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RESEARCH

Primary Peritoneal Serous Papillary Carcinoma: A Clinical and Pathological Study

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Abstract Primary peritoneal serous papillary carcinoma (PPSPC) is a rare primary tumor of the peritoneum that found predominantly in elderly and post-menopausal women. The aim of our study is to review the clinical and pathologic information of 22 patients, and then try to summarize clinical behavior and pathological characteristics of PPSPC, in order to be better recognized of this entity in future. We retrospectively reviewed the data from 22 patients with PPSPC treated at our hospital from 1992 to 2008. All paraffin blocks were recut for periodic acid-Schiff diastase and immunohistochemical staining for CD15, cytokeratin7(CK7), cytokeratin20 (CK20), S-100 protein, carcinoembryonic antigen (CEA), CA125, estrogen receptor(ER) and progesterone receptor(PR). The median age of the patients at the time of surgical staging was 56 years (range, 32–77 years). The most common presenting symptoms were abdominal distension (59.1%) and ascites (63.6%). Pretreatment CA125 levels were significant elevated in 90.5% patients. Optimal debulking was performed in 18 patients. All patients were consequently treated with platinum-based chemotherapy. Response to treatment is promising, and the median overall survival of all patients was 21.0 months (95% CI 16.9, 25.1 months). The positive rate of immunohistochemical staining was CD15 95.5%, CK7 90.9%, S-100 protein 68.2%, CA125 59.1%, CK20 31.8%, ER 31.8%, CEA 27.3% and PR 9.1%, respectively. Gynecologist should be aware of PPSPC when abdominal distension, gross ascites and a raised level of CA125 in women without ovarian enlargement. Immunohistochemical staining might be helpful as accessory criteria for the differential diagnosis among the PPSPC, peritoneal malignant mesothelioma (PMM), primary epithelial ovarian carcinoma (PEOC) and peritoneal carcinomatosis from the gastrointestinal tumors (SPCGT). Cytoreductive surgery combined with pre/postoperative platinum-based chemotherapy may be effective for PPSPC patients.

Keywords Primary peritoneal serous papillary carcinoma · Clinicopathology · Immunohistochemistry

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Primary Peritoneal serous papillary carcinoma (PPSPC) is a rare malignant tumor that originates from a single or multicentric focus of the peritoneum. Since Swerdlow reported the first case of PPSPC in 1959 [1], it has become recognized as a distinct clinicopathologic entity not uncommonly encountered by the gynecologist. Unfortunately, most patients with PPSPC display a paucity of symptoms for a long time and more than two thirds of patients often diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage III or IV disease at the time of initial presentation and treatment, which is the main reason for the unsatisfactory 5-year survival rate. Here, we conducted this retrospective study, in order to better recognition of this entity in future.

Methods

This study is a retrospective review about 22 patients with PPSPC diagnosed from November 1992 to October 2008 in

our hospital. PPSPC was defined according to the recommendation of the Gynecologic Oncology Group [2]. The clinicopathological information was obtained from medical records.

The clinical data included age at diagnosis, presenting symptoms, and preoperative serum tumor marker values, surgical stage (based on the FIGO stage of primary epithelial ovarian carcinoma,PEOC), type of surgical treatment,pathological grade, the first line of chemotherapy and follow-up. All patients were followed up to October 2008.

The pathological diagnosis and differentiate grade of PPSPC was based on the original pathologic report reviewed and signed by two certified pathologists. Grade 1 (well differentiated), Grade 2 (moderately differentiated) and Grade 3 (poorly differentiated). All specimens fixed in 10% formalin and embedded in paraffin were continuously recut in 4um sections for periodic acid-Schiff diastase and immunohistochemical staining.

Immunohistochemical staining was performed on representative tumor blocks using the avidin–biotin complex technique with antibodies to CD15, cytokeratin7(CK7), cytokeratin20(CK20), S-100 protein, carcinoembryonic antigen (CEA), CA125, estrogen receptor(ER) and progesterone receptor(PR). Information about the antibodies selected is given in Table 1. The results were evaluated with the percentage of stained tumor cells: negative is less than 5%; positive is equal to or more than 5%.

Results

Clinical Features

Over the period from 1992 to 2008, 768 patients with gynecological malignancies were treated in our hospital, including 22 cases (2.9%) of PPSPC, 169 cases (22.0%) of PEOC and seven cases (0.9%) of peritoneal malignant mesothelioma (PMM). The clinical characteristics of PPSPC patients are summarized in Table 2. The median age of the patients was 56.2 years (range, 32 to 77 years), and 14 patients (63.6%) were postmenopausal. The most common presenting symptoms were abdominal distension (59.1%) and abdominal pain (19.0%). Ascites were present in 63.6% of the cases. The preoperative CA125 values were significantly elevated in 90.5% patients with all stages and in 95% patients with stage II-IV patients.

All patients underwent surgical treatment, including total hysterectomy with salpingo-oophorectomy, omentectomy, appendectomy, extra pelvic lymphadenectomy, partial rectectomy or palliate surgery. Only one patient underwent the second-look laparotomy and no positive findings. One patient was first referred to general surgery owing to symptoms of abdominal distension resembling partial intestinal obstruction. During the operation, there was a solid mass in the Douglas pouch involved in anterior rectal wall, and numbers of small nodules on the surface of the peritoneum. So the initial impression was rectal tumor. And then the partial rectectomy was performed. But histological diagnosis showed serous papillary carcinoma. Optimal cytoreductive surgery almost without residual lesions was obtained in two patients, equal or less than 2 cm residual lesions in 16 patients.

The preoperative intraperitoneal cavity chemotherapy was performed in five patients with cisplatin 1~2 cycles in order to alleviate ascites. 6~8 courses of cisplatin, epirubicin, cyclophosphamide intravenous chemotherapy were administered in 10 patients following surgery, and 6~8 courses of paclitaxel plus platinum (cisplatin or carboplatin) in 12 patients.

Pathologic Features

The microscopic characteristics of PPSPC were almost identical to those of conventional PEOC. Microscopically, PPSPC showed papillary structures lined by one to several layers of cells ranging in shape from columnar to oval. The nuclei were enlarged, which resulted in a high nuclear-cytoplasmic ratio. Nucleoli were conscious and mitoses were numerous. The cytoplasm was modest amounts of eosinophilic. Psammoma bodies were present obviously in seven cases (Fig. 1a); Microscopic lesions near the ovarian surface were found in 14/22 patients with the depth less than 5 mm. There was no evidence of primary tumor in fallopian tubes or uterus.

In the immunohistochemical results, most PPSPC reacted for S-100 protien, CD15, CA 125, CK7 and CK20. The staining for CD15 was localized mainly in the cytoplasm and accumulated occasionally at the membrane of PPSPC cells (Fig. 1b). PMM was shown negative staining for CD 15(Fig. 1c). In most of the cases the patterns of immunoreactivity to S100, CK7 were mixed (Fig. 2b, c), and other antigen showed the highest intensity at the membrane. The positive immunohistochemical staining results are CD15 95.5%, CK7 90.9%, S-100 protein 68.2%, CA125 59.1%, CK20 31.8%, ER 31.8%, CEA 27.3% and PR 9.1%, respectively.

Follow Up

The median survival time of our series is 21.0 months (95% CI 16.9, 25.1 months). 12 patients died of the disease 4th~50th months after diagnosis, which included one grade 1 and stage II(survival 50 months) and 11 grade 2–3 and stage III-IV(survival 4–32 months). The 5-year survival rate was 34.4%. Patient 10 and 11 are staging IV, but they have

Table 1 Antibodies used for immunohistochemical analysis

Antibody	Clone	Source	Dilution	Pretreatment
CEA	II-7	DAKO, Ely, Cambridge, England	1:400	Trypsin
CD15	LeuM1	Becton Dickinson, Oxford, England	1:200	MWPC
CA 125	OV185:1	Vector, Peterborough, England	1:400	MWPC
ER	6F11	Vector	1:50	MWPC
PR	PGR636	DAKO	1:400	MWPC
Cytokeratin 7	OV-TLR12/30	DAKO	1:500	MWPC
Cytokeratin 20	Ks20.8	DAKO	1:500	MWPC
S-100	Anti-cow S-100 (r)	DAKO	1:400	MWPC

been alive more than 75 months without disease up to now. Although Patient 1 underwent three times operations and full-course chemotherapy after the third operation, she had been still died of the bowel obstruction eventually.

Discussion

To our knowledge, PMM, Müllerian tumor and metastatic tumor are three kinds of the female diffuse peritoneal neoplasms [3]. Because both PPSPC and PEOC are Müllerian tumors, arising from the mesothelium, theoretically, the clinical and histopathological features should be identically, specifically the serous variety. Several earlier studies have focused on characteristics of PPSPC in order to distinguish PPSPC from other tumors [4, 5]. Tews G et al. [6] suggested that the criteria to define PPSPC is ovaries normal in size or enlarged by a benign process, extraovarian involvement greater than ovarian involvement, and ovarian surface involvement less than 5 mm in depth

Table 2 Clinicopathologic features in 22 cases

Patient (n)	Age (y)	Symptoms or signs	CA125[a]	Stage	Grade	Surgical treatment	chemotherapy	Follow-up(m)
1	32	No symptom	nd	II[c]	I[b]	ls/th+lso+ap/rso+omt	PAC	Dod 50
2	38	AD	228.8	II[c]	III	th+so+cr+ap+omt+pl/sl	PAC	Ned 133
3	44	AD & AS	125.1	III[c]	II	th+so+cr+ap+omt	PT	Dod21
4	48	Vaginal bleeding	7.8	I	II	th+so+ap+omt	PAC	Ned 111
5	62	AD & AS	171.4	III[c]	II	th+so+cr+ap+omt	PAC	Dod19
6	38	AP	87.2	III	II[b]	ap+bio/ovarian bio	PT	Dod 11
7	67	AD & AS	>500	III[c]	II	th+so+cr+ap+omt	PAC	Dod 22
8	56	AD & AS	>500	IV[c]	III[b]	th+so+cr+ap+omt+pl	PAC	Dod 20
9	47	AD & AS	142.1	IV	II	omt+ovarian bio	PT	Dod 19
10	63	AD & AS	>500	IV[c]	III[b]	th+so+cr+ap+omt	PAC	Ned 91
11	54	AD & AS	>500	IV	III	th+so+cr+ap+omt	PAC	Ned 82
12	63	AD & AS	>500	IV	II	cr	PAC	Dod 4
13	60	AP	500	IV[c]	III	so+omt	PT	Awd 10
14	77	AP	32.38	III	III	rso+omt+cr+pl	PT	Awd 15
15	68	Pelvic mass	>500	III	III	th+so+cr+ap+omt	PT	Ned 25
16	70	AD & AS	>500	III[c]	II[b]	th+so+omt	PT	Ned 41
17	65	Pelvic mass &AS	>500	III[c]	II	th+so+omt	PT	Dod 11
18	57	AD & AS	474.5	III[c]	III[#]	th+so+omt	PT	Dod 15
19	43	AP & AS	>500	IV[c]	III	cr	PT	Dod 5
20	56	AP	>500	IV	III	th+so+cr+pl+omt	PAC	Dod 32
21	69	AD &AS	>500	III[c]	III	so+omt	PT	Awd 11
22	59	AD &AS	>500	III[c]	II[#]	th+so+cr+ap+omt+pl/sl	PT	Awd 5

[a] Preoperative serum tumor marker (U/mL). normal values:<35 u/ml; [b] with psammoma body; [c] with ovarian involvement;

AD Abdominal distension; *AS* ascites; *AP* Abdominal pain; *ls* laparoscopy; *th* total hysterectomy; *l/rso* left/right salpingo-oophorectomy; *ap* appendectomy; *omt* omentectomy; *cr* cytoreductive surgery; *pl* pelvic lymphadenectomy; *bio* biopsy; *dod* died of disease; *ned* no evidence of disease; *awd* alive with disease. *PAC* cisplatin+epirubicin+cyclophosphamide; *PT* paclitaxel + platinum

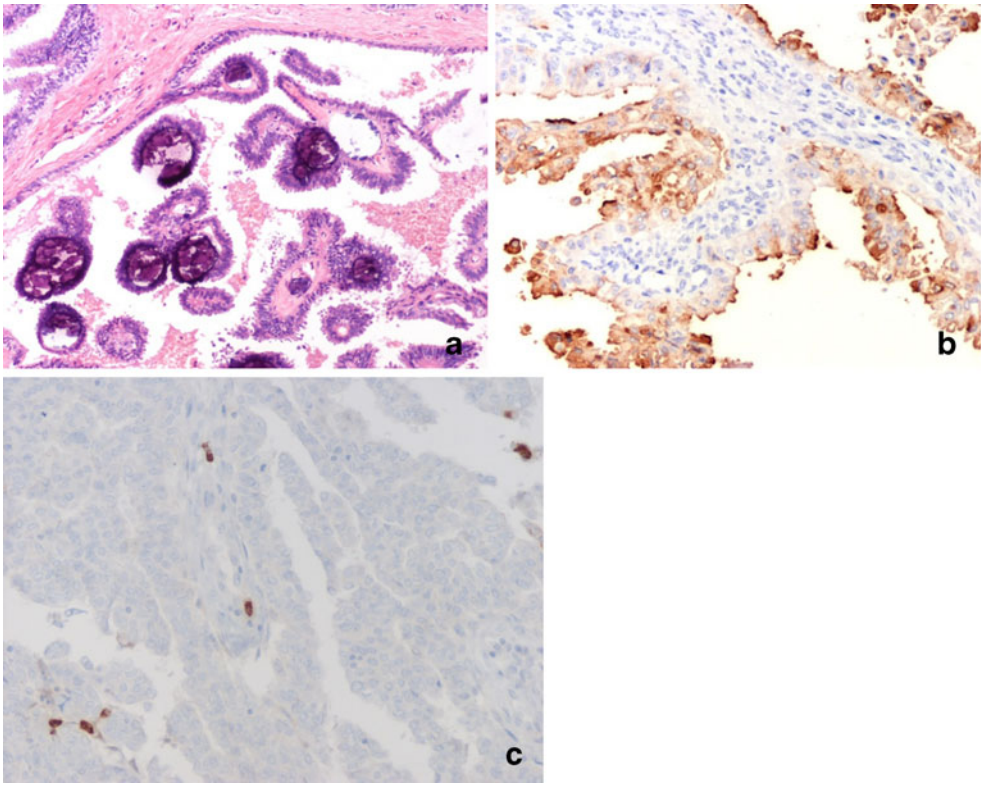

Fig. 1 PPSPC shows papillary structures lined by one to several layers of cells and psammoma bodies are present obviously (hematoxylin and eosin × 200). (**a**) Immunohistochemical staining of CD15 shows positive in the membrane and cytoplasm of tumor cell of PPSPC (immunohistochemical stain × 200).(**b**) Examples of PMM are shown negative staining for CD 15 (immunohistochemical stain × 200).(**c**)

and width. Using this clinical definition, all patients in our study meet the diagnostic criteria of PPSPC.

An epidemiologic study showed that approximately 23% to 27% of gynecological malignancies were PEOC, and nearly 10% of patients preoperative diagnosed with PEOC meet the diagnostic criteria for PPSPC [7]. The women diagnosed with PPSPC were on average significantly older than those diagnosed with PEOC [8]. Halperin R et al. [9] found that abdominal distension was the most common finding and more cases with abdominal distension caused

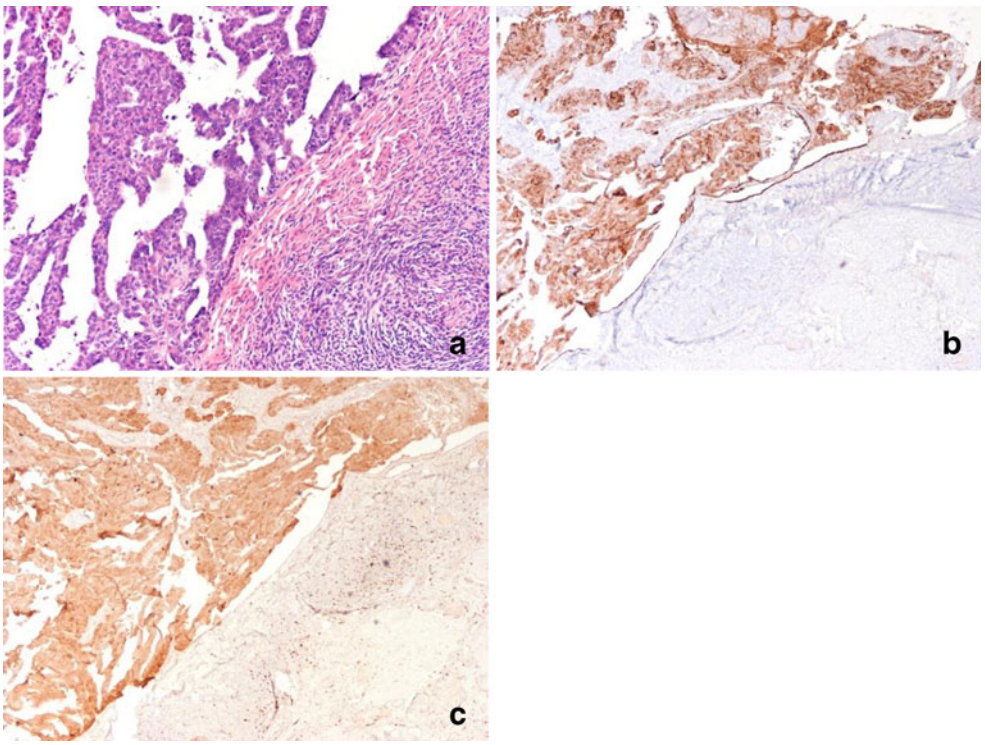

Fig. 2 Examples of PPSPC stained with hematoxylin and eosin (×200) (**a**) and in sections from the same tumor illustrated in A that show membranous and cytoplasmic immunostaining for CK7 (**b**) and Diffuse and strong immunoreactivity throughout the tumor cells for S-100(**c**) (immunohistochemical stain × 200)

by ascites in the PPSPC group than in the PEOC group. They also found that similar to the situation in patients with PEOC, serum CA125 level was elevated in most of the PPSPC patients, and it was not significantly different between two groups. Altaras et al. [10] described that CA125 values correlated with the clinical status of PPSPC, and it was considered to be the most effective serum tumor marker for diagnosis of PPSPC and follow up. In line with the results of previous studies, our study showed that about 22% of gynecological malignancies were PEOC. PPPSC was diagnosed at approximately 13.0% of the frequency of PEOC. The "typical" patients were almost postmenopausal women. Ascites were present in 63.6% of the cases; abnormal CA125 values occurred in all stage III–IV PPSPC patients except one patient and significantly positive correlated with clinical stage. Therefore, postmenopausal women presenting with abdominal distension, gross ascites and a raised level of CA125 should considered the possibility of PPSPC.

However, such clinical presentation does not be always specific to PPSPC. The signs and symptoms of PPSPC are often similar to those of PMM, PEOC and peritoneal carcinomatosis from metastatic gastrointestinal cancers (SPCGT). Zhou's study [11] demonstrated that proliferation of columnar neoplastic cell, presence of psammoma bodies and production of neutral mucin is thought to be the three specific histological features in PPSPC. It maybe helps us to distinguish PPSPC from other, but it is still difficult to distinguish all PEOC and peritoneal carcinomatosis. Recent evidence indicates that the immunohistochemistry about increasing availability of histogenetic markers plays an important role in the differential diagnosis of PPSPC [12].

CD15, also known as Leu-M1, is a trisaccharide with the structure Galbeta(1–4)Fucalpha(1–3)GlcNAc, which expressed on various adenocarcinomas such as PPSPC and PEOC. Therefore, it can't be used to distinguish PPSPC and PEOC. Since Sheibani first reported CD15 positivity in 47 (94%) of 50 pulmonary adenocarcinomas and in 0 of 28 mesotheliomas, CD15 immunostaining has often been used in the differential diagnosis between mesotheliomas and adenocarcinomas [13]. Zhou's study [11] showed that CD15 was characterized with positive rate of 88% in PPSPC and 0% in PMM. In1998, a large study on the role of immunohistochemistry in distinguishing PMM from peritoneal and ovarian serous carcinomas showed that CD15 was demonstrated 67% in the serous carcinomas, but none in the PMM [14]. Khoury et al. [15] also found similar results that CD15 had high specificity for the serous papillary carcinoma. Our study showed that CD15 was stained in 95.5% specimens, which implies that the PPSPC cells may originate from epithelial cells other than mesothelial cells.

Nevertheless, single tumor maker dose not enough to establish a correct diagnosis. Both CK7 and CK20 are the epithelial keratins that are used to investigate the site of origin of adenocarcinomas. Generally, CK7 is present in serous carcinomas but absent in gastrointestinal carcinomas. Contrarily, CK20 is common in gastrointestinal carcinoma but rare in serous carcinoma [16]. Although the positive rate for CK20 in our PPSPC cases was 31.8%, which is litter higher than the 10% to 30% rate previously reported, the combination of CK7 and CK20 markers provide more accurate prediction in distinguishing PPSPC from PMM [17].

CA125 is an epithelial membrane antigen that expressed in tissue derived from coelomic epithelium (mesothelial cells of the pleura, pericardium, and peritoneum) and Mullerian epithelium (tubal, endometrial, and endocervical). It is routinely used for diagnosis of PEOC and follows up. Zhou [11]'s report showed that CA125 expression was demonstrated 75% in the serous carcinomas, but none in the PMM. This finding indicates that CA125 is 100% specific for discriminating between serous carcinoma and PMM, and it is suitable for preliminary tumor screening (epithelial versus mesenchymal). The positive rate for CA125 in our PPSPC cases was 59.1%, which is little lower than the rate previously reported.

S100 protein is small acidic protein (10–12 kDa) that is also found in epithelial cells. The positive percentage (68.2%) of PPSPC for S100 in our study is similar to that in other reports [18]. However, S100 protein is also demonstrated in a variety of human neoplasm and normal tissues, including melanomas, glial cells, neurons, Schwann cells, Langerhans cells, macrophages, myoepithelium, and chondrocytes [19], which limits its practical utility.

CEA is one of the most widely used tumor markers. Its main application is mostly in gastrointestinal cancers, especially expression in colorectal malignancy. Previous report has demonstrated that CEA is sufficiently sensitive and/or specific to be diagnostically useful [20].Recently,

Table 3 Dominant immunohistochemical expressions in four different tumors

	CD15	CK7	S-100	CA125	CK20	ER	PR	CEA
PPSPC	+	+	+	+	−	±	±	−
PEOC	+	+	±	+	−	+	+	−
PMM	−	−	±	±	−	−	−	−
SPCGT	−	−	−	−	+	−	−	+

Attanoos et al. [17] investigated the expression of a variety of immunohistochemical markers, including CEA, in an attempt to determine whether immunohistochemical differences exist between PPSPC and other tumors. They found CEA was only rarely expressed in PPSPC. Our study showed that CEA expression was about 27.3%, but just only weak and focal cytoplasmic staining in PPSPC. So we think that CEA staining is helpful as the accessory criteria for the differential diagnosis between PPSPC and SPCGT.

Since PPSPC is always found in women, a hormonal influence was suspected. In breast and ovarian carcinomas, ER and PR can often be expressed, which has been suggested that they should be included in the panels of immunohistochemical markers used to determine the origin of metastatic carcinomas of unknown primary site [21, 22]. However, ER and PR are not common find in PPSPC. As reported in the previous literature by Halperin R [23], the percentages of ER and PR in PPSPC were 31% and 46%, respectively; in PEOC were 73% and 91%, which were significant statistical differences between PPSPC and PEOC. Our results indicated that ER and PR are expressed only 31.8% and 9.1% in all cases, respectively, which is almost consistent with mentioned report. That is to say they may become the helpful tumor makers for differential diagnosis between PPSPC and PEOC. Furthermore, ER and PR expressions are indicative of an intact estrogen pathway and might identify tumors that are hormonally responsive to hormonal therapy. Since PPSPC showed few ER and PR, hormonal therapy may be not suitable.

Up to now, the standard treatment for PPSPC has not been established. As the histological feature and biological behavior of PPSPC is supposed to be identical to that of PEOC, multimodality management including cytoreductive surgery and platinum-based chemotherapy, which is applied for stage III and IV of PEOC, would seem to be the optimal treatment to PPSPC [24]. Paclitaxel plus platinum-based chemotherapy in PPSPC was recommended by several investigations [25, 26]. The prognosis is seem to be better than other non-platinum-based chemotherapy, but still equal to or less than PEOC in same staging [5].

In conclusion, gynecologist should be aware of the existence of PPSPC when abdominal distension, gross ascites and a raised level of CA125 in women without ovarian enlargement. Immunohistochemical staining, such as CD15, CK7, CK20, S-100 protein, CEA, CA125, ER and PR are useful discriminatory markers for the differential diagnosis among the PPSPC, PMM, PEOC and SPCGT (summary in Table 3) and improvement for the PPSPC treatment planning. With the advances in cytoreductive surgery and chemotherapy, the prognosis of PPSPC will be improved in the future.

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