[症例報告]Endocrine Cell Carcinoma of the Gallbladder with Abnormal Serum CEA Levels: A Case Report

Endocrine Cell Carcinoma of the Gallbladder with Abnormal Serum CEA Levels: A Case Report

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ABSTRACT

Endocrine cell carcinoma (small cell carcinoma) of the gallbladder with elevated serum levels of carcinoembryonic antigen (CEA) in a 78-year-old Japanese woman is herein reported. The patient presented with a painless large mass in the right upper quadrant. Admission laboratory findings showed only an abnormal serum level of CEA. An abdominal ultrasonography (US) showed an echogenic large mass measuring 6 cm in diameter and several small gallstones. An abdominal computed tomography (CT) scan demonstrated a large hyperdensity mass occupying the body and neck of the gallbladder. At laparotomy, the gallbladder tumor showed hepatic infiltration and regional lymph node metastasis. Radical surgery for gallbladder carcinoma was thus performed. The gallbladder tumor was diagnosed to be Stage III. A large, sessile polypoid tumor measuring 6 cm in greatest dimension in the body and neck was found. The tumor was composed of intermediate cells which were histochemically and immunohistochemically positive for chromogranin A, neuron-specific enolase (NSE) and CEA. After being discharged, anticancer agents (Mitomycin C or cisplatin and 5-fluorouracil) was administered on an outpatient basis (small dose) for 2 years while taking great care to reduce any potential side effects. Finally, the patient died due to a recurrence of gallbladder carcinoma 27 months after surgery. *Ryukyu Med. J., 20(1)31~34, 2001*

Key words: endocrine cell carcinoma, small cell carcinoma, gallbladder, abnormal serum CEA

INTRODUCTION

A group of tumors of the gastrointestinal tract, including the gallbladder, originates in the neuroendocrine cells and is generally divided into two groups including carcinoid tumors (classical type)[1-3] and endocrine cell carcinomas (small cell carcinomas, atypical type).[4-7] Small cell carcinoma is a poorly differentiated carcinoma composed of small to intermediate cells with endocrine features[7]. Therefore, it is more appropriate to consider this tumor as a poorly differentiated endocrine carcinoma. In addition, its morphology and natural history closely resemble those of pulmonary and extrapulmonary small to intermediate cell carcinomas showing evidence of poor endocrine differentiation[7]. However, little is known about either the production of carcinoembryonic antigen (CEA) by endocrine cell carcinoma (small cell carcinoma) or its clinical implications. We herein report a case of endocrine cell carcinoma of the gallbladder with serum elevated levels of CEA.

CASE REPORT

A 78-year-old Japanese woman was hospitalized with a painless palpable mass in the right upper quadrant in December 1997. There was no history of right upper quadrant pain, fever, jaundice or appetite loss. Her past medical history was not contributory. On admission, the patient appeared well. On physical examination, she was well nourished with stable vital signs. An abdominal examination revealed a smooth-surfaced, firm and nontender mass measuring 8 cm in greatest dimension in the right upper quadrant which moved with respiration and was attached to the liver. The admission laboratory findings were all within the normal limits except for an elevated serum CEA (23.0 ng/ml) (normal, >5 ng/ml).

Abdominal ultrasonography (US) showed a heterogeneous echogenic large mass measuring 6 cm in diameter and several echogenic densities with acoustic shadows ranging from 2 to 5 mm in size suggestive of gallbladder stones. Abdominal computed tomography (CT) demonstrated a large hyperdensity mass occupying the neck and body of the gallbladder. Endoscopic retrograde cholangiography

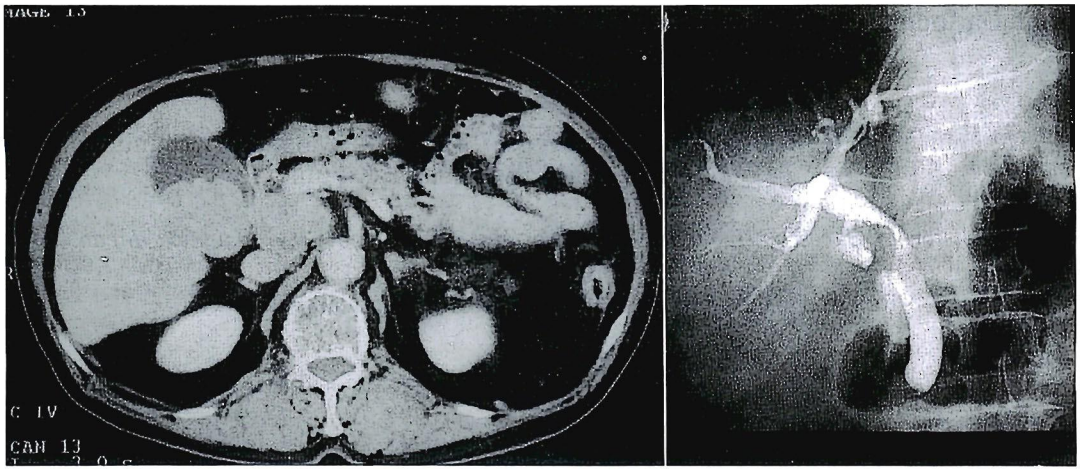

Fig. 1 Abdominal CT demonstrating a large, hyperdensity mass occupying the neck and body of the gallbladder (left) and ERC showing a filling defect in the middle portion of the common bile duct and occlusion of the cystic duct (right).

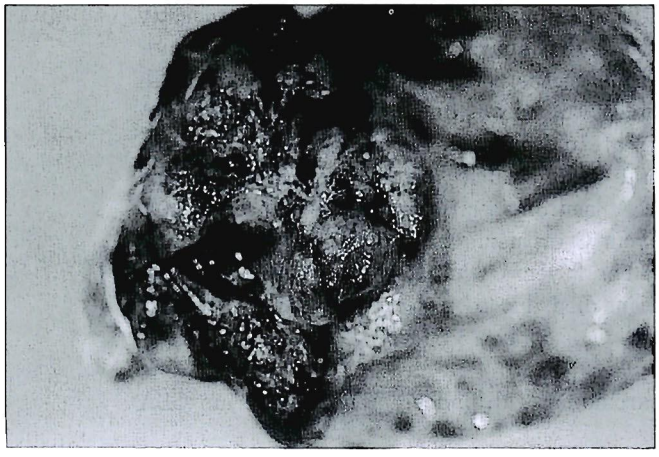

Fig. 2 The resected gallbladder showing a large, uneven and necrotic surfaced tumor measuring 6 × 4 × 3 cm in size.

showed a filling defect below the junction site of the cystic duct and the common duct, but the gallbladder was not outlined (Fig. 1). Hepatic arteriography revealed a fine irregular neovascularisation in the superficial branch of the cystic artery around the body and neck of the gallbladder.

An exploratory laparotomy was thus performed with a tentative diagnosis of advanced gallbladder carcinoma. Gallbladder carcinoma showed hepatic infiltration and regional lymph node metastasis. A cholecystectomy with a partial hepatic resection and a regional nodal dissection were performed. The gallbladder carcinoma was evaluated to be Stage III.

Grossly, the resected gallbladder was observed to be a gray-pinkish, sessile polypoid tumor measuring 6 × 4 × 3 cm located in the body and neck (Fig. 2). There were several small cholesterol gallstones. Histologically, the tumor was composed of nests and glandular structures of small to medium-sized, fusiform cells with hyperchromatic round

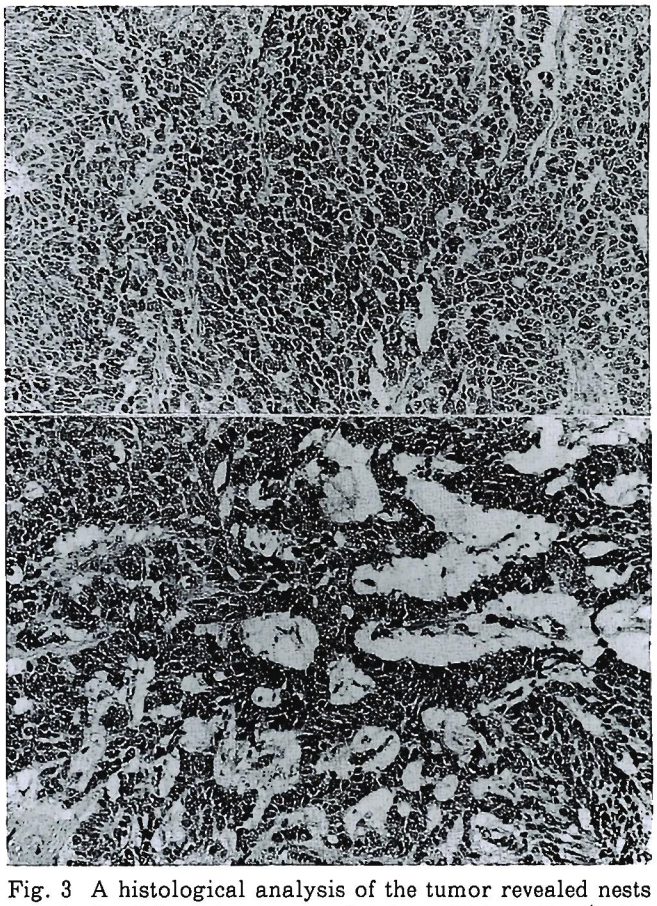

Fig. 3 A histological analysis of the tumor revealed nests and glandular structures of intermediate cells (both; hematoxylin-eosin, × 25).

to oval nuclei and poorly defined cytoplasmic borders. The sheets or nests of tumor cells were in trabecular arrangements within a delicate fibrous stroma (Fig.3). Histochemically and immunohistochemically, the tumor cells were positive for chromogranin A, neuron-specific

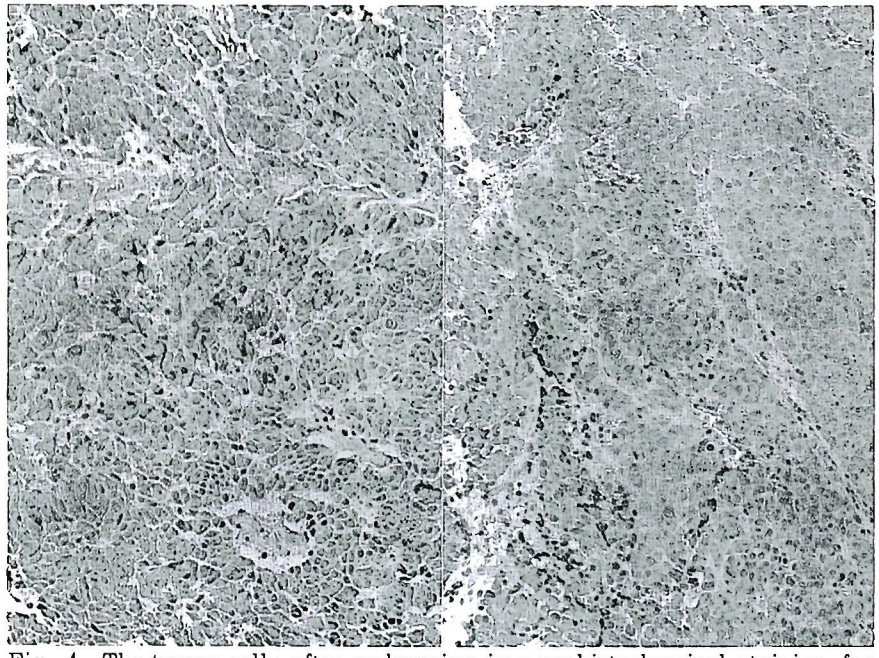

Fig. 4 The tumor cells after undergoing immunohistochemical staining for chromogranin and CEA showed a positive expression for chromogranin (left) and CEA (right) (both, ×50).

enolase (NSE) and CEA and were negative for keratin, epithelial membrane antigen (EMA) and neurofilament. Moreover, the tumor cells were negative for mucin staining (alcian blue and periodic acid-Schiff stains) (Fig. 4).

Postoperatively, an infuse A port was implanted in the right inguinal region for arterial infusion chemotherapy. Its tube was placed at the level of the 12th throracic vertebra. In five months, from February to June, 4 mg of Mitomycin C (MMC) per week and daily 5 fluorouracil (5-FU, 100 mg) were given. The serum CEA level increased to 60.2 ng/ml in April. Subsequently, the patient recieved 5 mg of cisplatin per week instead of MMC. Nevertheless, the serum CEA levels gradually increased to 232 ng/ml in June, 208 ng/ml in July, 360 ng/ml in August, and 364 ng/ml in October. The patient also developed obstructive jaundice (serum total bilirubin, 10.5 mg/nl). The patient was readmitted to our hospital and thereafter underwent percutaneous transhepatic biliary drainage (PTBD) in August. During hospitalization, cisplatin, 10 mg/m^2 was administered by intravenous piggyback (IVPB) in 100 ml normal saline (NS) over 30 minutes on Days 1 to 5 of each 4-week cycle. 5-FU, 250 mg/m^2 was administered by IVPB infusion on Days 1 to 5 of each 4-week cycle. Standard intravenous hydration and antiemetics were also used. This chemotherapy regimen was repeated for 3 cycles.

Finally, the patient died with clinical manifestations of recurrent gallbladder carcinoma 27 months after surgery.

DISCUSSION

So-called carcinoids (carcinoids) documented under the term carcinoid tumors, mainly including carcinoid tumors and endocrine cell carcinomas, are rare, and account for less than 2% of all tumors and usually arise from the gastrointestinal tract[8]. Primary gallbladder carcinoids account for approximately 1% of all carcinoids in the body. According to recent reports[9,10], only 86 cases of carcinoids of the gallbladder have been reported in the world and 53 cases of these cases have been described in the Japanese literature. Thus, the remaining 33 cases have been documented in the English literature. Of these 86 cases, there were 23 cases (26.7%) of carcinoid tumors and 63 cases (73.3%) of endocrine cell carcinomas, respectively. Our case demonstrated endocrine cell carcinoma (small cell carcinoma) composed of intermediate cells.

Recently, several studies have reviewed the reported cases in the literature regarding the morphologic features and biological behavior that distinguish carcinoid tumors from endocrine cell carcinomas[9-11]. There were no significant differences related to age or sex between the 2 groups. In carcinoid tumors, the tumors tended to mainly be located at the neck of the gallbladder (65.0%), whereas in endocine cell carcinomas, the tumors were mainly located from the fundus to the body (about 70%). The tumor size was extremely large in endocrine cell carcinoma (45.5 mm vs. 12.6 mm, $p < 0.001$). In carcinoid tumors, most of them formed a small yellowish polypoid lesion which resembled those of a non-neoplastic cholesterol polyp. Tumor invasion was within the muscular layer of the gallbladder

in more than half of all carcinoid tumors. In contrast, almost all endocrine cell carcinomas invaded beyond the subserosal layer of the gallbladder (96.3%). More than half of all endocrine cell carcinomas had metastasis at presentation (53.8%), whereas no carcinoid tumors had any metastatic or invasive characteristics while also demonstrating an extremely favorable prognosis. In this case, the tumor size was 6 cm in greatest diameter, and it was located in the body and neck. The tumor invaded beyond the serosa and also directly invaded the liver. As a result, this case was morphologically similar to those of endocrine cell carcinoma reported in the literature. The 5-year survival rate was 90.9% in carcinoid tumors and 17.4% in endocrine cell carcinomas. Our patient died 27 months after surgery.

Interestingly, endocrine cell carcinomas are composed of small cell carcinomas and adenocarcinomas which tend to intermingle with each other while also demonstrating an apparent transitional zone. Therefore, endocrine cell carcinoma cells may originate from multi-potential stem cells which have the ability to differentiate into various kinds of metaplastatic epithelia. On the other hand, the carcinoid tumors originate from endocrine cells, but not from multi-potential stem cells[12, 13]. As a result, the differences in the characteristics between the 2 groups are due to their origin. In this case, no nests of adenocarcinomas were observed. However, the serum elevated levels of CEA and immunohistochemical positivity for both chromogranin and CEA in the tumor cells may support the possibility of dual differentiation. In clinical practice, elevated serum levels of CEA were reported to be associated with an unfavorable prognosis of the corresponding patients[14]. This association thus needs to be futher elucidated.

In conclusion, in comparison with the carcinoid tumors, endocrine cell carcinomas are usually larger in size, have a metastatic or invasive character, and have also a poor prognosis. Nevertheless, if such tumors are confined to the gallbladder wall without any evidence of metastatic spread or direct invasion to the liver, then an appropriate hepatic resection and lymph node dissection may still lead to a favorable prognosis.

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