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Pathologic analyses of peritoneal nodules in gastric cancer patients during surgery—A single cancer center experience with diagnostic pitfalls

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ABSTRACT

Background: Gastric carcinoma (GC) is the second most common cause of cancer-related deaths worldwide. During operations, nodular lesions of the peritoneum are often sent for frozen section (FS). For pathologists, FS of the peritoneum is challenging due to sparse and discohesive tumor cells in a fibrotic background.

Methods: To explore diagnostic accuracy and diagnostic pitfalls of FS in this setting, we retrospectively collected 252 peritoneal biopsies in cases with GC from January 2006 to May 2017 and compared corresponding permanent sections and patient prognosis. After review, 6 cases (2.4%) were discrepant: positive conversion was identified in 5 cases due to scarce tumor cells associated with severe fibrosis and inflammation; negative conversion was identified in one case due to papillary mesothelial cell proliferation masquerading as carcinoma.

Results: Two hundred cases were finally confirmed as positive for tumor cells. Of these, 185 (92.5%) patients died of GC, with survival times ranging from 7 to 3574 (mean 415) days after operation. Fifty-two (20.6%) cases were negative for tumor, and pathologic findings included chronic inflammation with fibrosis (N = 25: associated with previous operation, 10; idiopathic, 15) and papillary mesothelial cell proliferation (N = 9). All 5 patients with frozen diagnosis converted to positive results died of GC during follow up. A total of 19 patients with peritoneal nodules diagnosed as benign on FS died with GC (79.0%), and their survival times ranged from 87 to 3649 (mean 833) days.

Conclusions: Peritoneal biopsies in patients with GC were mostly carcinoma, followed by chronic inflammation with fibrosis and papillary mesothelial cell proliferation. Deeper sections or intradepartmental consultations were helpful to reduce false negative diagnosis on FS.

1. Background

Gastric carcinoma (GC) is the fifth most common cancer worldwide and is the second most common cause of cancer-related deaths globally [23]. Although the incidence of GC has decreased substantially worldwide, its prognosis remains poor despite the use of multidisciplinary approaches for treatment and palliation because the majority of patients presenting with GC have advanced disease [4,8,9]. In addition, GC remains the second most common cancer and the third most common cause of death from cancer in Korea [12].

The peritoneal cavity and liver are the most common metastatic sites among patients with GC [22]. Peritoneal carcinomatosis (PC) is a common disseminated type of metastases and the most frequent pattern of recurrence in patients with GC [9,10]. Multiple peritoneal seeding of tumor cells compromises gastrectomy and is associated with poor prognosis because it can lead to bowel obstruction and malignant ascites [19,22]. However, there is a paucity of literature on the characteristics of patients with gastric PC. Virtually no studies have examined the pathologic features and diagnostic accuracy of intraoperative consultation (frozen section) [20].

Despite the availability of high resolution imaging techniques, exact diagnosis is not available before invasive procedures such as a laparoscopic biopsy [4,6,9,10]. In cases highly suspicious for PC, peritoneal biopsy before gastrectomy may facilitate surgical decision making,

Abbreviations: GC, gastric carcinoma; FS, frozen section; PC, peritoneal carcinomatosis; IHC, immunohistochemistry; H&E, hematoxylin and eosin

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enable exact diagnosis, avoid an unnecessary procedure, and permit assessment of the extent of disease [4,10,11]. In this clinical setting, suspicious lesions seen within the peritoneal cavity are often sent for FS analysis. For pathologists, these cases can be quite challenging due to the often sparse and discohesive nature of the infiltrate, particularly in poorly differentiated and signet ring cell carcinomas. Despite this difficulty in rendering a pathologic diagnosis during intraoperative consultation, the differential diagnosis and diagnostic pitfalls of peritoneal seeding nodules have not been formally evaluated. There is only one case report of a foreign body granuloma after gastric perforation mimicking peritoneal dissemination of GC [2].

To explore the diagnostic accuracy and diagnostic pitfalls during FS, we directly compared frozen and corresponding permanent sections of peritoneal biopsy specimens in a comprehensive cancer center in a GC prevalent area.

2. Materials and methods

We retrospectively collected 252 frozen peritoneal biopsy specimens in cases of GC from January 2006 to May 2017, and compared the findings with corresponding permanent sections and patient prognoses.

All excised peritoneal tissues were frozen in a cryostat machine and cut with a microtome. All diagnoses of original FS slides were made by pathologists with 10–20 years of experience. After FS, the tissue was fixed overnight in 10% buffered formalin and embedded in paraffin. All available FS slides and corresponding permanent hematoxylin and eosin (H&E) stained slides (4 μm) were examined.

For the degree of fibrosis and inflammation, we interpreted them as none (no fibrosis and inflammation), mild to moderate, and severe (fibrosis in > 50% of tumor volume and dense inflammatory cells infiltration) scored as 0, 1 and 2, respectively. Statistical analysis was performed using SPSS v25.0 software (IBM, NY, USA). Significant differences were evaluated using Wilcoxon signed rank test and a p values with less than 0.05 were considered to be statistically significant.

Tumor cells in frozen specimens were confirmed with pan-cytokeratin (CK AE1/AE3) (monoclonal mouse anti-human cytokeratin antibody, clone AE1/AE3, 1:500 dilution, Dako, Santa Clara, CA, USA) immunohistochemistry (IHC), and mesothelial cells were confirmed with calretinin (monoclonal mouse anti-human calretinin antibody, clone DAK Calret 1, 1:80 dilution, Dako, Santa Clara, CA, USA) and D2-40 antibody (monoclonal mouse anti-human podoplanin antibody, clone D2-40, 1:100 dilution, Dako, Santa Clara, CA, USA). Four pathologists (H. B, S.Y.H, K.T.J, and K.M.K) reviewed all slides and agreed upon the final diagnoses.

Intraoperative findings and electronic medical records were reviewed for patient prognosis. Written informed consent was obtained from all patients.

3. Results

Finally, 252 peritoneal biopsy specimens were analyzed with direct comparison of paired frozen and permanent slides. Patient age at diagnosis ranged from 21 to 83 years (mean, 57.1). The male to female ratio was 1.2:1. Of 252 cases, 196 (77.8%) were diagnosed as positive for tumor cells and 56 (22.2%) were diagnosed as negative for tumor cells during intraoperative consultation. There was no deferred case.

Two hundred cases (79.4%) were finally confirmed as positive for tumor cells, and 185 patients (92.5%) died of disease during follow up (follow up duration: 7 to 3574 days with a mean of 415 days). A total of 52 cases (20.6%) were confirmed as negative for tumor cells. A total of 31 patients (59.6%) were alive at the end of the study, with survival times ranging from 87 to 4189 (mean 1420) days after surgery (Table 1).

Out of 200 PC-positive cases, peritoneal lavage cytology was performed during operation in 126 cases and 64 of 126 cases (50.8%) were diagnosed as positive for tumor cells. Out of 52 PC-negative patients, cytology was performed in 33 cases and 3 of them were confirmed to be positive for tumor cells (9.1%), consisting 2 stages III and 1 stage IV patients (Table 1).

Table 1
Compared Clinical Characteristics of Peritoneal Seeding Positive Groups and Negative Groups.

Peritoneal seeding		Positive (200 cases)	Negative (52 cases)
Sex			
	Male	107 (53.5%)	30 (57.7%)
	Female	93 (46.5%)	22 (42.3%)
Mean age		56.5	62
Died during follow up			
	Yes	185 (92.5%)	19 (36.5%)
	No	9 (4.5%)	31 (59.6%)
	Loss	6 (3%)	2 (3.9%)
Survival times (days)		415 (7–3574)	1420 (87–4189)
Operation			
	No	154 (77%)	2 (3.8%)
	Subtotal gastrectomy	19 (9.5%)	28 (53.8%)
	Total gastrectomy	27 (13.5%)	22 (42.4%)
Peritoneal washing cytology			
	Not done	74 (37%)	19 (36.5%)
	Negative	62 (31%)	30 (57.7%)
	Positive	64 (32%)	3 (5.8%)
Clinical staging[a]			
	I	0	8 (15.4%)
	II	1 (0.5%)	7 (13.5%)
	III	16 (8%)	19 (36.5%)
	IV	183 (91.5%)	18 (34.6%)

[a] American Joint Committee on Cancer (AJCC) 8th cancer staging.

In total, 8 patients with clinical stage IV disease have received neoadjuvant chemotherapy and all but one case were died of disease during follow up and 4 of them were diagnosed with PC-positive. Unexpectedly, 9 patients with PC were alive at the end of the study, and 19 cases without PC died of GC. The clinicopathological characteristics of these cases are described in Table 2.

Pathologic examination of PC with long survival showed scarce tumor cells or extensive inflammatory cell infiltration including many neutrophils (Fig. 1). Out of total 252 cases, 139 cases (55.2%) were score 0, 95 cases (37.7%) were score 1, and 18 cases (7.1%) were score 2 for inflammation. For degree of fibrosis, 35 cases (13.9%) were score 0, 155 cases (61.5%) were score 1, and 62 cases (24.6%) were score 2. The degrees of inflammation ($p < 0.001$) and fibrosis ($p < 0.01$) were significantly higher in PC-positive cases compared to PC-negative patients. In PC-positive subgroup, surviving patients showed higher degree of inflammation compared to patients who died of disease with statistical significance ($p < 0.001$). All patients with PC with long survival were treated with adjuvant or palliative chemo-radiation therapy after surgery. Of patients with GC and peritoneal biopsy confirmed as negative who died of disease, 4 had pathologic stage IV GC (distant metastasis to liver, colon, and bone). The causes of death in these patients are described in Table 2.

After comparing frozen and permanent sections, discrepant diagnoses were made in 6 cases (2.4%). Positive conversion was confirmed in 5 cases. Fig. 2 shows a case with cancer cells scattered in dense fibrotic stroma admixed with inflammatory cells. In the permanent section slide, tumor cell nuclei were hyperchromatic, large, and positive by pan-cytokeratin IHC. Of the 4 remaining cases, 3 showed extensive fibrosis with desmoid-like features, and one showed dense inflammatory cell infiltration. Negative conversion was observed in one case where papillary proliferation of mesothelial cells mimicked metastatic adenocarcinoma on the FS slide. On the permanent slide, the cells were mainly located in the periphery of the peritoneal biopsies. The cells

Table 2
Compared Clinicopathological Characteristics Between Alive But Seeding Positive Groups and Dead But Seeding Negative Groups.

		Alive but seeding present (9 cases)	Dead but seeding negative (19 cases)
Sex			
	Male	3 (33.3%)	11 (57.9%)
	Female	6 (66.7%)	8 (42.1%)
Mean age		58.2 (39–70)	63.8 (32–83)
Survival times (days)		1062 (314–3574)	833 (87–3649)
Median duration of follow up (days)		591	524
Operation			
	No	4	2
	Subtotal gastrectomy	1	9
	Total gastrectomy	4	8
Resection margin status			
	Negative	4 (80%)	16 (94.1%)
	Positive	1 (20%)	1 (5.9%)
Lauren histologic type			
	Intestinal	1 (20%)	6 (35.3%)
	Diffuse	4 (80%)	9 (52.9%)
	Mixed	0	1 (5.9%)
	Indeterminate	0	1 (5.9%)
Clinical staging[a]			
	I	0	2 (10.5%)[b,c]
	II	0	0 (0%)
	III	1 (20%)	4 (21.1%)
	IV	4 (80%)	13 (68.4%)
Pathologic staging[a]			
	I	0	2 (10.5%)
	II	0	1 (5.2%)
	III	0	12 (63.2%)
	IV	5 (100%)	4 (21.1%)
Neoadjuvant chemotherapy			
	No	9 (100%)	16 (84.2%)
	Yes	0	3 (15.8%)
Postoperative therapy			
	No	0	4 (21.1%)
	Adjuvant	1 (12.5%)	4 (21.1%)
	Palliative	8 (87.5%)	11 (57.8%)
Cause of death			
	Medical problem	–	3 (15.8%)†
	Colon carcinoma	–	1 (5.2%)§
	Disease progression	–	15 (79.0%)

[a] American Joint Committee on Cancer (AJCC) 8th cancer staging.
[b] One patient dead due to other medical cause.
[c] One patient dead due to metachronous colon carcinoma.

were positive for calretinin and D2-40 IHC, confirming them as mesothelial cells rather than GC tumor cells (Fig. 3).

Peritoneal biopsies without tumor cells and representative pathologic findings were thoroughly reviewed, and the results are demonstrated in Fig. 4. Fibrosis with chronic inflammation was found in 25 cases (48.1%), and 10 cases (40%) had history of prior abdominal surgery. Papillary mesothelial proliferation (17.3%) was the second most common cause of a frozen consultation considered suspicious for peritoneal seeding nodule by surgeons (Table 3).

4. Discussion

To explore the diagnostic accuracy and diagnostic pitfalls during FS of the peritoneum, we directly compared frozen and permanent sections

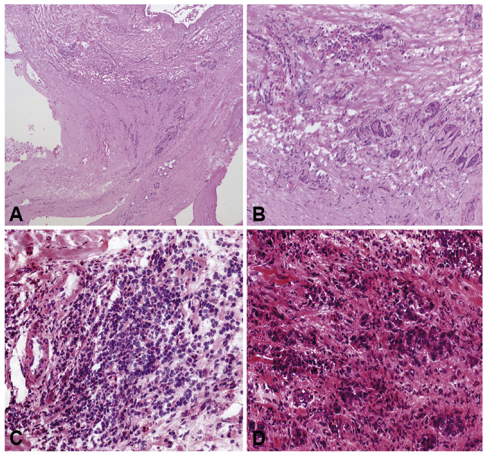

Fig. 1. Tumor cells in peritoneal seeding nodules of living patients. Inflammatory cells infiltration around tumor cells. (**a**) Scarce tumor cells with inflammatory cells in fibrotic stroma, low power field (×100). (**b**) High power field (×200). (**c** and **d**) Many inflammatory cells admixed with tumor cells.

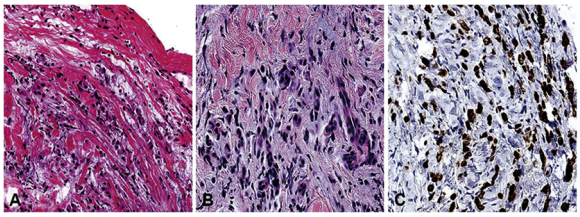

Fig. 2. Frozen and corresponding permanent H&E slides of positive conversion cases. (**a**) Frozen section. It was difficult to identify tumor cells due to many inflammatory cells and fibrosis. (**b**) Permanent section showed tumor cell infiltrates associated with fibrosis and admixed with numerous lymphocytes. (**c**) Tumor cells show strong positivity for AE1/AE3 (pan-cytokeratin) (H&E: hematoxylin and eosin).

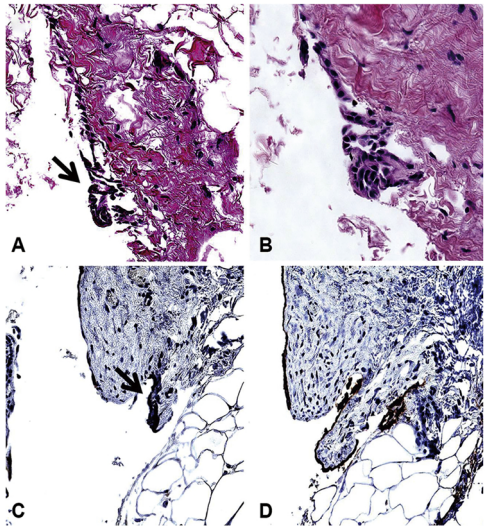

Fig. 3. Frozen and corresponding permanent H&E slides of negative conversion discrepant case. (**a**) Frozen slide showed hyperchromatic cells with papillary projections (black arrow). (**b**) Permanent slide showed bland mesothelial cells. Mesothelial cells were confirmed by calretinin (**c**) and D2-40 (**d**), immunohistochemistry. Mesothelial proliferation masquerades as carcinoma (H &E: hematoxylin and eosin).

of peritoneal biopsy specimens in a comprehensive cancer center in a GC prevalent area. We found discrepancies in 2.4% of cases. Marked chronic inflammation and fibrosis were the most frequent causes of

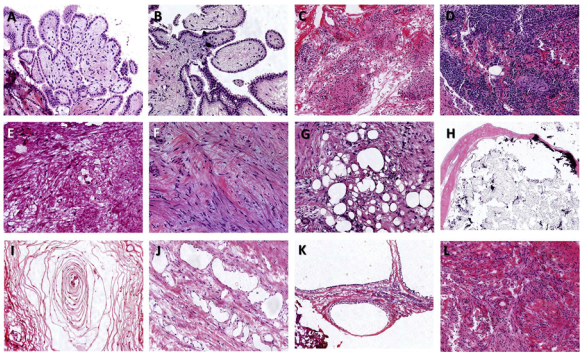

Fig. 4. Histology of peritoneal seeding negative group. Papillary mesothelial proliferation (**a** frozen sections; **b** corresponding permanent sections), chronic granulomatous inflammation (**c**, frozen; **d**, permanent), chronic inflammation with fibrosis (**e**, frozen; **f**, permanent), fat necrosis and calcification (**g** and **h**), edematous nerve (**i**), ectatic vessels (j), mesothelial inclusions (**k**), and incidental extra-gastrointestinal stromal tumor (**l**).

Table 3
Causes of Frozen Consultation of Suspicious Peritoneal Seeding Nodules During Gastric Carcinoma Surgery.

Final pathologic diagnoses	Number of case
Fibrosis with chronic inflammation	25
Prior abdominal operation history	10
Idiopathic	15
Papillary mesothelial proliferation	9
Ectatic vessels	5
Mesothelial inclusions	3
Fat necrosis with calcification	3
Extra-gastrointestinal stromal tumor	2
Chronic granulomatous inflammation	2
Edematous nerves	2
Castleman's disease	1
Total	52

discrepancy.

Intraoperative consultation (frozen section) is one of the most important, difficult, and stressful tasks of pathologists [1]. Carrying out an intraoperative consultation requires experience, knowledge of clinical information, the capacity to make quick decisions under pressure, and a keen awareness of the method's limitations [13]. Three acceptable purposes for a FS are: (1) to establish the presence and nature of a lesion; (2) to determine the adequacy of surgical margins; and (3) to establish whether the tissue obtained contains diagnosable material or whether additional sampling is indicated [18]. PC is a common disseminated type of metastasis and the most frequent pattern of recurrence in patients with GC, especially diffuse-type cancer by Lauren classification [9,10]. PC compromises gastrectomy and is associated with poor prognosis because it can lead to bowel obstruction and malignant ascites [19,22]. In this clinical setting, suspicious lesions seen within the peritoneal cavity are often sent for FS diagnosis. For pathologists, these cases are challenging because GC is often comprised of sparse and discohesive cancer cells, particularly in cases with poorly differentiated or signet ring cell histology. These tumor cells do not form glandular structures, are often small or inconspicuous, and may resemble histiocytes, plasma cells, or lymphocytes [21]. Despite the importance and difficulty of evaluating FS in GC, the differential diagnosis and diagnostic pitfalls of peritoneal seeding nodules on FS have not been extensively evaluated. In this study, we explored the diagnostic accuracy and pitfalls during FS of peritoneal seeding nodules in patients with GC.

The overall accuracy of FS in several hospitals of the United States and United Kingdom is about 95.8% (88.9–98.9) [16]. The accuracy of FS in the present study was 97.6%. Discrepant results were observed in 6 cases (2.4%). In all discrepant cases, intra-departmental consultation, deeper sections, or recuts were not performed. In 32 cases (12.7%), intra-departmental consultation with a more experienced pathologist was performed. In 43 cases (17.1%), deeper cuts were obtained. In those cases, the diagnostic accuracy was 100%. In 6 cases with discrepancy, all the patients had been underwent gastrectomy because surgeon based on their clinical decision and operability and all of them received palliative chemotherapy.

For FS diagnosis of peritoneal biopsies, precise pathologic features and the diagnostic accuracy of intraoperative consultation have not been reported. There is one case report of a foreign body granuloma after gastric perforation mimicking peritoneal dissemination of GC [2]. Basaran et al. reported that the main causes of discrepant cases are misinterpretation and sampling error [3]. In our study, the main reason for discrepancy was misinterpretation of the original FS. Five cases with positive conversion showed tumor cells scattered in dense fibrotic stroma admixed with chronic inflammatory cells. In the FS, discrimination of tumor cells and inflammatory cells is very challenging. In the corresponding permanent slide, tumor cell nuclei were hyperchromatic, large, and positive for pan-cytokeratin IHC. Negative conversion was observed in one case with papillary proliferation of mesothelial cells mimicking metastatic adenocarcinoma on the FS slide. From this study, we found that, when cells are larger and more hyperchromatic than background stromal or inflammatory cells on FS, more caution is needed. Deeper sections or recuts may help to identify obvious cancer cells in this circumstance. We also found many cases of papillary mesothelial cell proliferations on peritoneal biopsy, which warrant further caution.

By the end of follow up, 92.5% of patients with peritoneal seeding had died. Unexpectedly, 9 cases with PC were alive: 5 patients received palliative gastrectomy and postoperative chemotherapy and 4 patients were treated with palliative chemotherapy. Li et al., reported that complete gross peritonectomy following gastrectomy confers a survival benefit to GC patients with PC and postoperative chemotherapy improves survival regardless of peritonectomy [15]. Thorough pathologic examination of long term survivors with PC showed scarce tumor cells in a dense fibrotic background or extensive inflammatory cell infiltration. Inflammatory reactions may be a favorable predictive or prognostic factor in GC patients [5,7,14,17]. Based on these findings, our long term survivors of GC with PC may be caused by intensive treatment and inflammatory reactions within the tumor.

In contrast, 19 GC patients without PC were died and 15 (79.0%) of them were died of GC progression. We carefully reviewed all peritoneal biopsy slides but failed to identify any tumor cells on both frozen and corresponding permanent sections. Peritoneal sampling error could account for this unexpected result because we found cancer cells in peritoneal cytologic examinations [3]. In the remaining cases, acute kidney injury, metachronous carcinoma other than GC, and other medical illnesses were the causes of death.

In conclusion, peritoneal biopsies in patients with GC were mostly carcinoma (200 cases), followed by chronic inflammation with fibrosis (25 cases) and papillary mesothelial cell proliferation (9 cases). Caution is needed to identify scarce cancer cells, and deeper sections or intradepartmental consultations are helpful to reduce false negative diagnosis on FS.

5. Conclusion

GC is common cancer in Korea and worldwide and its prognosis is still poor due to the majority of patients presenting with GC have advanced stage such as PC. During gastrectomy, nodular lesions in peritoneum are often sent for FS. For pathologists, this is challenging due to sparse and discohesive tumor cells in a fibrotic background. Despite the importance and difficulty of evaluating FS in GC, the differential diagnosis and diagnostic pitfalls of peritoneal seeding nodules on FS have not been extensively evaluated. The current study reveals peritoneal

biopsies in patients with GC were mostly carcinoma, followed by chronic inflammation with fibrosis and papillary mesothelial cell proliferation. Cases with deeper sections or intradepartmental consultations have 100% accuracy. Pathologists need more prudence when FS slides show hypercellularity with fibrotic background and should understand exact clinical history of patients. Deeper cut or consultations were helpful to reduce false negative diagnosis on FS of peritoneal biopsies in GC patients.

Ethics approval and consent to participate

Written, informed consent to donate their tissues and clinical data for research from all patients.

Consent for publication

Not applicable.

Availability of data and material

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

HB searched and reviewed all slides, collected clinicopahologic data, and wrote the manuscript; HK has been involved in drafting the manuscript and revising it critically for important intellectual content; JC has been involved in the statistical test; SYH, KTJ, and KMK reviewed and approved the pathologic diagnoses; YJ, HHK, and HJ made critical assessment of the article; All authors reviewed and approved the final version of the manuscript.

Conflicts of interest and source of funding

The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

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