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Clinical characteristics of primary peritoneal carcinoma patients: a single-institution experience involving 8 patients

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ABSTRACT

Primary peritoneal carcinoma (PPC) is treated similarly to advanced epithelial ovarian carcinoma (aEOC); however, the standard approach for the management of PPC is controversial. The objective of this study was to evaluate the clinical features and prognosis of those patients. A retrospective analysis was performed of eight patients with PPC between January 2008 and December 2015. Clinicopathologic parameters, the diagnostic modality, treatment, and oncologic outcome were analyzed. The median age at the time of diagnosis was 72.5 years (range: 55–79), with a median follow-up of 26.5 months (range, 5–74). Most of the PPC developed with carcinomatosis peritonei involving ascites, while some cases developed sporadically in the peritoneal or extraperitoneal cavity without ascites. The most common initial symptom was abdominal fullness, and other symptoms were inguinal tumor, paralysis of the extremities, and respiratory disorder. The preoperative CA125 value was elevated in all patients. In four patients who did not undergo primary surgery, the final diagnoses were determined by the ascites cytology and radiological image. Initial or interval debulking surgery was performed in only two patients. All patients were treated with paclitaxel or docetaxel plus carboplatin. Five showed a complete response (CR), and one showed a partial response (PR). Among the five patients with CR, the median progression-free and overall survival periods were 15 (12–26) and 41.5 (32–74) months, respectively. Three patients without carcinomatosis peritonei showed a relatively favorable prognosis. The management of PPC is generally consistent with that of aEOC; however, in atypical cases, the treatment method should be considered individually.

Key Words: Primary peritoneal carcinoma, diagnosis, clinical outcome, peritoneal metastasis

INTRODUCTION

Primary peritoneal carcinoma (PPC) is histologically similar to epithelial ovarian carcinoma (EOC). The Gynecologic Oncology Group (GOG) has developed criteria to define PPC: 1) Both ovaries are normal in size or enlarged by a benign process; 2) The involvement in extraovarian sites is greater than the involvement on the surface of either ovary; 3) Microscopically, the ovaries are not involved with the tumor or exhibit only serosal or cortical invasions with dimensions

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smaller than 5×5 mm; 4) The histopathological and cytological characteristics of the tumor are predominantly of the serous type.[1,2] Previous studies revealed that PPC and EOC show similar clinical characteristics.[3,4] Accordingly, the mainstream treatment for PPC is cytoreductive surgery followed by platinum-based chemotherapy in the same way as advanced EOC. However, recent molecular and epidemiological studies have shown some differences between PPC and EOC.[2,5-7]

The objective of this retrospective study was to evaluate the clinical features and prognosis of patients with PPC.

PATIENTS AND METHODS

We reviewed medical records of patients with PPC at our institution between January 2008 and December 2015. Clinicopathologic parameters, the diagnostic modality, treatment, and oncologic outcome were retrospectively analyzed. Four PPC patients were diagnosed based on GOG criteria by surgery, and the other four patients were diagnosed by the ascites cytology and radiological image. In three cases, cell block cytology was performed and immunohistochemical analysis was done to determine serous type adenocarcinoma derived from ovary or peritoneum, which is generally positive for cancer antigen (CA125) and cytokeratin 7 (CK7), sometimes positive for Ber-EP4 , while generally negative for cytokeratin 20 (CK20). Calretinin and D2-40 are the marker which are usually positive in mesothelioma, and negative in serous type EOC and PPC. Wilm's tumor suppressor gene (WT-1) is also the mesothelioma marker; however it is sometimes positive in serous type EOC and PPC. In all cases, systemic computed tomography (CT) scan, gastroscopy and colonoscopy were performed to exclude cancers derived from digestive tract, breast, and other sites. Those patients were classified according to the 2014 FIGO staging system. Several patients underwent debulking surgery, which consisted of metastasectomy in the intra- and/or extra-peritoneal cavity, bilateral salpingo-oophorectomy, hysterectomy, and omentectomy. All patients received chemotherapy in combination with carboplatin (area under the curve, 5) and paclitaxel (180 mg/m^2) or docetaxel (70 mg/m^2) every 3 weeks. Chemotherapy involved at least 6 cycles or was continued until lesions detected on radiological images disappeared. Radiotherapy with Gamma knife was performed in the patients who had a brain metastasis. Patients were followed-up by clinical, biochemical, and radiological examinations every 1–3 months after treatment. The diagnosis of recurrence was determined when recurring lesions were detected on radiological images.

RESULTS

There were eight patients diagnosed with and treated for PPC during the study period. Patients' characteristics are shown in Table 1. The median age at the time of diagnosis was 72.5 years (range, 55–79). All patients were multipara. The most common initial symptom was abdominal fullness, and other symptoms were an inguinal tumor, paralysis of the extremities, and respiratory disorder. In case 4, involving a right inguinal tumor, it took seven months before the final diagnosis was determined. Cervical Pap (Papanicolaou) cytology was "NILM" (Negative for Intraepithelial Lesion or Malignancy) in all patients. Endometrial cytology was positive in one patient. Five patients had a large amount of ascites, and adenocarcinoma cell clusters were detected in ascites. The pretreatment CA125 value was highly elevated in all patients. CT showed massive ascites and peritoneal dissemination in five patients, and bilateral pleural effusion in one (Fig.1). In case 3, CT identified cervical, pelvic, and multiple para-aortic sites

Table 1 Patients' characteristics

Case	Age	Parity	PS[#1]	Initial symptom	Prehospital duration (Mo)[#2]	Pap cytology	Endometrial cytology	Ascites cytology	CA125 value[#3] (U/mL)
1	74	G2P2	3	Abdominal fullness	1	NILM	*N.A.*	AC	2,870
2	79	G2P2	2	Abdominal fullness	0	NILM	Negative	AC	878
3	59	G2P2	2	Abdominal fullness	1	NILM	*N.A.*	*N.A.*	749
4	55	G3P2	1	Rt. inguinal tumor	7	NILM	Negative	*N.A.*	1,026
5	64	G3P1	3	Abdominal fullness	0	NILM	Positive	AC	646
6	71	G3P2	2	Paralysis of extremities	1	NILM	Negative	N.A.	833
7	74	G8P5	3	Abdominal fullness	1	NILM	*N.A.*	AC	> 5,000
8	77	G4P4	3	Respiratory disorder	0	NILM	Negative	AC	3,610

#1: Performance status (Eastern Cooperative Oncology Group), #2: Duration from the beginning of initial symptom to hospital visit, #3: Pretreatment CA125 value, NILM: negative for intraepithelial lesion or malignancy, AC: adenocarcinoma, *N.A.*: not applicable

of lymphadenopathy (Fig.2A-B). In case 4, magnetic resonance imaging (MRI) of the pelvis showed a right inguinal simple-cystic tumor, whose capsule was thick and contrasted (Fig.2C-D). In case 6, CT of the abdomen detected a 7.0×5.0×4.0-cm solid tumor located in the upper right portion, and MRI of the brain revealed the enhanced mass in the left parietal lobe (Fig.2E-F).

Table 2 shows the diagnostic modality, treatment, and oncologic outcome. In three patients who had no ascites, the final diagnosis was histopathologically determined by surgery. In five patients who had massive ascites, case 1 was diagnosed by surgery while the others were diagnosed clinically by ascites cytology, radiological images and tumor markers without surgery. In three cases, cell block cytology was performed and immunohistochemical staining of the ascitic cells was positive for CA125, CK7, Ber-EP4, and WT-1, but negative for CK20, Calretinin, and D2-40 (data not shown). In case 8, pleural effusion cell block cytology was performed and shows same immunohistochemical characteristics.

Initial or interval debulking surgery was performed in case 4 or 8, respectively, and then optimal debulking (residual tumor ≤ 1 cm) was achieved. Three patients underwent surgery only for diagnosis, and two did not receive surgery. Case 7 is planned to undergo interval debulking surgery.

All patients received platinum-based chemotherapy. Bevacizumab (15 mg/kg) was added to the chemotherapy after interval debulking surgery in case 8. In case 6, the brain metastatic tumor completely disappeared by radiotherapy with Gamma knife. The median follow-up was 26.5 months (range, 5–74). Five patients showed a complete response (CR), one patient showed a partial response (PR) but no remission, and two patients are undergoing treatment. Among the five patients with CR, one showed platinum-resistance recurrence and a favorable prognosis. In contrast, four showed platinum-sensitive recurrence and their median progression-free and overall survival periods were 15 months (12–26) and 41.5 months (32–74), respectively. In another point of view, the three patients who had no ascites showed better prognosis than that of the patients who had malignant ascites. Overall survival periods of the patients without ascites were 49 months (32–74) and those of the patients with ascites were 25 months (19–34). Patients who initially had malignant ascites experienced recurrence as carcinomatosis peritonei.

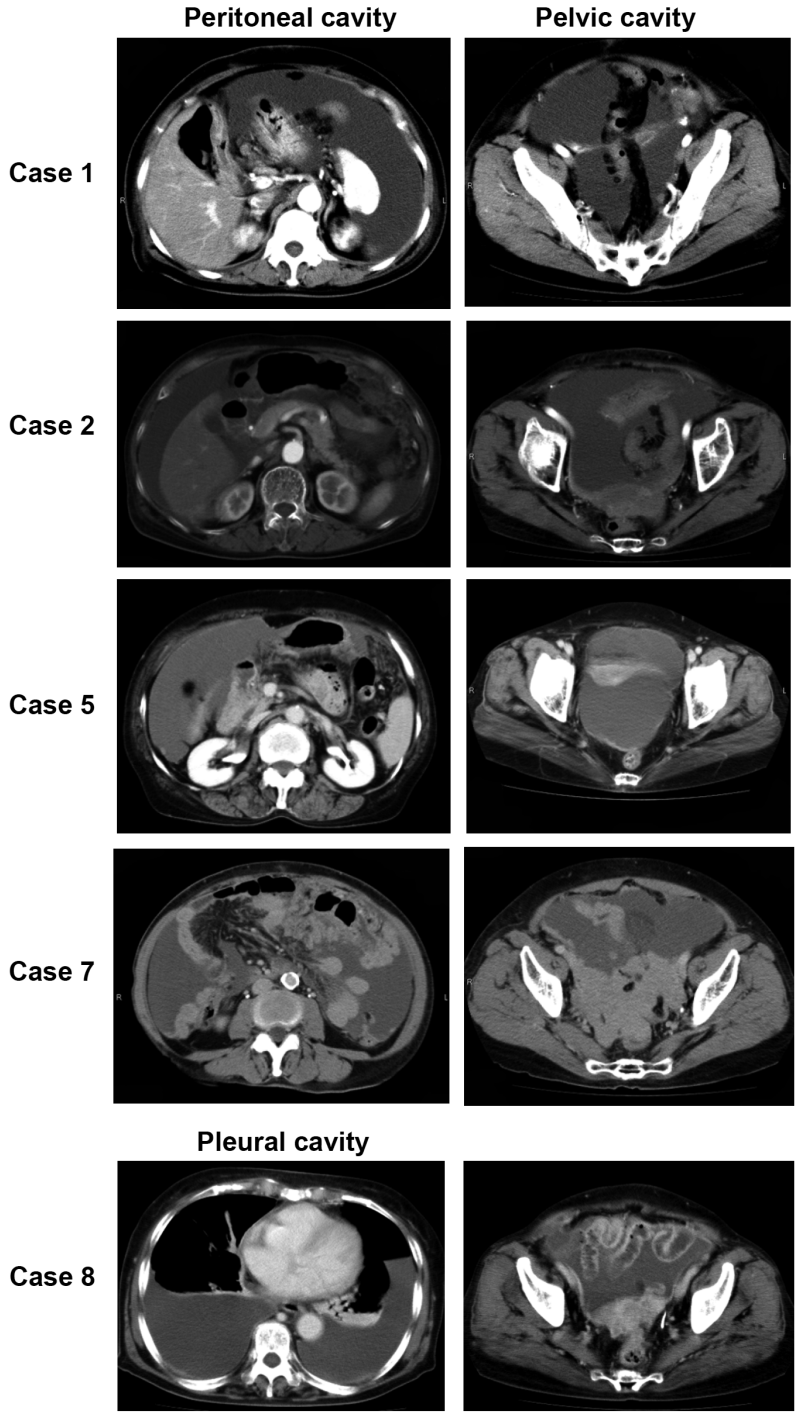

Fig. 1 Representative abdominal and/or pleural appearance in each case
Computed tomography (CT) showed massive ascites and peritoneal dissemination in cases 1, 2, 5, 7, and 8, and bilateral pleural effusion in case 8.

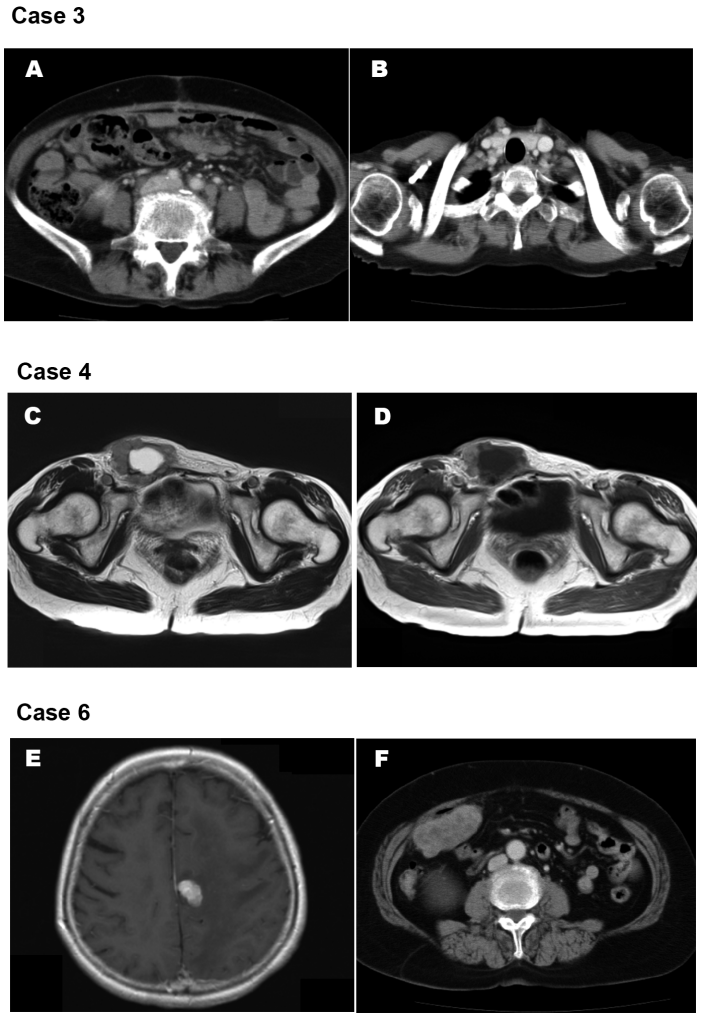

Fig. 2 Representative metastatic lesions in each case
A-B: Case 3: CT scans showed cervical, pelvic, and multiple para-aortic sites of lymphadenopathy. C-D: Case 4: Magnetic resonance imaging (MRI) of the pelvis showed a right inguinal simple-cystic tumor, whose capsule was thick and contrasted. E-F: Case 6: CT of the abdomen showed a 7.0×5.0×4.0-cm solid tumor located in the upper right portion, and MRI of the brain showed the enhanced mass in the left parietal lobe.

Table 2 Clinical characteristics and oncologic outcome

Case	FIGO stage[#1]	Final diagnosis	Surgery	Histological type	Chemotherapy	PFS (Mo)	Recurrence site	OS (Mo)	Prognosis
1	IIIC	Surgery	Probe laparotomy	Serous AC	TC (6), DC (4)	No remission	Carcinomatosis	25	DOD
2	IIIC	Image / cytology	*N.A.*	*N.A.*	TC (7)	3	Carcinomatosis	19	DOD
3	IVB	Surgery	Metastasectomy[#3] + USO	AC	TC (6)	12	Brain, PAN	74	AWD
4	IVB	Surgery	ATH + BSO + OM+ Metastasectomy[#4]	Undifferentiated AC	TC (6)	13	PLN	49	AWD
5	IIIC	Image / cytology[#2]	*N.A.*	*N.A.*	TC (12)	17	Carcinomatosis	34	AWD
6	IVB	Surgery	Metastasectomy[#3]	AC	TC (3), DC (3)	26	Pelvic dissemination	32	AWD
7	IIIC	Image / cytology[#2]	*N.A.*	*N.A.*	TC(7)	Ongoing	*N.A.*	6	AWD
8	IVA	Image / cytology[#2]	ATH + BSO + OM+ Metastasectomy[#4]	Serous AC	TC(3)[#5], TC+BEV(1)	Ongoing	*N.A.*	5	AWD

#1: International Federation of Gynecology and Obstetrics (2014), #2: Cell block cytology, #3: Metastasectomy in the peritoneal cavity, #4: Metastasectomy in the inguinal tumor, #5: Neoadjuvant chemotherapy, AC: Adenocarcinoma, TC: Paclitaxel plus carboplatin, DC: Docetaxel plus carboplatin, BEV: Bevacizumab, PFS: Progression-free survival, PAN: Para-aortic lymph node, PLN: Pelvic lymph node, OS: Overall survival, DOD: Died of the disease, AWD: Alive with disease

DISCUSSION

The differences between PPC and EOC were investigated in previous studies. According to prior reports, the median age of PPC patients was 64 years, and such patients were older than those with EOC.[2,8] In the current study, the median age at the time of diagnosis was 72.5 years (range, 55–79), and 5 of 8 patients were septuagenarian. The most common symptoms of PPC are abdominal fullness, abdominal pain, a palpable abdominal mass because of massive ascites, and peritoneal dissemination.[9,10]

Earlier studies showed that the endometrial cytology was useful for the early detection of epithelial ovarian, fallopian tube, or primary peritoneal carcinoma.[11] In our study, the endometrial cytology was positive in one case. Here, we reported three PPC patients who had no ascites. In case 3, we preoperatively identified cervical, pelvic, and multiple para-aortic sites of lymphadenopathy by CT. Initially, malignant lymphoma was suspected. During the initial surgery, we detected peritoneal dissemination on the omentum and surface of the left adnexa uteri, then partial resection of the omentum and left salpingo-oophorectomy were performed. Immunohistochemical approach led to the final diagnosis. Yun *et al.* reported two PPC patients who presented with cervical lymphadenopathy.[12] In case 4, the right inguinal tumor was first suspected to be a hydrocele of the canal of Nuck but the tumor developed gradually, and herniorrhaphy was performed. The operation revealed that it was a malignant tumor which arose in the peritoneum of the hernia sac. In case 6, the initial symptom was a gradually progressing paralysis on her right side. MRI of the brain indicated a metastatic tumor. CT detected the primary lesion in the abdominal cavity. Gastroscopy and colonoscopy examination results were normal. The patient underwent exploratory laparotomy by a general surgeon, and the tumor was located on the serosal layer of the transverse colon and omentum. Since no lesions were found except for those tumors, partial resection of the transverse colon was performed. The final diagnosis was determined by an immunohistochemical approach. Kim *et al.* reported a case of localized PPC presenting as a solitary colonic mass.[13]

Previous studies reported that debulking surgery improved the prognosis of PPC as well as EOC patients, and neoadjuvant chemotherapy (NAC) was more often required to achieve optimal debulking surgery in PPC.[14] The accuracy of diagnosis is a problem before NAC; however, a Japanese trial showed that clinical diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal carcinoma with cytology, radiological images and tumor markers had a high positive predictive value.[15] In our study, the patients' age and performance status were considered, and four patients were not pathologically but clinically diagnosed. This study indicates that PPC patients tend to be older and have a less favorable performance status. Thus, we think that clinical diagnosis and neoadjuvant chemotherapy followed by interval debulking surgery may be the best treatment strategy for those patients. On the other hand, the abovementioned study pointed out that clinical diagnosis was insufficient for staging. Among 56 patients who were clinically diagnosed with stage IIIC/IV, 7 patients (12.5%) turned out to be under stage IIIB by laparoscopic surgery.[15] In our study, three patients had never received surgery, and consequently they may have been overdiagnosed. Laparoscopic surgery is less invasive and thought to be applicable for patients with a poor PS. In addition, observing intraperitoneal conditions with a laparoscope, we can check if there is any peritoneal dissemination involving the bowels, and administer Bevacizumab to the patients safely.

Our retrospective analysis was too preliminary and had several limitations, such as the small number of cases and variable follow-up length, precluding a definite conclusion. However, this study indicated that there were several development patterns of PPC and those patterns might be related to the patients' prognosis. Most of the PPC developed at multiple sites in the abdominal cavity with malignant ascites, while some developed sporadically in the peritoneal or extraperitoneal cavity without ascites, and others showed systemic lymphadenopathy. Three patients who had no ascites had not received debulking surgery; however, they showed a relatively favorable prognosis. PPC patients without carcinomatosis peritonei may show a good oncologic outcome without debulking surgery if they are sensitive to platinum-based chemotherapy. The management of PPC is generally referred to that of advanced EOC; however, in atypical cases, the treatment method should be considered individually. This retrospective study involved a small number of PPC patients and had various limitations, thus, to clarify a more appropriate strategy for PPC, we would like to accumulate more cases and reconfirm the current results in the future.

CONFLICT OF INTEREST STATEMENT

All authors declare that there are no conflicts of interest, nor any financial or personal relationships with other people or organizations that could inappropriately influence the work.

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