Primary Small Cell Carcinoma of the Stomach Successfully Treated With Cisplatin and Etoposide

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We report a 44-year-old man with primary gastric small cell carcinoma who showed a remarkable response to chemotherapy specific for pulmonary small cell carcinoma. The patient had been admitted to another local hospital because of intermittent epigastralgia. An upper gastrointestinal examination there revealed an ulcerative tumor, 5 cm in diameter, on the lesser curvature side of the cardia, and endoscopic biopsy reported adenocarcinoma. Computed tomography revealed a mass over the lesser curvature of the stomach and some enlarged regional lymph nodes. Radical total gastrectomy, lymph node dissection, Roux-en-Y esophagojejunostomy and splenectomy were performed at our hospital. Pathology revealed gastric mucosa infiltrated by small-sized tumor cells with scanty cytoplasm and hyperchromatic nuclei. Immunohistochemically, the tumor cells were positive for synaptophysin, chromogranin A, and CD56. Primary gastric small cell carcinoma was diagnosed. The postoperative course, complicated by shock due to bleeding, wound infection and intra-abdominal abscess, took more than 2 months to resolve. Follow-up computed tomography showed tumor recurrence with multiple enlarged lymph nodes in the aortocaval region and hepatic hilum. The patient received palliative chemotherapy consisting of cisplatin 80 mg/m^2 on day 1 and etoposide 80 mg/m^2 on days 1–3 every 28 days, and had partial response to the chemotherapy, with a progression-free survival of 10 months. Chemotherapy with cisplatin and etoposide used for small cell carcinoma of the lung is a good treatment for gastric small cell carcinoma. [*J Chin Med Assoc* 2009;72(11):598–602]

Key Words: chemotherapy, small cell carcinoma, stomach

Introduction

Although accounting for only 0.1% of all gastric cancers, gastric small cell carcinoma (SCC) is extremely aggressive and spreads systemically even at an early clinical stage.[1–3] The prognosis is poor.[2–5] Most patients die within 1 year, and effective therapy is still lacking.[4–8] Due to the similarity of biological characteristics of gastric and pulmonary SCC, chemotherapy regimens specific for pulmonary SCC have been proposed for treatment of gastric SCC, but the experience is still rare.[9–11] In this report, we present a patient with primary gastric SCC who underwent surgery and had remarkable response to the palliative chemotherapy specific for pulmonary SCC.

Case Report

A 44-year-old man was admitted to Taipei Veterans General Hospital on May 28, 2006 due to intermittent epigastralgia for 2 months. His past clinical history and family history were noncontributory. The physical examination was not remarkable. On admission, serum levels of α-fetoprotein, carcinoembryonic antigen and cancer antigen 19-9 were all normal.

Upper gastrointestinal endoscopy done at another local hospital revealed an ulcerative tumor, approximately 5 cm in diameter, located on the lesser curvature side of the cardia near the esophagogastric junction. The histological report revealed adenocarcinoma. Computed tomography (CT) revealed a mass over the

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lesser curvature and some enlarged locoregional lymph nodes. Chest CT did not detect any lung metastasis. Radical total gastrectomy, modified D2 lymph node dissection, Roux-en-Y esophagojejunostomy and splenectomy were performed on May 30, 2006. Intraoperative cytological examination of peritoneal washings was negative for malignancy. Macroscopically, the resected specimen showed an ulcerative tumor measuring 80 × 50 mm, with invasion to the esophagus (Figure 1). Microscopically, the tumor had hyperchromatic cells with little cytoplasm in a nest and sheet arrangement. The tumor invaded the gastric serosal layer. Lymphovascular tumor emboli and perineural invasion were also observed. Immunohistochemically, the tumor cells were positive for synaptophysin, chromogranin A, and CD56 (Figure 2). Primary gastric SCC was diagnosed. The AJCC (American Joint Committee on Cancer) stage was T3N2M0, stage IIIB.

The postoperative course was complicated by hypovolemic shock due to bleeding from the splenic artery, wound infection and intra-abdominal abscess. It took more than 2 months to overcome these episodes. Follow-up CT (Figures 3A and 3B) in August 2006 revealed multiple enlarged lymph nodes in the aortocaval region and hepatic hilum. The tumor extended along the liver surface, from the subphrenic region and falciform ligament to the right portal region and bare area. Chemotherapy consisting of cisplatin 80 mg/m^2 on day 1 combined with etoposide

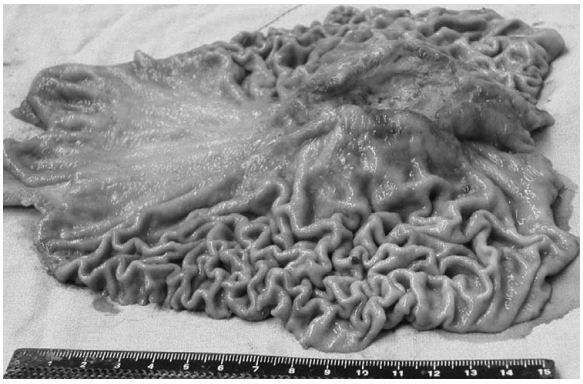

Figure 1. Macroscopic findings of the resected stomach: an ulcerative tumor measuring 80 × 50 mm, with invasion to the esophagus.

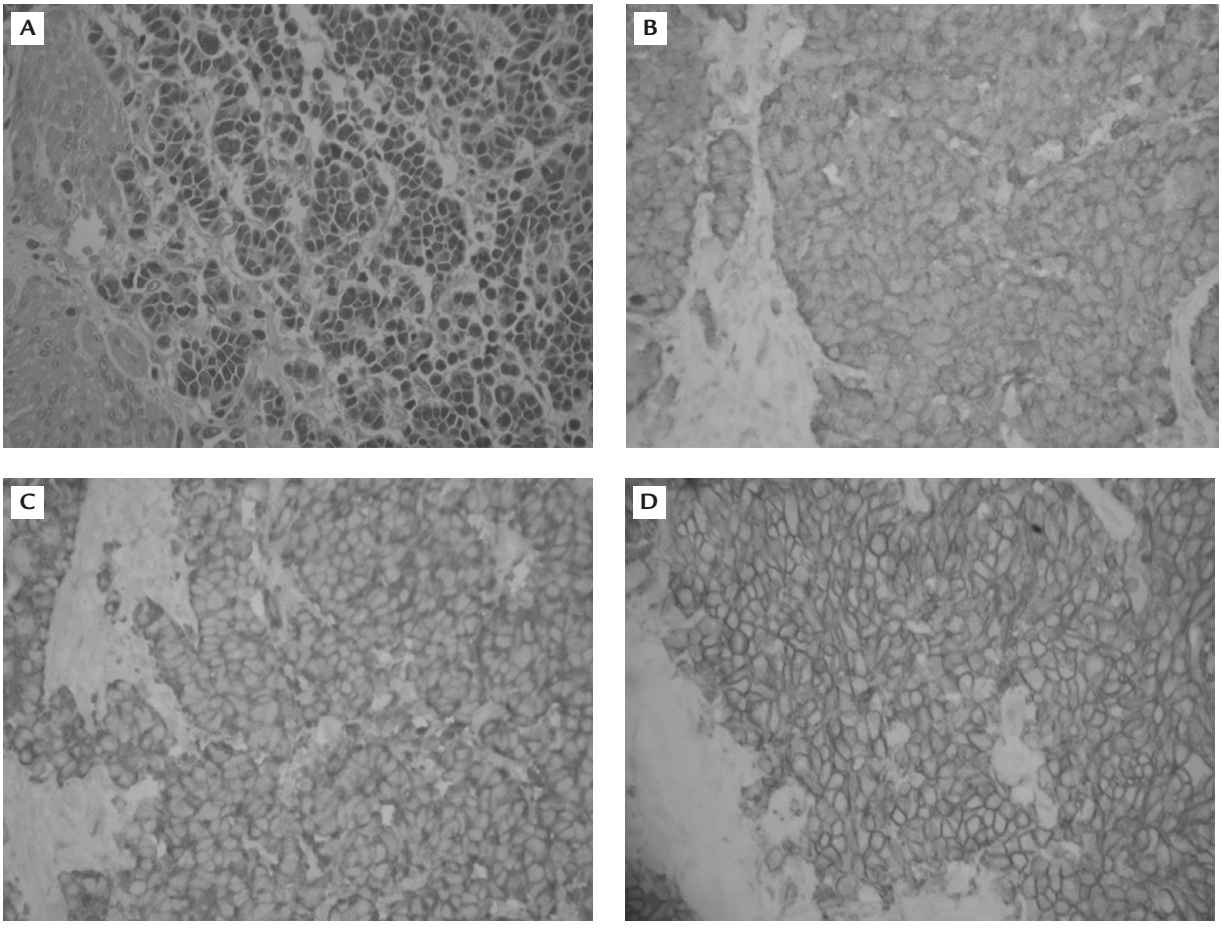

Figure 2. (A) Microscopic findings of the gastric tumor (hematoxylin & eosin, 400×). The tumor cells were also positive for: (B) CD56; (C) synaptophysin; (D) chromogranin A.

80 mg/m^2 on days 1–3 every 28 days for 12 courses was administered.[11]

CT scan (Figures 3C and 3D) in November 2006 revealed remarkable reduction of the tumor along the liver surface and of the lymph node metastases (partial response according to RECIST [Response Evaluation Criteria In Solid Tumors]). The chemotherapy was well tolerated, and no major toxicity was observed. The disease remained under control until CT in June 2007 revealed progression of lymph node metastases and peritoneal seeding. Second-line chemotherapy was given, with a regimen of intravenous ifosfamide at 1,000 mg/m^2 with equidose mesna as a 30-minute infusion, followed by 50 mg oral etoposide daily for 10 days.[12] Therapy was repeated every 3 weeks for 3 courses. The disease progressed relentlessly and the patient died in October 2007.

Discussion

Primary gastric SCC, first reported in 1976, is extremely rare and accounts for only 0.1% of all gastric carcinoma.[1] Even in all gastrointestinal SCC, gastric SCC represents only 11%.[13] Primary gastric SCC is also rare in Japan, where the incidence of gastric adenocarcinoma is much higher than in Western countries. Kusayanagi et al reviewed previous literature from 1976 to July 2001, which yielded only 37 cases.[6] Of them, 89% (33 cases) were Japanese and 11% (4 cases) were from Western countries.

The histological features of gastric SCC are similar to those of pulmonary SCC, demonstrating very scanty cytoplasm, small-sized oval nuclei, and multiple mitotic figures.[4] Microscopically, gastric SCC is divided into 2 types: a pure type and a composite type consisting of glandular and/or squamous differentiation.[7] The pure type was more common (60%) in previous reports.[5,6,8] Han et al hypothesized that the histologically different components of the composite type originated from the same progenitor cell, which was supported by *P53* and *K-ras* mutational analysis.[14]

Gastric SCC is difficult to diagnose preoperatively, as observed in this patient. Most patients are diagnosed as having undifferentiated adenocarcinoma, common types of gastric adenocarcinoma or even lymphoma

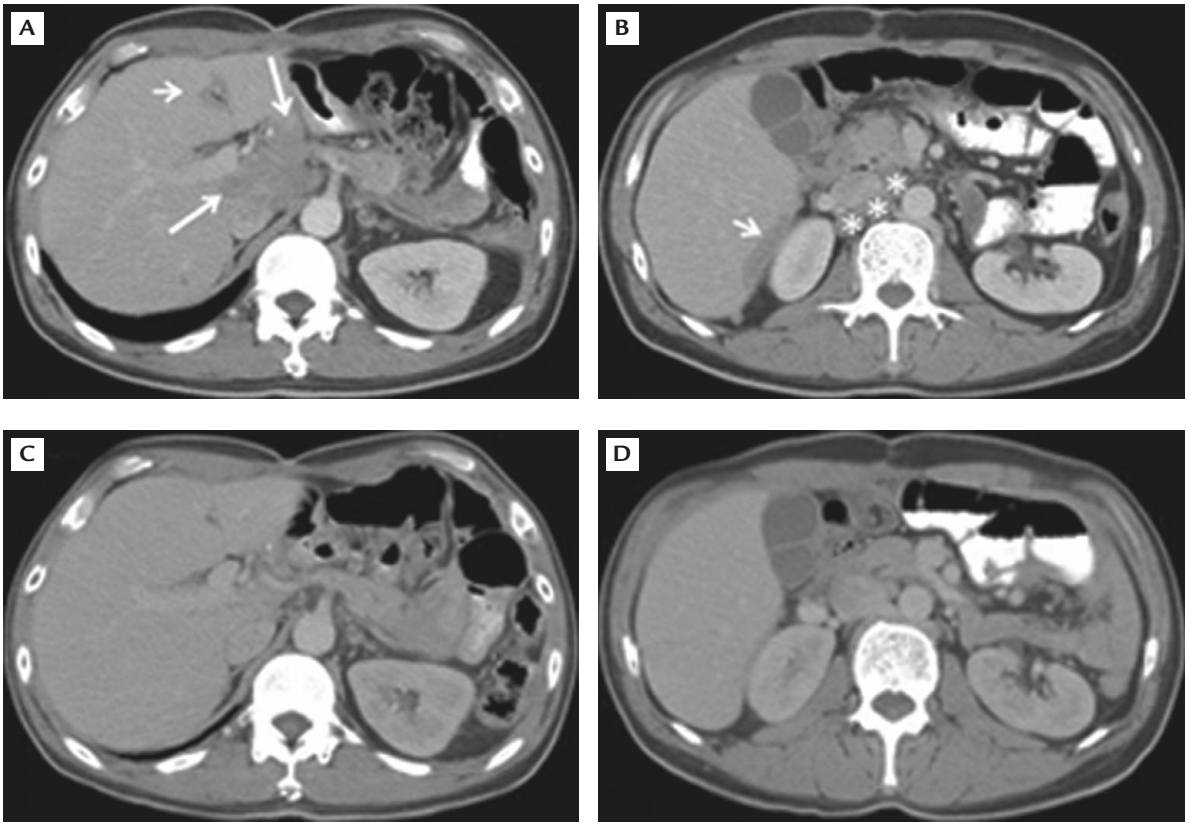

Figure 3. Abdominal computed tomography scans: (A, B) before and (C, D) 3 months after chemotherapy. (A) Hepatic hilar nodes (long arrows) and left hilar fissure node (short arrow). (B) Aortocaval and retrocaval nodes and tumor seeding over the right subhepatic region (arrow). (C) and (D) show remarkable reduction of the tumor along the liver surface and of the lymph node metastases.

until the pathology of the resected stomach demonstrates SCC.[4,6,15–17] In 1 study, only 40% of patients were diagnosed correctly before surgery.[6] The reasons may be that histological heterogeneity is common and biopsy specimens of mucosa tend to contain only normal tissue because SCC is located mainly in the submucosa. Immunohistochemical examination is very valuable for the diagnosis of gastric SCC. Gastric SCC, which shares immunohistochemical similarity with lung SCC, is distinct for its positive reaction to chromogranin-A, synaptophysin, neuron-specific enolase, CD56 and S-100 protein as well as presence of neurosecretory granules.[5,13,18]

Bone marrow biopsy is an important staging procedure for small cell lung cancer, and most authors also recommend using staging studies similar to pulmonary SCC for extrapulmonary SCC.[19] In this patient, the initial pathological report at another local hospital was adenocarcinoma. So bone marrow biopsy was not performed and the patient received surgery directly. Follow-up CT showed the tumor to be extensive disease, and further bone marrow biopsy was not performed.

Gastric SCC is as clinically aggressive as lung SCC and has a poor prognosis, with a median survival of 7 months.[2–5] When diagnosed, gastric SCC shows a high incidence of vasculolymphatic invasion, marked deep infiltration and distant metastases.[2,3] In 1 review, 63% (24/38) of patients died within 1 year of being diagnosed with gastric SCC.[6]

The standard treatment for gastric SCC has not been established. Operation and/or postoperative chemotherapy were used in most of the studies, but the results were not satisfactory.[3–4,16–18] Because of the similarity of clinical and biological characteristics shared by gastric and pulmonary SCC, O'Byrne et al reported that chemotherapy with cyclophosphamide, doxorubicin, and etoposide was effective,[9] while Shimada et al reported that TS-1 and cisplatin were useful,[10] as opposed to the conventional chemotherapy regimens such as 5-fluorouracil and mitomycin for gastric adenocarcinoma. The most commonly used combination chemotherapy regimen for patients with extensive-stage lung SCC is etoposide and cisplatin.[20] Futagami et al reported a case of gastric SCC with multiple liver and lung metastases who was successfully treated with cisplatin and etoposide.[11] Accordingly, we used chemotherapy with cisplatin 80 mg/m^2 on day 1 combined with etoposide 80 mg/m^2 on days 1–3 every 28 days. After 3 months of treatment, the reduction in metastases was remarkable and the disease was under good control for 10 months. The duration of response was 7 months, and progression-free survival was 10 months in this patient. According to previous reports, most patients die within 1 year of being diagnosed with gastric SCC,[2–8] while our patient survived for 17 months. The patient tolerated the chemotherapy well and no major side effects were observed. His quality of life was satisfactory.

In conclusion, although a standard treatment for gastric SCC has not been established, intensive chemotherapy should be considered to promote long-term survival, and chemotherapy with cisplatin and etoposide is effective in the treatment of primary gastric SCC. Larger trials are needed to further prove the efficacy of this regimen and to determine the best treatment for gastric SCC.

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