Early Gastric Cancer Recurrence Following Curative Resection Presenting as Biliary Tract Dilatation, Pancreatic Duct Dilatation and Intestinal Wall Thickening

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Abstract

Early gastric cancer, especially cancer confined to the mucosa (stage T1a), is known to have a high cure rate with rare recurrence. We herein report the case of a 40-year-old female who initially presented with biliary tract dilatation, pancreatic duct dilatation and intestinal wall thickening 3 years after curative resection of pT1aN0 stage gastric cancer. The intestinal resection specimen revealed tumor cells spreading through the subserosa to the submucosa sparing mucosal membrane, which made exploratory laparotomy the only approach to confirm the diagnosis. It is always important to be aware of malignancy recurrence and clinicians should not hesitate to choose exploratory laparotomy to avoid any delay in the diagnosis and treatment.

Key words: early gastric cancer, recurrence, retroperitoneal dissemination

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Introduction

Early gastric cancer (EGC) is defined as gastric carcinoma confined to the mucosa or submucosa regardless of lymph node metastasis and tumor size, according to the Japanese Classification of Gastric Carcinoma (1). EGC has been demonstrated to be a “curable” malignant tumor with a favorable prognosis after curative resection; the overall 5- and 10-year survival rates were 95.9% and 95.9% for stage T1a in Japan, respectively (2).

Despite the very favorable prognosis of EGC, recurrence has been reported to occur in up to 2.2% of the patients, with distant recurrence via hematogenous spread most frequent (47.1%), followed by peritoneal recurrence (23.5%) (3). The symptoms caused by peritoneal recurrence include intestinal obstruction, massive ascites, and ureteral obstruction. Peritoneal fluid cytology is useful for the diagnosis of this condition. However, we herein report a case of EGC in which biliary tract dilatation, pancreatic duct dilatation and intestinal wall thickening were the initial presentations of recurrence. Exploratory laparotomy was the only approach to confirm the diagnosis.

Case Report

A 40-year-old woman with a previous history of pT1aN0 EGC (signet ring cell carcinoma with poorly differentiated adenocarcinoma component and negative lymphovascular involvement) (Fig. 1) curatively resected by laparoscopy-assisted distal gastrectomy 3 years earlier presented with a 2-wk history of epigastric pain, nausea and anorexia. A blood test showed increased liver, biliary and pancreatic enzymes (Table 1). An abdominal computed tomography (CT) scan revealed biliary tract and pancreatic duct dilatation with diffuse enlargement of the pancreas (Fig. 2a, b). The subsequent work-up, including magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasonography (EUS), revealed no signs of obstruction in the biliary tract or pancreatic duct (Fig. 3). CT also showed hydronephrosis and thickening of the intestinal wall in the duodenum, ascending colon and rectum, which was due to severe edema.

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confirmed by an endoscopy examination (Fig. 2c-f). Biopsies from the stomach, duodenum, colon and peritoneal fluid cytology showed no signs of malignancy. A liver biopsy was also performed to investigate the cause of liver dysfunction and showed no signs of other diseases such as drug-induced hepatitis, autoimmune hepatitis, primary biliary cirrhosis or primary sclerosing cholangitis. Based on the diffuse enlargement of the pancreas and pancreatic duct dilatation, a potential diagnosis of autoimmune pancreatitis (AIP) was suspected. Although a normal serum IgG4 level and no fibrous tissue surrounding the abdominal aorta were atypical for the diagnosis, hydronephrosis and intestinal symptoms were thought to be retroperitoneal fibrosis symptoms. Because steroid reactivity is proposed as one of the diagnostic criteria for IgG4-negative AIP in the Japanese Consensus Guidelines for Autoimmune Pancreatitis (4), corticosteroid therapy was administered; however, it did not improve her symptoms. A CT scan 13 days after the initiation of corticosteroid therapy showed a slight resolution in the duodenal wall thickening, but no definite change in any other organs. Intravenous hyperalimentation was induced because of the intestinal symptoms, and the patient was monitored regularly on an outpatient basis. One month later she presented with perforated appendicitis. Emergent laparotomy was performed, and the resected appendix showed poorly differentiated adenocarcinoma spreading through the subserosa to the submucosa sparing mucosal membrane (Fig. 4). The round ligament of the liver also taken as a specimen showed adenocarcinoma infiltration. Immunochemical staining revealed similar patterns of cytokeratin and CDX2 staining between the poorly differentiated adenocarcinoma component in primary gastric cancer and adenocarcinoma found in the appendix. Both of them presented as CK7-positive, CK20-positive and CDX2-negative, which was a consistent finding that the metastasis had originated from a poorly differentiated focus (Fig. 5). Systemic chemotherapy consisting of TS-1 100 mg/
day (3 weeks on, 2 weeks off) and cisplatin (CDDP) (day 8) was started. Following the second cycle of chemotherapy, the intestinal symptoms resolved completely and her liver, biliary and pancreatic enzymes also recovered to the normal ranges. CT showed resolution of biliary tract dilatation, pancreatic duct dilatation and intestinal wall thickening (Fig. 6a, b). Endoscopy revealed resolution of the duodenum wall edema (Fig. 6c). The patient received a total of 8 courses of TS-1 and CDDP and currently shows no sign of progression 12 months after recurrence. The complete therapeutic course is illustrated in Fig. 7.

Discussion

In the present case, we discovered two important clinical issues. Gastric cancer recurrence can present as biliary tract dilatation, pancreatic duct dilatation and intestinal wall thickening. Therefore, it is important to be aware of malignancy recurrence and clinicians should not hesitate to choose exploratory laparotomy to avoid diagnosis and treatment delay.

First, gastric cancer recurrence can present as biliary tract dilatation, pancreatic duct dilatation and intestinal wall thickening. Previous studies have reported that retroperitoneal dissemination is one of the common presentations of the disease progression. It occurs through a number of mechanisms, such as tumor cells spreading across the peritoneal cavity when the tumor involves the entire thickness of the gastric wall (trans-mesothelial metastasis), leakage of the tumor cells from the lymphatic vessels (trans-lymphatic metastasis), iatrogenic dissemination caused by the operation itself and other potential causes. Many metastasis-related factors, including adhesion molecules, matrix proteases, motility factors and angiogenic factors, are involved in the formation of peritoneal dissemination (5). Ascites and ureteral obstruction are well known presentations for this condition (6). However, presentations similar to the current case are rare, which thus made the diagnosis difficult. Rectal stenosis is well known as Schnitzler’s metastasis (7-9), however, most of the previously reported cases are derived from advanced gastric cancer and thus accompanied by other obvious distant or lymph node metastases. A diagnosis could easily be made by peritoneal fluid cytology or rectal biopsy. There are also cases of recurrent gastric cancer causing duodenal stenosis or obstructive jaundice (10), however, Lee et al. summarized that jaundice could either be explained by lymphadenopathy in the hepatoduodenal ligament (93%) or direct tumor invasion (7%) (11). Our case is unique in that biopsies from the stomach, duodenum, colon, liver and peritoneal fluid cytology showed no signs of malignancy and no obvious mass-forming metastasis was detected. The tumor cells only existed through the subserosa to the submucosa sparing mucosal membrane. The lesions spread widely to several organs similar to ‘skip lesions.’ This strange tumor cell distribution supports, and could be explained by, the former metastasis model. That is to say, the trans-lymphatic
metastasis only took place in our case without the transmesothelial process, as the lymphovascular structure distributes through the intestine sparing mucosal membrane. The reported cases (8-10), similar to our case, demonstrated that these intestinal symptoms or jaundice could successfully be treated by 2 to 3 cycles of chemotherapy, although some publication bias may exist. Further reports should be accumulated to clarify the mechanisms of gastric cancer recurrence.

Second, it is always important to be aware of malignancy recurrence and clinicians should not hesitate to choose exploratory laparotomy to avoid diagnosis and treatment delay.
Figure 7. The complete course of therapy in this case. Corticosteroid therapy had a slight effect but failed to completely treat the patient. Liver, biliary and pancreatic enzymes recovered to the normal ranges after chemotherapy. TS-1: tegafur, gimeracil, oteracil, CDDP: cisplatin

Table 2. Case Reports that Mentioned the Recurrence of pT1aN0 Gastric Cancer.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age(y)</th>
<th>Sex</th>
<th>Time to recurrence</th>
<th>Histologic type</th>
<th>Tumor site</th>
<th>Operation</th>
<th>Initial recurrence site</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15</td>
<td>50</td>
<td>Male</td>
<td>10 years</td>
<td>por</td>
<td>Lower</td>
<td>Distal gastrectomy</td>
<td>Bone marrow</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>61</td>
<td>Male</td>
<td>5 years and 7 months</td>
<td>sig</td>
<td>Lower</td>
<td>Distal gastrectomy</td>
<td>Lymph node</td>
</tr>
<tr>
<td>present case</td>
<td>40</td>
<td>Female</td>
<td>3 years and 7 months</td>
<td>sig, por</td>
<td>Lower</td>
<td>Distal gastrectomy</td>
<td>Retroperitoneum</td>
<td>Alive</td>
</tr>
</tbody>
</table>

por: poorly differentiated adenocarcinoma, sig: signet ring cell carcinoma

In our case, no signs of malignancy were detected by the biopsy. Furthermore, reexamination of the primary EGC specimen by making additional slices, performing D2-40, Elastica van Gieson (EVG) staining and reevaluating the dissected regional lymph node revealed that the previous diagnosis of pT1aN0 without lymphovascular involvement was correct. None of the 19 dissected regional lymph nodes [stations nos. 1, 3, 4d, 4sb, 5, 6, 7 according to the Japanese Classification of Gastric Carcinoma (1)] were positive for metastasis. Therefore, the resection was believed to be curative according to the standard pathological criteria. These findings made it challenging for us to diagnose the patient with gastric cancer recurrence and conduct chemotherapy.

Although EGC is known to have a high cure rate, a small but innegligible number of recurrences have been reported. Triboulet et al. (12) reported the recurrence rates of signet ring cell (SRC) EGC and non-SRC EGC to be 5.8% vs. 8.8% (p=0.223) respectively, and peritoneal carcinomatosis recurrence rates to be 1.9% vs. 1.6% (p=0.838) respectively. According to Saka et al. (13), even EGC without lymph node metastasis recurs with an incidence of 0.6-0.7%. Nam et al. (14) reported that the following factors were predictive factors of lymph node metastasis in T1a gastric cancer: tumor size larger than 4 cm, the presence of middle and lower stomach cancer, poorly differentiated adenocarcinoma and signet ring cell carcinoma. However, in terms of pT1aN0 EGC, recurrence cases that have been reported are much less (15, 16) (Table 2), and thus the predictive factors for recurrence in pT1aN0 cancer have not yet been proposed. Further cases should therefore be accumulated to clarify the risk factors.

We must keep in mind that recurrence could potentially occur even in a case of a curative resection of EGC and clinicians should not hesitate to choose exploratory laparotomy if necessary. Our case may be a representative case that emphasizes the importance of a careful follow-up for those who have a previous history of malignancy.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

The authors state that they have no Conflict of Interest (COI).

References

1. Japanese Gastric Cancer Association. Japanese Classification of