vs. 4 months, $p = 0.022$) and for tumor diameters < 5 vs. ≥ 5 cm (mean = 26.6 vs. 17.7 months, median = 11 vs. 5 months, $p = 0.028$). These authors suggest several reasons for the better prognosis of Japanese patients, including genetic variation, earlier detection, and more sophisticated surgical procedures. In a report on CSGB cases in 36 Japanese patients, stage 4 cases had a significantly poorer prognosis than did stage 1–3 cases (5-year survival rate: 75.0% vs. 14.3%, $p = 0.04$); however, there is a possibility of long-term survival when radical resection is performed and distant metastasis is absent [15]. The 5-year survival rate after curative resection for CSGB is 88.9% when the invasion is restricted to the muscularis propria [18].

The first choice of treatment for CSGB is radical resection. The effectiveness of radiation therapy and chemotherapy has not been established, and these treatments have reportedly not improved prognosis [17]. In the report by Wada *et al.*, recurrence-free survival was more than 5 years following radical resection and long-term postoperative gemcitabine chemotherapy for a CSGB with portal vein and liver invasion [10]. Owing to the poor prognosis of CGSB, Wada *et al.* recommend careful follow up with chemotherapy for 2–3 years. For stage 4 CSGB, which has an extremely poor prognosis, it is important to perform staging laparoscopy and tissue biopsy to avoid unnecessary surgery and to maintain quality of life [19]. The effectiveness of postoperative adjuvant chemotherapy for biliary tract cancer has not yet been established, but we chose S-1 therapy based on a previous report [20]. The tumor in our case was less than 5 cm in diameter and T2a in depth, and there were no lymph node metastases or distant metastases, which may have contributed to the patient's long-term survival with no recurrence.

Further case studies are needed to clarify the characteristics of this rare tumor and to find out the best treatment options to treat this disease.

CONCLUSION

We reported a rare case of CSGB with long-term survival after radical resection and postoperative adjuvant chemotherapy with S-1. Further case studies are needed to clarify the characteristics of this rare tumor and to identify the best treatment options.

INFORMED CONSENT

Informed consent was obtained from the patient for submission of this paper in accordance with the COPE guideline.

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