Surg Today (2007) 37:995–999
DOI 10.1007/s00595-007-3501-0

SURGERY TODAY

Alpha-Fetoprotein-Producing Early Gastric Cancer of the Remnant Stomach: Report of a Case

YUTAKA SHIBATA[1], KOUHEI SATO[1], MASASHI KODAMA[1], and HIROSHI NANJYO[2]

[1]Department of Surgery, Kotou General Hospital, 37 Kawasaki, Hachirogata-machi, Minamiakita-gun, Akita 018-1605, Japan
[2]Division of Clinical Pathology, School of Medicine, Akita University, Akita, Japan

Abstract
A 67-year-old man initially underwent a distal gastrectomy for early gastric cancer (T1, N0, M0; Stage IA) in March 1995. During the follow-up period, an elevation of the serum α-fetoprotein (AFP) level (98.8 ng/ml) and a liver tumor (S4) were detected. A left hepatectomy was performed in December 1996. Immunohistochemically, AFP-positive cells were present in both the primary gastric tumor and metastasized liver tumor. The serum AFP level normalized immediately, but it elevated again to 22.4 ng/ml. An endoscopic examination revealed a protruding lesion in the remnant stomach. A total resection of the remnant stomach was performed in February 2005. The tumor was evaluated T1, N0, M0; Stage IA, with positive staining for AFP. The patient has survived without any sign of recurrence for more than 11 years after the first diagnosis of cancer. To the best of our knowledge, this is the first case of a long-term survival of AFP-producing gastric cancer with successfully resected metachronous liver metastasis and gastric remnant carcinoma.

Key words α-Fetoprotein-producing early gastric cancer · Recurrence · Long-term survival

Introduction

α-Fetoprotein (AFP)-producing gastric carcinoma is a relatively rare malignant neoplasm of the stomach that accounts for approximately 2.7%–8.0% of all gastric malignant tumors.[1–3] The prognosis of AFP-producing gastric cancer has been reported to be very poor due to the high incidence of liver metastasis which accounts for 33%–72% of all cases.[1–4] Although the tumor is an early gastric cancer, AFP-producing gastric cancer tends to show liver metastasis, blood vessel invasion, or lymphatic vessel invasion, and it also often recurs in the liver after surgery.[5–8] Some authors have reported that AFP-producing gastric cancer showed an aggressive clinical behavior and a low 5-year survival rate, in comparison with ordinary gastric cancers.[1,2] There have so far been very few reports of a long survival with metastasis from AFP-producing gastric cancer.[9,10] We herein describe the rare case of a patient with long-term survival after undergoing resections of metachronous liver metastasis and gastric remnant carcinoma from an AFP-producing early gastric cancer.

Reprint requests to: Y. Shibata
Received: November 8, 2006 / Accepted: February 21, 2007

Case Report

A 67-year-old man initially underwent a distal gastrectomy with lymph node dissection, and Billroth-I reconstruction for an early gastric cancer on March 1995. The resected specimen showed a depressive lesion surrounded by slight elevation (IIc + IIa), 27 × 15 mm, located on the anterior wall of the lower part of the stomach. Microscopically, the tumor was a moderately differentiated adenocarcinoma massively invading to the submucosal layer, with severe venous invasion, and no lymph node metastasis (Fig. 1a). No evidence of liver metastasis was detected by preoperative computed tomography (CT) findings and an intraoperative exploration.

At the follow-up examination 18 months after surgery, the serum AFP level increased gradually to 98.8 ng/ml (Fig. 2), and a liver tumor was subsequently detected at segment 4 (S4) by abdominal CT. An examination was performed to determine whether the liver tumor was a primary hepatocellular carcinoma or metastasis from an early gastric cancer. Selective hepatic angiography showed a homogeneously stained hypervascular tumor in S4 (Fig. 3a). Computed tomography showed a tumor

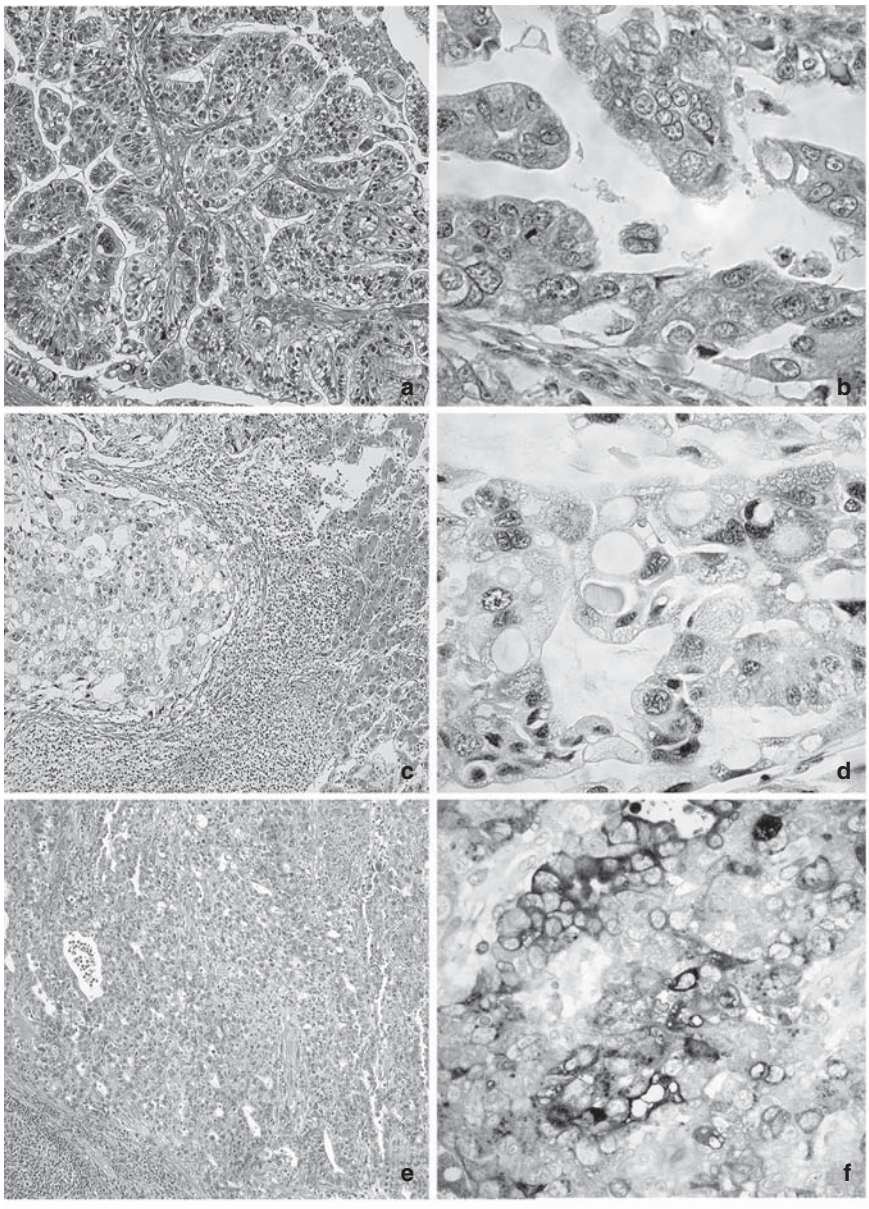

Fig. 1. Histological findings of the primary gastric cancer (**a,b**), the metastatic liver tumor (**c,d**), and the gastric remnant tumor (**e,f**). Hematoxylin–eosin staining (×10) (**a,c,e**) and positive immunostaining for α-fetoprotein (×40) (**b,d,f**)

enhanced by contrast medium. These findings were compatible with hepatocellular carcinoma, but he had no serologic evidence of either a hepatitis B or C virus infection and his liver function was normal. Under a provisional diagnosis of a liver tumor, thought to be a hepatocellular carcinoma, a left hepatectomy was performed on December 1996. The resected specimen contained a well-defined tumor, measuring 35 × 35 mm, and no cirrhotic change (Fig. 3b). A histological examination revealed the tumor to be a moderately differentiated adenocarcinoma and it was metastasis from an early gastric cancer (Fig. 1c). Furthermore, the tumor cells in the both primary gastric and metastatic lesions were immunohistochemically positive for AFP (Fig. 1b,d). The patient's serum AFP level had been elevated at 281.5 ng/ml before hepatectomy, but decreased to 11.8 ng/ml postoperatively (Fig. 2). A definite clinical diagnosis of liver metastasis from AFP-gastric cancer was established based on the patient's preoperative high levels of serum AFP and an immunohistochemical examination of the tumors. According to his request, he had been treated with Uracil-ftorafur (600 mg/day) oral administration for about 3 years postoperatively, without transarterial infusion chemotherapy.

During a follow-up examination at 8 years after a left hepatectomy, the serum AFP level became elevated again to 22.4 ng/ml in December 2004 (Fig. 2). An upper gastrointestinal series and endoscopy showed a protrud-

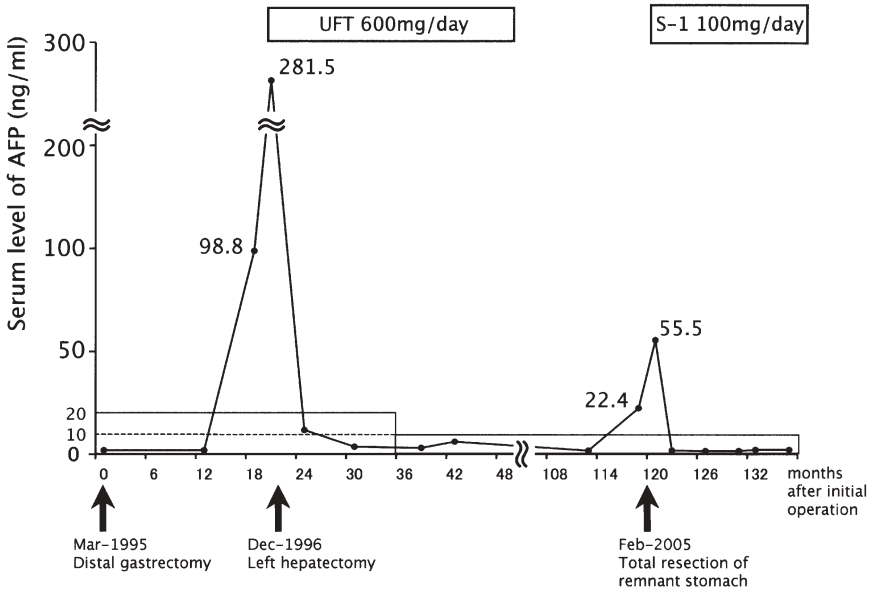

Fig. 2. Clinical course and changes in the serum level of α-fetoprotein (*AFP*). Normal AFP level: <20 ng/ml (0–36 months after initial operation), <10 ng/ml (over 36 months after initial operation). *UFT*, Uracil-ftorafur; *S-1*, tegafur–gimeracil–oteracil potassium

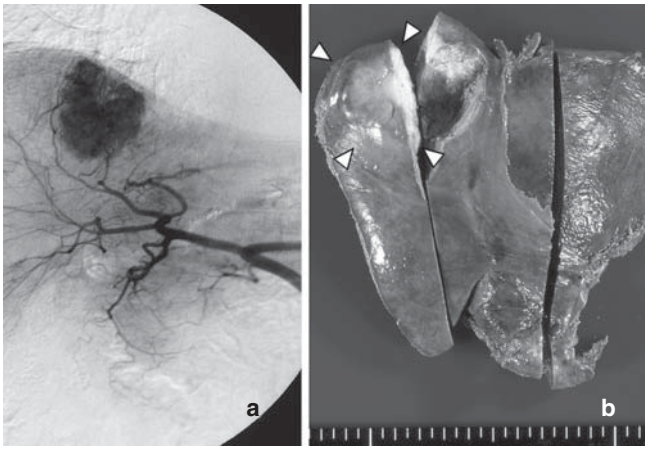

Fig. 3. a Selective hepatic angiography showing a homogeneously stained hypervascular tumor in S4. **b** Gross appearance of the primary tumor showed a size of 35 × 35 mm in diameter (*arrowheads*)

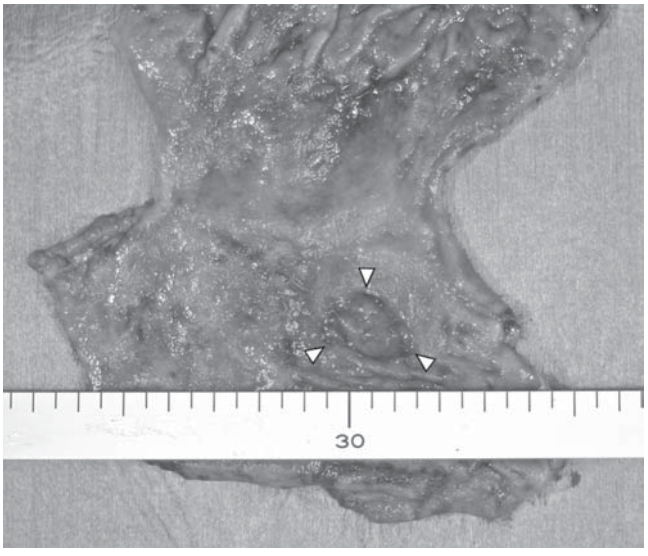

Fig. 4. A macroscopic view showing a protruding lesion, measuring about 25 × 20 mm in diameter, in the posterior wall of the remnant stomach (*arrowheads*)

ing lesion, about 25 mm in diameter, at the posterior wall of lesser curvature on the gastric remnant. There was no apparent finding of distant metastasis. A total resection of the remnant stomach including perigastric lymph node dissection was performed in February 2005. Macroscopically, an elevated tumor measuring 25 × 20 mm was seen in the posterior wall of the remnant stomach (Fig. 4). A microscopic examination revealed poorly differentiated adenocarcinoma invading no deeper than the submucosal layer, with positive staining for AFP (Fig. 1e,f). The final diagnosis was SM2, por, ly1, v3, N0; Stage Ia. The postoperative course was uneventful and the serum AFP level normalized immediately after the operation. The patient has been treated orally with S-1 (tegafur–gimeracil–oteracil potassium) (100 mg/day). For more than 11 years after the initial operation, there has been no sign of recurrence, and his serum AFP level has also remained within the normal range.

Discussion

α-Fetoprotein-producing gastric cancers are relatively rare lesions, which account for approximately 2.7%–

8.0% of all gastric tumors.[1–3] In recent years, case reports of AFP-producing gastric cancer have been increasing, however, many cases of AFP-producing gastric cancer are advanced stages and the prognosis is poor.[1–4] The 5-year survival rate post curative resection has been reported to be only 8.3%.[1] Adachi et al. examined 270 cases of AFP-producing gastric cancer reported in the Japanese literature and showed the overall 5-year survival rate after a gastrectomy to be 22%, and median survival period was only 14 months.[4] According to some reports, AFP-producing gastric cancers have higher malignant potential (high proliferative activity, weak apoptosis, rich neovascularization, and higher frequency of c-Met expression) compared to AFP-negative gastric cancers.[11,12] These biological characteristics of AFP-producing gastric cancer might be one explanation for the poorer prognosis while also reflecting its aggressive behavior.

Even if the tumor is an early-stage gastric cancer, AFP-producing gastric cancer has a tendency to cause liver metastasis, lymph node metastasis, and lymphatic and venous invasion of the gastric wall.[5–8] It is generally considered that the prognosis of AFP-producing gastric cancer is poor because of frequent liver metastasis.[1–4] Metastatic liver tumors from AFP-producing gastric cancer cannot be resected curatively in the majority of cases due to the multiplicity of metastases.[2,5,7,8] Few cases of resected liver metastasis from gastric cancer have been reported.[6,10,13] The interval of metachronous liver metastasis was shorter in AFP-producing gastric cancer,[1] thus suggesting that AFP-producing gastric carcinomas have a highly aggressive nature. Chang et al. have reported, even if no metastasis is present preoperatively, that liver metastasis can occur within a year after surgery,[5] as well as in our case. In our patient, liver metastasis occurred within a relatively short period after an initial gastrectomy. It is likely that a curative resection of primary lesion and early detection of solitary liver metastasis caused a good outcome in our patient. Furthermore, liver metastasis and remnant gastric recurrence were detected first by the elevation of his serum AFP level prior to the appearance of the symptom and image detection. The serum AFP levels are generally understood to elevate in association with recurrence except in a rare case.[14] Therefore, patients with AFP-producing gastric cancer should be carefully observed for the early detection and treatment of possible recurrent disease by measuring the serum AFP levels as a follow-up marker.

Gastric remnant recurrence from AFP-producing gastric cancer is extremely rare. Yoshida et al. reported a patient with AFP-producing gastric cancer arising from the remnant stomach after a distal gastrectomy for a benign gastric ulcer.[10] In the present case, it is especially noteworthy that AFP-producing gastric cancer originated again in the gastric remnant after distal gastrectomy for AFP-producing gastric cancer. Furthermore, the interval between the initial gastrectomy and the occurrence of gastric remnant recurrence has been very long, i.e., about 10 years. Xing et al. described *Helicobacter pylori* infection and the reflux of bile and pancreatic juice to be two important risk factors for secondary stomach carcinogenesis in the remnant stomach mucosa.[15] However, the mechanisms of carcinogenesis of gastric remnant cancer after distal gastrectomy remain unclear. Furthermore, no previous studies have been reported concerning the cellular or molecular mechanisms to explain the carcinogenesis of AFP-producing gastric cancers due to the small number of long-term survivors. Therefore, it is difficult to elucidate whether the gastric remnant tumor in our patient was recurrence or a newly developed cancer. A further accumulation of such cases is therefore needed to establish the mechanisms of carcinogenesis of this disease.

Kono et al. concluded that surgical resection of liver metastasis from AFP-producing gastric cancers was unsatisfactory and the development of a novel multimodal therapy is needed.[2] However, a standard chemotherapy for AFP-producing gastric cancer has not yet been established. We attempted treatment with TS-1, a novel oral derivative of 5-fluorouracil. Its effect against some cases of AFP-producing gastric cancer has also been reported.[16,17] Further studies on the effective chemotherapy for AFP-producing gastric cancers are therefore certainly required.

In conclusion, we encountered a long-term survival case of AFP-producing gastric cancer with liver metastasis, especially with gastric remnant metastasis. The surgical resections are an effective treatment even for these metastases from AFP-producing gastric cancer. The serum AFP level is therefore considered to be a good indicator for the early development of metastasis.

References

1. Chang YC, Nagasue N, Abe S, Taniura H, Kumar DD, Nakamura T. Comparison between the clinicopathologic features of AFP-positive and AFP-negative gastric cancers. Am J Gastroenterol 1992;87:321–5.
2. Kono K, Amemiya H, Sekikawa T, Iizuka H, Takahashi A, Fujii H, et al. Clinicopathologic features of gastric cancers producing alpha-fetoprotein. Dig Surg 2002;19:359–65.
3. Chen J, Rocken C, Treiber G, Jentsch-Ulrich K, Malfertheiner P, Ebert MP. Clinical implications of alpha-fetoprotein expression in gastric adenocarcinoma. Dig Dis 2003;21:357–62.
4. Adachi Y, Tsuchihashi J, Shiraishi N, Yasuda K, Etoh T, Kitano S. AFP-producing gastric carcinoma: multivariate analysis of prognostic factors in 270 patients. Oncology 2003;65:95–101.
5. Chang YC, Nagasue N, Abe S, Kohno H, Kumar DD, Nakamura T. alpha Fetoprotein producing early gastric cancer with liver metastasis: report of three cases. Gut 1991;32:542–5.

6. Tsurumachi T, Yamamoto H, Watanabe K, Honda I, Watanabe S, Yamada S, et al. Resection of liver metastasis from alpha-fetoprotein-producing early gastric cancer: report of a case. Surg Today 1997;27:563–6.
7. Kubota O, Suzuki T, Takahashi T, Kosukegawa M, Yamashita K, Mori S, et al. A case of AFP-producing early gastric carcinoma with rapid growth liver metastasis. Hepatogastroenterology 2001;48:1206–8.
8. Aoyagi K, Koufuji K, Yano S, Miyagi M, Koga A, Takeda J, et al. Alpha-fetoprotein-producing early gastric cancer: report of two cases. Kurume Med J 2003;50:63–6.
9. Nakahashi C, Kinoshita T, Konishi M, Nakagohri T, Inoue K, Oda T, et al. Long-term survival achieved by repeated resections of metachronous pulmonary and adrenal metastases of alpha-fetoprotein-producing gastric cancer: report of a case. Surg Today 2004;34:784–7.
10. Yoshida H, Mamada Y, Taniai N, Mizuguchi Y, Nakamura Y, Nomura T, et al. Ruptured metastatic liver tumor from an alpha-fetoprotein-producing gastric cancer. J Nippon Med Sch 2005; 72:236–41.
11. Koide N, Nishio A, Igarashi J, Kajikawa S, Adachi W, Amano J. Alpha-fetoprotein-producing gastric cancer: histochemical analysis of cell proliferation, apoptosis, and angiogenesis. Am J Gastroenterol 1999;94:1658–63.
12. Amemiya H, Kono K, Mori Y, Takahashi A, Ichihara F, Iizuka H, et al. High frequency of c-Met expression in gastric cancers producing alpha-fetoprotein. Oncology 2000;59:145–51.
13. Sato Y, Nishimaki T, Date K, Shirai Y, Kurosaki I, Saito Y, et al. Successful resection of metachronous liver metastasis from alpha-fetoprotein-producing gastric cancer: report of a case. Surg Today 1999;29:1075–8.
14. Tomiyama K, Takahashi M, Fujii T, Kunisue H, Kanaya Y, Maruyama S, et al. A rare case of recurrent alpha-fetoprotein-producing gastric cancer without re-elevation of serum AFP. J Int Med Res 2006;34:109–14.
15. Xing C, Kato S, Matsukura N, Matsuda N, Xu H, Takashi E, et al. Interleukin-8, cyclo-oxygenase-2, and trefoil factor family 1 gene expression and their association with Helicobacter pylori infection in the remnant stomach. Surg Today 2005;35:1026–32.
16. Okazaki M, Yamamura J, Kawasaki Y, Ohtsuru M, Kobayakawa K, Yasuda S, et al. A case of advanced gastric cancer producing alpha fetoprotein with multiple liver metastases responding to TS-1 after TAE (in Japanese with English abstract). Gan To Kagaku Ryoho 2001;28:2073–7.
17. Hatta W, Kumagai S, Imamura J, Oikawa T, Asano Y, Fujita H, et al. A case of curatively resected AFP producing gastric cancer that responded remarkably to 1 course of TS-1 and showed complete loss of multiple liver metastatic tumors (in Japanese with English abstract). Gan To Kagaku Ryoho 2005;32:855–8.