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Case Report

An Early Gastric Cancer Patient With Pleural Metastatic Recurrence

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A 72-year-old male patient was diagnosed with depressed-type gastric cancer in the body of stomach [preoperative diagnosis: T2 (MP), N0, M0, P0, H0, cStage IB] and underwent distal gastrectomy and D2 dissection in January 2011. The pathological classification was T1b (SM), por2, 24 × 45 mm, ly3, v1, N2 (6/14), M0, P0, CY0, H0, fStage IIA. Continuous increase of serum carbohydrate antigen 19-9 (CA19-9) followed 1-year postoperative S-1 adjuvant chemotherapy, so S-1 was resumed despite not identifying the site of recurrence. In December 2012, pleural metastasis was suspected based on fluorine 18-fluorodeoxyglucose FDG standardized uptake value 14 × 23 mm in size on the right diaphragm (pleural cavity side) found on positron emission tomography-computed tomography. No other metastasis was found. Serum CA19-9 continued to increase. In April 2013, the patient underwent thoracoscopic removal of pleural metastasis on the right diaphragm (cytology of pleural effusion: class II). Pleural metastasis of gastric cancer was diagnosed based on the same histology as the gastric tumor. Elastica van Gieson (EvG) staining showed intravascular tumor thrombus, suggesting hematogenous metastasis. The tumor markers temporarily decreased after the surgery, but started to increase again. The patient is being treated with chemotherapy on an outpatient basis.

Key words: Early gastric cancer – Pleural metastasis – FDG-PET

While lymph node, peritoneal, and liver metastases are common after gastrectomy, pleural metastatic recurrence is rare.[1] The frequency of distal metastasis of early gastric cancer is about 0.14%[2] and postoperative recurrence is generally infrequent.[3–5] Postoperative pleural metastatic recurrence of early gastric cancer is extremely rare. Removal of pleural metastatic lesion has not been

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reported. We report a case of pleural metastasis removal in a patient with early gastric cancer and discuss related literature.

Case Report

A 72-year-old man consulted the department of internal medicine with upper abdominal distension in December 2010. Endoscopy revealed a depressed-type cancer in the midposterior wall of the gastric corpus (biopsy: group V, adenocarcinoma). The patient was referred to our department and admitted. He had a right nephrectomy for renal cell cancer in 1997. Laboratory tests revealed mild anemia, renal impairment due to having a single kidney, and normal tumor markers. Advanced gastric cancer in the midpostural wall of the gastric corpus with no lymph node or distal metastasis was found by abdominal computed tomography (CT). The cancer was diagnosed as T2, N0, M0, P0, H0, cStage IB. At the operation, an expose beyond the serosa was not seen in the stomach and an induration in lesser curvature lymph node was seen. Distal gastrectomy with lymphadectomy was performed in January 2011. The macroscopic appearance of the resected stomach showed a depressed-type lesion (size of 24 × 15 mm) in the midposterior wall of the gastric corpus (Fig. 1). The microscopic examination showed that the tumor had invaded into the submucosal layer (SM invasion) with lymphovascular infiltration (Fig. 2). The histological tumor finding was: M, post, 24 × 45 mm, IIc, fT1b (SM 2.7 mm), N2 (6/14), ly3, v1, M0, P0, CY0, H0, fStage IIA. The postoperative course was good. The patient was discharged with an improved condition. We performed S-1 adjuvant chemotherapy for 1 year postoperation (March 2011–February 2012) with a decreased dose (80 mg/body) due to renal impairment associated with the single kidney. In July 2012, the tumor markers started to increase [carcinoembryonic antigen (CEA): 8 ng/mL; carbohydrate antigen 19-9 (CA19-9): 114 U/mL]. In September, further increase was noted (CEA, 9.9 ng/mL; CA19-9, 233 U/mL). Abdominal CT failed to detect the metastatic lesion. Oral S-1 was resumed for possible recurrence while searching for the metastatic lesion. In December 2012, positron emission tomography–CT (PET-CT) showed a standardized uptake value (SUV) of fluorine 18-fluorodeoxyglucose positron emission tomography (FDG-PET) the size of 14 × 23 mm (SUV max: 5.4) on the right diaphragm (pleural cavity side; Fig. 3). In March 2013, pleural metastatic recurrence from gastric cancer was diagnosed based on the CT showing an enlarged mass; the increased tumor markers (CEA, 29.4 ng/mL; CA19-9, 372.2 U/mL); and the clinical course. No other metastasis was found. In April 2013, thoracoscopic removal of pleural metastatic recurrence on the right diaphragm was performed (cytology of pleural effusion: class II). The resected tumor was an elastic and soft node the size of 3 cm. The cross-sectional surface was solid and yellow in color (Fig. 4). The microscopic examination showed a solid proliferation of sharply marinated tumor cells with oval

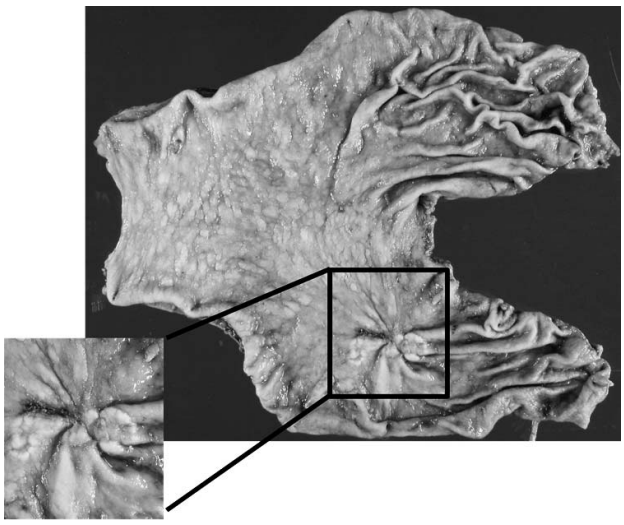


Fig. 1. The macroscopic examination showed a depressed-type lesion (size of 24 × 15 mm) in the midposterior wall of the gastric corpus.

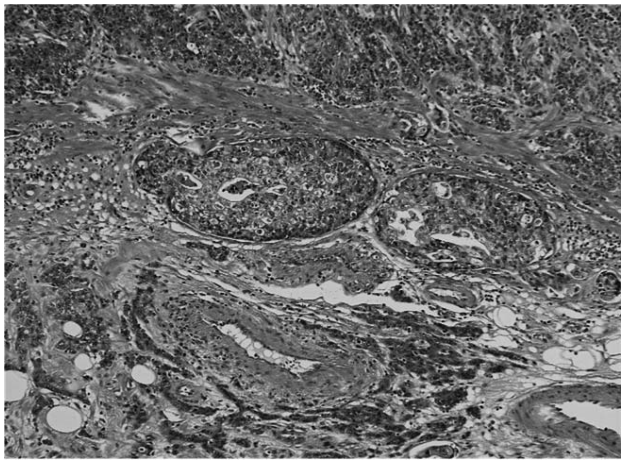
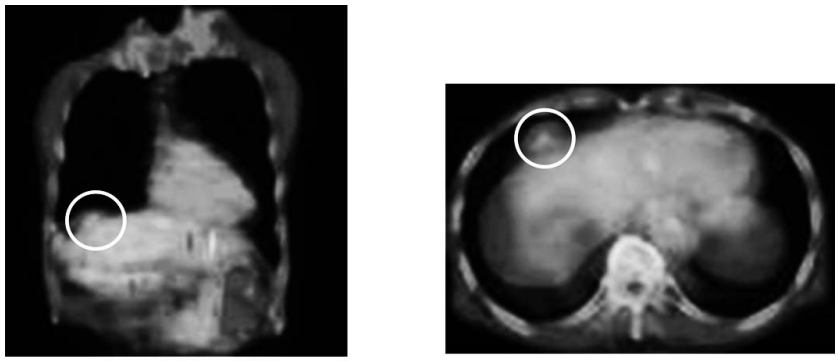


Fig. 2. The microscopic examination showed that the tumor invasion was submucosal layer (SM invasion) with lymphovascular infiltration.



(a) (b)

Fig. 3. PET-CT showed an SUV of FDG-PET the size of 14 × 23 mm (SUV max: 5.4) on the right diaphragm (pleural cavity side).

nuclei and clear cytoplasm. Poorly differentiated adenocarcinoma was diagnosed. Elastica van Gieson (EvG) staining showed an intravascular tumor thrombosis (Fig. 5). Based on the positive CEA staining and strong-positive human epidermal receptor 2 (HER2) staining as in the primary lesion, pleural metastatic recurrence from gastric cancer was diagnosed (Fig. 6). Although the patient had a history of renal cell carcinoma, the histology was different from clear cell renal cell carcinoma (positive CK7/CK20/CD10 and negative vimentin). In May 2013, because the tumor markers started to increase again (CEA, 45.5 ng/mL; CA19-9, 1064 U/mL), a second-line treatment with weekly paclitaxel and trastuzumab was started. The tumor markers temporarily decreased (CEA, 32.3 ng/mL; CA19-9, 204.7 U/mL), but increased again after 7 cycles of chemotherapy (CEA, 143 ng/mL; CA19-9, 171 U/mL). In December 2013, the treatment was switched to CPT-11 and trastuzumab due to mediastinal lymph node and pleural metastasis found by thoracoabdominal CT. The patient is currently being treated with chemotherapy on an outpatient basis (3 years and 7 months after the initial surgery, 1 year and 4 months after the removal of a recurrent lesion).

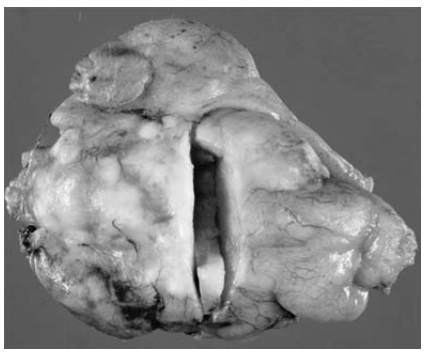
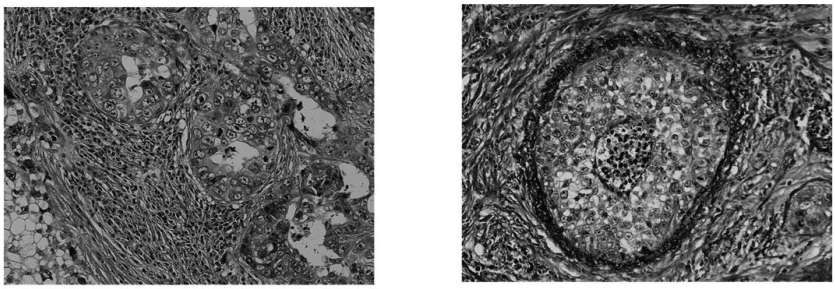


Fig. 4. The cross-sectional surface of the resected tumor was solid and yellow in color.

Discussion

Early gastric cancer has a good prognosis in general. The recurrence rate is from 1.4% to 2.4%.[3–5] Common risk factors for postoperative recurrence of early gastric cancer include submucosal (SM) infiltration, lymph node metastasis, differentiated tumor, and miscellaneous tumor with a combination of protrusion and depression.[3] Lymphovascular infiltration and multiple cancers have also been identified as risk factors.[4,5] This patient with multiple risk factors for recurrence such as lymph node metastasis, lymph vascular infiltration, and SM invasion had a tumor marker increase at about 1 year after the initial surgery and was diagnosed with pleural metastatic recurrence based on the diagnostic images and a resected sample. Mochizuki *et al*[4] reported many early gastric cancer patients with recurrence within 2 years had lymph node metastasis and lymphovascular infiltration. While studies have reported post-gastrectomy pleural metastatic recurrence diagnosed based on pleural fluid retention or empyema,[6,7] it is a rare recurrence type with the frequency of 1.9% (1/52 patients) based on autopsy samples of recurrent gastric cancer.[1] According to a case report by Saka *et al*[8] on early gastric cancer with pleural metastatic recurrence at 11 months' postoperation, pleural metastasis was found in 5% of early gastric cancer recurrence with lymph node metastasis. Mochizuki *et al*[4,5] also reported a patient with early multiple gastric cancer with lymphovascular infiltration and lymph node metastasis had pleural recurrence with bone metastasis at 98 months' postoperation. Eun Jung Hwang *et al*[9] reported pleural metastasis in an early gastric cancer patient immediately after

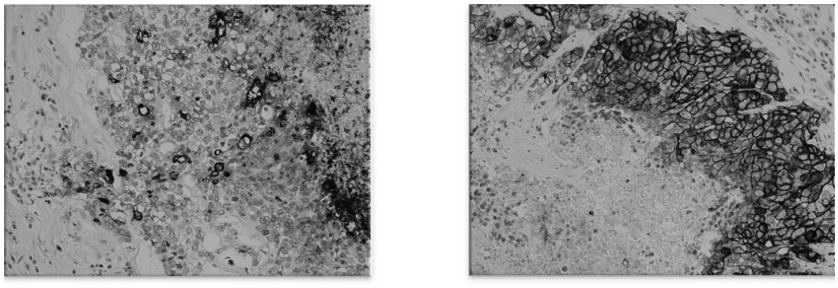


(a) (b)

Fig. 5. (a) HE staining showed a poorly differentiated adenocarcinoma. (b) EvG staining showed an intravascular tumor thrombosis.

endoscopic submucosal dissection. No study has reported a clinical course to recurrence. In this patient, the tumor markers increased 1 year post-operation. PET-CT to search for the recurrence lesion found FDG-PET SUV on the right diaphragm (pleural cavity side). PET-CT is also useful for the diagnosis of recurrent gastric cancer and deciding on future treatment.[10] Sensitivity may vary depending on the histology.[11] The diagnosis of pleural metastasis was reported in a patient with well-differentiated cancer. In a case of signet ring cell cancer or poorly differentiated adenocarcinoma (por2), FDG SUV may be false-negative.[6] In this patient with por2 cancer, SUV was confirmed. Making a definitive diagnosis of metastatic gastric cancer was based on concurrent immunohistochemistry staining of pleural fluid[9] or thoracoscopic pleural biopsy.[6] The diagnosis is generally difficult, although their usefulness has been reported. In this patient, we could perform a histopathological search on the completely resected metastatic lesion, which was diagnosed based on the same characteristics as the primary gastric lesion, such as por2, positive CEA staining, and strong-positive HER2 staining. Amano *et al*[6] also made a diagnosis of metastasis based on the similarity of histological findings and consistent immunostaining outcome. The route of metastasis was thought to be hematogenous based on the venous invasion in the primary lesion and intravascular tumor thrombosis in the metastatic lesion. Lymphatic invasion in the submucosal layer is considered to be the most important factor for gastric cancer metastasis.[9] Pleural metastasis suggestive of lymphatic route has also been reported.[6] The pleural metastasis cannot be explained based on a single metastatic route in this patient because of severe lymph node invasion and following mediastinal lymph node metastasis and pleural metastatic recurrence.

Recurrence prevention is crucial. D2 lymph node dissection and postoperative adjuvant chemotherapy are necessary to prevent recurrence of early gastric cancer.[4] Saka *et al*[8] emphasized the significance of the lymph node metastasis count and suggested the advantage of postoperative adjuvant chemotherapy specifically in patients with pN2 or higher lesions based on a multivariate analysis. S-1 adjuvant chemotherapy is currently recommended in patients with pStage II, IIIA, or III B cancer, except T1 based on the data from the adjuvant chemotherapy trial of TS-1 for gastric cancer (ACTS-GC) study.[12] Although this patient had a T1 tumor, S-1 adjuvant chemotherapy was performed for 1 year after surgery in accordance with the ACTS-GC study[12] because of



(a) (b)

Fig. 6. (a) Immunostaining examination showed the positive CEA staining. (b) Immunostaining examination showed the strong-positive HER2 staining.

severe lymph node and lymphatic invasion. The recommended dose of chemotherapy drugs could not be used because of renal impairment. The tumor markers increased immediately after the 1-year chemotherapy was completed, and pleural metastatic recurrence was found within 2 years postoperation. Early gastric cancer patients with severe lymph node metastasis and lymphatic invasion may need more aggressive postoperative adjuvant chemotherapy.

Conclusion

We reported a case of an early gastric cancer patient with pleural metastatic recurrence that was completely removed.

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