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Is cell block technique useful to predict histological type in patients with ovarian mass and/or body cavity fluids?

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ABSTRACT

The cell block (CB) technique is a generalized method utilized for the diagnostic evaluation of body cavity fluids. Ascites cytology is one of the most important diagnostic processes for epithelial ovarian cancer. However, in clinical practice, the usefulness of the CB method to diagnose this tumor remains unelucidated. Between 2008 and 2017, 15 peritoneal or pleural fluid samples obtained from patients with ovarian or peritoneal carcinoma or other gastrointestinal malignancies were preoperatively subjected to a diagnostic evaluation to predict the histological type and original organ. The CBs were made from 10% formalin neutral buffer solution fixed sediments of fluid samples after cytological smears were made by conventional method. Four-μm thickness sections were prepared from the cell blocks and stained with immunohistochemical method, using 16 kinds of antibodies and hematoxylin eosin staining method. The cellularity, architectural patterns, and morphological details were also studied. The median (range) age of patients was 73 (35–87) years. The clinical features were identified as follows: pleural effusion in 4, ovarian mass in 7, peritoneal dissemination in 12, para-aortic nodal swelling in one, and liver tumor in one (some overlapping). Five patients had a history of prior malignancy. Finally, we could accurately diagnose the histological type in 9 patients based on subsequent biopsy, surgery, and autopsy. In all 9 women, the clinical diagnosis, CB diagnosis and final pathological diagnosis were consistent. The CB technique may be a helpful modality for evaluating fluid cytology to obtain a final histopathologic diagnosis.

Keywords: epithelial ovarian cancer, cell block technique, histological type, carcinomatosis, fluid cytology

Abbreviations:
CB: Cell block
IHC: immunohistochemistry
POC: primary ovarian carcinoma
HGSC: high-grade serous ovarian carcinoma
PPC: primary peritoneal carcinoma
ER: estrogen receptor
PgR: progesterone receptor

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INTRODUCTION

Primary ovarian carcinoma (POC) is one of the most aggressive malignancies among cancers of the female reproductive system. The recent Cancer Statistics in United States estimated that 22,440 women were newly diagnosed, and 14, 080 died of this tumor.[1] According to Japanese Registry and Statistics, the total number of cases and mortality were 9,804 and 4,758, respectively, in 2016.[2] In contrast to other gynecologic cancers such as cervical, endometrial, and vulvar cancer, this tumor frequently causes no apparent symptoms in the early stages.[3] However, an abdominal mass and/or fullness is a major symptom in women with disease as the tumor enlarges. Clinically, reflecting the fact that the ovary is an intra-abdominal organ, ovarian carcinoma can readily expand into the peritoneal cavity. Therefore, at the initial diagnosis, the majority of this tumor is stage III or higher. As a result, curative and complete surgical resection is not an option for most patients.[3] The majority of those patients have multiple peritoneal metastases with a large amount of ascites, including the Pouch of Douglas, small bowel mesentery, ileocecal junction, paracolic gutters, hepatorenal fossa, and right subphrenic space.[4] The primary cytology of ascites is essential for an accurate diagnosis, therapeutic decision, and prognosis.[5] However, diagnosing cells as being either malignant or benign 'reactive mesothelial cells' in serous effusions is a common diagnostic problem.[6] In addition, these tumors are sometimes considered to have originated from non-ovarian organs as metastatic lesions since ovary is a common site of metastasis from many cancers.[3] In particular, we have frequently encountered difficulty in distinguishing between primary ovarian carcinoma and metastasis from other organs until obtaining the final histological findings.[7] Particularly, to discriminate primary and metastatic ovarian carcinomas is of marked clinical importance, because an accurate diagnosis promotes the appropriate selection of chemotherapy, leading to a better oncologic outcome. Actually, the standard chemotherapeutic agents for patients with POC and colorectal mucinous carcinomas are individually defined as the taxane plus platinum combination and fluoropyrimidines, respectively. Therefore, an expert physician sincerely wants to know the accurate pathological diagnosis to appropriately conduct subsequent therapy. However, the morphological examination of cytological samples is not a highly sensitive diagnostic tool to distinguish primary from metastatic carcinoma in ascites. The cell block (CB) technique, which is traditional a method for evaluating body cavity effusion, is frequently helpful when cytological abnormalities are misleading. However, in clinical, the utility of CB methods to diagnose this tumor remains unelucidated. The current study was conducted to examine whether CB using a panel of a variety of antibodies can help improve the accuracy of diagnosing ovarian carcinoma.

MATERIALS AND METHODS

Patients

Between 2008 and 2017, 15 peritoneal or pleural fluid samples obtained from patients with primary ovarian or peritoneal carcinoma or other gastrointestinal malignancies were preoperatively subjected to a diagnostic evaluation to predict the histological type and original organ. Clinicopathologic parameters, the diagnostic modality, treatment, and oncologic outcome were retrospectively analyzed. In all cases, the CB technique accompanied by immunohistochemical (IHC) analyses was conducted to distinguish primary carcinomas derived from the ovary, fallopian tube, and peritoneum from metastatic carcinoma from other organs. The sections were immunostained with primary antibodies against the following targets (clinical significance: source: clone): Ber-EP4 (adenocarcinoma: Agilent: Ber-EP4), calretinin (malignant mesothelioma: Life

Technologies: DC8), p53 (serous POC/peritoneal carcinoma: Roche: DO-7), CDX2 (gastric carcinoma/colorectal carcinoma/mucinous POC: Roche: EPR2764Y), CK5/6 (malignant mesothelioma: Roche: D5/16B4), CK7 (POC/ gastric carcinoma/colorectal carcinoma/ malignant mesothelioma: Roche: SP52), CK20 (POC/ gastric carcinoma/colorectal carcinoma/ malignant mesothelioma: Roche: SP52), podoplanin (malignant mesothelioma: Roche: D2-40), EMA (Roche; E29), ER (estrogen receptor) (serous POC/peritoneal carcinoma: Roche: SP1), PgR (progesterone receptor) (serous POC/peritoneal carcinoma: Roche: IE2), TTF-1 (Thyroid carcinoma/lung carcinoma: Roche: SP141), CEA (mucinous POC, carcinoma from gastrointestinal tract: Nichirei Bioscience: COL-1), CA125 (serous POC/peritoneal carcinoma/inflammation: Agilent: M11), WT-1 (serous POC/peritoneal carcinoma/inflammation/ malignant mesothelioma: Agilent: 6F-H2), CA19-9 (Pancreatic carcinoma/cholangiocarcinoma/ serous POC/peritoneal carcinoma: Agilent: 116-NS-19-9), mammaglobin (Breast carcinoma: Agilent: 304-1A5). The cellularity, architectural patterns, morphological details, and cytoplasmic and nuclear details were also studied. In all cases, systemic computed tomography (CT), gastroscopy, and colonoscopy were performed to exclude cancers derived from the digestive tract, breast, and other sites. This study was approved by the ethics committee of Ekisaikai Hospital.

The cell block technique

The 10 mL fluid was centrifuged at 2,500 rpm for 5 minutes. Cytological smears were prepared from the sediment after discarding the supernatant and added 10% neutral buffered formalin and fixed for 20 minutes. After supernatant was discarded, sodium alginate was added and centrifuged 5 minutes. The sediment was used to make a paraffin block. The paraffin embedding 4-μm-thick sections were made from paraffin cell blocks and they were used to stain with immunohistochemical and hematoxylin eosin staining methods.

RESULTS

Clinical backgrounds of these 15 patients are shown in Table 1. The median age at the time of diagnosis was 73 years (range, 35–87). Based on several imaging analyses, the presence of an ovarian mass, pleural effusion, peritoneal dissemination, swelling of a para-aortic lymph node, and a liver mass were identified in 7 (No. 2, 3, 4, 8, 10, 14, and 15), 4 (No. 3, 8, 11, and 12), 12 (all patients excluding for No. 12, 13, and 15 patient), 1 (No. 8), and 1 (No. 14) patient, respectively (some overlapping). Representative diagnostic images (CT or MRI) of Patients No.1, 2, 6, and 9 are shown in Figure 1. Five patients had a history of previous cancer. In one patient, detailed investigation of the gastrointestinal tract detected the presence of a tumor. Table 2 shows the estimated original tumor based on IHC staining. Because of a limitation of reagents, multiple IHC staining was not performed in Patient No.13, 14, and 15. Based on the IHC activity, a four-tiered semiquantitative score was assigned according to the intensity and area of stained cells as follows: (–): negative, (±): weak, (+): medium, and (++): strong. Through this analyses, we suspected serous primary ovarian carcinoma (POC) or primary peritoneal carcinoma (PPC) in Patients No.1 to 11. Although Patients No.2 and 6 had a history of breast carcinoma, their samples were negative for mammaglobin. Thus, in these women, breast carcinoma was likely to be negative. In Patient No.4 who had a history of gastric carcinoma, POC (HGSC) or PPC was suspected because of positive CA125 and ER expressions. From Patients No.12 to 15, we only detected adenocarcinoma, without more detailed pathological diagnosis. Representative images of each histological feature in Patients No.5, 6, and 14 are shown in Figure 2.

Table 3 shows summary of cytological diagnosis, IHC findings of cell block methods, and

final histological results. In CB specimens of Patients No. 1–7, the possibility of malignant mesothelioma was excluded as a result of IHC, including calretinin, podoplanin, CK5/6, and BerEP4. Since the samples of those patients were positive for CA125 and p53 and negative for CDX2, these results were consistent with HGSC or PPC as a final diagnosis. In samples from Patients No. 8–10, histological architectures were similar to those of No. 1–7; however, p53 overexpression was not detected, being consistent with low-grade serous carcinoma. Because those in Patients No. 13–15 were positive for CEA, CA19-9, and CDX2, carcinomas from the gastrointestinal tract were suspected. Finally, we could accurately diagnose the histological type in 9 patients based on subsequent biopsy, surgery, and autopsy followed by CB diagnosis. In 6 of 9 women, we could speculate on the precise pathology. Nevertheless, in the remaining 3 of the 9 patients, we could predict adenocarcinoma originated from the gastrointestinal tract. Namely, in these 9 patients, the clinical diagnosis, CB diagnosis with or without IHC technique, and final pathological diagnosis were consistent. Among six patients who were not given a final pathological diagnosis, 5 women (No. 4, 6, 7, 9, and 10) were tentatively considered to have PPC or POC based on the results of CB, and underwent primary chemotherapy with a positive therapeutic effect. Nevertheless, in the remaining 1 patient, we could not accurately diagnose its histological type by either clinical diagnosis including image and conventional cytological analysis or the CB-IHC technique. At present, No. 4 is alive with disease, and No.6 died of disease after transient clinical remission.

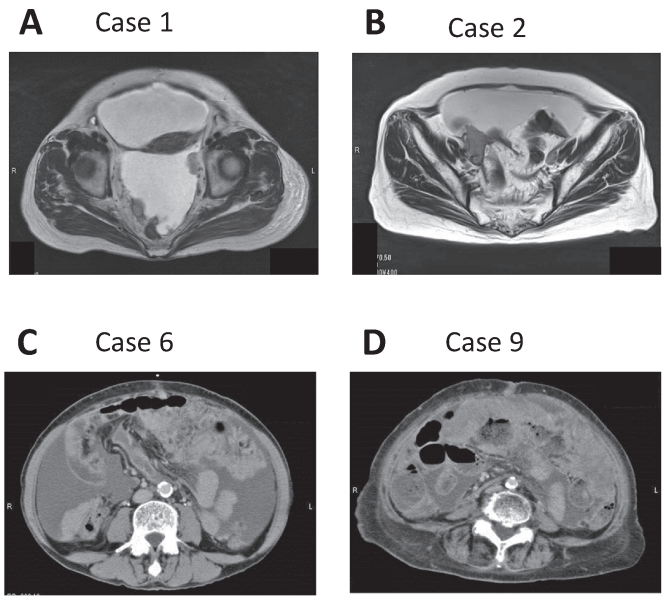

Fig. 1 Representative diagnostic images
Fig. 1A: Case 1 (MRI).
Fig. 1B: Case 2 (MRI).
Fig. 1C: Case 6 (CT).
Fig: 1D: Case 9 (CT).

Table 1 Characteristics of patients

Patient No.	Age	Main image findings*			Ascites	Other metastatic site	Major symptoms	History of cancer	Abnormal findings in GI tract
		Pleural effusion	Ovarian mass	Peritoneal dissemination					
1	75	(–)	(–)	Grossly	Large	PC	Ascites	(–)	(–)
2	71	(–)	(+)	Paucity	Large	PC	Ascites	BC	(–)
3	71	(+)	(+)	Grossly	Large	PC	OM, Ascites, PE	(–)	(–)
4	67	(–)	(+)	Grossly	Large	PC	Ascites	GC	(–)
5	64	(–)	(–)	Paucity	Large	PC	Ascites	(–)	(–)
6	74	(–)	(–)	Paucity	Large	PC	Ascites	BC	(–)
7	74	(–)	(–)	Paucity	Large	PC	Ascites	(–)	(–)
8	37	(+)	(+)	Grossly	Large	PAN swelling	OM, Ascites, PE	(–)	(–)
9	87	(–)	(–)	Paucity	Large	PC	Ascites	(–)	(–)
10	55	(–)	(+)	Paucity	Small	PC	OM, Ascites	(–)	(–)
11	77	(+)	(–)	Paucity	Large	PC	Ascites, PE	(–)	(–)
12	73	(+)	(–)	No	Large	PC	Ascites, PE	(–)	(–)
13	76	(–)	(–)	No	Large	PC	Ascites	CRC, GC	CRC, GC
14	75	(–)	(+)	Paucity	Large	Liver	OM, liver mass	(–)	Ascending colon tumor
15	35	(–)	(+)	No	Small	PC	PM	CRC (appendix)	CRC (appendix)

*CT and/or MRI findings and/or PET (positron emission tomography)-CT, PC: peritoneal carcinomatosis, PAN: paraaortic lymph node, PE: pleural effusion, OM: ovarian mass, PM: pelvic mass, BC: breast carcinoma, GC: gastric carcinoma, CRC: colorectal carcinoma, GI tract: gastrointestinal tract.

Table 2 Summary of immunohistochemical findings using cell block methods

Patient No.	Sample	Cal-retinin	podo-planin	CK5/6	CA125	CK7	CK20	ER	PgR	WT1	BerEP4	CEA	CA19-9	CDX2	TTF1	mamma-globin	p53 OE	Estimated disease at clini-cal diagnosis
1	Ascites	(–)	(–)	(++)	(++)	(++)	(–)	(++)	(–)	(–)	(++)	(±)	(+)	(–)	(–)	(–)	(++)	sEOC, PPC
2	Ascites	(–)	(–)	(–)	(++)	(++)	(–)	(++)	(–)	(++)	(++)	(–)	(±)	(–)	(–)	(–)	(++)	sEOC, PPC
3	PE	(±)	(±)	(±)	(++)	(++)	(±)	(++)	(+)	(++)	(++)	(–)	(++)	(–)	(–)	(–)	(++)	sEOC, PPC
4	Ascites	(–)	(±)	(±)	(++)	(++)	(–)	(++)	(–)	(++)	(++)	(–)	(++)	(–)	(–)	(–)	(++)	sEOC, PPC
5	Ascites	(±)	(+)	(–)	(++)	(++)	(–)	(–)	(–)	(+)	(++)	(–)	(–)	(–)	(–)	(–)	(++)	sEOC, PPC
6	Ascites	(–)	(±)	(–)	(++)	(++)	(–)	(++)	(–)	(++)	(++)	(±)	(++)	(–)	(–)	(–)	(++)	sEOC, PPC
7	Ascites	(–)	(–)	(±)	(++)	(++)	(–)	(–)	(+)	(+)	(++)	(+)	(±)	(–)	(–)	(–)	(++)	sEOC, PPC
8	Ascites	(–)	(–)	(±)	(++)	(++)	(–)	(+)	(–)	(+)	(++)	(++)	(–)	(–)	(–)	(–)	(–)	sEOC, PPC
9	Ascites	(–)	(–)	(–)	(++)	(++)	(–)	(++)	(–)	(+)	(++)	(–)	(–)	(–)	(–)	(–)	(–)	sEOC, PPC
10	Ascites	(+)	(+)	(±)	(+)	(±)	(–)	(++)	(±)	(++)	(–)	(–)	(–)	(–)	(–)	(–)	(–)	sEOC, PPC
11	PE	(±)	(±)	(+)	(++)	(++)	(–)	(–)	(–)	(–)	(++)	(++)	(++)	(–)	(–)	(–)	(++)	sEOC, PPC
12	Ascites	(–)	(–)	(±)	(±)	(++)	(–)	(–)	(–)	(–)	(++)	(++)	(++)	(–)	(–)	(–)	(++)	AC
13	Ascites	(–)	(–)	(–)	(±)	(–)	(–)	(–)	(–)	(–)	(++)	(++)	(+)	(++)	(–)	(–)	(++)	AC
14	Ascites	(–)	(–)	(±)	(+)	(+)	(–)	(–)	(–)	(+)	(+)	(++)	(++)	(+)	(–)	(–)	(–)	AC
15	Ascites	(–)	(–)	(–)	(±)	(±)	(±)	(–)	(–)	(–)	(++)	(++)	(++)	(++)	(–)	(–)	(++)	AC

Based on the immunostaining activity, a semiquantitative classification was assigned according to the intensity and area of stained cells. The classification is as follows: (–): negative, (±): weak, (+): medium, and (++): strong. IHC intensity: PE: pleural effusion, sEOC serous epithelial carcinoma, AC: adenocarcinoma, PPC: peritoneal carcinoma.

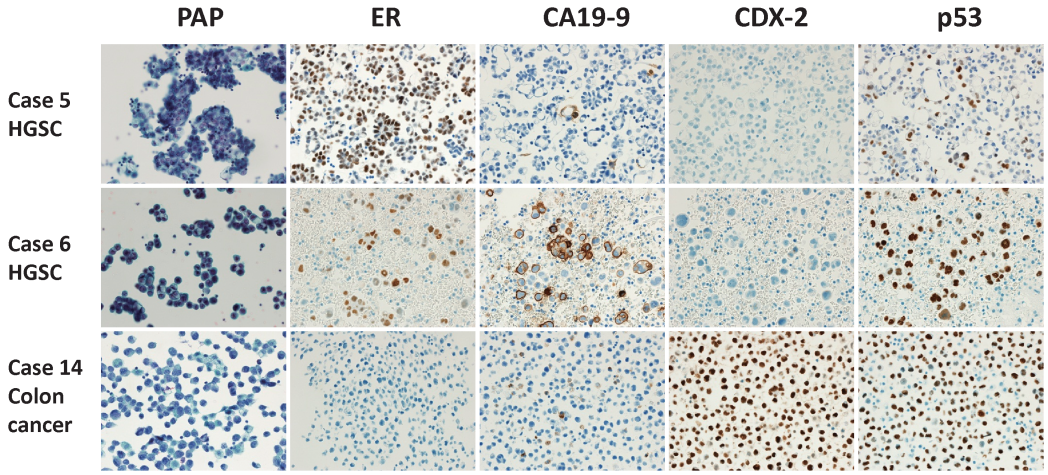

Fig. 2 Representative images of immunohistochemical staining for ER, CA19-9, and CDX-2. (×400)
HGSC: high-grade serous carcinoma.

DISCUSSION

Because the ovary exists in the abdominal cavity, POC can easily spread to other parts of the peritoneal cavity. Thus, frequently in clinical practice, widespread intraabdominal disease with peritoneal metastases is present, referred to as peritoneal carcinomatosis.[3]

HGSC is the most frequent subcategory identified in women with POC. Although patients with HGSC are asymptomatic, the majority of them have numerous intraperitoneal disseminations and a marked amount of ascites at the initial diagnosis. On the other hand, the accumulation of malignant pleural effusion is one of the most common symptoms of stage IV POC or breast carcinoma. A positive cytology is required for a stage IVA diagnosis. Thus, an accurate cytological diagnosis of POC/HGSC based on ascites and/or pleural effusion is crucial for appropriate staging and decision-making in clinical practice, particularly in women scheduled for fluid cytology before undergoing preoperative chemotherapy. In contrast, according to a variety of prior reports, cytological examination based on morphological features is not necessarily an accurate diagnostic modality to discriminate an intrafluid tumor from reactive mesothelial cells, which often resemble malignancy in a conventional smear.[5,8] Actually, it is difficult to precisely discriminate reactive mesothelial cells from tumor cells by morphologic characteristics alone.

The CB technique is a traditional diagnostic modality used for evaluating body fluids, including ascites and pleural effusion. One of the benefits of the CB method is the ability to obtain multiple sections for IHC staining. According to earlier studies, calretinin is a specific and sensitive indicator of both malignant and normal mesothelial cells, while all metastatic adenocarcinomas display negative nuclear staining to calretinin.[5,9] Also, Cytokeratin 5/6 (CK 5/6) is a suitable marker for the identification of mesothelioma or reactive mesothelial cells.[10] The mesothelial cells exhibit strong membrane IHC activity when stained with cytokeratin.[9,10] Based on the current study, in a half of patients, the possibility of malignant mesothelioma was excluded based on results of IHC, including calretinin, podoplanin, CK5/6, and BerEP4. In addition, according to positive IHC findings of CA125 and p53 and negative CDX2, we could make a final diagnosis of HGSC or PPC as a final diagnosis. Furthermore, we could accurately diagnose the histological type in the majority of patients (9 patients) based on subsequent biopsy, surgery, and autopsy followed by

CB diagnosis. Finally, we could accurately diagnose the histological type in 9 patients based on subsequent biopsy, surgery, and autopsy followed by CB diagnosis. In all 9 women, the clinical diagnosis, CB diagnosis with or without IHC technique, and final pathological diagnosis were consistent. Among six patients who were not given a final pathological diagnosis, 5 women were tentatively considered to have PPC or POC based on the results of CB, and underwent primary chemotherapy with a positive therapeutic effect. Taken together, in 14 of the 15 (93.3%) women, we could predict its histological type. Although further study is necessary, these results indicate that the CB technique using IHC staining as wells as conventional cytology may be useful to accurately diagnose its pathological type and predict the following clinical outcome.

The ovary is a comparatively frequent site of metastasis from other extra-ovarian malignancies, being a common site of metastasis from a variety of cancers. In fact, it is very difficult to accurately estimate the incidence of metastatic ovarian carcinoma due to different methods of pathological assessment and analysis. In addition, there is also wide geographical variation in the incidence of common gastric, breast, and colorectal carcinomas as well as changing incidences in many populations in recent decades.[7] Indeed, about 4% of women with carcinoma from the gastrointestinal tract had a risk of ovarian metastasis during the course of their disease.[11-13] The most and second most frequent original tumors were colorectal (43%, N=62) and gastric (29%, N=42) carcinoma, respectively.[14] Regarding body fluid, as well as endometrial and ovarian carcinoma, gastric, pancreatic, and colorectal malignancies are frequently associated with malignant ascites.[1] The major extra-abdominal tumors from malignant ascites are breast and lung carcinomas and lymphoma. In the current study, in two patients (No.2 and 6) who had a history of breast carcinoma, breast carcinoma was ruled out because of negative IHC staining for mammaglobin. In one patient (No.4) who had a history of gastric carcinoma, HGSC or PPC was suspected because of positive CA125 and ER expressions. Furthermore, in two patients with positive IHC staining for CEA, CA19-9, and CDX2, carcinoma from the gastrointestinal tract was suspected. Similarly, TTF-1 nuclear staining proved useful for lung carcinomas, ER/PR staining helped to identify primary disease of the breast, and CDX2 nuclear staining proved an intestinal origin. Furthermore, the immunohistochemical staining pattern of cytokeratins 7 and 20 (CK7/20) is useful to distinguish primary and metastatic OC from gastrointestinal tract tumors.[15,16] In the almost universally CK7-negative metastases of lower gastrointestinal tract origin, coordinate expressions of CDX2 (83%) and cytokeratin 20 (86%) were equivalent. CDX2 was comparable to CK20 in distinguishing metastases of lower gastrointestinal tract origin (CK7-negative and CDX2/CK20-positive) from primary ovarian tumors and metastases of upper gastrointestinal tract origin (CK7-positive and CDX2/CK20 variable).[17] Thus, even if patients have a history of malignancy, IHC examination specific for breast and the gastrointestinal tract-derived carcinoma is helpful for both accurate and exclusive diagnoses.

In summary, the CB technique definitively increased the detection of malignancy in body cavity effusion when used as an adjunct to conventional smears. Morphological and architectural features are better identified with the CB technique, improving sensitivity. In this study, we could accurately diagnose serous POC or peritoneal carcinoma in the majority of patients. Thus, the current study demonstrated that the CB technique was useful for accurate pathological diagnosis of original carcinoma from ascites and/or pleural effusion, leading to appropriate staging and decision-making in clinical practice, especially for women undergoing neoadjuvant chemotherapy.

Table 3 Summary of cytological diagnosis, IHC findings of cell block methods, and final histological results

Patient No.	Sample of cytology	Cytological diagnosis	Clinical diagnosis w/o CB-IHC	Estimated disease with CB-IHC	Histological examination	
					Sampling Tissue	Final pathological diagnosis
1	Ascites	poorly diff. AC	POC or PPC	POC or PPC[#3]	PDT	PPC
2	Ascites	AC	POC or PPC	POC or PPC[#3]	PDT (autopsy)	PPC
3	PE	AC	POC or PPC	POC or PPC[#3]	Ovary	PPC
4	Ascites	AC	POC or PPC	POC or PPC[#3]	*NA*	(–)
5	Ascites	AC	POC or PPC	POC or PPC[#3]	PDT (autopsy)	PPC
6	Ascites	AC	POC or PPC	POC or PPC[#3]	*NA*	(–)
7	Ascites	AC	POC or PPC	POC or PPC[#3]	*NA*	(–)
8	Ascites	AC	POC or PPC	POC [#4]	RPN	POC
9	Ascites	AC	POC or PPC	POC[#4]	*NA*	(–)
10	Ascites	AC	POC or PPC	POC (atycal LGSC)	*NA*	(–)
11	PE	AC	POC or PPC	POC or PPC (atypical)	PDT (autopsy)	PPC
12	Ascites	AC	Unknown	Origin unknown[#1]	*NA*	(–)
13	Ascites	AC	GC	CRC or GC (CRC<GC)	PDT	GC
14	Ascites	Malignant cells	OC ≤ CRC	Carcinoma from GI tract + RM	Liver metastasis	CRC[#2]
15	Ascites	AC	Metastatic OC	Carcinoma from GI tract + RM	Ovary	CRC

CB-IHC: cell-block with or without immunohistochemical staining technique, PE: pleural effusion, AC: adenocarcinoma,
POC: primary ovarian carcinoma, PPC: primary peritoneal carcinoma, RM: reactive mesothelial cells, CRC: colorectal carcinoma,
GC: gastric carcinoma: PDT: peritoneal disseminated tumor, NA: not applicable, #1: suspicious for Cholangiocarcinoma or pancreatic carcinoma,
#2: moderately defferentiated adenocarcinoma (tub2), #3: high-grade serous carcinoma, #4: low-grade serous carcinoma.

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AUTHOR CONTRIBUTION STATEMENT

Data collection, analysis, and interpretation: Z. Maseki, T. Misawa, Writing draft: H. Kajiyama, Pathological evaluation: E. Nishikawa, T. Satake, Supervision throughout this work: T. Misawa, F. Kikkawa, Revising manuscript: T. Misawa

CONFLICT OF INTEREST

The authors have nothing to disclose.

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