



Case report

Two cases of resected gallbladder carcinosarcoma with a contrasting course

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ABSTRACT

Introduction: Carcinosarcoma of the gallbladder is a rare tumor with both carcinoma and sarcoma components. **Case presentation:** In this paper, we report two cases. The first case is of a man in his 60s who was preoperatively diagnosed with gallbladder carcinosarcoma and has achieved 6 years and 6 months survival through aggressive surgical treatment. The second case is of a woman in her 70s who was diagnosed with locally advanced gallbladder cancer; she underwent multidisciplinary treatment for the same, but died 8 months after the surgery. While the primary disorder was the same in both cases, the clinical courses contrasted sharply. **Discussion:** There is no established chemotherapy or radiation therapy for gallbladder carcinosarcoma, and the only curative treatment is surgery. However, it has a very poor prognosis. **Conclusion:** Carcinosarcoma of the gallbladder may progress very rapidly, and the treatment management should be carefully decided.

1. Introduction

Carcinosarcoma is a tumor that has both carcinoma and sarcoma components in the same mass. The tumor has been documented in different organs, but is relatively rare in the gallbladder, occurring for less than 1% of all gallbladder cancers [1]. Only about 100 cases of CSGB have been previously reported. There is no effective adjuvant treatment for carcinosarcoma, and radical resection is considered the only curative option. Therefore, carcinosarcoma of the gallbladder (CSGB) is considered to have a similar or worse prognosis than adenocarcinoma of the gallbladder [2].

Here, we report two patients with CSGB. Both cases were highly advanced, but with multidisciplinary treatment, we performed the curative resection. These patients had contrasting postoperative courses despite appropriate perioperative management. One patient had an unfortunate course, but the other achieved the longest survival time to date. This work was reported in accordance with the SCARE 2020

criteria [3].

2. Case presentation

2.1. Case 1

A 68-year-old man with no significant medical history presented to his local physician with a complaint of jaundice. He was referred to our hospital for diagnosis. He had no symptoms other than jaundice, and physical examination, including vital signs, was unremarkable. Laboratory data showed liver disorder, marked elevation of the enzymes associated with biliary obstruction (total bilirubin 13.1 mg/dL, alkaline phosphatase 4080 IU/L), and elevated serum carbohydrate antigen 19-9 (CA19-9 429 U/mL). There was no elevation in the serum carcinoembryonic antigen level (CEA 1.4 ng/mL). Contrast-enhanced computed tomography (CE-CT) showed a large enhancing mass arising from the cystic duct into the common bile duct. The lymph nodes on the dorsal

Abbreviations: CSGB, carcinosarcoma of the gallbladder; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CE-CT, contrast-enhanced computed tomography; EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration; UICC, Union for International Cancer Control; GCS, gemcitabine, cisplatin, and tegafur/gimeracil/oteracil potassium.

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side of the pancreatic head were enlarged and the right hepatic artery was infiltrated by the tumor (Fig. 1).

Since trans-papillary biopsy did not provide a definitive diagnosis, biopsy was performed using endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA). The microscopic examination of the specimen revealed the existence of both cytokeratin (CK)-AE1/AE3 positive papillary growth component and vimentin-positive round cell component in the tumor. Therefore, the patient was diagnosed with CSGB. Because the expected remnant liver volume was underestimated, after percutaneous transhepatic embolization of the right branch of the portal vein, an extended right hepatectomy and regional lymph node dissection were performed. The pancreatic head and the transverse colon had been infiltrated by the metastatic lymph node, and a pancreaticoduodenectomy and a partial colon resection were also performed.

The macroscopic examination showed an expanding tumor, 9.0 × 8.0 × 6.5 cm in size, originating from the cystic duct and compressing the liver and pancreas. The microscopic examination revealed a spindle cell proliferation in a large part of the tumor, which was vimentin-positive by immunostaining. In addition, a well-differentiated CK-AE1/AE3 positive ductal adenocarcinoma was also found in the tumor, which led to the diagnosis of CSGB (Fig. 2). Osteogenesis was observed in a small portion of the sarcoma component. Lymph node metastasis was observed only in the dorsal part of the pancreatic head. The tumor invaded the liver, but not the pancreas or the colon. The final stage according to the classification of malignant tumors by Union for International Cancer Control (UICC) was IIIB (T3N1M0). The patient had a pancreatic fistula as postoperative complications, which was treated with drainage and discharged on the 30th postoperative day.

He underwent follow-up with routine imaging and laboratory studies and is alive 6 years and 6 months after surgery without any recurrence.

2.2. Case 2

A 71-year-old woman visited her local doctor with a complaint of jaundice. An abdominal ultrasonography showed a large tumor occupying the liver and gallbladder, and she was referred to our hospital. She had a history of HBV infection.

She had no other symptoms except jaundice, and physical examination revealed a mass on the right costal region. Laboratory data showed mildly elevated biliary enzymes and normal CEA and elevated CA19-9 (126 U/mL). CE-CT showed a 12-cm tumor in the gallbladder invading the anterior and medial segment of the liver. There was no distant metastasis, but a 9-cm lymph node was found in the hepatoduodenal ligament (Fig. 3). A trans-papillary biopsy revealed adenocarcinoma, and an EUS-FNA biopsy showed that the enlarged lymph node was also a metastatic lesion, leading to the diagnosis of locally advanced gallbladder cancer. In-hospital multidisciplinary team

conferences, so-called cancer board, concluded that the long-term prognosis could not be obtained based on the up-front surgery, then a preceding chemotherapy strategy was decided [4].

She received gemcitabine, cisplatin, and tegafur/gimeracil/oteracil potassium (GCS) therapy, which was approved in Japan in 2018 [5]. The serum CA19-9 level (12.6 U/mL) decreased to below the cut-off level after 12 courses of GCS therapy. The tumor shrank markedly from 12 cm to 5 cm, and radical surgery was performed 8 months after diagnosis. Since the lymph node in the hepatoduodenal ligament were suspected to infiltrated the pancreatic head, a pancreaticoduodenectomy with gallbladder bed resection of the liver and dissection of regional lymphadenectomy was performed.

Macroscopically, the tumor was a papillary growth measuring 5.0 × 3.7 × 2.2 cm, bulging in the lumen of the gallbladder fundus with hepatic infiltration (Fig. 4). The lymph node in the hepatoduodenal ligament was 7.5 × 5.5 × 3.8 cm. The microscopic examination revealed an area of spindle tumor cells growing in bundles in the gallbladder and an area of polygonal tumor cells with mucous components infiltrating the liver. The tumor invasion to other organs was only in the liver. Immunostaining showed positivity for CK-AE1/AE3 and vimentin, which suggested carcinosarcoma (Fig. 5). In addition, in the intermediate area between the carcinoma and sarcoma, polygonal tumor cells with an eosinophilic component were present, and immunostaining showed CK-AE1/AE3, chromogranin A, and synaptophysin positivity, indicating neuroendocrine carcinoma. The lymph node in the hepatoduodenal ligament was a metastasis from the carcinoma component. Preoperative chemotherapy resulted in 60% necrosis of the carcinoma component, but there was no treatment effect on the sarcoma component. The final stage was classified as IVB (T3N2M0) using the classification of UICC. The patient developed a pancreatic fistula and hepatic dissection abscess as postoperative complications. These were treated with drainage and the patient was discharged on postoperative day 69.

Four months after surgery, a follow-up CT revealed multiple nodules in the liver. Percutaneous transhepatic biopsy indicated sarcoma recurrence. The medical oncologist administered chemotherapy with doxorubicin; however, the tumor continued to grow. She died 8 months after surgery.

3. Discussion

Gallbladder cancer is the most common tumor of the biliary tract. Among them, carcinosarcoma is a relatively rare malignant tumor with a combination of carcinoma and sarcoma within the same mass. Carcinosarcoma is found in all organs, and is most frequently reported in the pharynx, mammary gland, and lungs, while it is rare in the gallbladder. The female to male ratio for CSGB is 3.25:1. The average age of incidence is 68.8 years [6]. The first report was made by Landsteiner et al. in 1907. Since then, the number of reports has been increasing, but there



Fig. 1. Contrast-enhanced computed tomography (CE-CT) showed a large enhancing mass lesion growing from the gallbladder duct into the common bile duct. It was also found that the lymph nodes on the dorsal side of the pancreatic head were enlarged, and the right hepatic artery was infiltrated by the tumor (arrow head).

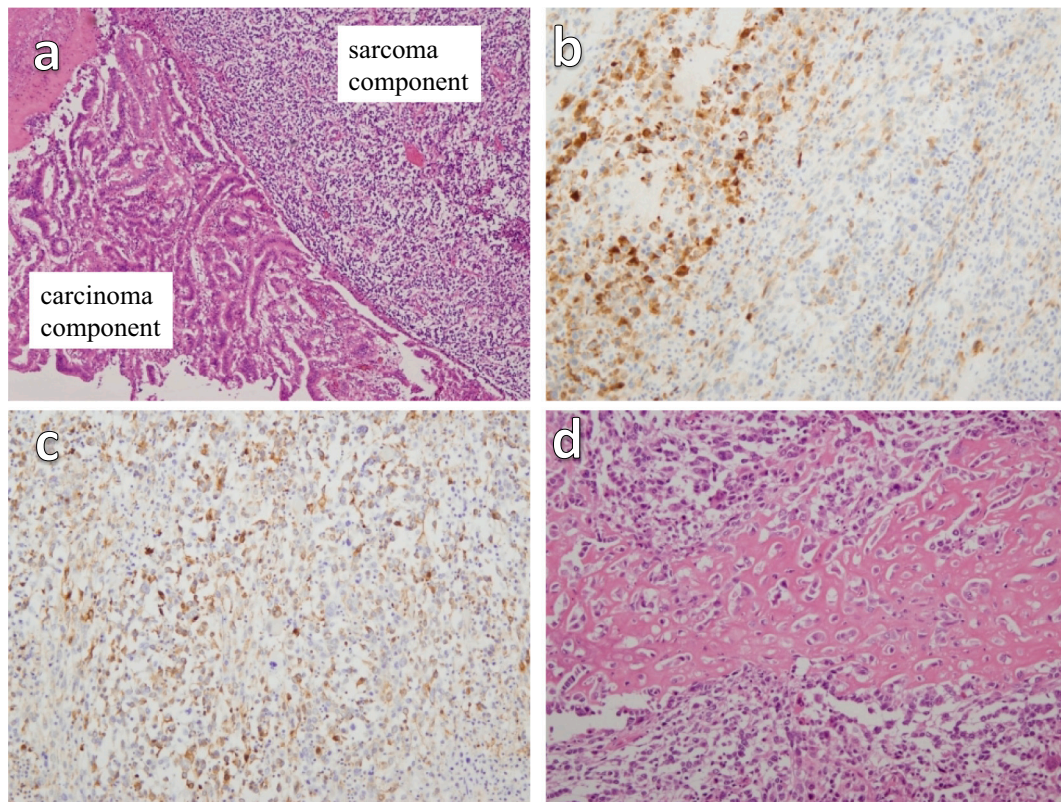


Fig. 2. (a) Microscopic examination revealed a substantial growth of spindle cells and a well differentiated ductal adenocarcinoma. HE staining. (b) Microphotography showed CK-AE1/AE3 positive in the carcinoma components. (c) Microphotography also showed vimentin positive in the sarcoma components. (d) Osteogenesis was observed in a small portion of the sarcoma component. HE staining.

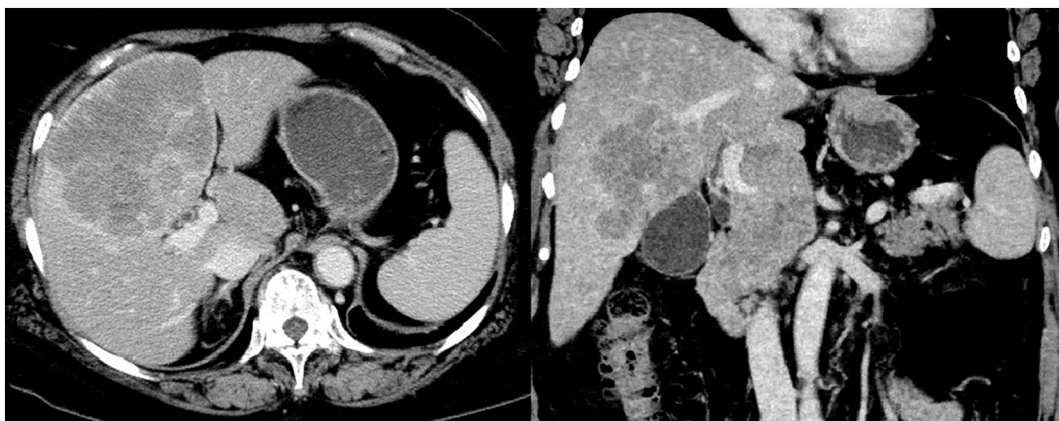


Fig. 3. CE-CT showed a tumor measuring 12 cm in diameter in the gallbladder invading into the liver. There was no distant metastasis, but a 9-cm lymph node was found in the hepatoduodenal ligament.

are only around 100 reports in English [7].

The histogenesis and natural history of carcinosarcoma are not clear. They are typically categorized into “true carcinosarcoma” and “so-called carcinosarcoma”. “True carcinosarcoma” is thought to be the result of a collision between a carcinoma and a sarcoma, occurring separately. On the other hand, “so-called carcinosarcoma” is considered to arise from very poorly differentiated carcinoma cells that have developed sarcomatous differentiation, morphologically and immunohistologically losing their epithelial features and expressing stromal cell features [8]. It is sometimes referred to as sarcomatoid or spindle cell carcinoma [9]. In both our cases, the sarcoma component was negative for epithelial markers, suggesting that the lesions were “true carcinosarcoma”.

The mesenchymal component usually has undifferentiated spindle and stellate cells with various proportions of heterogeneous elements such as chondrosarcoma, osteosarcoma, rhabdomyosarcoma, and leiomyosarcoma [10]. In the epithelial component, adenocarcinoma is most commonly observed (79.2%), followed by squamous cell carcinoma (9.4%) [6]. Neuroendocrine differentiation, as in Case 2, is very rare and has only been reported in one case of CSGB [11].

CSGB, like carcinoma of the gallbladder, is most commonly associated with abdominal pain, anorexia, vomiting, and jaundice, but has no specific symptoms [12]. Epithelial tumor markers such as CEA, CA19-9 are not specific. Imaging studies are a potential way to diagnose CSGB preoperatively. CSGB has been reported to have two imaging features –

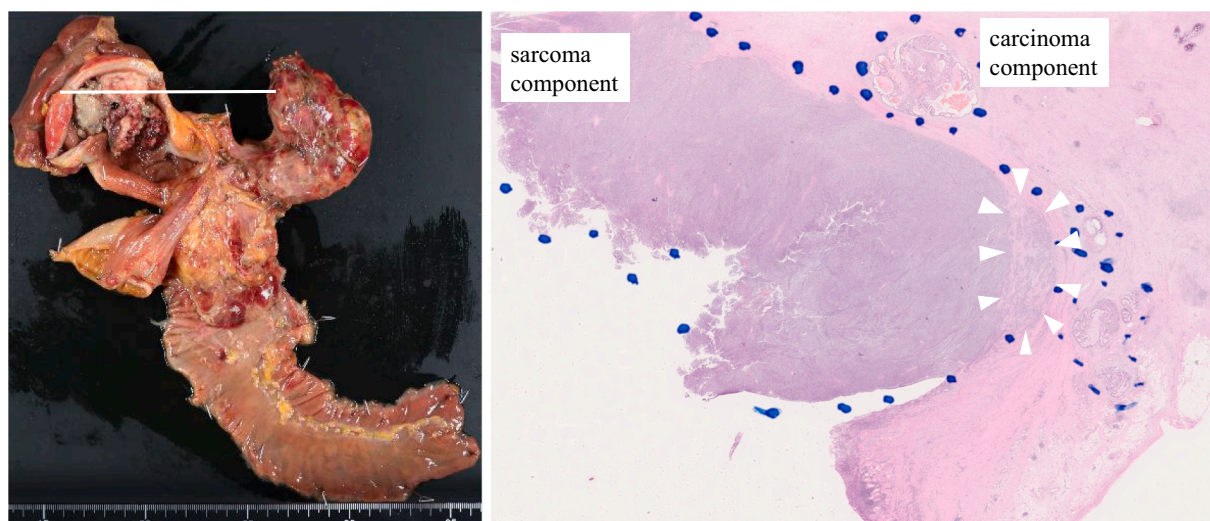


Fig. 4. Macroscopically, the tumor was a papillary growth measuring $5.0 \times 3.7 \times 2.2$ cm, bulging in the lumen of the gallbladder fundus with hepatic invasion. The area enclosed by the arrow heads is the site of neuroendocrine differentiation.

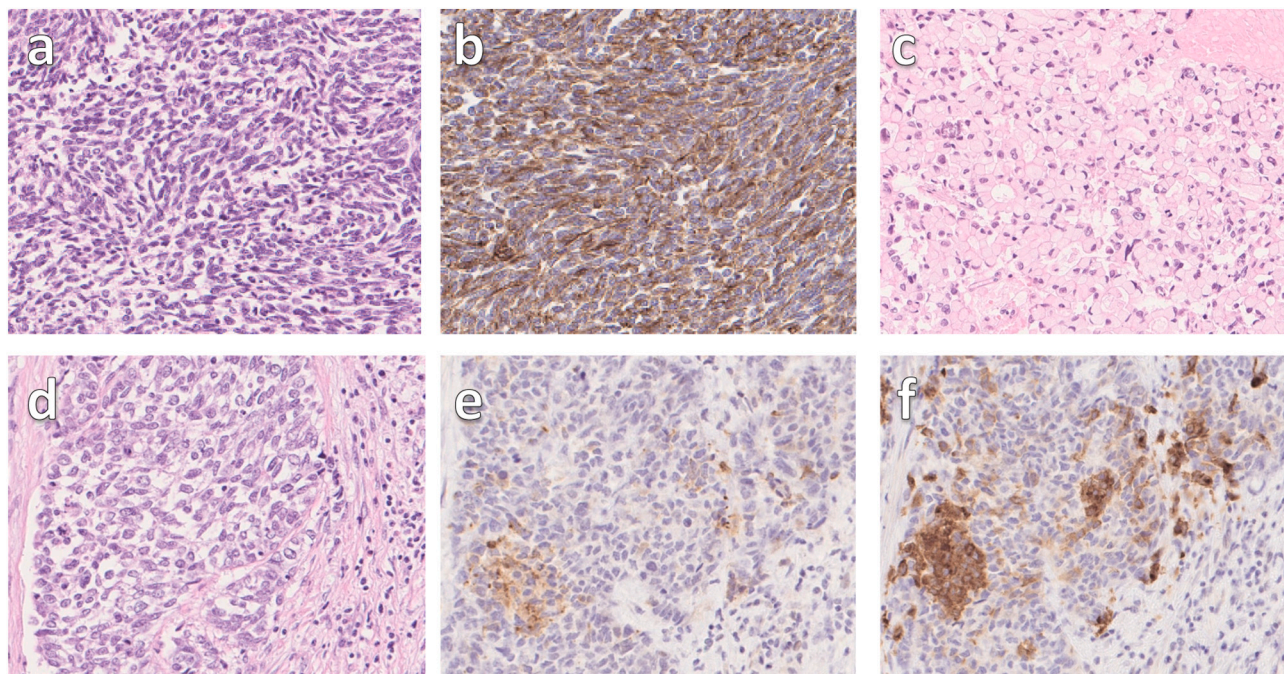


Fig. 5. (a) The sarcoma component of spindle tumor cells. HE. (b) Microphotography showed vimentin positive in the sarcoma components. (c) The carcinoma components of polygonal tumor cells with mucous components. HE. (d), (e), (f) Microphotography showed polygonal tumor cells with an eosinophilic component in the area between the carcinoma and sarcoma. Immunostaining showed positive chromogranin A, and synaptophysin respectively, indicating neuroendocrine carcinoma.

the papillary growth in the gallbladder, which tends to keep the outer margin of the gallbladder even, if the tumor forms a large mass, and speckled calcification within the tumor [13]. However, these findings are not seen in all cases of CSGB. This makes it difficult to make a proper diagnosis preoperatively. Thus, the preoperative diagnosis is usually gallbladder carcinoma, and the therapeutic strategy is often based on this diagnosis. There have been no cases of CSGB correctly diagnosed preoperatively as in case 1.

A few reports have been reported on the chemotherapy of the carcinosarcoma [9,14–16]. Even if chemotherapy is administered, it is usually based on the adjuvant therapy for gallbladder cancer. However, most of the cases recur early due to liver metastasis [17]. Due to the

rarity of CSGB, no effective regimen has been established at this time [18]. Radiotherapy has been reported to be ineffective. Case 2 is the first case in which not only preoperative chemotherapy but also chemotherapy was given for recurrent sarcoma. In addition, there is no previous report on the use of GCS therapy as an adjuvant therapy, and GCS therapy had effect only on the epithelial component but not the mesenchymal component.

Surgery is undoubtedly the only method of curative treatment. The surgical strategy is usually the same as for adenocarcinoma of the gallbladder: simple cholecystectomy or extended cholecystectomy including liver bed resection and pancreaticoduodenectomy. In CSGB, since most of these cases presented with a large mass invading into

adjacent organs, an extended cholecystectomy is often performed [2]. However, despite the aggressive surgical treatment for CSGB, the prognosis after resection is very poor. Okabayashi et al. and Zhang et al. reported a median survival of 7 months and 5 months, respectively, with a 3-year survival rate of 31% and 16%, respectively [2,6]. Although the prognostic factors have not been fully investigated, Okabayashi et al. reported that extension till the muscularis propria depth and Stage II are good prognostic factors, while Zhang et al. reported having a maximum diameter of less than 5 cm is a good prognostic factor. To the best of our knowledge, our patient (case 1) has the longest survival (78 months) among all the cases of highly advanced CSGB reported [15]. It is uncertain why the course of Case 2 was poor, but controlling the carcinoma component was not enough; we also needed to consider controlling the sarcoma component.

4. Conclusion

It is necessary to fully understand the limitations of surgical treatment for highly malignant carcinosarcoma. The progression of CSGB is usually rapid, and its therapeutic management should be carefully determined.

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Ethical approval

The institutional review board of the Sapporo Medical University Hospital approved the study protocol (302-29). Due to the retrospective study of this type, the applicable legal and ethical principles pertaining to the protection of human subjects provide for a waiver of approval from a research ethics committee.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contributions

TK and YK: Performed the surgery on the patients.
 TK, YK, TK, AM and TH: Full access to all the data in the study and take responsibility for the integrity of the data.
 TK and YK: Acquisition or interpretation of data.
 TK and YK: Drafting of the manuscript.
 YK, TK, AM, and TH: Critical revision of the manuscript for important intellectual content.
 IT: Study supervision.

Registration of research studies

Our case report is not first-in-human. Therefore, in accordance with

the Guidance of Research Registry, we did not register our case report at <http://www.researchregistry.com>.

Guarantor

Yasutoshi Kimura (Corresponding author and Guarantor).

Provenance and peer review

Not commissioned, externally peer-reviewed.

Declaration of competing interest

The authors declare that they have no competing interests.

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