Case Report

Alpha Fetoprotein Producing Early Gastric Cancer with Metachronous Liver Metastasis—A Report of Two Cases—

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AFP-producing early gastric cancer is extremely rare, and its characteristics and prognosis have not yet been clarified. We report two cases of AFP-producing early gastric cancer with metachronous multiple liver metastases after curative resection.

Case 1 : A 53-year-old woman with epigastralgia was found to have a depressive lesion in the middle portion of the stomach by gastroendoscopy. The preoperative serum level of AFP was 32 ng/ml. Pylorus-preserving gastrectomy with D1 lymph node dissection was performed. The resected specimen showed a depressive tumor of 18×14 mm with histological findings of p0, sm, n0 and positive for AFP staining. Ten months later, the serum AFP level elevated to 70,520 ng/ml, and liver metastasis was identified. In spite of liver resection, and chemotherapy, she died 22 months after the first operation.

Case 2 : A 52-year-old man with epigastralgia was found to have a depressive lesion in the lower third portion of the stomach by gastroendoscopy. The preoperative serum level of AFP was 332 ng/ml. Distal gastrectomy with D2 lymph node dissection was performed. The resected specimen showed a depressive lesion surrounded by slight elevation of 27×18 mm. Histological findings were p0, sm, n0 and reactive for AFP staining. An elevated serum AFP level (620 ng/ml) and multiple liver metastases were detected by abdominal CT seven months later and he died 16 months after surgery.

We must keep in mind the high malignant potential of AFP-producing early gastric cancer, and should observe patients carefully using echogram, CT and the serum AFP level.

Key Words : liver metastasis, early gastric cancer, AFP-producing gastric cancer

Introduction

Alpha fetoprotein (AFP), a glycoprotein normally produced by the fetal liver and yolk sac, was initially considered a specific tumor marker for hepatocellular carcinoma and yolk sac tumor. With the advent of a more sensitive radioimmunoassay, AFP was frequently found in gastrointestinal malignancies, with gastric cancer being the most common. Since AFP-producing gastric cancer was first described in 1970¹⁾, case reports have increased as the AFP

assay is commonly performed. The most reported cases are advanced cancers at the time of presentation, and AFP-producing early gastric cancer is extremely rare. AFP-producing gastric cancer has been reported as having aggressive behavior and a poor prognosis, however, the characteristics of patients with AFP non-producing early gastric cancer have not yet been clarified. We herein report two cases of AFP-producing early gastric cancer that died of metachronous multiple liver metastases after curative resection.

Case Report

Case 1: A 53-year-old woman with epigastralgia consulted a hospital and early gastric cancer was detected by gastroendoscopy. She was admitted to the Second Department of Surgery, Gifu University School of Medicine Hospital for surgical treatment on January 5, 1998. On admission, her physical condition was good and a blood examination revealed no liver dysfunction except an abnormal serum AFP value of 32 ng/ml. Other tumor markers, such as CEA and CA19-9 were within the normal range. Gastroendoscopy revealed a small-sized depressive lesion in the middle portion of the stomach, and a biopsy specimen revealed moderately differentiated tubular adenocarcinoma. The findings of the tumor were described in accordance with the General Rules for Gastric Cancer Study and Pathology²⁾. With a diagnosis of early gastric cancer with elevated serum AFP level, she underwent pylorus-preserving gastrectomy with D1 lymph node dissection. The resected specimen revealed a slight depression (IIc), 18×14 mm in size, in the middle portion (Fig. 1). Microscopically, the tumor was composed of poorly differentiated adenocarcinoma and moderately differentiated tubular adenocarcinoma, but partially

contained a yolk sac tumor-like area showing a loose vacuolated network with meshes or cystic spaces and a labyrinthine structure (Fig. 2a, b).

Fig. 1 Resected specimen showed a slightly depressive lesion of 18×14 mm in the middle portion of the stomach (↑).

Fig. 2 a) Photomicrograph showing a tumor with submucosal invasion mainly composed of poorly differentiated adenocarcinoma and moderately differentiated tubular adenocarcinoma (HE×20). b) The tumor partially contained a yolk sac tumor-like area showing a loose vacuolated network with meshes or cystic spaces and a labyrinthine structure (HE×400). c) The tumor cells were reactive for AFP staining (AFP×40).

a
b
c

Fig. 3 The resected specimen showed a depressive lesion surrounded by slight elevation (IIa+IIc), 27×18 mm, in the lower third portion of the stomach (↑).

Tumor invasion was limited to the submucosal layer, but a moderate degree of venous involvement was observed. There was no lymph node involvement. An immunohistological study indicated positive reactivity for AFP (Fig. 2c). The postoperative clinical course was uneventful for 10 months; however, when she visited our institute again, the serum AFP, which had decreased to the normal range after surgery, had again increased to an extremely high level (70,520 ng/ml) and abdominal CT revealed two metastatic lesions in the lateral lobe of the liver. Lateral segmentectomy was performed and the remnant stomach removed. In spite of surgery, metastases appeared in the liver, lung and paraaortic lymph nodes in a short period, and she died 22 months after the first operation.

Case 2: A 52-year-old man with epigastral-gia consulted the First Department of Medicine of Gifu University Hospital. As early gastric cancer was detected by gastroendoscopy, he was referred to our surgical department on June 8, 1984. On admission, physical and laboratory examinations showed no abnormal findings except for a high serum level of AFP (86 ng/ml). Upper gastrointestinal series and gastroendoscopy revealed a superficial elevated

Fig. 4 a) The tumor was mainly composed of medullary - growing poorly differentiated adenocarcinoma with clear cytoplasm and large bizarre nuclei, invading the submucosal layer (HE×10). b) In some areas, tumor cells with an abundant eosinophilic cytoplasm proliferated in a solid or trabecular fashion (hepatoid pattern) (HE×200). c) The tumor cells were reactive for AFP staining (AFP×100).

a
b
c

lesion with central depression in the lower third portion. Pathological diagnosis from the biopsy specimen was poorly differentiated adenocar-

cinoma. Distal gastrectomy with D2 lymph node dissection was performed under the diagnosis of early gastric cancer with a high serum level of AFP. The resected specimen showed a depressive lesion surrounded by slight elevation (IIa+IIc), 27×18 mm in size in the lower third portion (Fig. 3). Microscopically, the tumor was mainly composed of medullary-growing poorly differentiated adenocarcinoma with clear cytoplasm and large bizarre nuclei, invading the submucosal layer (Fig. 4a). In some areas, tumor cells with abundant eosinophilic cytoplasm proliferated in a solid or trabecular fashion (hepatoid pattern) (Fig. 4b). Remarkable venous and lymphatic involvement was detected, but there was no lymph node involvement. The tumor cells were strongly reactive for AFP by immunohistochemical study (Fig. 4c). This case was conclusively determined as T1 (sm) N0 M0 stage, an early cancer producing AFP. The postoperative course was uneventful for 6 months, but the serum AFP level elevated to 620 ng/ml and CT and echogram revealed multiple liver metastases. In spite of intra-arterial infusion chemotherapy with 5-FU, Adriamycin and Mitomycin C, he died from progressive liver dysfunction from the rapid growth of metastatic tumors 6 months after surgery.

Discussion

AFP was previously considered a specific marker for hepatoma, but as the sensitivity of the serum AFP assay has improved, case reports of cancer in other organs have been increasing. Bourreille et al.¹⁾ first reported a case of serum AFP-positive gastric cancer in 1970. Okita et al.³⁾ revealed the presence of AFP in gastric cancer cells by immunofluorescence technique and, since then, the concept of AFP-producing gastric cancer has been developing. The incidence of AFP-producing gastric

cancer has been reported as ranging from 1.3% to 15%⁴⁾⁻⁶⁾. In most cases, tumors are detected in an advanced condition, and cases with early cancers are extremely rare.

However, the definition of AFP-producing gastric cancer has not yet been clearly established. Takahashi et al.⁶⁾ listed three conditions: a) high level of serum AFP changing in parallel with the extent of the illness, b) positive reactivity for AFP immunohistochemical staining, and c) AFP staining in cancer tissue grafted to a nude mouse. Murakami et al.⁷⁾ reported that criteria a) and b) were essential. He demonstrated that the level of serum AFP and immunohistochemical reactivity are not always correlated. According to our study, of 16 cases with a high serum AFP value without liver disease, 13 cases were positive and 3 cases had negative immunohistochemistry in spite of a decreased serum AFP level after gastrectomy⁸⁾. Kubo et al.⁹⁾ reported such patients with a high level of AFP, changing in parallel with the extent of the illness, as having AFP-producing gastric cancer unless the existence of AFP in the cancer cells was confirmed. This discrepancy seems to be due to the heterogeneity of gastric cancer.

Some reports⁴⁾⁵⁾⁻¹⁰⁾ have demonstrated that AFP-producing gastric cancer is associated with a poor prognosis due to the high incidence of lymphatic and venous microinvasion in the gastric wall, and the high frequency of synchronous and metachronous liver metastasis. Consequently, the survival rate for patients with AFP-producing gastric cancer is significantly poorer than for the AFP-negative group. According to the analysis of 19 cases in our department, the same phenomena, such as poor prognosis and a high incidence of liver metastasis, were observed. Regarding AFP-producing early gastric cancer, Tsurumachi¹¹⁾ analyzed 23 cases and reported as follows: the

majority of patients were male (16 of 23), ranging in age from 48 to 78 years. The serum AFP level ranged from 16 to 245,600 ng/ml and 13 of 21 cases (62%) were macroscopically IIa+IIc type.

Eight of 21 cases (43.5%) showed liver metastasis within 2 years post-surgery, and the mortality was very high (8/21, 38.1%). In our cases, the preoperative serum AFP levels were 32 ng/ml, and 332 ng/ml, and the macroscopical types were IIc, IIa+IIc, respectively. Both cases had venous microinvasion in the gastric wall, and showed multiple liver metastases within one year following marked elevation of the serum AFP level.

In contrast to the excellent prognosis of patients with early gastric cancer, the mortality rate of patients with AFP-producing gastric cancer is significantly poor, 66.7% (2/3) in our department. In a comparison of characteristics, YC Chang et al.⁵⁾ showed the possibility that, even with the same degree of lymphatic or venous invasion, AFP-producing early gastric cancer has a stronger tendency to metastasize to the liver. Kono et al.¹⁰⁾ demonstrated its highly malignant characteristics from the point of the higher frequency of high c-Met expression. We found that AFP-positive tumors showed a higher labeling index of proliferating cell nuclear antigen than AFP-negative tumors (44.1 vs. 63.9)⁸⁾.

Histopathologically, the typical features of AFP-producing gastric cancer are undifferentiated cancer cells with clear or eosinophilic, abundant cytoplasm and pleomorphic large round nuclei, indicated as "hepatoid adenocarcinoma" by Ishikura¹²⁾. However, Ooi et al.¹³⁾ showed that AFP-producing gastric cancer is not always derived from hepatoid differentiation of the foregut, but sometimes from poorly differentiated solid medullary components. Motoyama¹⁴⁾ proposed that AFP-producing

gastric cancer should be divided into three subtypes: (i) hepatoid type, (ii) yolk sac tumor-like type, and (iii) fetal gastrointestinal type. Case 1 showed a small area of yolk sac tumor-like appearance in the poorly differentiated medullary component, and Case 2 demonstrated a hepatoid appearance in the poorly differentiated medullary component.

Generally, adjuvant chemotherapy is not necessary for patients with early gastric cancer, but it must be performed for patients with AFP-producing gastric cancer, considering the poor prognosis of these cases. However, good regimens of adjuvant chemotherapy for AFP-producing gastric cancer have not yet been established. Some authors¹⁵⁾¹⁶⁾ have published case reports showing the efficacy of chemotherapy with combinations of etoposide, adriamycin and cisplatin (EAP), and the combination of cisplatin and 5-FU. These combinations are candidates for the recommended regimen of adjuvant chemotherapy for AFP-producing gastric cancer.

Early gastric cancer is generally considered to have a favorable prognosis, but we must consider the special characteristics of AFP-producing early gastric cancer, such as the high frequency of liver metastasis and the poor prognosis. Patients should therefore be carefully observed for the early detection of liver metastasis by echogram and CT, as well as serum AFP monitoring as a follow-up marker.

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