

Gallbladder carcinoma with a large monolocular cystic cancerous component

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Abstract. The monolocular cystic formation associated with gallbladder carcinoma is an extremely rare condition. A 79-year-old female suffering from upper abdominal pain and distention was admitted to our hospital. Ultrasonography and computed tomography revealed a monolocular cyst with an irregular wall thickness of 15 cm in diameter concomitant with a solid mass of 8 cm in diameter around the gallbladder bed. During celiotomy, the tumor was found to have a large pale gray cystic component at the fundus of the gallbladder, and disseminated nodules were observed in the peritoneum. We diagnosed the patient with gallbladder carcinoma and performed a simple cholecystectomy that included the tumor without systematic lymphadenectomy. On the cut face of the gallbladder, the lumen was occupied by a solid neoplasm. The cyst included a large amount of serous fluid and protruded continuously from the body of the gallbladder, but it did not communicate with the gallbladder lumen. Although the mechanism responsible for the development of cyst-forming papillary carcinoma of the gallbladder remains unknown, the present case is crucial for understanding the mechanism of cystogenesis in gallbladder carcinoma.

Introduction

Primary gallbladder carcinoma shows a variety of growth patterns, some of which spread expansively to form a mass while others infiltrate diffusely and deeply into the gallbladder wall or the surrounding organs. Numerous studies

have been conducted on gallbladder carcinoma with cystic formation, such as cystadenocarcinoma of the gallbladder (1-4) and Rokitansky-Aschoff sinus (RAS)-associated gallbladder carcinoma (5-7). In these tumors, it is normal that the cancerous cystic component is multilocular or not large in size. This study evaluated the clinicopathological findings and analyzed the morphogenesis of a gallbladder carcinoma showing a large malignant cystic growth.

Case report

A 79-year-old Japanese female suffering from upper abdominal pain and distention was admitted to our hospital. The patient had previous illness of note nor a family history of disease. A large mass was palpable in the right upper quadrant of the abdomen. The patient's lactate dehydrogenase was elevated to 413 IU/l (normal range <230), and two serum tumor markers, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), were both elevated at 3.4 ng/ml (normal range <2.5) and 1465.3 U/ml (normal range <37), respectively. Abdominal radiography showed an oval radio-opaque shape of 15 cm in diameter in the right upper abdomen (Fig. 1). Ultrasonography (Fig. 2) and computed tomography (CT) (Fig. 3) revealed the tumor to be a monolocular cyst with an irregular wall thickness of 15 cm in diameter concomitant with a solid mass of 8 cm in diameter around the gallbladder bed, suspected to be a tumor originating from the gallbladder. Endoscopic examinations of the alimentary tract showed no abnormalities. During celiotomy, the tumor with a large pale gray cystic component was identified at the fundus of the gallbladder. The tumor fibrously adhered to the liver, duodenum, and greater omentum, but it appeared to have only partially infiltrated into the transverse colon. A number of small nodules suspected to be tumor dissemination were scattered on the peritoneum. Gallbladder cancer with peritoneal dissemination was diagnosed. Although curative resection for the tumor was impossible, a simple cholecystectomy was performed that included the tumor without systematic lymphadenectomy, and a partial resection of the transverse colon was added due to its tight adhesion by the tumor cyst.

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Figure 1. An oval-shaped tumor was suspected upon abdominal radiography.



Figure 2. Abdominal ultrasonography showed a large cystic tumor with a solid component at the liver bed.



Figure 3. Enhanced computed tomography showed a large cystic tumor (arrow) with a solid component (arrow head).

The gross appearance of the excised gallbladder with the monocular large cyst is shown in Fig. 4. On the cut face of the gallbladder, the lumen was occupied by a solid neoplasm. The cyst included a large amount of serous fluid and protruded continuously from the body of the gallbladder,

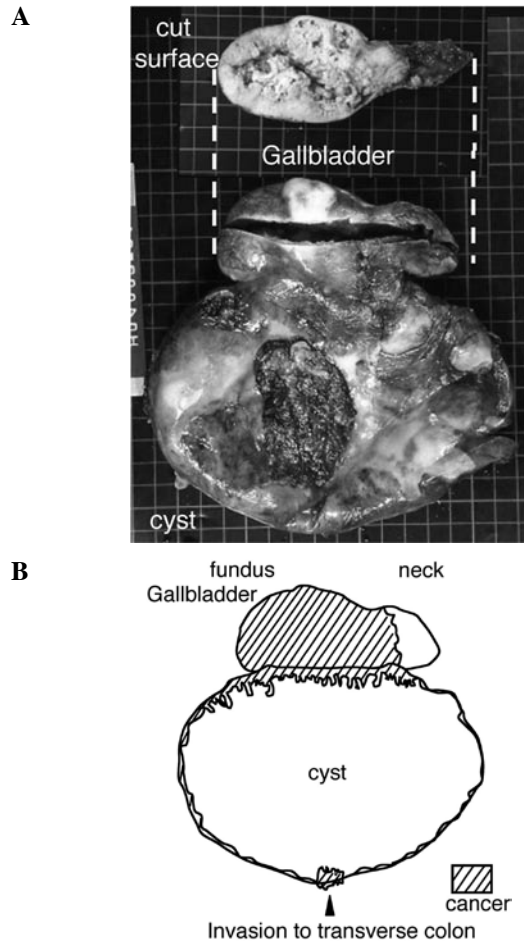


Figure 4. (A) Gross appearance of the excised specimen showed that the gallbladder was occupied by a solid tumor and a monocular cyst. (B) The gallbladder, except for the neck and the wall of a large cyst, was covered with non-neoplastic low papillary columnar epithelium and papillary adenocarcinoma microscopically.

but was not part of the gallbladder lumen. Microscopic examination suggested that the internal wall of the cyst was covered with non-neoplastic low papillary columnar epithelium and papillary adenocarcinoma. However, the remainder of the cyst was composed of papillary carcinoma (Figs. 4B and 5A). A macroscopic solid mass observed in the gallbladder lumen also consisted microscopically of various-sized cystic components composed of papillary adenocarcinoma (Fig. 5B).

Immunohistochemical examinations showed that the cancer cells of the gallbladder and the large cyst were positive for cytokeratin 7 and CEA, and were negative for mesothelin and calretinin. The immunohistochemical findings proved that the carcinoma was derived from gallbladder epithelium. Further immunohistochemical studies [E-cadherin, epidermal growth factor (EGF) and hepatocyte growth factor (HGF)] were performed to determine the morphogenesis of this tumor. The cancer cells of the gallbladder and large cystic lesion showed positive staining for E-cadherin (Fig. 6A), EGF (Fig. 6B) and HGF (Fig. 6C).

The postoperative clinical course of the patient was uneventful. Some anti-cancer chemotherapy was recommended, but the patient refused to undergo this treatment. The patient succumbed to the disease at 185 days post-surgery.

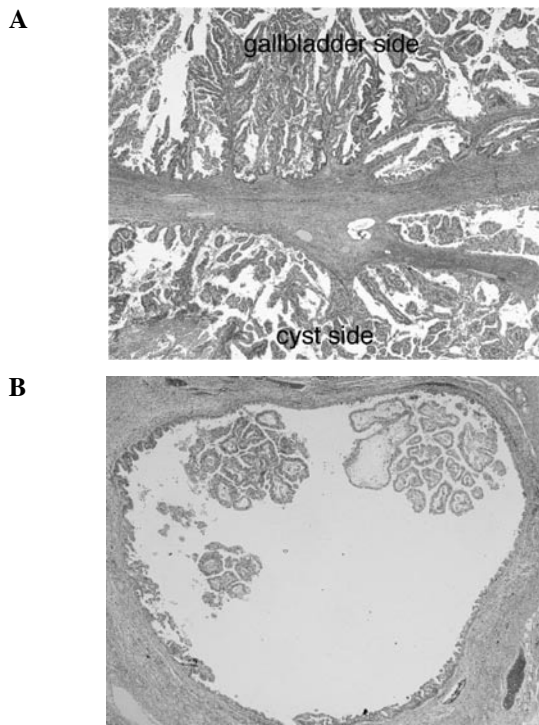


Figure 5. (A) The microscopic appearance of the cyst showed papillary adenocarcinoma similar to the gallbladder. (B) Cancer cells organized into various sized cystic structures in the gallbladder wall.

Discussion

The key interest of this case involved cystic formation, which was associated with gallbladder carcinoma cells. Various hypotheses have been documented regarding the genesis of the cystic structure in gallbladder mucosal tissues. Essentially, there are two types of cysts: acquired and congenital. Acquired cysts develop as a result of RAS, pericholecystic adhesion, parasites (8) or closed communication between the diverticulum and the gallbladder caused by inflammation or a tumor (9). With regard to gallbladder carcinoma, the cysts are presumed to originate in the RAS, diverticulum or to be associated with congenital cysts (5-7,9). However, gallbladder carcinoma with a large monolocular cystic cancerous component is an extremely rare condition. To the best of our knowledge, there has been only one case report of gallbladder carcinoma accompanied by a large malignant epithelium-covered cyst of more than 10 cm in diameter (9). Sworn and Gay (9) reported an epithelium-covered cyst of 16 cm in diameter associated with gallbladder carcinoma. The cyst was lined by papillary gallbladder epithelium with carcinoma *in situ* in various parts. Similar to the present case, no communication between the cyst and the gallbladder lumen was found, and the cyst contained serous fluid. The authors hypothesized that the cyst was acquired by the occlusion of the communication of a fundal diverticulum and the gallbladder. The tumor epithelium-covered cysts can probably be regarded as a special subtype of papillary carcinoma, and are different from cystadenocarcinoma of the gallbladder in which malignant cyst formation is likely the dominant type of growth.

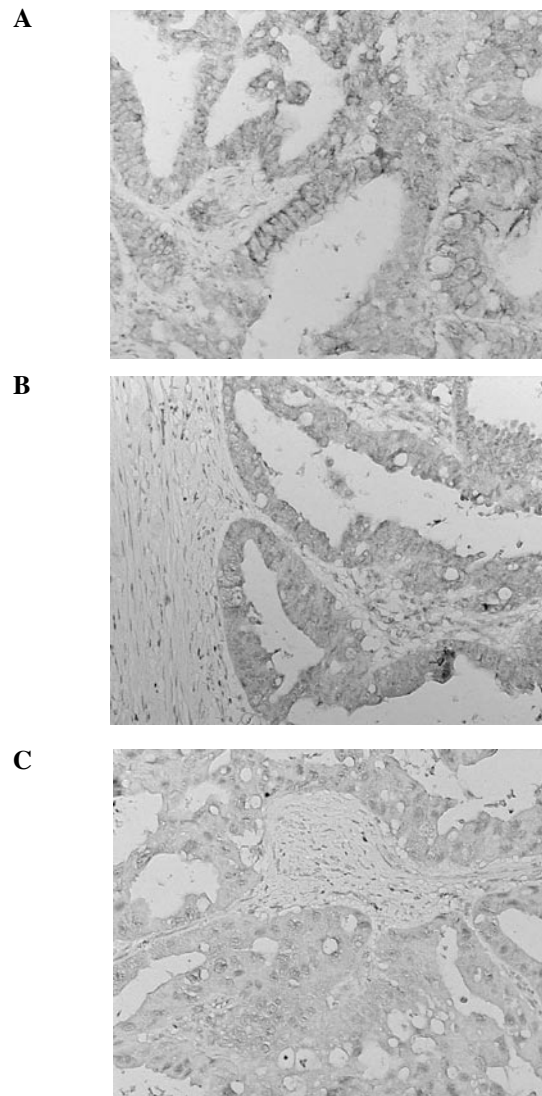


Figure 6. Immunohistochemical studies showed that the cancer cells were positively stained for (A) E-cadherin, (B) epidermal growth factor and (C) hepatocyte growth factor.

One of the possible mechanisms underlying the formation of these cysts is the occlusion of the communication between RAS or a blockage in the communication between the diverticulum and gallbladder due to inflammation or cancer growth. The present case showed large and small cancerous lesions forming various cystic structures, suggesting that the large cysts may have arisen following the transition from one of the small cysts in the solid gallbladder carcinoma (Fig. 5B). Therefore, we speculate that this characteristic papillary adenocarcinoma results in the formation of cysts.

We previously reported the acquisition of cysts from gallbladder epithelial and gallbladder cancer cells *in vitro*, and confirmed that the expression of EGF, HGF and E-cadherin were essential to the cystogenesis of these gallbladder cancer cells (10-13). We confirmed that EGF, HGF and E-cadherin were expressed in the cancer cells of both the gallbladder and large cyst *in vivo*. Although the results of immunohistochemical analyses are not sufficient to clarify the mechanism underlying the cyst-forming growth in our case, it is compatible with the previous hypothesis.

In conclusion, this study reports a rare case of gallbladder carcinoma with a large monolocular cystic carcinoma component. Although the mechanism responsible for the development of cyst-forming papillary carcinoma of the gallbladder remains unknown, the present case is crucial for understanding the mechanism of cystogenesis in gallbladder carcinoma. We anticipate that as additional case reports accumulate, it is likely that the nature of cyst-forming papillary carcinoma may be proven and the entity established as a unique carcinoma.

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