Case report

A patient with 43 synchronous early gastric carcinomas with a Krukenberg tumor and pericardial metastasis

YOSHIFUMI BABA¹, SHINJI ISHIKAWA¹, KOUJI IKEDA¹, SHINOBU HONDA¹, NOBUTOMO MIYANARI¹, KEN-ICHI IYAMA², and HIDEO BABA¹

¹Department of Gastroenterological Surgery, Graduate School of Medical Science, Kumamoto University, 1-1-1 Honjo, Kumamoto 860-8556, Japan

²Department of Surgical Pathology, Graduate School of Medical Science, Kumamoto University, Kumamoto, Japan

Abstract

A 53-year-old Japanese woman with bilateral ovarian tumors consulted our department. Gastroendoscopy disclosed 16 superficial depressed gastric lesions, and the histopathological diagnosis of the biopsy specimens was poorly differentiated adenocarcinoma and signet-ring cell carcinoma. Computed tomography (CT), ultrasonography (US), and positron emission tomography (PET) examinations revealed no other metastasis except for that observed in the ovaries. We performed a total gastrectomy with radical lymph node dissection and bilateral ovarian resection. A postoperative histological examination revealed 43 isolated gastric lesions which were scattered over the entire resected stomach; they were all confined to the mucosa. Cancer cell invasion in the lymphatics was detected only in the submucosal region beneath the main tumor. Both ovarian tumors were diagnosed as metastasis of signet-ring cell carcinoma (Krukenberg tumor). Adjuvant chemotherapy with irinotecan (CPT-11) and low-dose cisplatin (CDDP) was given on an outpatient basis, but 1 year after the surgery, carcinomatous pericarditis occurred. Administration of mitomycin C (MMC) into the pericardial space was performed twice; however, unfortunately, the patient died 13 months after surgery.

Key words Synchronous early gastric carcinomas · Krukenberg tumor · Pericardial metastasis

aforsaid four patients, the histological type was signet-ring cell carcinoma for all lesions in three patients, and moderately differentiated adenocarcinoma in the main tumor and signet-ring cell carcinoma in the other lesions in one patient.

Of interest, a Krukenberg tumor is often detected in advanced gastric carcinoma but not in early gastric carcinoma. In Japan, only seven cases of gastric intramucosal carcinoma with a Krukenberg tumor have been reported since 1970 [7,8]. Pericardial metastasis from early gastric carcinoma is very rare. To our knowledge, only one case has been reported in which pericarditis carcinomatosa was initially diagnosed, and subsequently early gastric carcinoma was found [9,10]. The administration of anticancer drugs into the pericardial space has been reported to be effective for pericardial metastasis [9,11]. However, the effect was temporary and most of these patients eventually died 3–8 months after undergoing treatment.

We herein report a patient with 43 synchronous early gastric carcinomas with bilateral metastatic ovarian tumors. The patient demonstrated cardiac tamponade due to pericarditis carcinomatosa, which appeared 1 year after surgery.

Introduction

It has been reported that approximately 6% to 14% of gastric carcinomas include multiple lesions [1–5]. Only four patients with more than 40 synchronous gastric carcinomas have previously been reported [6]. Only one of these patients had multiple cancer lesions definitely confined to the mucosa and the submucosal layer. In the

Case report

A 53 year-old Japanese woman complained of a lower abdominal mass, and visited a local medical doctor in May 2004. She had no family history of malignancy and no significant past history. Bilateral ovarian tumors were confirmed by computed tomography (CT; Fig 1A), and metastatic tumors were thus suspected. She was referred for detailed checking and treatment to the Department of Gynecology at our hospital in July 2004, and she then consulted our department (The Department of Gastroenterological Surgery) to undergo a detailed examination of her gastrointestinal tract.

Fig. 1A,B. Preoperative clinical findings in the patient reported in this study. **A** Computed tomography (CT) of the pelvis shows bilateral cystic ovarian tumors measuring 7 cm in diameter (the right tumor) and 4 cm in diameter (the left tumor). The arrows show the right tumor. **B** Gastroendoscopy shows a wide superficial depressed (IIc) lesion with an ulcer in the greater curvature of the middle-third area (arrowhead). This lesion was considered to be the main tumor

An endoscopic examination of the upper digestive tract revealed 16 superficial depressed lesions located from the cardia to the antrum. A wide superficial depressed lesion, which measured 1.5×1.0 cm in size, with an ulcer scar, was found in the greater curvature of the middle-third area, and it was considered to be the main tumor (Fig. 1B). Biopsy specimens, which were obtained from 6 lesions, revealed poorly differentiated adenocarcinoma and signet-ring cell carcinoma. Tumor markers (carcinoembryonic antigen [CEA], carbohydrate antigen [CA] 19-9, and α -fetoprotein [AFP]) were all within the normal ranges. There was no evidence of hepatic metastasis, lung metastasis, or peritoneal metastasis, based on the findings of ultrasonography (US), CT, and positron emission tomography (PET), the bilateral ovarian tumors being the only metastases found. Total colonoscopy also showed no abnormal findings.

We performed an operation in July 2004. We first confirmed the peritoneal lavage cytology findings to be negative, and CEA mRNA and cytokeratin (CK) 20 mRNA in peritoneal washes were found to be negative using ultrarapid quantitative reverse transcription polymerase chain reaction (RT-PCR). We performed a total gastrectomy with a radical lymph node dissection and an ovarian resection.

Serially cut sections of the whole resected stomach were submitted to histological examination. Forty-three isolated lesions of signet-ring cell carcinoma and poorly differentiated adenocarcinoma within the mucosal layer were scattered over the entire resected stomach (Fig. 2A, B). Cancer cell invasion in the lymphatics was de-

tected only in the submucosal region beneath the main tumor (Fig. 2C) in the greater curvature of the middle-third area, but not in the other lesions. Lymph node metastasis was found in 18 of 22 dissected lymph nodes. Both ovarian tumors (Fig. 3) had metastasis of signet-ring cells, and they were diagnosed as metastasis of gastric cancer (Krukenberg tumor). Other gastric mucosa specimens showed multifocal atrophic gastritis with *Helicobacter pylori* infection, according to the updated Sydney System [12]. The grade of chronic inflammation was moderate, and inflammation was very uniformly distributed in the antrum and corpus. Glandular atrophy with intestinal metaplasia of a mild grade was demonstrated in both the antrum and corpus.

The postoperative course was uneventful. For adjuvant chemotherapy, we first treated the patient with S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan), but discontinued this treatment due to the occurrence of serious side effects, consisting of skin eruptions. Next, chemotherapy with irinotecan (CPT-11) and low-dose cisplatin (CDDP) was administered on an outpatient basis [13]. Because of general fatigue and bone marrow suppression, she and her family decided to terminate the chemotherapy, in April 2005.

In July 2005, she was admitted with mild dyspnea. A chest X-ray showed an increased cardiothoracic ratio, and ultrasonographic echocardiography disclosed massive pericardial effusion (Fig. 4A). Cardiac tamponade was diagnosed and pericardiocentesis yielded 570 ml of serous pericardial effusion. Cytology suggested the presence of signet-ring cell carcinoma (Fig. 4B). Al-

Fig. 2A–C. Macroscopic and microscopic findings of the resected stomach. **A** Schematic presentation of the 43 superficial lesions with cancer cells seen on the histological examination. The *arrow* shows the main tumor with submucosal lymphatic infiltration. **B** Microscopic findings. All 43 lesions had both

signet-ring cell carcinoma and poorly differentiated adenocarcinoma. **C** Microscopic view of the main tumor. Lymphatic invasion was seen in the submucosa (*arrow*). **B** H&E, $\times 200$; **C** H&E, $\times 100$

though a drainage tube was placed and 8 mg mitomycin C (MMC) was administered into the pericardial space, her general status gradually worsened, and she died in August 2005.

Discussion

We experienced a patient demonstrating multiple synchronous gastric carcinomas, with 43 lesions. In general, four histological points are important for the differential diagnosis of multiple gastric cancer lesions. The first

is to confirm whether surface spreading lesions connect with each other in the mucosa. The second is to confirm whether the carcinoma cells that are spread widely throughout the submucosa have infiltrated to the mucosa. The third is to determine whether there is intramural metastasis through the lymphatic vessels or the veins, and the fourth is to determine whether there are multiple synchronous lesions. In our patient, detailed histological examination revealed a lack of continuousness in both the mucosa and the submucosa, which revealed that the first and the second points could be ruled out. It was found that all the lesions were confined

Fig. 3A,B. Macroscopic findings of the resected ovarian tumors; **A** right tumor; **B** left tumor

Fig. 4A,B. Pericardial metastasis at 1 year after surgery. **A** Echocardiography, revealing massive pericardial effusion (arrow-heads). **B** Cytological findings of the pericardial effusion demonstrated signet-ring cell carcinoma

to the mucosa, and cancer cell invasion of the lymphatic vessels was observed only beneath the main tumor. For this reason, we ruled out the third point. According to Moertel et al. [14], primary multiple gastric cancer is defined as follows: (1) each lesion is histopathologically malignant; (2) each lesion is separated from another by the normal gastric wall; (3) each lesion is not the result of either local extension or metastasis from another lesion. Our case met the criteria of this definition. As a result, we diagnosed these lesions to be synchronous multiple gastric carcinomas.

The primary lesion of a Krukenberg tumor is mostly advanced gastric carcinoma, and early gastric carcinoma with a Krukenberg tumor is rare [7,8]. The pathways of

metastasis from early gastric carcinoma to the ovary have been considered to be via peritoneal spread and via lymphatic and vascular pathways. In our patient, no intraoperative findings of peritoneal metastasis were observed, and no free cancer cells were detected in the peritoneal washes by either cytological examination or RT-PCR of CEA, and CK-20 mRNA [15]. According to these findings, although lymphatic invasion or the vascular pathway could have been the cause of the ovarian metastasis in our patient, the possibility of the peritoneal spread was undeniable.

Listrom and Fenoglio-Preiser [16] have described that gastric lymphatics normally begin as a plexus of vessels immediately superficial to, within, and below the

muscularis mucosa. The upper two-thirds of the gastric lamina propria is normally devoid of lymphatics. This distribution is also maintained in neoplastic tissues. However, in patients with atrophic gastritis, in whom the overall height of the gastric mucosa is known to markedly decrease, lymphatic capillaries may be found near the surface epithelium, and cancer cells in the mucosa may infiltrate the lymphatic vessels easily. Furthermore, Sano [17] reported that destruction of the muscularis mucosa by histological ulceration could cause an interchange between the lymph flow in the mucosa and the submucosa, which thus could result in an increased risk of lymph node metastasis. In our patient, the gastric mucosa other than the cancer showed atrophic gastritis, while the main tumor in the greater curvature of the middle-third area had an ulceration. Due to such ulcerations, even though the cancer cells in all lesions were confined to the mucosa, cancer cells may therefore have infiltrated into the lymphatic vessels, and thus metastasized to the many lymph nodes and the ovaries.

Cardiac tamponade arising from gastric cancer is uncommon [9,10]. Fraser et al. [18] reviewed the literature concerning malignant pericardial effusion and described the primary tumor to be in the lung in 14 of 19 patients, and in the stomach in only 2 of 19. Edward et al. [19], based on autopsy examination data, reported the incidence of pericardial metastasis to be 12.9% (4/31) for esophageal cancer, 16.7% (35/209) for lung cancers, 13.3% (8/60) for breast cancer, and only 5.1% (2/39) for gastric cancers. Furthermore, most patients with pericardial metastasis had advanced gastric carcinomas, and pericardial metastasis from early gastric carcinoma was very rare.

In conclusion, we herein reported a rare case of a patient with 43 synchronous multicentric gastric carcinomas, all of which were confined to the mucosa, except for cancer cell invasion observed in the lymphatic vessels. In this patient, with Krukenberg tumors, cardiac tamponade, due to carcinomatous pericarditis, appeared 1 year after surgery.

References

- Esaki Y, Hirokawa K, Yamashiro M. Multiple gastric cancers in the aged with special reference to intramucosal cancers. *Cancer* 1987;59:560–5.
- Mitudomi T, Watanabe A, Matsusaka T, Fujinaga Y, Fuchigami T, Iwashita T. A clinicopathological study of synchronous multiple gastric cancer. *Br J Cancer* 1989;76:237–40.
- Kosaka T, Miwa K, Yonemura Y, Urade M, Takenaga S, Miyazaki I, et al. A clinicopathological study on multiple gastric cancers with special reference to distal gastrectomy. *Cancer* 1990; 65:2602–5.
- Isozaki H, Okajima K, Hu X, Fujii K, Sako S. Multiple early gastric carcinomas, Clinicopathological features and histogenesis. *Cancer* 1996;78:78–86.
- Kodama M, Tur GE, Shiozawa N, Koyama K. Clinicopathological features of multiple primary gastric carcinoma. *J Surg Oncol* 1996; 62:57–61.
- Ozeki Y, Hino A, Hayasi M, Goto H, Masao S, Hirose H, et al. Multiple gastric cancers exhibiting more than 80 foci; report of case (in Japanese). *I to Cho (Stomach and Intestine)* 1989; 25:467–72.
- Kakushima N, Kamoshida T, Hirai S, Hotta S, Hirayama T, Oka Y, et al. Early gastric cancer with Krukenberg tumor and review of cases of intramucosal gastric cancers with Krukenberg tumor. *J Gastroenterol* 2003;38:1176–80.
- Takenoue T, Yamada Y, Miyagawa S, Akiyama Y, Nagawa H. Krukenberg tumor from gastric mucosal carcinoma without lymphatic or venous invasion. *Hepatogastroenterology* 2001;48: 1211–4.
- Moriyama A, Murata I, Kuroda T, Yoshikawa I, Tabaru A, Otsuki M, et al. Pericardiac metastasis from advanced gastric cancer. *J Gastroenterol* 1995;30:512–6.
- Sakai Y, Minouchi K, Ohta H, Annen Y, Sugimoto T. Cardiac tamponade originating from primary gastric signet ring cell carcinoma. *J Gastroenterol* 1999;34:250–2.
- Kobayashi T, Nakashima R, Kimura K. Management of metastatic pericardial effusion. *Jpn J Clin Oncol* 1971;1:137–46.
- Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney System. *Am J Surg Pathol* 1996;20:1161–81.
- Shimada S, Yagi Y, Shiomori K, Kuramoto M, Ogawa M. Second line chemotherapy with combined irinotecan and low-dose cisplatin for patients with metastatic gastric carcinoma resistant to 5-fluorouracil. *Oncol Rep* 2003;10:687–91.
- Moertel CG, Bargain JA, Soule EH. Multiple gastric cancers. *Gastroenterology* 1957;32:1095–103.
- Marutuka T, Shimada S, Shiomori K, Hayashi N, Yagi Y, Ogawa M, et al. Mechanisms of peritoneal metastasis after operation for non-serosa-invasive gastric carcinoma: an ultrarapid detection system for intraperitoneal free cancer cells and a prophylactic strategy for peritoneal metastasis. *Clin Cancer Res* 2003;9: 678–85.
- Listrom MB, Fenoglio-Preiser CM. Lymphatic distribution of the stomach in normal, inflammatory, hyperplastic, and neoplastic tissue. *Gastroenterology* 1987;93:506–14.
- Sano R. Pathological analysis of 300 cases of early gastric cancer with special reference to cancer associated with ulceration. *Gann Monograph on Cancer Research*. Tokyo: University of Tokyo Press; 1971. p. 81–9.
- Fraser RS, Vilorio JB, Wang NS. Cardiac tamponade as a presentation of extracardiac malignancy. *Cancer* 1980;45:1697–704.
- Edward C, Klatt MD, Danel R. Cardiac metastasis. *Cancer* 1990;65:1456–9.