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Primary peritoneal serous papillary carcinoma: a case series

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Abstract

Purpose To present the clinical and laboratory characteristics, as well as the management, of patients with primary peritoneal serous papillary carcinoma (PPSPC).

Methods This is a retrospective study of 19 patients with PPSPC who underwent debulking surgery followed by first line chemotherapy and were managed in Metaxa Memorial Cancer Hospital between January 2002 and December 2017.

Results The median age of the patients was found to be 66 years (range 44–76 years). Clinical presentation of PPSPC included abdominal distention and pain, constipation, as well as loss of appetite and weight gain. Two of the patients did not mention any symptomatology and the disease was suspected by an abnormal cervical smear and elevated CA125 levels respectively. Biomarkers measurement during the initial management of the patients revealed abnormal values of CA125 for all the participants (median value 565 U/ml). Human epididymis secretory protein 4 (HE4) and ratios of blood count were also measured. Perioperative Peritoneal Cancer Index ranged from 6 to 20. Optimal debulking was achieved in 5 cases. All patients were staged as IIIC and IVA PPSPC and received standard chemotherapy with paclitaxel and carboplatin, whereas bevacizumab was added in the 5 most recent cases. Median overall survival was 29 months.

Conclusion PPSPC is a rare malignancy, the management of which should take place in tertiary oncology centers.

Keywords Primary peritoneal serous carcinoma · Primary peritoneal serous papillary carcinoma · PPSPC · PPSC · Peritoneal malignancy

Introduction

Primary peritoneal carcinoma is a rare malignancy arising from peritoneal epithelium and it was firstly described by Swerdlow in 1959 as "mesothelioma of pelvic peritoneum" [1]. Primary peritoneal serous papillary carcinoma (PPSPC) is the most common histologic type among primary peritoneal malignancies, the incidence of which was 0.62 per 100,000 women in US population from 2011 to 2014, according to the United States Cancer Statistics. The worldwide incidence is unknown because of the lack of large multicenter studies [2, 3].

PPSPC shares the same clinical presentation with primary ovarian serous carcinoma and the two entities are indistinguishable immunohistochemically. In order to distinguish PPSPC from papillary serous adenocarcinoma of the ovary, the Gynecology Oncology Group has set specific criteria [4], and thus a patient is classified as having PPSPC when:

(i). Ovaries are absent, normal-sized or enlarged due to a benign mass.

We clarify that the results of our preliminary study were presented as an e-poster in European Gynecologic Oncology Congress 2017, Vienna. The complete presentation of our study accompanied with an analysis, are submitted in this manuscript.

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(ii) Extraovarian involvement is greater than involvement of ovarian surface.
(iii) Ovarian involvement is either limited to the surface or measures less than 5 × 5 mm within the cortex.
(iv) Serous histopathological/cytological characteristics.

The age-specific peak incidence of peritoneal cancer is 75–79 years, similar to that of ovarian cancer but older compared to fallopian tube cancer (70–74 years) [3]. The clinical and histological resemblance between ovarian, tubal and peritoneal serous carcinomas has given rise to a multitude of theories in the literature concerning the potential common origin of these malignancies [5–8]. Symptoms resulting predominantly from excessive ascites in advanced stages, elevated values of CA125 and typical imaging findings such as diffuse peritoneal disease, omental infiltration and absence of ovarian pathology, may be indicative for diagnosing PPSPC. Cytoreductive surgery is the standard of care for such patients with the intention to achieve complete cytoreduction, followed by adjuvant chemotherapy [9].

We aim to present a case series of patients with PPSPC managed in our department, focused on the main clinical and laboratory characteristics of the disease.

Methods

This is a retrospective study of 19 patients with PPSPC who were treated between 2002 and 2017 in the Gynaecological Oncology Department of Metaxa Memorial Cancer Hospital, Piraeus, Greece. All the patients were discussed preoperatively in tumor board meetings by a multidisciplinary team. Initial diagnosis and management included abdominal and chest CT, transvaginal U/S and diagnostic laparoscopy in order to gain a biopsy for diagnostic purposes and to assess the resectability of the disease. With these results, comorbidities and Performance Status based on the ECOG Scale were also taken into account and the patients were either treated with primary debulking or neoadjuvant approach [10]. Based on this protocol, only 19 patients were identified as candidates for primary debulking.

Our electronic database and medical notes were retrospectively studied for each individual, and clinical and pathological data was collected. The data included the age and symptoms at diagnosis, comorbidities for each patient, the preoperative CA125 values, the stage of the disease, information about the operative findings as well as the surgical techniques used, the amount of residual disease, and subsequent surgical complications. Preoperative HE4 levels of the last four patients were also obtained. Furthermore each individual's response to chemotherapy was recorded and the overall survival was calculated.

In addition to CA125 and HE4 values, which are well established biomarkers for both PPSPC and ovarian serous carcinoma, we also calculated the values of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). It has been suggested that these inflammatory markers are associated with ovarian cancer survival by Zhu et al. [11].

Peritoneal Cancer Index (PCI) scoring system, described by Jacquet and Sugarbaker, was used to estimate the extent of the disease in the peritoneal cavity based on the operative findings [12]. The amount of residual disease (R) was recorded and categorized into 3 groups based on the size of the largest residual mass: R0, $R \leq 1$ cm and $R > 1$ cm. R0 corresponds to complete macroscopic resection of the disease. It is worth noting that the term 'optimal debulking' is often used when $R \leq 1$ cm is achieved. Along with (R) score we used the Completeness of Cytoreduction Score (CC score). CC score classification includes the four subgroups 0, 1, 2, and 3 where residential disease is no visible, < 2.5 mm, 2.5 mm − 2.5 cm and > 2.5 cm respectively [13].

Patients were categorized into 3 groups (low, intermediate and high) based on the Surgical Complexity Score as defined by Aletti et al., depending on the extent of surgical interventions [14]. The modified Classification of Surgical Complications, as proposed by Dindo et al. in 2004, was used to define and grade postoperative complications [15].

After surgery they received first-line chemotherapy. Data regarding each individual's response to chemotherapy was collected, based on radiological and laboratory findings according to the revised RECIST guideline [16].

Results

The median age of the patients was 66 years old ranging from 44 to 76 years old. All of them were postmenopausal, except for two patients, one premenopausal referring menstrual disorders and one with normal menstrual cycle respectively. Six patients were staged as IVA primary peritoneal carcinoma due to the presence of malignant pleural effusion, whereas the remaining 13 were staged as IIIC in accordance with FIGO staging classification. None of the patients was diagnosed with distant metastasis during the initial investigation with abdominal and chest CT scans. Eight patients were fully active at the time of diagnosis, while regarding the 6 patients staged as IVA, 5 and 1 had grade 2 and 3 Performance Status respectively.

Clinically PPSPC usually presented with abdominal distention and pain (17/19 cases) as well as loss of appetite (14/19), while 6 patients complained of constipation. Dyspnea was mentioned by 6 patients. Two of the patients did not report any symptoms and the only findings suggesting the disease were glandular atypia on

routine Papanicolaou smear, and elevated CA125 levels in a patient with a history of hysterectomy and bilateral salpingoophorectomy due to CINIII respectively.

All patients except for one had abnormal values of CA125 at the time of initial diagnosis, ranging from 119 to 12767.3 U/ml, with a median value of 565 U/ml. Apart from CA125, we estimated HE4 levels and ratios of blood count during the preoperative evaluation of our patients. Specifically, HE4 of the four most recent patients was measured and the average was 372.85 pmol/l, ranging between 185 and 627 pmol/l. Median values of NLR (neutrophil-to-lymphocyte ratio) and PLR (platelet-to-lymphocyte ratio) were calculated for all patients studied and the median values were found to be 5.94 (range 1.7–17.93) and 140 (range 68.9–625.9) respectively.

Intraoperative PCI was estimated based on Sugarbaker's staging and it ranged from 6 to 20 (median 13). Total abdominal hysterectomy and bilateral salpingo-oophorectomy combined with supracolic omentectomy was performed on all our patients. However there was not any other surgical intervention to the 8 patients that were managed before 2009, therefore resulting in a low surgical complexity score. In 2009 a new surgical protocol was introduced in our department, which emphasized the importance for extensive surgical efforts and complete removal of macroscopic disease, based on recent studies [17–19]. Thereafter, intermediate and high surgical complexity scores were achieved in 8 and 3 patients respectively. Optimal debulking was achieved in 5 cases.

Three patients presented with Grade I postoperative complications, which included two surgical site infections opened at the bedside and one atrial fibrillation caused by low K^+ level. Five patients required a blood transfusion and one was administered with total parenteral nutrition (Grade II Surgical Complications). One patient required reoperation for hemorrhage while another was admitted to intensive care unit postoperatively due to renal insufficiency requiring dialysis (Grade IIIb and IVa respectively). Eight patients had an uneventful postoperative course (Table 1).

All patients received six cycles of fist line chemotherapy with paclitaxel and carboplatin, whereas bevacizumab was added in the 5 most recent cases. Six and five patients demonstrated complete and partial response to chemotherapy respectively, while in five cases the disease appeared to be stable. The remaining three cases demonstrated progressive disease during the follow-up, and the overall survival in these cases was found to be worse compared to the rest cohort. Median overall survival was 29 months, ranging from 13 to 46 months (Table 2).

Table 1 Patient characteristics

Patient characteristics	
Number of patients	19
Age	
Range (median)	44–76 (66)
Stage	
IIIC	13
IVA	6
Preoperative CA125 (U/ml)	
Range (median)	6.5–12,767 (565)
Performance status	
Grade 0	8
Grade 1	5
Grade 2	5
Grade 3	1
PCI (median)	6–20 (13)
Residual disease (R)	
R0	1
R < 1 cm	4
R > 1 cm	14
CC score	
CC-0	1
CC-1	4
CC-2	9
CC-3	5
Surgical complexity score	
Low	8
Intermediate	8
High	3
Surgical complications	
Grade I	3
Grade II	6
Grade III	1
Grade IV	1

PCI Peritoneal carcinomatosis index

CC score Completeness of cytoreduction score

Table 2 Chemotherapy response and overall survival

Chemotherapy and overall survival	
Chemotherapy regimen	
Carboplatin + paclitaxel	14
Carboplatin + paclitaxel + bevacizumab	5
Chemotherapy response	
Complete response	6
Partial response	5
Stable disease	5
Progressive disease	3
Overall survival	
Range (median)	13–46 (29)

Discussion

Two theories have been proposed in the past to explain the development of PPSPC. The first suggested the malignant transformation of embryonic germ cells that remain along the gonadal embryonic pathway, whereas the second assumed that carcinogenesis takes place in the coelemic epithelium lining the abdominal cavity [5]. In the last decade, accumulating evidence suggests that most extrauterine high-grade serous carcinomas originate from the fimbriated end of the fallopian tubes. Serous tubal intraepithelial carcinoma is a precursor lesion of the fallopian tubes that has been found in many cases of both primary ovarian and peritoneal serous carcinomas and is considered to be the source of a significant proportion of these diseases [6–8]. Based on the latter theory, it is of great interest that one of our patients had a history of bilateral salpingoophorectomy two years before the diagnosis of PPSPC. Possible illustrations have been reported in the literature in order to explain the development of PPSPC in the absence of fallopian tubes, predominantly in BRCA mutation carriers with a history of a prophylactic bilateral salpingoophorectomy [20].

Risk factors for developing PPSPC include female gender, age and BRCA mutations [21]. Although most cases have been reported almost exclusively in elderly, postmenopausal women, PPSPC has been diagnosed also in men and one child [22, 23]. In comparison with ovarian serous carcinoma, PPSPC patients have been found in some studies to be older, more often obese and with higher parity [21].

PPSPC spreads mainly intraperitoneally and diffusively involves the abdominal and pelvic peritoneum. However, lymphatic and bloodborne metastases have been reported including metastasis in lungs, brain, breast and axillary lymph nodes [24–28].Concerning our study group, no distant metastasis was found either preoperatively or during postoperative follow up.

Typical imaging findings that may indicate PPSPC preoperatively include massive ascites, parietal peritoneal nodules or masses, omental infiltration or caking and absence of an obvious ovarian mass or another primary tumor of gastrointestinal or genital origin [29, 30]. Regarding our cohort, ascites was found in all patients except for 2, while omental and/or peritoneal nodules were found in 15 patients. In 3 cases, ovarian pathology with benign characteristics was described. It is, however, not always trustworthy to evaluate the morphology and size of the ovaries based on CT findings. Thus, both an intraoperative assessment, either laparoscopically or through an exploratory laparotomy, and mainly histological examination will lead to a reliable diagnosis of PPSPC. On account of this we performed diagnostic laparoscopy to every patient. It is crucial to be mentioned that 10% of the cases initially diagnosed as ovarian serous carcinoma, will meet the criteria for PPSPC [31].

Our routine laboratory investigation included not only CA125 and HE4, but also NLR and PLR. The later biomarkers have been used as prognostic factors preoperatively in patients with ovarian and endometrial cancer, while no investigation has been carried out yet concerning their diagnostic accuracy in peritoneal cancer. Thus, we are not able to reach reliable conclusions based on these laboratory tests at present.

Although early stages of the disease may be asymptomatic, most patients in advanced stages complain of abdominal distension, abdominal lump, diffuse nonspecific abdominal pain, vomiting, weight gaining and dyspnea secondary to massive ascites [32]. The majority of the patients involved in our study presented with the aforementioned symptoms. The late-appeared, non-specific symptomatology is the reason why the majority of the patients are staged as IIIC or IV at the time of initial diagnosis, resulting in a decreased overall survival.

Concerning the prognosis of PPSPC, in the majority of studies overall survival has been found to be worse compared to ovarian cancer patients (range between 7.8 and 25 months less for PPSPC), while some investigators suggest a similar OS for both malignancies [21]. Median overall survival of patients managed in our department was 29 months. Specific factors have been found to have a significant positive impact on overall survival, and these include the age of the patient at diagnosis (< 70 years), good performance status (grade 0), optimal debulking and a high serum CA125 regression rate during the preoperative neoadjuvant chemotherapy [28].

Surgery is used to both efficiently stage the disease and as a therapeutic modality. It should include total abdominal hysterectomy and bilateral salpingo-oopherectomy with supracolic omentectomy, and debulking of as much gross tumor as possible to achieve complete cytoreduction. There is considerable evidence that the volume of residual disease is reversely correlated to patient survival [9]. This was also found in our study as the single patient that had complete cytoreduction survived for 46 months.

In a systematic review, Steihagen and Sehouli reported the involvement of pelvic and paraaortic lymph nodes in two-thirds of patients with PPSPC, and they pointed out the potential benefit of systematic retroperitoneal lymphadenectomy when optimal cytoreduction is achieved [24]. Regarding our cohort, only two patients underwent both pelvic and paraaortic lymph node dissection. It is worth noting that a recent randomized trial showed no survival benefit of systematic lymphadenectomy in patients with advanced ovarian cancer who had undergone macroscopically complete

resection and had normal lymph nodes both before and during surgery [33].

Platinum-based chemotherapy has been found to have high response rate, while other newer chemotherapeutic agents such as taxanes, topoisomerase I inhibitors, gemcitabine, and vinorelbine, alone or in combinations, can result in the improvement of median survival [34]. Bevacizumab is an antiangiogenic drug that has been approved not only for the treatment of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal carcinoma recurrence, but also combined with conventional drugs in first and second line chemotherapy in ovarian cancer. Concerning the protocol of its usage, it is combined with carboplatin and either paclitaxel or gemcitabine, and then it is administered alone [35, 36]. Furthermore, it has recently been demonstrated that olaparib improves progression-free survival when it is used as a maintenance treatment in patients with advanced ovarian cancer and BRCA1/2 mutations [37].

Intraperitoneal chemotherapy has recently demonstrated a survival benefit in patients with PPSPC when compared to those treated with surgery alone or surgery in combination with systemic chemotherapy. The role of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) after debulking surgery is still under exploration. Recently, Ceresoli et al. pointed out that HIPEC can affect the relapse pattern with lesser peritoneal recurrence and better overall survival, while van Driel et al. showed an improved survival of patients with ovarian cancer who underwent HIPEC in addition to interval debulking surgery (IDS) vs IDS alone [38, 39].

As limitations of our study the retrospective type of our investigation and the relatively small number of patients included could be considered. PPSCP is a rare disease and for this reason we identified 19 patients in a 15-year period with limited data for the analyzed parameters regarding the cohort. We should clarify that the included 19 patients refer to the ones who underwent primary debulking surgery. Therefore one could criticize that sparse conclusions can be drawn. Further limitations include the non-inclusion of a control group e.g. an ovarian cancer group, and the unavailability of the BRCA testing data. Based on our findings we can highlight in our cohort a trend towards maximal surgical effort during debulking approach of PPSPC patients.

Our intention is to present the main characteristics of the patients with PPSPC, as well as their management, comparing them with those found in the literature. Given the small total number of patients having been reported, large multicenter investigation should be carried out, concerning predominantly preoperative diagnostic management and therapeutic approach.

Authors contribution NB: data collection, data analysis, manuscript writing, EV: data collection, manuscript writing, manuscript editing, GV: project development, data analysis, NK: project development, validation, CI: project development, data analysis, manuscript editing.

Compliance with ethical standards

Conflict of interest We declare that we do not have any conflict of interest.

Informed consent Informed consent was obtained from all alive individual participants or, in case of deceased patients, from their next of kin.

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