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PRIMARY FALLOPIAN TUBE CARCINOMA: A REVIEW OF A SINGLE INSTITUTION EXPERIENCE

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ABSTRACT **Background:** Primary fallopian tube carcinoma (PFTC) is rare. Herein, we investigate the clinico- pathological characteristics and response to cytoreductive surgery & appropriate therapies for PFTC.

Materials and Methods: A retrospective observational study of 5 women with a histopathologic diagnosis of PFTC from January 2004 to Dec 2018.

Results: The mean age at diagnosis was 53 years (range, 46 to 62 years), and the mean follow-up period was 51 months. All (100%) patients were postmenopausal. Eighty percent had an ECOG score of 0-1.The most common clinical presentation was nonspecific pelvic pain (100%), followed by abnormal vaginal bleeding (80%), and adnexal mass of unknown origin (40%). Three (60%) patients were assumed preoperatively as primarily in the ovary. All patients were diagnosed postoperatively; Primary optimal cytoreductive surgery was achievable in 4/4 (100%) in advanced disease. Only 1 (20%) patient was in Stage IIA & four (80%) in Stage IIB - IIIB. The serous type histology was predominant (60%), 60 % were of grade 2 and 40% of high grade. All showed complete response (CR) to adjuvant paclitaxel and carboplatin (P+C).The mean progression-free survival (PFS) rate was 43.6 months and mean Overall survival (OS) was 51 months.

Conclusion: PFTC is infrequently diagnosed preoperatively or intraoperatively due to its rarity, and has nonspecific presentation. Radical cytoreductive surgery, followed by postoperative adjuvant chemotherapy P+C is a standard treatment by which the survival potential of PFTC can be greatly enhanced.

KEYWORDS : primary fallopian tube carcinoma, prognosis, chemotherapy.

INTRODUCTION

Fallopian tube malignancy may be primary or secondary. PFTC is rare and accounts for 0.3-1.6 % of all malignancies of the female genital tract [1]. Over 3000 cases with PFTC described in the literature [2–4]. It occurs in post-menopausal women. The etiology is unknown. Hormonal, reproductive, epithelial ovarian cancer (EOC) might also increase PFTC risk [5,6]. High parity and the use of oral contraceptives decrease the risk of PFTC [7].

The symptom complex of hydrops tubae profluens (Latzko triad), in which a patient presents with a pelvic mass, pelvic pain and profuse watery vaginal discharge and the pain being relieved after vaginal discharge is rarely encountered, but is almost pathognomonic. The diagnosis is rarely achieved pre-operatively because of misleading imaging and relatively limited clinical experience, but may be suspected in cases of postmenopausal bleeding with negative diagnostic curettage [8]. In most of the cases, preoperative diagnosis was ovarian carcinoma but surgical findings and histology confirmed fallopian tube carcinoma. Frozen section study is much helpful in making intraoperative diagnosis.

Currently, the guidelines for ovarian cancers is used for the management of PFTC, and the International Federation of Gynecology and Obstetrics (FIGO) staging system for epithelial ovarian cancer have been adapted for PFTC. Patients with PFTC are more likely to present with early-stage tumors and to have better survival than ovarian cancer [9,10]. Recently, several studies have reported an increase in the incidence of PFTC, especially among the higher social classes. Rising incidence of PFTC inspired us to investigate the clinic-pathological features and treatment of this unique malignancy.

2. MATERIAL AND METHODS

We retrospectively reviewed the records of 5 patients who were diagnosed postoperatively with pathologically confirmed PFTC between January 2004 and December 2018. Medical records were analyzed for demographic characteristics (age at diagnosis, parity, presenting signs and symptoms, menopausal status, serum CA 125 levels), surgical findings (surgical procedure, residual tumor tissue, the numbers of excised and positive lymph nodes, the presence or absence of ascites), and the adjuvant chemotherapy prescribed, clinical outcome at follow-up, date of recurrence, date of the last medical examination, and the date of death. Staging was done as per FIGO classification [11]. Histological grading was done as Grade 1 - well-differentiated, Grade 2 - moderately differentiated, and Grade 3 - poorly differentiated tumors. Complete resection was defined as no residual tumor measuring >1 cm in maximal dimension after the initial surgery.

All 5 patients underwent surgery followed by chemotherapy (4 patients received P+C and one patient received docetaxel). There were two chemotherapy protocols: P+C and docetaxel. Response to chemotherapy and surgery was evaluated by computed tomography or ultrasound according to World Health Organization (WHO) criteria. Patients with tumors assessed by CT scan (≥10 mm) or by ultrasonography (≥20 mm) were classified as measurable disease. Nonmeasurable disease included cystic lesions and ascites. Patients with measurable disease after primary cytoreductive surgery were assessed for objective response. Pelvic and abdominal CT scan or USG and chest X-ray were repeated after the third and the sixth treatment courses.

The recurrence was defined based on CA 125 or imaging findings. PFS time was defined as the interval between the date of primary surgery to detection of recurrence of PFTC or the end of the follow-up when no disease was detected. OS was calculated from the date of registration to date of death or the last follow up.

3. RESULTS

Patient demographics are shown in Table 1. The mean age was 53 years (range 46–62 years). Mean parity was 3 (range 2–4) and all 5 women were postmenopausal. The most common clinical presentation was abdominal pain 100%, abnormal vaginal bleeding 80%, abdominal distension and discharge per vaginum 40%. Abdominal pain with distension were encountered in 2/5 (40%) (Table 2) and irregular bleeding and vaginal discharge were noted in 2/5 (40%) of the women. four patients 80% had an ECOG score of 0-1(Table 1). In 2/5 (40%) of women, pre operative diagnosis was adnexal mass and in rest of 60% it was ovarian mass.

The preoperative serum CA-125 levels in early stage disease was 32 U/mL in 1 woman and 100 to 428U/mL in 4 women in advanced stage. An elevated CA- 125 had a positive correlation with higher stage disease. Distribution of primary tumor size was 3–8 cm.

Staging laparotomy was done in one patient with clinically apparent early stage disease. In advanced stages, primary optimal cytoreductive surgery was achievable in 4/4 (100%). Final staging could categorize 1/5 (20%) of women into early stage disease (Stage IIA and grade 2 Figure 1 and 2) and 4/5 (80 %) into advanced stage (IIB–IIIB and grades G2, and 3) Table 1. Two patient (40%) had grade 3 and 3/5 (60%) had grade 2 tumors. Microscopic and macroscopic pelvic nodal disease was observed only in advanced stage disease 1/5 (20%). All 5/5 (100%) women had received adjuvant chemotherapy. Complete response was achieved in one woman (20%) with docetaxel and in four women (80%) with P+C, Tables 1 and 2.

One women (20%) in early stage disease is alive with NED. Four women were alive at the end of 3 years and the longest survivor has completed 5.5 years. In this series, the mean follow-up from the time of initial surgery was 51 months (range, 26-67 months). Four patients (80%) had experienced recurrence at the time of the review. Two patients (40%) were lost to follow up.

They had mean PFS of 43.6 months (range 12–67months) and mean OS 51 months (range 26–67 months), Tables 2.

Table 1. Details of women characteristics

Age (mean and range)	53 yrs. (range 46–62 years)
Postmenopausal	100%
ECOG performance score	
0	40%
1	40%
2	20%
3	0
Final histopathology	
Sq cell ca Mod. Diff.	20%
Mod. differentiated Adeno carcinoma	20%
Mod. differentiated serous Adeno carcinoma	20%
High grade Papillary serous adeno carcinoma	40%
Histological grade	
1	0%
2	60%
3	40%
FIGO stage	
Early stage	
(IIA and grades 2)	1/5 (20%)
Advanced stage	
(IIB/III and grades 2, 3)	4/5 (80%)
Surgical procedure	
Optimal debulking surgery (Early & advanced stage)	5/5(100%)
Chemotherapy response	
Single agent Docetaxel was administered in 1 advanced stage disease	1/5 (20%)
Paclitaxel and Carboplatin combination in Early & advanced stage disease	4/5 (80%)

Table 2. Summary of women characteristics and treatment.

S. No.	Age	Parity	Stage	Menauposal/ Past / family his	Presenting comp.	Pre op investigation USG/CT	Pre op CA-125 U/m	Surgical procedure	HPR/grade	Adjuvant Chemotheapy	PFS	OS
1.	50	P3L3	IIIA	PM--	Pain abdomen & bleeding PV	Rt tubo-ovarian mass	354	TAH + BSO + omentectomy	High grade papillary adeno ca	6 cycle P+C	12 M	26 M
2.	56	P4L4	IIB	PM - -	Bleeding PV Pain Abd	Lt ovary enlarged 5.6x5.4 cm	164	TAH + BSO + omentectomy	High grade papillary adeno ca	6 cycle P+C	60 M	63 M
3.	62	P2L2	IIIB	PM - -	Pain & Distension Abd., Bleeding & Discharge PV	Pelvic mass 5.5x3.8x3.5 cm	428	TAH + BSO + omentectomy +node dissetion	MD Adeno ca	6 cycle P+C	26 M	36 M
4.	48	P3L2	IIIA	PM - -	Pain & Distension Abd	Pelvic mass 8.1x3.5 cm	127	TAH + BSO + omentectomy	MD Sq cell ca	6 cycle P+C	67 M	63 M
5.	46	P4L4	IIA	PM - -	Pain, Bleeding & Discharge PV	Ovarian ca	32	TAH + BSO + omentectomy	MD Adeno ca	6 cycle Docetaxel	53 M	67 M

P: parity; L: living children; his.: history; PM: postmenopausal; comp.: complaints; USG: abdominopelvic ultra sound; Adj. CT: adjuvant chemotherapy; ca.: carcinoma; TAH: total abdominal hysterectomy; BS0: bilateral salphingooophorectomy; P+ C: paclitaxel + carboplatin; PFS: progression-free survival; M: months; HPR: histopathology report; abd.: abdominal; Ut.: uterus.

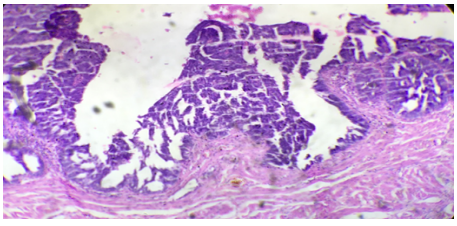

Fig.1 Serous carcinoma showing slit-like glandular spaces admixed with compex papillae and psammoma bodies. H/E stain 100 X.

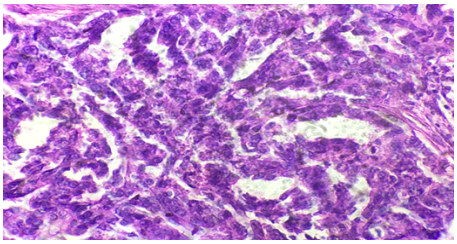

Fig.2 High power showing papillary serous adenocarcinoma. H/E stain 400 X.

4. DISCUSSION

This current study includes 5 patients of PFTC from a single institution between January 2004 and December 2018. In the literature, the mean age of patients with PFTC is 55 years [12]. The average age of the patients in our study was 53, while 80% of the patients were younger than 60 years and 20% were older than 60 years. All 5/5 (100%) of the women were postmenopausal which were in accordance with the literature.

The symptoms of the patients in our study were consistent with the literature. Abdominal pain 100%, abnormal vaginal bleeding 80%, abdominal distension and discharge per vaginum 40%. Other authors report the incidence of pain, distension of abdomen and palpable mass in 39-42% of their series [5]. The pathognomonic Latzko triad symptoms of PFTC [8], was not found in any of our patient. However, none of these symptoms are specific, and this triad was reported in only 3--15% of PFTC cases [2].

In literature the preoperative diagnosis rate is 0.3–15% [5,6]. Preoperative diagnosis is usually ovarian tumor or pelvic masses and most often, it is difficult to distinguish from ovarian cancer [1]. In our series, 60% were preoperatively presumed to be ovarian cancer and remaining 40% as undefined adnexal mass which is consistent with literature. Although intra-operative frozen section is much helpful to make intra-operative diagnosis, but this was not employed in our cases.

There is no specific tumor marker for PFTC. However, CA-125 is often used as a tumor marker for fallopian tube carcinomas like ovarian malignancy. CA-125 levels are lower in the early stages but higher at advanced stages [1] and is an independent prognostic factor for disease-free survival and overall survival. The CA-125 was found to be 32U/mL in one women (20 %) in early stage disease and in advanced stage (80 %) it was ranged from 100–428 U/mL (normal limit 35 U/mL). However, in this study, no correlation with prognosis was identified.

Imaging studies such as ultrasound, computed tomography, or MRI may help in diagnosing PFTC, however MRI is considered a better method for detecting tumor infiltration of extratubal organs. Although they are nonspecific, and their findings mimic other pelvic diseases such as tubo-ovarian abscess or ovarian tumor, several findings may provide a diagnostic clue preoperatively. Transvaginal Color Doppler and computed tomography or the use of endometrial cytology combined with CA-125 levels may help in early detection [8].

Primary optimal cytoreductive surgery was achieved in all patients. Most of our patients were moderately differentiated (60%) with histopathologic findings of serous adenocarcinoma 60%, nonserous adenocarcinoma 20% and squamous cell carcinoma 20 %. Tumor grade & histology of the patients included in our study was consistent with the literature [1]. In our study, due to few number of cases we failed to establish association between the grade, type of histology and survival probability. Most of studies failed to establish such association of grade as significant prognostic factor [8], except Shamshirsaz et al [13] and Kietpeerakool et al [14]. Wethington *et al*. reported that 48% of patients had serous adenocarcinoma and 52% had nonserous adenocarcinoma [2].

Although data is limited with the use of P+C as the first line treatment in PFTC, the last decade has witnessed the experiences shared by Gemignani et al. [15]. He reported 24 patients with advanced stage in 71%, of them 96%, 90% had overall survival at the end of 1 year and 3 years respectively. Median disease PFS of 27 months for the entire population. They concluded excellent survival in the optimally cytoreduced patients treated with adjuvant treatment using paclitaxel-based chemotherapy regimen.

Cytoreductive surgery followed by chemotherapy as adjuvant or radiotherapy for the residual disease has been recommended as a routine treatment of PFTC for decades. Pectasides et al [16] and Cormio et al [17] reported that in advanced PFTC treated with chemotherapy regimen contain P+C for 6 cycles show significant survival benefit and suggesting as the new treatment recommendation. Optimally cytoreduced patients with PFTC followed by paclitaxel-based chemotherapy regimen shown excellent survival [15]. Several recent studies suggested that the platinum and paclitaxel based chemotherapy regimen should be taken as the standard treatment in patients with PFTC [3, 18]. One of the largest series consisting of 101 women with PFTC was reported by Lingjie Bao et al. in 2016 [8], where patients treated with 6 cycles of carboplatin and paclitaxel therapy shown that 5-year OS and 5-year DFS were significantly higher than those of patients treated with fewer than 6 cycles (78.2 ± 5.2 vs 43.4 ± 8.6, 69.1 ± 5.8 vs 31.4 ± 8.2, respectively).

In our series, a total of 4/5 (80%) patients were administered 6 cycles of P+C regimen and 1/5 (20%) patient received 6 cycle of docetaxel as single agent. In the present series we had 100% overall response rate to both the adjuvant chemotherapy regimen. Recurrence occurred in 3 patients with advanced stage, each having PFS of 12, 26 & 60 months and OS of 26, 36 & 63 months. The most important prognostic factors for survival appear to be early stage of disease [3,15] and optimal cytoreduction [15]. Similar observations was found in the present study where one woman in early stage disease is alive without clinical, radiological, or biochemical evidence of recurrence.

This study is also limited because of its sample size. The incidence of PFTC is low, and its clinical manifestations are rather heterogeneous. Based on this experience, we would like to suggest that PFTC be considered in postmenopausal woman presenting with vaginal bleeding, discharge, or lower abdominal pain. Intraoperative frozen section may help in diagnosis and optimal cytoreductive surgery of this rare disease. Radical cytoreductive surgery, followed by postoperative P+C based chemotherapy for 6 cycles are recommended for the treatment for patients with PFTC.

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