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Case report

Early gastric cancer with Krukenberg tumor and review of cases of intramucosal gastric cancers with Krukenberg tumor

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A 47-year-old woman was admitted because of hypermenorrhea. Transvaginal ultrasonography revealed an ovarian tumor and myoma uteri, and total hysterectomy with bilateral salpingo-oophorectomy was performed. Histology revealed signet-ring cell carcinoma in the right ovary. In order to find out the primary site of this tumor, gastroendoscopy was performed after the operation, and showed a IIc lesion in the lower body of the stomach; biopsy specimens showed signet-ring cell carcinoma similar to that in the right ovary. Total gastrectomy revealed that the lesion was an early gastric cancer confined to the mucosa, but there was lymphatic invasion slightly beneath the muscularis mucosa, with regional lymph node metastasis. In the light of a review of the seven cases of early gastric cancer with Krukenberg tumor previously reported, lymphatic metastasis seemed to be the most likely pathway of ovarian metastasis in early gastric cancers.

Key words: early gastric cancer, Krukenberg tumor

Introduction

The primary lesion of Krukenberg tumor is an advanced gastric cancer in most cases. Rare cases of early gastric cancer with Krukenberg tumor have been reported, but the pathway of metastasis still remains to be elucidated. We experienced a patient with early gastric cancer with Krukenberg tumor, in whom the primary lesion showed minimal lymphatic invasion beneath the muscularis mucosa, which suggested that early lymphatic permeation of the cancer cells may have been one of the metastatic routes.

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Case report

A slightly obese 47-year-old woman presented with hypermenorrhea in March 2001. She had no family history of malignancy, and she did not have any significant past history, except for borderline hypertension with no medication. Hematological tests revealed slight anemia (hemoglobin [Hb], 11.2 g/dl) and mild elevation of hepatic enzymes, but tumor markers (carcinoembryonic antigen [CEA], carbohydrate antigen [CA]19-9, CA125, CA72-4, and alpha-fetoprotein [AFP]) were all within normal limits. Transvaginal ultrasonography revealed a tumor in the right ovary and leiomyoma of the uterus. Suspecting ovarian cancer, we performed total hysterectomy with bilateral salpingo-oophorectomy, on May 1, 2001. Pathologically, the right ovary measured 11 × 6 cm in size (Fig. 1a) and there was diffuse stromal proliferation of signet-ring cancer cells (Fig. 1b). Angiolymphatic permeation of cancer cells was prominent in the hilar area of the ovary and fallopian tube. There was a slight amount of ascites, but cytology was negative. In order to find out the primary site of this tumor, further examinations were performed after the operation. Gastroendoscopy (Fig. 2) and double-contrast examination (Fig. 3) revealed a 3 × 2-cm-sized shallow depressed (IIc) lesion (*Japanese classification of gastric carcinoma*[1]) in the lower body of the stomach. Biopsy specimen showed signet-ring cell carcinoma. Total colonoscopy showed no abnormal findings. There was no evidence of lymph node metastasis or hepatic metastasis from the findings of the abdominal ultrasonography and computed tomography (CT), and total gastrectomy with regional lymph node dissection was performed on July 2, 2001. Grossly, the tumor was 4.3 × 1.3 cm in size. The lesion was cut in sections of 3-mm width and was scrutinized in serial sections (Fig. 4a). Slight fibrosis was seen in a small portion of the submucosa, but there was no cancer invasion in this part (Fig. 4b). Minimal lymphatic invasion, slightly beneath the

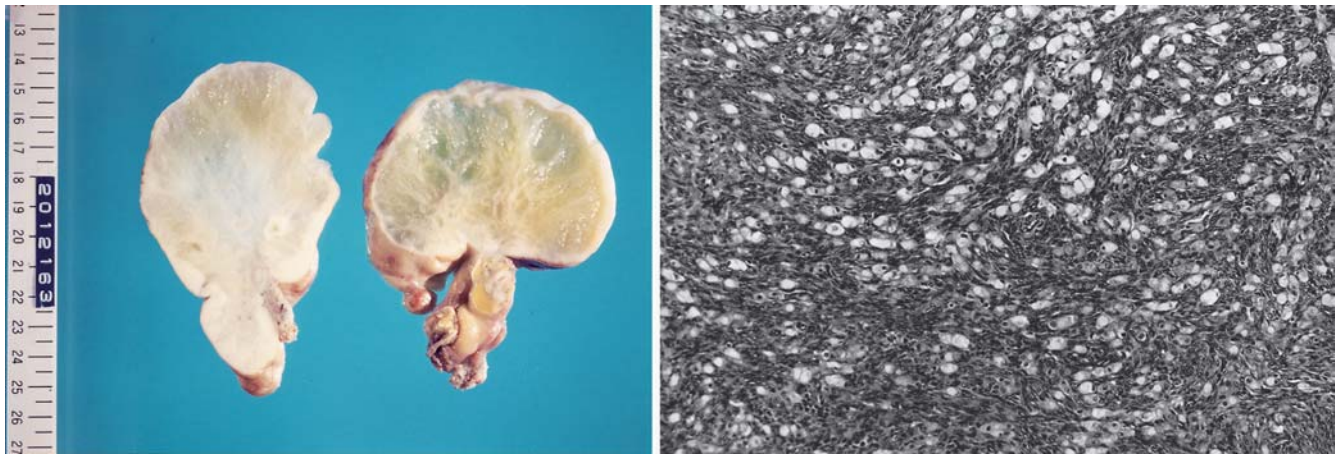


Fig. 1. a The resected right ovary measured 11 × 6cm in size. The cut surface was edematous and took on greenish hue. **b** Histology revealed diffuse stromal proliferation of signet-ring cancer cells. H&E, × 100

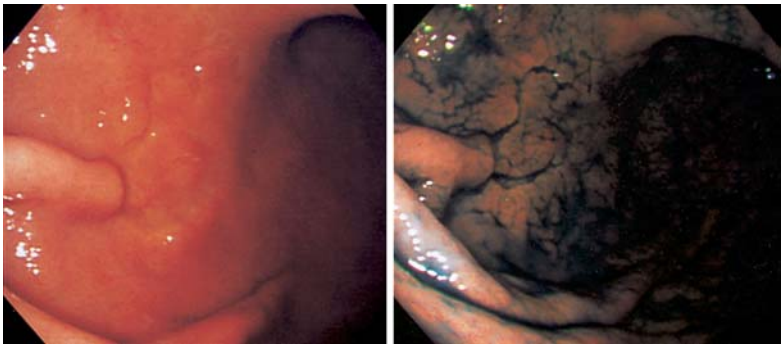


Fig. 2. Gastroendoscopy showed a well demarcated 3 × 2-cm-sized shallow depressed lesion in the lower body of the stomach

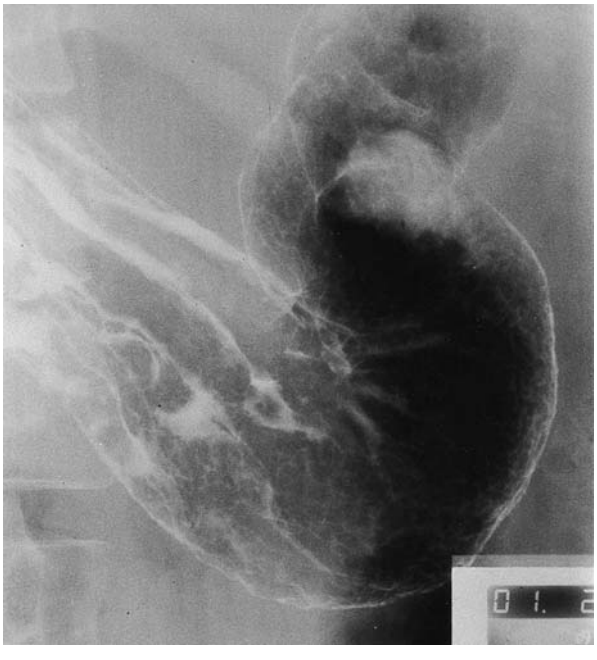
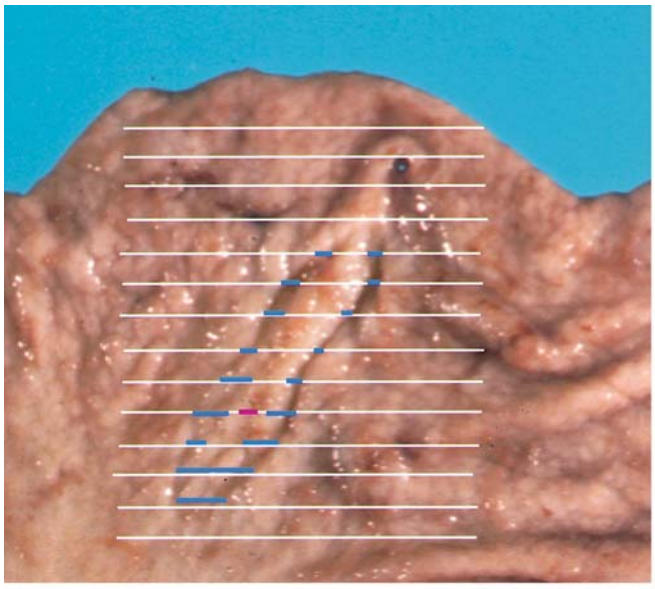


Fig. 3. Double-contrast examination revealed a 3 × 2-cm-sized shallow depressed lesion in the lower body of the stomach

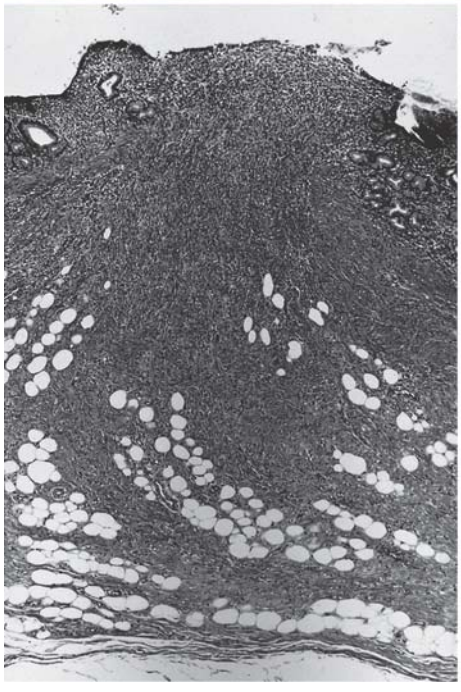
muscularis mucosa, was suspected in one part of the edge of the lesion (Fig. 4c). The cancer cells within the lymph vessel were positively stained with anticytokeratin monoclonal antibody. The gastric mucosa other than the cancer showed severe atrophic gastritis. Metastasis was found in 10 of 26 lymph nodes dissected. Thus, the lesion was diagnosed as early gastric carcinoma, signet-ring cell type, T1, N2 (nos. 3, 4, 7, 9), H0, P0, M1 (OTH), stage IV. The patient's postoperative course was uneventful, and chemotherapy with methotrexate (MTX)/5-fluorouracil (5-FU) was given. She was discharged after four courses of the regimen without untoward effects. Follow-up abdominal CT, performed in December 2002, showed no signs of recurrence.

Discussion

Krukenberg tumors are metastatic neoplasms from primary lesions in the gastrointestinal tract, in particular from carcinomas of the stomach. They are invariably bilateral, the stroma usually appears quite pronounced,



a



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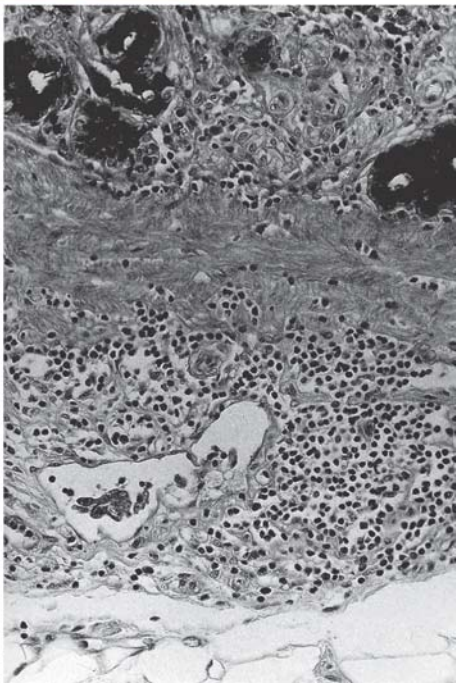

c

Fig. 4. **a** Macroscopic view of the lesion (4.3 × 1.3 cm). *Blue lines* show the presence of cancer, and the *red line* shows the part with slight fibrosis seen in the submucosa. **b** Microscopic view of the part which showed slight fibrosis in a small portion of the submucosa. There was no cancer invasion in this part. **c** The edge of the lesion. Minimal lymphatic invasion was seen slightly beneath the muscularis mucosa. **a** Periodic acid schiff (PAS), ×200; **b** H&E, ×40

and a mucus-producing carcinoma is present, with numerous signet-ring cells.[2] The average age at diagnosis is reported to be 40 to 50 years, and it is more common in premenopausal women than in postmenopausal women.[3–4] The prognosis is poor, and it worsens if the primary tumor is identified after the metastasis to the ovary is discovered.[4] The median survival after the diagnosis of Krukenberg tumor is reported to be 7 to 14 months.[3–7] Resection of the primary lesion may have a role in the management of Krukenberg tumor of stomach origin, but no effective therapy has been reported so far.[5] Because the tumor in our patient was diagnosed after oophorectomy, in consideration of her age and the evidence of lymph node metastasis, we decided to give her postoperative therapy and chose a chemotherapy regimen for advanced gastric cancer which could be continued in the outpatient department.

Unilateral Krukenberg tumor is, allegedly, exceptional.[7,8] Our case was diagnosed as a unilateral ovarian tumor, but from the gross appearance of the section of the specimen, together with the microscopic findings of signet-ring cells, we concluded that it was a metastasis from the early gastric cancer found after the surgery.

In Japan, seven cases of gastric intramucosal cancer with Krukenberg tumor have been reported since 1970 (Table 1).[9–13] The average age was relatively young, and

Table 1. Reported cases of Krukenberg tumor arising from intramucosal gastric cancer in Japan

No.	Year	Author	Age (years)	Type	Size (cm)	ly v n	Other factors
1.	1970	Nagasako	31	IIc, sig	1.2	n (+)	Ascites, pregnancy
2.	1977	Sajima	41	IIc, muc	4.0	?	Ascites, carcinomatous emboli
3.	1997	Igarashi[9]	29	IIcIIa, sig	2.0	ly1v0n4 (perigastric and others)	Pregnancy
4.	1999	Hatakeyama[10]	46	IIc, sig	3.0	ly0v0n3 (no. 13)	Ascites, myoma uteri
5.	2000	Hashimoto[11]	35	IIc, sig	1.5	ly0v0n2 (nos. 3, 4 d, 7)	
6.	1999	Nokubi[12]	56	IIb, sig	0.2 (×4)	n4	Carcinomatous emboli
7.	2001	Takenoue[13]	49	IIc, sig	1.6	ly0v0n0	Myoma uteri, carcinomatous emboli

ly, lymphatic invasion; v, venous invasion; n, lymph node metastasis; sig, signet ring cell; muc, mucinous

the ovarian tumor was diagnosed concurrently or before the primary lesion in all patients, except for the last one, in whom the ovarian tumor was noted 18 months after gastrectomy. All of the primary lesions were IIc, and histologic types were either poorly differentiated adenocarcinoma or signet-ring cell carcinoma. In five patients, there was lymphatic invasion and/or lymph node metastasis, and in three, ascites was present. In our patient, the primary lesion was suspected to be an intramucosal cancers, because the minimal lymphatic invasion beneath the muscularis mucosa was not noticed until the results of serial sections were examined. The chance of lymph node metastasis of gastric cancer is associated with tumor size larger than 30 mm, undifferentiated histological type, lymphatic-vascular involvement, and massive submucosal penetration. Patients with gastric cancer invading the submucosa without the first three of these factors, but with submucosal penetration of less than 500 μm, have a minimal risk of lymph node metastasis (0–3.1%), but, if the submucosal penetration is more than 500 μm, the risk would increase markedly, up to 20%.[14] On applying these criteria, the gastric tumor in our patient met the criteria for size, histology, and lymphatic invasion which may have increased the risk of lymph node and ovarian metastasis.

Thus far, three possible pathways of metastasis to the ovary have been considered: via peritoneal spread, and via lymphatic and vascular pathways.[15] Lymphatic metastasis is thought to be the most common route for spreading into the ovaries, and this pathway is plausible in five of the reported patients, because of the evidence of lymphatic invasion. Another important histologic feature frequently observed in Krukenberg tumors is carcinomatous emboli, a feature which was reported in four patients (including ours); this feature is often recognized in the ovarian hilus, mesoovarium, and mesosalpinx because these tissues contain a large number of lymphatics and blood vessels.[16] Among the reported patients, metastasis was seen in gastric regional lymph nodes, but there was no report of metastasis in ovarian regional lymph nodes; this fact, taken together with the anatomical one-way lymphatic flow, suggests that the cancer cells may be spread to the ovary after entering the systemic circulation via the lymphatic system and thoracic duct. Two patients presented with carcinomatous lymphangiomatosis and bone metastasis soon after the diagnosis of Krukenberg tumor was made, and this suggests the possibility of early invasion of cancer cells into the systemic circulation.

Ascites is a common feature in Krukenberg tumor, and Woodruff and Novak[17] reported that 22 of 48 patients had ascites at the time of diagnosis. The presence of ascites is a bad prognostic sign, and it may be the pathway of metastasis to the ovary in advanced gastric cancer. Among the patients reported, two had ascites with positive cytology. In both patients, the disease relapsed within a few months after surgery, with carcinomatous peritonitis. However, lymph node metastasis was also present from the time of their first surgeries, so it is difficult to judge whether the ovarian metastasis was first and caused the ascites, or vice versa. In our patient, from the findings of lymphatic invasion with lymph node metastasis, and her long survival after the operation without recurrence, lymphatic metastasis is the most suspected.

Listrom and Fenoglio-Preiser[18] have reported 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. But in patients with severe atrophic gastritis, in which condition the overall height of the gastric mucosa is markedly decreased, lymphatic capillaries may be found near the surface epithelium. So, in patients such as ours, even if the cancer lesion is confined to the mucosa, cancer cells may have a chance to enter the lymphatic capillaries, resulting in lymph node metastasis as well as lymphatic metastasis to distant organs. For the seven reported patients, however, there was no information given

about evidence of gastric atrophy or serum pepsinogen values.

In regard to other risk factors of early metastasis to the ovary from gastric mucosal cancers, six of the seven reported patients were premenopausal including two who were pregnant, and two with myoma uteri. Gastric cancer with positive estrogen receptor has been discussed as a risk factor for poor prognosis,[19] but of the seven reported patients, only one was examined for estrogen receptor, and was negative, and in our patient, estrogen receptor was negative too. In addition, immunohistological staining for CA19-9, p53, Ki67, and E-cadherin—which are thought to enhance the proliferation potency and metastatic potential of malignant tumors—was performed in our patient; however, the results were all negative.

We experienced a patient with unilateral Krukenberg tumor derived from early gastric cancer. The primary lesion was an intramucosal tumor with minimal lymphatic invasion beneath the muscularis mucosa, revealed by serial section analysis, and lymph node metastasis was shown. This case suggested that early lymphatic permeation of the cancer cells may be one of the metastatic routes for Krukenberg tumor. In premenopausal women with ovarian tumors, close investigation of the stomach and regional lymph nodes is considered to be mandatory for detecting the primary lesion and the metastasis pathway.

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