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Case report

A case of aggressive neuroendocrine carcinoma of the stomach

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Abstract

An 18 cm × 16 cm × 10 cm tumor of the stomach, invading the left lobe of the liver, pancreatic body and tail, and transverse colon, with peritoneal deposits on the major omentum, was resected by total gastrectomy plus left hepatic lobectomy, transverse colectomy, distal pancreatectomy, splenectomy, and omentectomy. Histopathologically, the tumor consisted of large uniform cells with significant nuclear atypia, showing solid growth patterns with occasional small nests without adenocarcinoma components. Immunohistochemical investigations of the neoplastic cells confirmed the tumor as a neuroendocrine (NE) carcinoma. Molecular analyses disclosed loss of heterozygosity at the *MEN1* gene locus on chromosome 11q13.

Recurrence occurred at the hepatic hilus and incurred obstructive jaundice 2 months after surgery. Following percutaneous transhepatic biliary drainage, intensive chemotherapy (20 mg/m^2 cisplatin on days 1–5 div, 100 mg/m^2 etoposide on days 1, 3, and 5 div, and 800 mg/m^2 5-fluorouracil on days 1–5 bolus iv) was started. The recurrent tumor shrank dramatically, and could not be detected on image modalities after five courses of chemotherapy. The patient was well and free of symptoms without biliary drainage for 5 months. Then he began to present with jaundice again, and died of acute massive dissemination 7 months after surgery.

An aggressive form of NE carcinoma has been known to be associated with an extremely poor prognosis. However, it is notable that treatment with extensive surgery and intensive chemotherapy could contribute to an improvement in quality of life even if the beneficial effect lasted for only half a year.

Key words Neuroendocrine carcinoma · Stomach · Chemotherapy · Loss of heterozygosity

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Introduction

Neuroendocrine (NE) carcinoma of the stomach is an uncommon tumor, usually associated with highly malignant biological behavior and extremely poor prognosis [1–3]. In this report, we describe a case of advanced gastric NE cancer treated with surgery and chemotherapy.

Case report

Clinical course

A 58-year-old Japanese man with no remarkable previous history and no familial history was admitted because of severe upper abdominal pain in May 2001. Upper alimentary tract endoscopy revealed an ulcerative lesion on the lesser curvature in the body of the stomach. Biopsy specimens revealed a poorly differentiated carcinoma composed of relatively large atypical cells without the formation of tubules or lobules.

Immunohistochemical staining suggested the presence of NE carcinoma. A barium meal study indicated a voluminous lesion on the lesser curvature of the gastric body (Fig. 1). Abdominal computed tomography (CT) showed a mass in the left upper abdominal cavity involving the lateral segment of the liver and the pancreatic body (Fig. 2). No pituitary lesion was shown on brain CT. Endocrinological studies, including measurements of serum gastrin, insulin, glucagon, somatostatin, ACTH, prolactin, and serotonin, did not reveal any abnormality.

The patient could not eat, and his severe abdominal pain persisted. With the patient's informed consent, surgery was performed in June, 2001, after the diagnosis of a sporadic NE carcinoma of the stomach. The tumor had invaded not only the liver and pancreas, as had been expected preoperatively, but also the spleen and

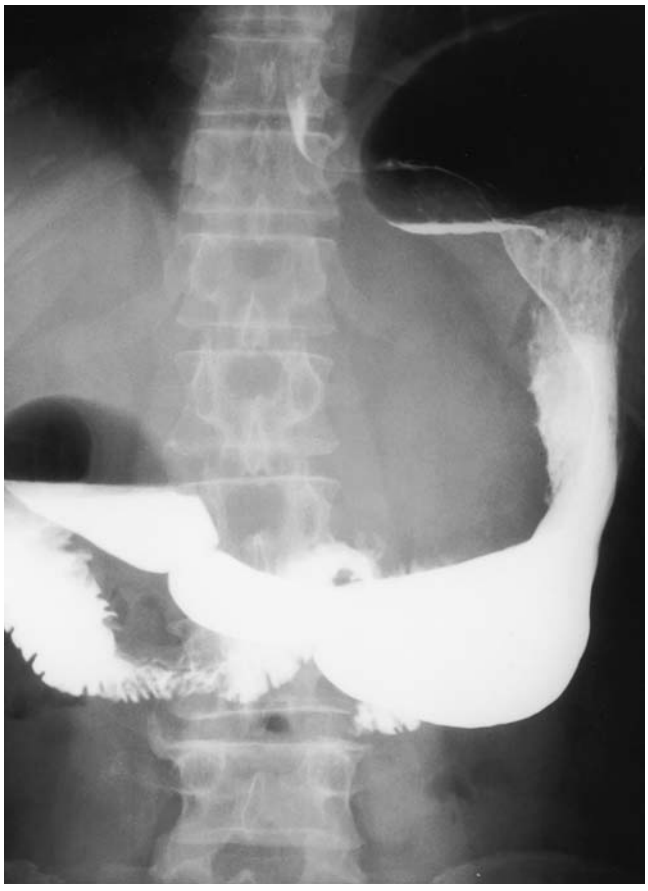

Fig. 1. Upper gastrointestinal radiograph with barium

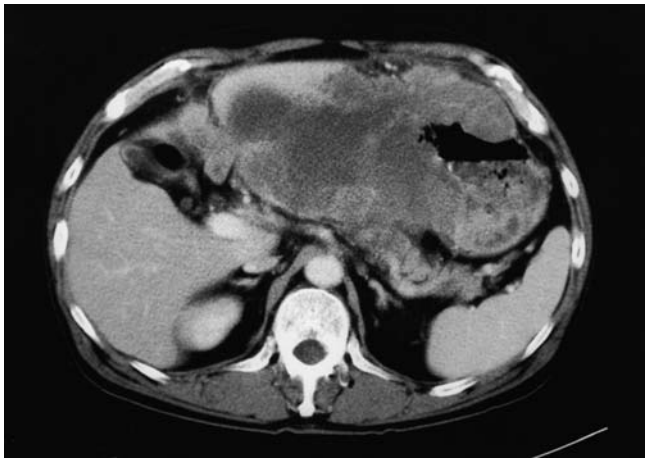

Fig. 2. CT scan, revealing a large gastric tumor invading the lateral segment of the liver and pancreatic body

transverse colon. Metastatic deposits on the omentum and cytological findings of malignant cells in ascites were also confirmed. Since it was technically feasible, palliative resection was chosen in the hope of attaining pain control and feeding per os. Total gastrectomy, left lobectomy of the liver, distal pancreatectomy, and splenectomy were performed. The resected specimen was 30 cm × 24 cm × 10 cm, and the gastric tumor was 18 cm × 16 cm × 10 cm (Fig. 3). Residual lesions were macroscopically negligible.

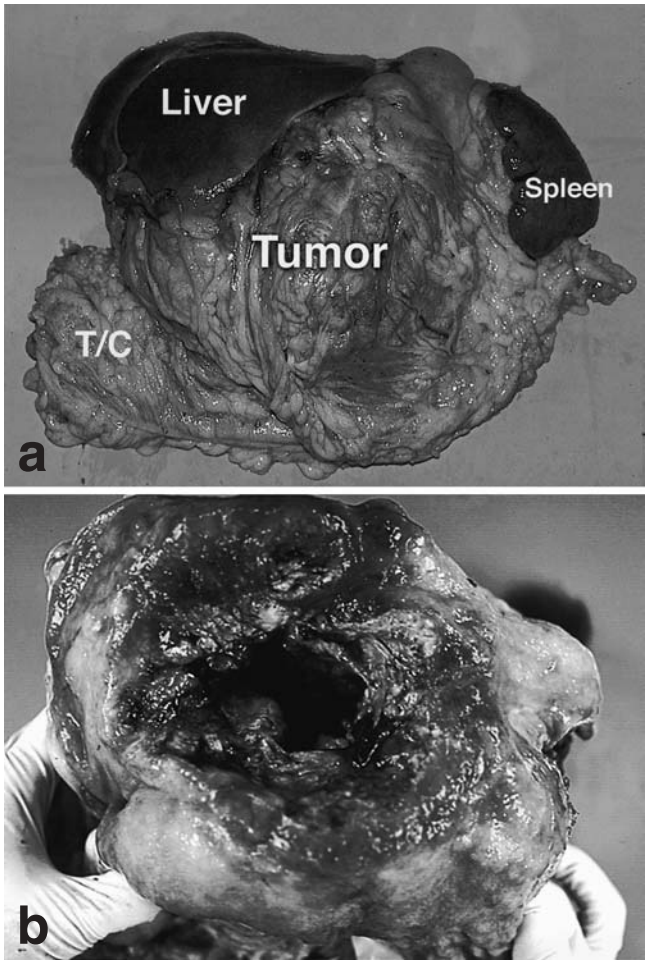

Fig. 3. Resected specimens. **a** Outer surface; **b** luminal aspect of the stomach. *T/C*, transverse colon

Two months after surgery, the patient presented with jaundice and a mass was detected at the hepatic hilus. After percutaneous transhepatic biliary drainage, intensive chemotherapy (20 mg/m^2 cisplatin on days 1–5 div, 100 mg/m^2 etoposide on days 1, 3, and 5 div, and 800 mg/m^2 5-fluorouracil on days 1–5 bolus iv) was started. After five courses of chemotherapy, the recurrent tumor shrank dramatuilly. The patient was discharged from the hospital with sufficient feeding per os, but he later began to present with jaundice again, and died of acute massive dissemination 7 months after surgery.

Histological findings

Histopathologically, the gastric tumor consisted of relatively large pleomorphic cells growing diffusely, without the formation of tubules or lobules (Fig. 4). The non-

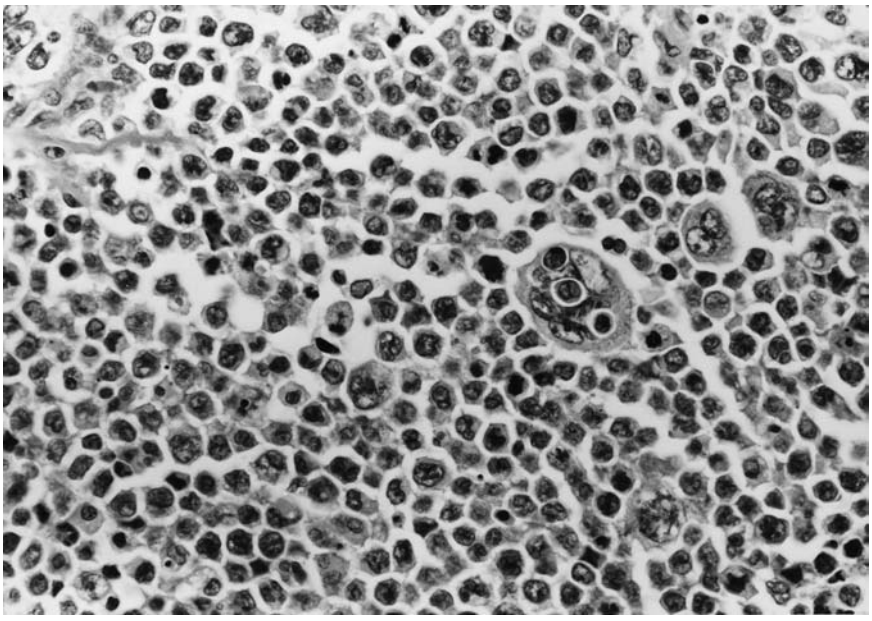

Fig. 4. Histological findings. The tumor consisted of relatively large pleomorphic cells growing diffusely without the formation of tubules or lobules. Hematoxylin–eosin staining

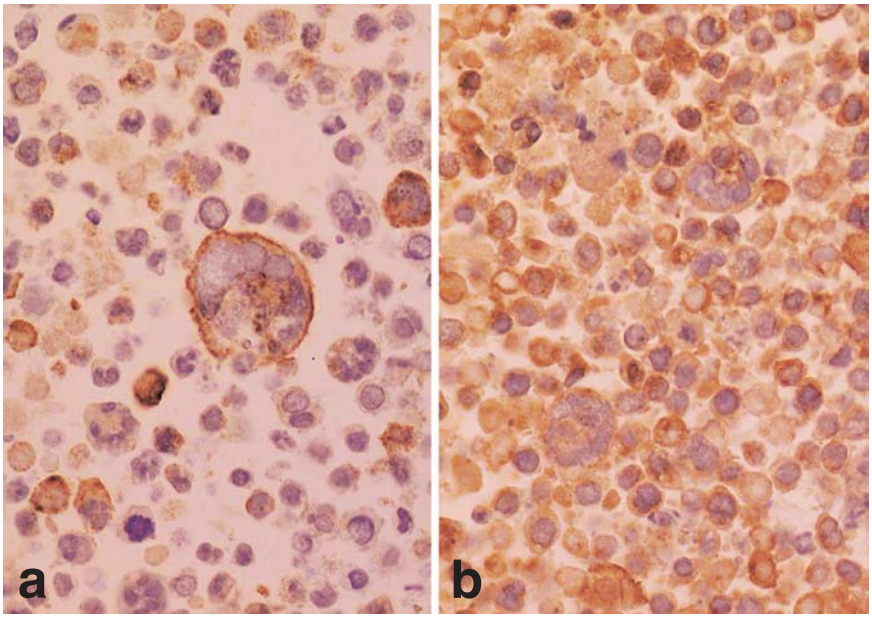

Fig. 5. Immunohistochemical staining for **a** chromogranine A, and **b** synaptophysin. The percentages of positive cells for chromogranin and synaptophysin were approximately 40% and 80%, respectively

cancerous gastric mucosa was not accompanied by chronic atrophic gastritis (CAG) or type A gastritis.

Immunohistochemical staining was positive for chromogranine A, synaptophysin, AE1/AE3, CAM5.2, KL1, CD56, and p53, and negative for epithelial membrane antigen (EMA), lymphocyte antigens (LCA), vimentin, and HCG (Fig. 5). Cell proliferation marker Ki67 was rated as over 50%. From these findings, we diagnosed the tumor as a NE carcinoma of the non-small-cell type.

Molecular investigations

After the diagnosis of NE carcinoma, we further attempted to elucidate the molecular basis of tumorigenesis in terms of multiple endocrine neoplasia (MEN).

After the approval of the Ethics Committee of Jichi Medical School for genetic investigations and the informed consent of the patient, we investigated the presence or absence of germline *MEN1* gene mutation. The entire *MEN1* coding region (exons 2–10) was amplified

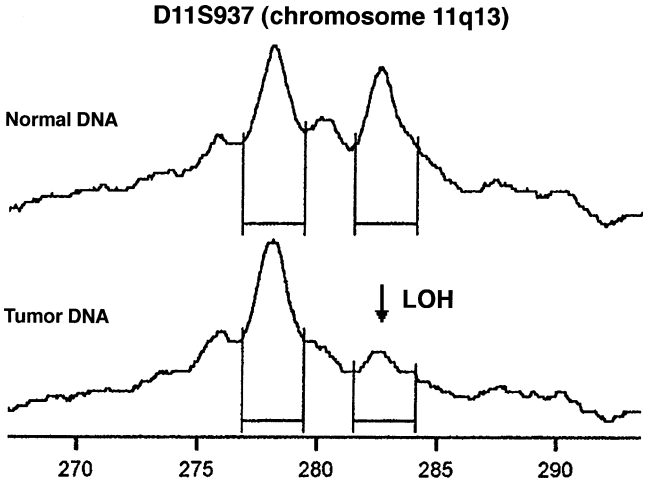

Fig. 6. LOH analysis showing allelic loss at locus D11S937

from genomic DNA by polymerase chain reaction, and was subjected to direct sequencing analysis on an ABI 3100 Genetic Analyzer (PE Applied Biosystems, Foster City, CA, USA). DNA extracted from peripheral blood cells and the tumor of the patient was analyzed for allelic loss using a polymorphic microsatellite marker (D11S937) flanking the *MEN1* gene on chromosome 11q13. No abnormality was found in the peripheral blood cells, but allelic loss was detected at the D11S937 loci in the tumor (Fig. 6).

Discussion

In recent years, gastric NE tumors have been classified into four subgroups, mainly based upon their clinicopathological features [1,2]. Type I histologically mimics a classical carcinoid tumor of the gastrointestinal tract, possibly arises in type A gastritis or autoimmune gastritis, usually represents small and multiple neoplasms, and has an excellent prognosis after resection, even though there are exceptions [4,5]. Type II, which is histologically similar to type I, is usually associated with MEN1, especially with Zollinger–Ellison syndrome [6,7]. The prognosis of this type is generally good, even though there are occasional exceptions [8]. Type III is a solitary sporadic carcinoid, quite often infiltrating the muscularis propria and the serosa. Distant metastasis is frequent, resulting in a poor prognosis [9]. Type IV is an uncommon tumor, usually single, large, poorly differentiated, and highly malignant, with an extremely poor prognosis [1–3,10]. Mean survival rates of 6.5–14.9 months have been reported [9,10].

The present case of an extremely large NE cancer of the stomach apparently belonged to Type IV. Rindi et al. [9] reported a poorly differentiated NE carcinoma of 4.2 cm (range 1.5–7.0 cm) in mean diameter. According to Matsui et al. [3], the average size of 33 NE carcinomas was 6.4 cm (range 2.0–14 cm). The largest known NE carcinoma was reported by Bordi et al. [8] to be 16 cm. The present tumor seems to be the largest ever reported.

Even with such an extensive growth on preoperative imaging and an extremely miserable prospect for treatment, we resorted to aggressive, but technically feasible, surgery after obtaining informed consent from the patient. Chemotherapy was added immediately after recurrence. Moertel et al. [11] reported that 18 patients with NE carcinomas (small and large bowel, pancreas, and stomach) were treated with a regimen of etoposide, 130 mg/m^2/day, for 3 days, plus cisplatin 45 mg/m^2/day on days 2 and 3. This regimen achieved an overall regression rate of 67%, and a median survival of 19 months. Thus, the combined chemotherapy seems to be effective to a certain degree. Nonetheless, the toxicity of the regimen in the previous reports could not be ignored.

Ryoo et al. [12] conducted a pilot study to evaluate the safety and possible efficacy of adjuvant chemotherapy with cisplatin, etoposide, and 5-fluorouracil (PEF) after curative resection of gastric adenocarcinoma involving the esophagogastric junction. Three cycles of adjuvant PEF chemotherapy with cisplatin (20 mg/m^2/day iv on days 1–5), etoposide (100 mg/m^2/day iv on days 1, 3, and 5), and 5-fluorouracil (800 mg/m^2/day div on days 1–5) were given every 3 weeks after curative resection. The toxicities after PEF were reported to be tolerable. We applied this regimen to the present case of aggressive NE carcinoma of the stomach. The disappearance of the recurrent tumor and no severe side effects may suggest the feasibility of PEF for aggressive NE carcinoma. Thus, treatment with extensive surgery and intensive chemotherapy could contribute to an improvement in the quality of life even for a patient with extremely poor prognosis. Nonetheless, the effect of chemotherapy was temporary in our case.

As for tumorigenesis, loss of heterozygosity (LOH) at the *MEN1* locus, commonly found in type II gastric carcinoid tumors, is known to play an important role in tumorigenesis [7]. In contrast, information has been scanty for other types of NE tumors [13]. D'Adda et al. [14] reported that LOH on 11q13–14 was found in some sporadic gastric carcinoids: 52% (13/25) in type I, 25% (1/4) in type III, and 100% (2/2) in type IV (NE carcinoma). The relatively low rate of LOH in type III suggests the presence of different genetic mechanisms in this subgroup, whereas the high incidence in types I and IV may be more closely associated with the *MEN1* gene and/or a more telomeic tumor suppressor gene in the pathogenesis of these sporadic NE tumors. The present case also seems to imply the involvement of *MEN1* in its tumorigenesis. Han et al. [15] reported that a high rate

of LOH on chromosomes 8p suggests the possible presence of tumor suppressor genes associated with the development of gastric NE tumors. Therefore, LOH in 11q13 is not exclusive to gastric NE tumors. More research is mandatory to elucidate the role of allelic loss in the tumorigenesis and clinical features of NE tumors.

In conclusion, we have documented an advanced NE carcinoma of the stomach managed with extended surgery and intensive chemotherapy.

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