Primary Peritoneal Carcinoma: Regional Cancer Institute Experience

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Received: 8 April 2014 / Accepted: 5 August 2014 / Published online: 13 August 2014
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Abstract Primary peritoneal serous carcinoma (PPSC) is a rare malignancy that arises primarily from peritoneal surface epithelium. However there are limited studies on these tumors even in world literature. To study the clinical, pathologic profile, outcome and prognostic features of PPSC. A 5 year retrospective study of PPSC diagnosed and treated at our centre was conducted. The pathological specimen of PPSC diagnosed from January 2008 to December 2012 were reviewed by gynaecopathologists. The diagnosis was based on GOG criteria, complemented with IHC. Majority of the patients underwent upfront de-bulking surgery. Postoperatively, six cycles of combination chemotherapy with paclitaxel (175 mg/m²) and carboplatin (AUC 6) was administered every 3 weekly. These patients were analysed for progression free survival (PFS), this was correlated with stage and surgical adequacy. The median age of presentation was 56 years. The total number of ovarian cancers treated during study period was 374. The 30 cases were clinically suspected to have primary peritoneal carcinoma (PPC) on pre- and intra-operative gross findings, but further evaluation with histopathological examination, IHC and GOG criteria revealed only 10 cases were genuine PPSC. The remaining 20 cases; 13 were found to poorly differentiated ovarian carcinomas, six were primary fallopian tube carcinoma and one was appendicular carcinoma. The 10 (2.7 %) cases of the 374 were eligible for the PPSC analysis. The two (20 %) of the 10 cases had family

history of breast and ovarian cancers, two (20 %) cases were diagnosed as abdominal tuberculosis (TB) prior referral to our centre. Radiological presentation includes gross ascites, with omental caking and normal adnexa. The eight (80 %) of 10 cases presented with stage IIIC and other two cases (20 %) with stage IV disease. The eight (80 %) of 10 cases underwent upfront surgery; six (75 %) of these eight cases had optimal cytoreduction, i.e. residual disease (RD) <1 cm or no visible disease (R0) and other two (25 %) suboptimal cytoreduction. The two (20 %) of 10 cases with stage IV disease received neoadjuvant chemotherapy (NACT) followed by interval cytoreduction. After debulking surgery the most useful IHC marker include CK7+, CK20-, CA125+, WT-1+, and GCDPF-. At median follow up of 24 months (range 3–60 months), the median progression free survival (PFS) was 22 months, while the estimated 5 year PFS was 18 %. Stage IV disease and suboptimal surgery had poor outcome. The PPSC presents with advanced stage disease and are observed to be misdiagnosed abdominal TB in tropical countries. The GOG criteria and IHC complement the diagnosis. These have poor outcome despite optimal care, highlighting need for larger studies on this disease.

Keywords Abdominal TB · Primary peritoneal carcinoma · Regional cancer institute

Introduction

Primary peritoneal serous carcinoma (PPSC) is a rare malignancy compared to their ovarian counterpart (6 vs. 120 cases per million respectively) [1]. These tumors arise primarily from peritoneal surface epithelium. The epithelial layer of the ovary and the peritoneum share a common embryonal heritage, deriving from coelomic epithelium early in life [2]. The recent new data in the pathogenesis of PPSC suggests the

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origin and its precursors lesion starts in fallopian tubes as serous tubal in situ carcinoma (STIC), stage 0 but grows preferentially at remote site in the peritoneum [3, 4]. The PPSC are staged and treated in a similar way to epithelial ovarian tumors. However these tumors present with advanced stage and have a shorter survival when compared to their ovarian counterpart [5]. And there are limited studies on these tumors even in world literature [6].

Since these are rare and there is dearth of data, we conducted the present study to analyse its demographic profile, clinical, radiologic, pathologic features and outcome of this disease.

Material and Methods

This retrospective study included PPSC diagnosed and treated at our institute during January 2008 to December 2012. The case records of these patients were analyzed in detail for clinical profile, immunohistochemistry, treatment given and outcome. The departmental policy for cytoreductive surgery in advanced stage ovarian cancers is upfront cytoreduction for patient having good performance status (WHO performance score 0–1), serum albumin >3 g/dl and clinical/radiological evaluation revealing resectable disease. The resectable disease is defined as; the visible tumor deposits on the peritoneal surface, bowel, omental, spleen, diaphragm, liver surface and enlarged retroperitoneal nodes below the renal vessels, and the disease was considered as unresectable, when the tumor deposits in the porta-hepatis, liver parenchymal metastasis, multiple bowel carcinomatosis, multiple bowel mesenteric tumor deposits and enlarged retroperitoneal nodes above the renal hilum. The patients having poor performance status (WHO performance score >2), low serum albumin <3 g/dl and stage IV disease receive three cycles of neoadjuvant chemotherapy (NACT) followed by interval cytoreductive surgery. The histopathological study was done by Gynaec-oncopathologist and the GOG criteria was used for diagnosis [7] which include: i) both ovaries must be normal in size or enlarged by a benign process, ii) the involvement in the extra-ovarian sites must be greater than the involvement on the surface of either ovary, iii) the ovarian tumor component must be either nonexistent, confined to ovarian surface epithelium without stromal invasion, or involving the cortical stroma with tumor size up to 5×5 mm; (Fig. 1) and iv) serous histology is present (Fig. 2). The diagnosis was established on the basis of the final histopathological and immunohistochemistry (IHC) examination after definitive surgery. The IHC markers used were CK7 (clone: OV-TL, company: BioGenex), CA125 (clone: OV185:1, company: BioGenex), WT-1 (clone: EP1131Y, company: BioGenex), CK20 (clone: IT-Ks20.8, company: BioGenex), GCDFFP-15 (clone: 23A3, company: Novocastra), P53, (company: Dako) ER(company: Dako),

Fig. 1 Showing the ovarian tumor component confined to ovarian surface epithelium involving the cortical stroma with tumor size up to 5×5 mm($10\times$), insert showing higher magnification at $40\times$

and PR(company: Dako). These patients were classified according to 2009 FIGO staging system. The adjuvant 6 cycles of combination chemotherapy with paclitaxel (175 mg/m^2) and carboplatin (AUC 6) was administered every 3 weekly. The patients were followed up by clinical, biochemical and radiological examination every 3 months after therapy. The progression free survival (PFS) and overall survival (OS) was evaluated for all patients using the Kaplan Meier curve (SPSS 19 - SPSS Inc, USA). Stage of disease and extent of resection were correlated with overall survival using the Log Rank test

Results

The total number of ovarian cancers treated during study period was 374. The 30 cases were clinically suspected to have primary peritoneal carcinoma (PPC) on pre- and intra-operative gross findings, but further evaluation with histopathological examination, IHC and GOG criteria revealed only 10 cases were genuine PPSC. The remaining 20 cases; 13 were found to be poorly differentiated ovarian carcinomas, six were primary fallopian tube carcinoma and one was appendicular

Fig. 2 photomicrograph showing omentum serous histology $10\times$, insert showing higher magnification at $40\times$

Table 1 clinical features, stage and treatment given

Demographic profile	
Total number of Ovarian cancers	374
PPSC cases (analyzed)	10
Median age	56 years (range 45–72)
Post-menopausal	8
Misdiagnosed and treated for Tuberculosis	2
Family history of breast/ovarian cancer	2
CA125 mIU/ml	Mean 566 (range 46–2350)
Stage of disease	
IIIc	8
IV	2
Therapy	
Upfront cytoreduction surgery	8
-Optimal	6
-Suboptimal	2
Neoadjuvant chemotherapy	2

carcinoma. The 10 (2.7 %) cases of the 374 were eligible for the PPSC analysis (Table 1). The median age was 56 (range 45–72) years. Majority, eight (80 %) of 10 were postmenopausal. Two (20 %) of 10 cases had a family history of breast and ovarian cancer in first degree relative aged <50 years, these patients and their relatives were counselled about testing for BRCA mutations; however it was not done due to logistic reason. Abdominal distension with vague pain was the most common presentation. Two (20 %) of 10 patients were misdiagnosed to have abdominal tuberculosis (TB) and received therapy for the same prior referral to our centre. The radiological study detected gross ascites and omental caking in all cases with normal adnexa or adnexa not visualized in most cases which was confirmed on intra-operative findings

(Figs. 3 and 4). All patients had raised CA125 levels mean 566 (46–2340 mIU/ml). Peritoneal fluid cytology study revealed malignant cells in all cases, with specific histology being adenocarcinoma. IHC revealed CK7+, CK20-, CA125+, WT-1+, and GCDFP- in all cases. The P53 positive staining observed in 3 cases (30 %) and another 3 cases (30 %) revealed ER and PR positive staining.

The eight (80 %) of 10 cases underwent upfront surgery; six (75 %) of these eight cases had optimal cytoreduction, i.e. residual disease (RD) <1 cm or no visible disease (R0) and other two (25 %) suboptimal cytoreduction. The two (20 %) of 10 cases presented with malignant pleural effusion, stage IV disease received three cycles of neoadjuvant chemotherapy (NACT) followed by interval cytoreduction. These two patients had complete response to NACT and optimal interval cytoreduction. The median follow up was 24 months (range 3–60 months). The median PFS was 22 months, while the estimated 5 year PFS was 18 % (Fig. 5). The patient's with suboptimal cytoreduction and stage IV disease had worse prognosis.

Discussion

Primary peritoneal cancer is a rare tumour which occurs in female with a median age of 62 years [8, 9]. The median age in our study was 56 years and 80 % stage IIIC at diagnosis. In our scenario, abdominal tuberculosis is a common differential diagnosis and may lead to delay in proper management of PPSC.

PPSC has a distinct genetic profile when compared to epithelial ovarian tumour. These tumours have a higher expression of BRCA1 and TP53; but KRAS expression is

Fig. 4 Intra-operative picture; Omental Cake in primary peritoneal serous carcinoma

infrequent [8]. In an ovarian cancer screening program involving familial cancer patients, where seven cases of PPSC was diagnosed in 1261 participants; only 2 had elevated CA125 levels, ultrasonographic (USG) abnormalities in two patients and three patients carried BRCA1 mutation [10]. In our study all patients had raised CA125 levels, all patients had USG abnormalities and two patients had history suggestive of familial cancer.

IHC helps in differentiating PPSC from other tumours and is only complimentary. PPSC is usually positive for CK-7, CA125, ER, and WT-1 [11]. GCDPF-15(gross cystic disease fluid protein) is a marker for breast and salivary gland tumours and is usually negative for mullerian origin tumors [12]. These tumours are also positive for HER-2/neu (34.4 %), p53 (71.9 %), bcl-2 (9.4 %), and nm23-H1 (100 %) [13]. P53 was positive in three cases in

Fig. 5 Progression Free Survival Curve

our study. Other markers were not done due to logistic reasons.

In our study all patients were stage IIIc/IV at diagnosis; this is similar to world data. The adjuvant treatment of choice of PPSC is platinum-paclitaxel combination [14]. Using this combination the median Progression free survival reported is 17 months and overall survival is 40 months, however this is significantly better in those who are optimally debulked [14]. Our number is too small to comment on survival, in our study the median PFS was 22 months. The 5 year survival in similar stage ovarian counterpart is around 25–30 % in stage IIIC and 15–20 % in stage IV disease, we noted a similar estimated event free survival [15].

In conclusion: The PPSC presents with advanced stage disease and are observed to be misdiagnosed abdominal TB in tropical countries. The GOG criteria and IHC complement the diagnosis. These have poor outcome despite optimal care, highlighting need for larger studies on this disease.

Conflict of Interest authors declare no conflict of interests.

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