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ORIGINAL ARTICLE

Peritoneal dissemination in early gastric cancer: importance of the lymphatic route

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Abstract The current paradigm concerning the mechanism of peritoneal dissemination of gastric cancer is that it occurs through an invasive process in which cancer cells directly penetrate the gastric wall and exfoliate into the peritoneal cavity. However, some experimental studies suggest the lymphatic route as an alternative. We present five early gastric cancer cases, which support this alternative pathway of peritoneal dissemination without direct invasion in the serosa. We investigated all patients with early gastric cancer who underwent curative gastrectomy between September 2002 and February 2015 at the Shizuoka Cancer Center, Japan. We examined them by intraoperative peritoneal lavage cytology and frozen section diagnosis of peritoneal nodules during laparotomy. Peritoneal dissemination was defined as peritoneal metastasis by positive cytology or histological diagnosis. Among 1509 early gastric cancers, five cases (0.3 %, 95 % CI 0.1–0.8 %) presented peritoneal dissemination detected by lavage cytology and frozen section diagnosis of peritoneal nodules. Histological examination revealed that the primary tumors invaded the submucosal layer using the lymphatic route, through which they metastasized to regional lymph nodes. Our data indicate that gastric cancer may give rise to peritoneal dissemination even at an early stage, probably through the lymphatic route without direct invasion into the serosa.

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Introduction

Gastric cancer is the fourth most common cancer with over 989,600 new cases and 738,000 deaths estimated worldwide per year [1]. The mortality represents 10 % of total cancer-related deaths. Peritoneal dissemination worsens the prognosis of gastric cancer patients because it causes severe ascites, bowel obstruction, and hydronephrosis, resulting in deterioration of general condition [2, 3]. Peritoneal dissemination was detected in 14 % of gastric cancer patients at initial examination, associated with a median survival of only 4 months [4]. The 5-year survival rate of gastric cancer with peritoneal dissemination, detected by peritoneal lavage cytology at surgery, is only 2 % [5]. Although systemic polychemotherapy has improved survival for gastric cancer patients with peritoneal dissemination, its effect is still inadequate [6–9]. Moreover, only a limited number of patients can sustain the combination of cytoreductive surgery and intraperitoneal chemotherapy [10–13].

In general, peritoneal dissemination occurs through direct invasion of the serosa, when cancer cells penetrate the gastric wall, exfoliate into the peritoneal cavity, and then lodge onto the peritoneum. Some reports, however, suggest an alternative dissemination route to peritoneal metastasis through lymphatics [14–16]. The Krukenberg tumor, a metastatic tumor in the ovary usually of a primary gastric cancer, might not be caused by direct invasion but by lymphatic spread [17]. Often, however, it is quite difficult to identify the route responsible for peritoneal dissemination because it usually occurs in end-stage cancer patients with tumor invasion through multiple routes, including blood vessel, lymphatics, and direct invasion through the serosal surface.

In addition, adjuvant chemotherapy for advanced or recurrent cases complicates the analysis of the responsible mechanism.

We present here five cases of early gastric cancer with simultaneous metastatic nodules and/or free cancer cells in the peritoneal cavity at the time of the surgery. These cases suggest the presence of an alternative pathway of peritoneal dissemination of gastric cancer, without a step of direct invasion through the serosal membrane.

Materials and methods

Case selection

A review of the institutional database of the Shizuoka Cancer Center, Japan, identified all patients with early gastric cancer, defined as cancer invading up to the submucosal layer, who underwent curative gastrectomy at the Shizuoka Cancer Center between September 2002 and February 2015. All patients gave their written informed consent for gastrectomy, and this study was approved by the institutional review board (institutional code number: 25-J42-25-1-3). Exclusion criteria were the following: patients with history of advanced cancer in other organs, recurrent cases, synchronous gastric cancers, and preoperative chemotherapy or radiation therapy for gastric cancer. Peritoneal dissemination was defined by histological diagnosis of peritoneal metastasis and/or by peritoneal lavage cytology positive for cancer cells.

Operation and pathological evaluation

Gastrectomy and lymphadenectomy were performed according to the guidelines of the Japanese Gastric Cancer Association (JGCA) [18]. All patients underwent intraoperative peritoneal lavage cytology using a wash solution with 100–200 mL of physiological saline in the left subphrenic and the pelvic space. Macroscopic peritoneal metastases detected by the surgeon were confirmed by intraoperative pathological diagnosis. The lavage was centrifuged at 1800 rpm for 1 min and fixed on glass slides using the autosmear method. The specimens were stained by Papanicolaou and Alcian Blue/PAS methods. Immunostaining with antibodies against CEA (Leica Microsystems, Wetzlar, Germany, dilution 1:5000) and Ber-EP4 (Dako Japan, Tokyo, Japan, dilution 1:200) was performed to confirm the cytological diagnosis. Cytology was determined by experienced cytoscreeners and cytopathologists. Definite malignancy was defined as positive in this study.

All resected specimens were fixed in 10 % formalin solution at room temperature. A set of step-cut sections including the whole tumor was prepared at 5-mm intervals based on the sectioning manual of JGCA [19]. Paraffin-embedded sections were routinely stained with hematoxylin and eosin. For observations of vascular invasion and mucin phenotype, Elastica–Masson or Elastica van Gieson stains and immunostaining using antibodies against D2-40 (Dako Japan, Tokyo, Japan, dilution 1:200), CDX2 (Dako Japan, Tokyo, Japan, dilution 1:100), MUC2 (Leica Microsystems, Wetzlar, Germany, dilution 1:200), MUC5AC (Leica Microsystems, Wetzlar, Germany, dilution 1:200), and MUC6 (Leica Microsystems, Wetzlar, Germany, dilution 1:100) were performed. Pathological diagnosis was performed by experts in gastrointestinal pathology, according to the Japanese classification [19]. Resected lymph nodes were also examined as well as tumor nodules (Ex), which were defined as an extramural tumor deposit without lymph node structure, discontinuous from the primary tumor [20, 21].

Table 1 Clinicopathological features of 1509 early gastric cancers

Age, mean ± SD	63 ± 11
Sex, male, *n* (%)	954 (63)
Tumor location, *n* (%)	
Upper third	287 (19)
Middle third	747 (50)
Lower third	475 (31)
Macroscopic type[a], *n* (%)	
Elevated (0-I, 0-IIa)	260 (17)
Flat and depressed (0-IIb, 0-IIc, 0-III)	1249 (83)
Size of tumor, mean ± SD, mm	36 ± 20
Histological differentiation, *n* (%)	
Differentiated type (pap, tub1, tub2)	831 (55)
Undifferentiated type (por, sig)	649 (43)
Others	29 (2)
Depth of invasion, *n* (%)	
M	665 (44)
SM	844 (56)
Vascular involvement, positive, *n* (%)	
ly	374 (25)
v	213 (14)
Lymph node metastasis, positive, *n* (%)	220 (15)
Liver metastasis, positive, *n* (%)	1 (0.07)
Cytological lavage examination, positive, *n* (%)	4 (0.3)
Peritoneal mass formation, *n* (%)	2 (0.1)

SD standard deviation, *pap* papillary adenocarcinoma, *tub1* well-differentiated tubular adenocarcinoma, *tub2* moderately differentiated tubular adenocarcinoma, *por* poorly differentiated adenocarcinoma, *sig* signet ring cell carcinoma, *M* mucosa, *SM* submucosa, *ly* lymphatic involvement, *v* venous involvement

[a] Macroscopic type was classified according to the Japanese classification of gastric carcinoma: 0-I, protruding type; 0-IIa, superficial elevated type; 0-IIb, superficial flat type; 0-IIc, superficial depressed type; 0-III, excavated type

Table 2 The details of five patients with peritoneal carcinomatosis from gastric cancer

Case	Age, years	Sex	CT findings	Tumor location	Macroscopic type	Tumor size, mm	Surgery; adjuvant therapy
1	81	Male	Heterogeneous enhancement, 50-mm protruding lesion with regional lymph node metastasis No ascites and distant metastasis	Lower third, lesser curvature	0-I + 0-IIc	46	DG None
2	81	Female	No visual gastric lesion Lymph node metastasis and hydronephrosis of the right kidney	Middle third, greater curvature	0-IIc	15	PR None
3	54	Male	No visual gastric lesion Massive lymph node metastasis around the celiac trunk, superior mesenteric artery and aorta	Middle third, posterior wall	0-IIc + 0-IIb	99	DG Intraperitoneal chemotherapy
4	64	Female	No significant findings	Middle third, lesser curvature	0-IIc	47	DG S-1
5	77	Female	No significant findings	Lower third, posterior wall	0-IIc + 0-III	12	ESD followed by DG S-1

CT computed tomography, *0-I* protruding type, *0-IIb* superficial flat type, *0-IIc* superficial depressed type, *PR* partial resection, *DG* distal gastrectomy, *ESD* endoscopic submucosal dissection, *S-1* tegafur/gimeracil/oteracil potassium

Table 3 The details of five patients with peritoneal carcinomatosis from gastric cancer

Case	Histology	Depth, μm	INF	ly/v	DR	Single infiltrating cells	Immunohistological findings	Positive LN; positive LN/total LN; Ex/positive LN	CY	P	Status; cause of death	Period of survival, month
1	Tubular adenocarcinoma (tub2)	SM 1250	b	+++/+	+	+	CDX2 (focal +) MUC2 (-) MUC5AC (-) MUC6 (-)	+ 15/56 5/15	+	+	Dead Gastric cancer (debility, rectal stenosis due to Schnitzler metastasis)	16
2	Poorly cohesive carcinoma (por2)	SM 875	b	+++/−	−	+	CDX2 (−) MUC2 (−) MUC5AC (−) MUC6 (−)	+ 2/2 0/2	−	+	Dead Gastric cancer (septic shock due to hydronephrosis)	7
3	Poorly cohesive carcinoma (por2)	SM 2750	c	++/−	+	+	CDX2 (−) MUC2 (−) MUC5AC (diffuse +) MUC6 (diffuse +)	+ 35/78 5/35	+	−	Dead Gastric cancer (acute renal failure due to renal−artery involvement)	3
4	Poorly cohesive carcinoma (sig)	SM 80	c	+/−	−	+	CDX2 (focal +) MUC2 (−) MUC5AC (diffuse +) MUC6 (focal +)	+ 1/34 0/1	+	−	Alive	99
5	Tubular adenocarcinoma (tub1)	SM 2000	b	++/−	+	+	CDX2 (+) MUC2 (focal +) MUC5AC (diffuse +) MUC6 (+)	+ 1/25 0/1	+	−	Alive	12

por 2 poorly differentiated adenocarcinoma, non-solid type, *sig* signet ring cell carcinoma, *tub 2* moderately differentiated tubular adenocarcinoma, *SM* submucosal cancer, *INF* tumor infiltrative pattern, *INF a* expansive growth, *INF b* intermediate pattern, *INF c* infiltrative growth, *ly* lymphatic involvement, *v* venous involvement, *DR* desmoplastic reaction, *LN* lymph node, *Ex* extranodal metastasis, *CY* cytological examination, *P* peritoneal metastasis

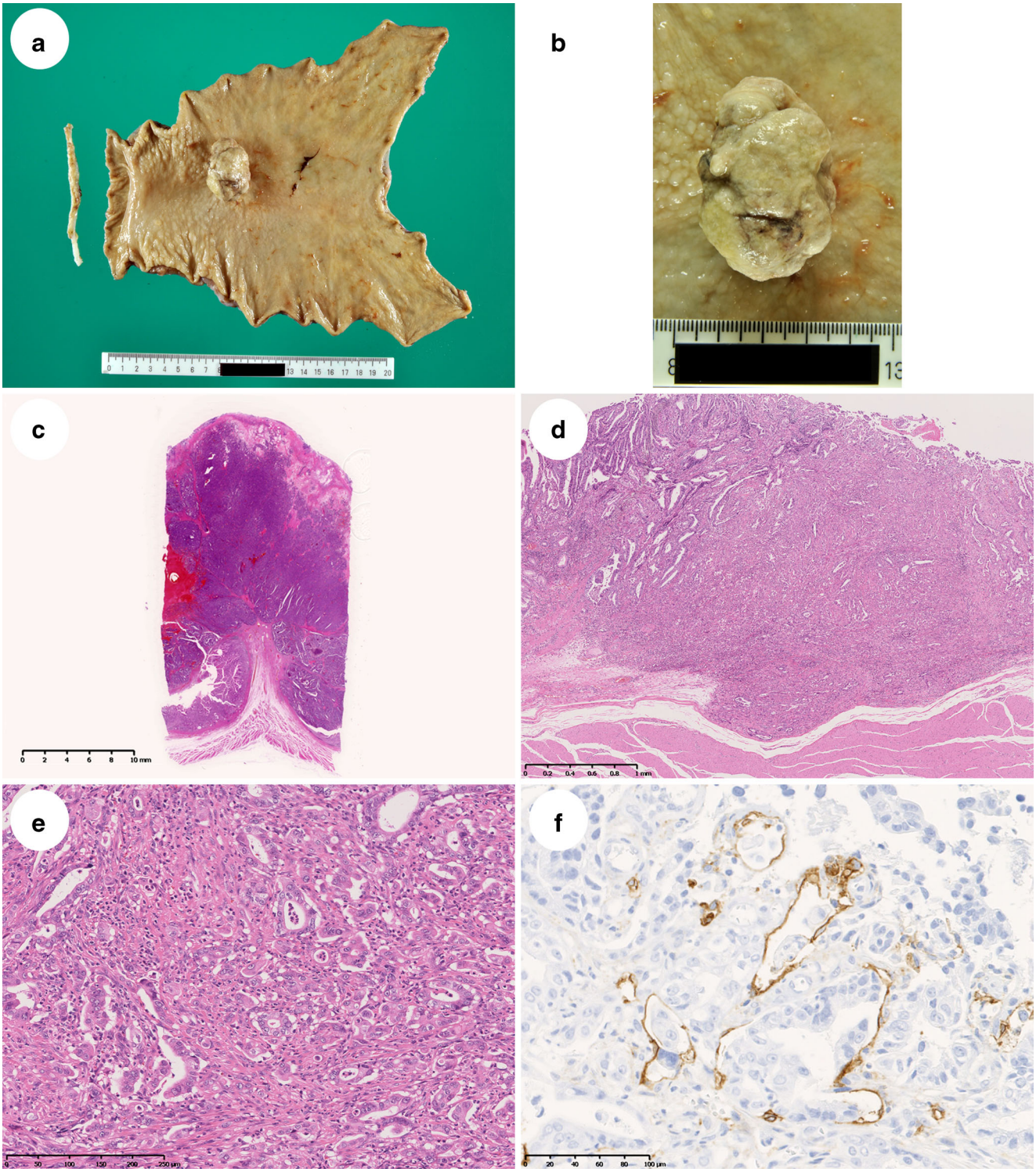

Fig. 1 Morphologies of a representative case (case 1 in Tables 2 and 3). **a**, **b** Macroscopic images of the primary tumor showing a pedunculated protruding tumor at the lesser curvature of the antrum. **c**, **d** Histological findings. Moderately differentiated tubular adenocarcinoma mostly grows in the mucosal layer (**c**), whereas some cancer cells massively invade into the submucosal layer (**d**) (H&E stain). **e** Single-cell infiltration and desmoplastic reaction are observed (H&E stain). **f** Lymphatic invasion of cancer cells. Immunohistochemistry using D2-40 antibody shows multiple cancer cell emboli within lymphatic vessels. **g** Histology of a regional lymph node with massive metastasis of cancer cells (H&E stain). **h** Peritoneal lavage cytology showing clusters of cancer cells (Papanicolaou stain). **i** Histology of peritoneal dissemination forming a metastatic nodule in the subserosal layer of the gastric wall (H&E stain)

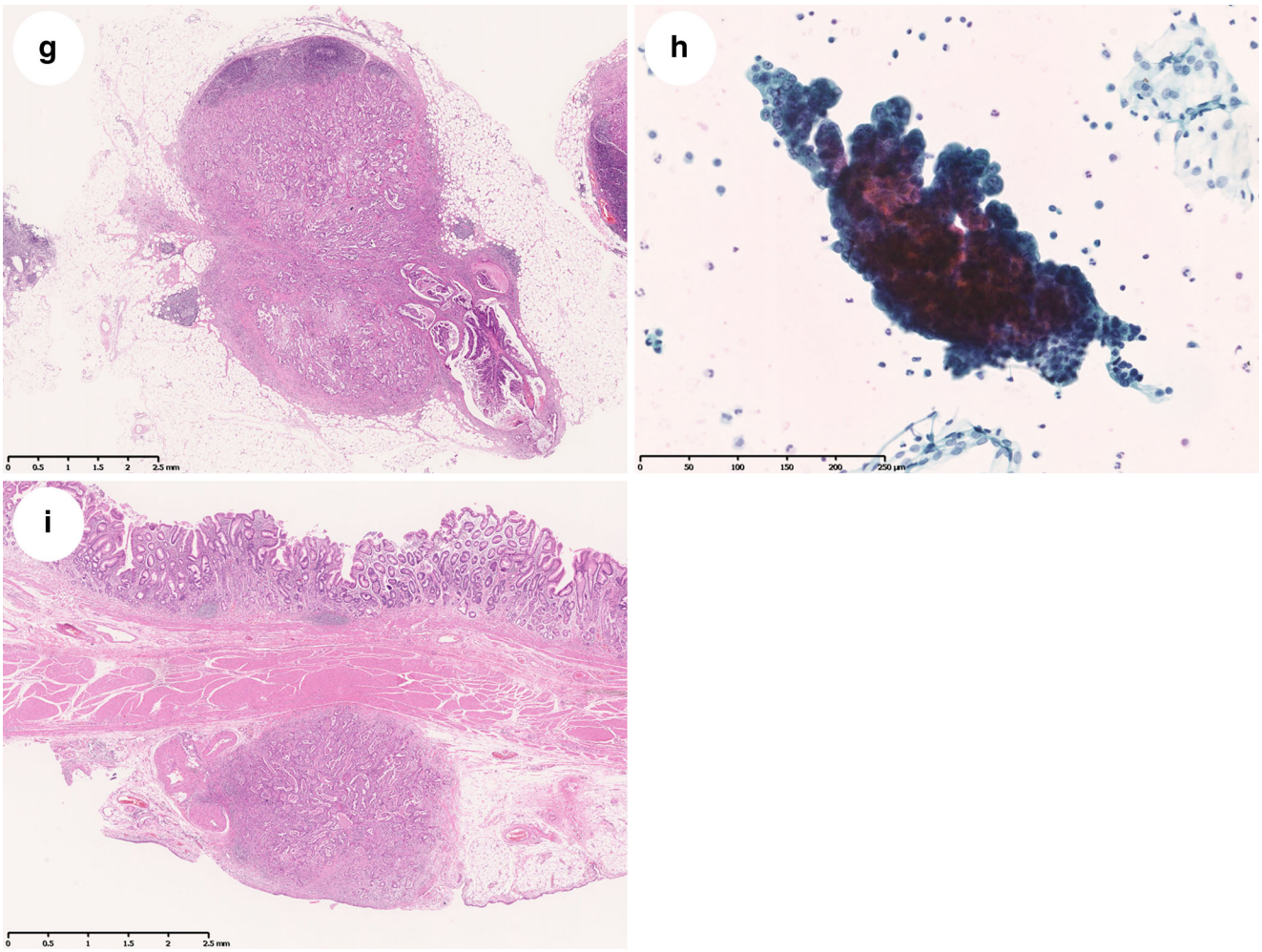

Fig. 1 (continued)

Statistical analysis

All variables were presented with the mean and the standard deviation and 95 % confidence interval (CI), calculated using the binomial distribution. Overall survival curve was calculated using the Kaplan–Meier method with the date of the initial treatment as the starting point. Statistical analyses were performed using the JMP statistical analysis software (version 11.0; SAS Institute Inc., North Carolina, USA).

Results

Clinical and pathological findings of 1509 early gastric cancers resected by gastrectomy are summarized in Table 1. Peritoneal dissemination was detected in five cases (0.3 %, 95 % CI 0.1–0.8 %) of early gastric cancer using cytological lavage examination (four cases) and histological observation (two cases). One case was detected by both methods. Clinicopathological information of these patients is shown in Tables 2 and 3. Representative morphology of the primary tumor and metastasis of case 1 are shown in Fig. 1. In three cases, preoperative examination using computed tomography pointed out lymph node metastasis. Pathological examination revealed that in two cases, the cancer was of a differentiated type, and in three cases, the cancer was undifferentiated. Moreover, single cell invasion was observed in all cases. A desmoplastic reaction was detected in three cases. Based on mucin expression pattern, two cases were classified as gastric type, one as mixed gastric and intestinal type, and two as null type. All five tumors showed submucosal invasion and lymph node metastasis, while two had extensive lymph node metastasis (35/78 (pN3b) and 15/56 (pN3a)). All primary tumors were accompanied by lymphatic involvement, whereas venous involvement was present in one case.

The median survival time was 12 months (3–99 months). Three patients died of peritoneal dissemination-associated conditions: urothelial infection caused by ureteral obstruction,

acute renal failure due to renal-artery involvement, and intestinal obstruction. Two patients, 12 and 99 months after surgery followed by adjuvant chemotherapy, are still alive.

Discussion

We present here five early gastric cancer cases with peritoneal dissemination detected at the time of surgery. While some reports have described recurrent cases of peritoneal dissemination after surgery for early gastric cancer [22, 23], no report has provided evidence for an indirect pathway for peritoneal metastasis. Although these cases are extremely rare (5 in 1509 early gastric cancers), they might contribute to our understanding of the mechanism of peritoneal metastasis in gastric cancer.

In general, peritoneal dissemination occurs in advanced gastric cancer or in recurrent cases [22–30]. In advanced cases, however, it would be difficult to specify the exact mechanism of peritoneal dissemination because of the complicated condition involving every dissemination route, such as blood vessel, lymphatics, and direct invasion to the serosa. Moreover, recurrent cases may be affected by previous surgeries that may have caused the dissemination of cancer cells to the peritoneum, thus overcoming the natural course of metastasis formation. Therefore, we focused on early gastric cancer cases after an initial operation because we could get complete information on the primary tumor and on the metastatic lesions in the peritoneum and in the dissected lymph nodes.

As a result, we found five gastric cancer cases with peritoneal dissemination, in which direct invasion into the peritoneum could be excluded. Interestingly, all were submucosal cancers with lymphatic invasion and lymph node metastases. Recently, a case report on early gastric cancer with peritoneal dissemination detected by cytological examination was published. The case showed submucosal invasion with lymphatic involvement [16]. The findings in all five cases demonstrate that peritoneal dissemination can occur without transmural invasion of cancer cells to the gastric wall. We propose a possible process of peritoneal dissemination via a lymphatic route, in which cancer cells enter into the lymphatic vessels in the submucosal layer, transfer to the lymphatics on the serosa and/or the regional lymph node to form a secondary tumor, and then disseminate to the peritoneum. Alternatively, cancer cells could be directly shed into the peritoneal cavity from the metastatic lymph nodes or from the lymphatic channel on the peritoneum [15, 31]. In both cases, the lymphatics may be an important route for peritoneal dissemination of gastric cancer [17]. In our study, the incidence of peritoneal dissemination was extremely rare in early gastric cancer, even with submucosal invasion and lymphatic involvement (348 cases), indicating that in addition to the lymphatics, other factors might be involved in the establishment of peritoneal metastasis. However, our data suggest the possibility that lymphatic involvement in early gastric cancer can cause not only lymph node metastasis but also peritoneal dissemination, thus implying that peritoneal metastasis via a lymphatic route may occur also in advanced gastric cancer.

Since the incidence of peritoneal dissemination in our study is low, the data obtained cannot be used for clinical diagnosis or therapy. However, our findings could help elucidate the mechanism of peritoneal dissemination in early- and late-stage gastric cancers.

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Compliance with ethical standards All participants gave their written informed consent, and this study was approved by the institutional review board (institutional code number: 25-J42-25-1-3).

Competing interests The authors declare no competing interests.

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