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Case series

“A Concealed Malignancy” A Case Series of Primary Fallopian Tube Carcinoma and its Diagnostic Challenges

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Background: Primary fallopian tube carcinoma remains a diagnostic challenge due to its rarity and nonspecific clinical presentation. Its insidious nature often leads to misdiagnosis, with the true diagnosis emerging only on histopathology. This case series presents four cases of fallopian tube cancer managed in our institution over a five-year period, highlighting the diverse clinical presentations and diagnostic hurdles.

Methods and Results: The four cases, encompassing a range of ages, exhibited distinct symptoms. The first case, a 44-year-old patient, presented with recurrent vaginal discharge followed by supraclavicular node involvement suggestive of metastasis. The second case, a 58-year-old patient, presented with vaginal spotting and a pelvic mass mimicking an ovarian tumor. The third and fourth cases, a 71-year-old and a 66-year-old respectively, presented with gradually enlarging abdominal masses, initially attributed to an adnexal mass. Intraoperative findings revealed a thinned and dilated fallopian tube in the first and third cases, an unidentified right fallopian tube with an adnexal mass in the second case, and a left fallopian tube transformed into a tan, irregular mass in the fourth case. Histopathology confirmed high-grade fallopian tube serous carcinoma in all cases. This case series emphasizes the importance of raising suspicion for primary fallopian tube carcinoma in patients with suggestive clinical features. Timely investigations and early detection are crucial for effective management and improving patient outcomes.

Conclusion: This study underscores the varied presentation of this rare malignancy and serves as a reminder to avoid misdiagnosis and ensure prompt and appropriate treatment strategies.

Introduction

Primary fallopian tube carcinoma (PFTC) is an unusual tumor of the female genital tract with an incidence of less than 0.14-1.18% of all genital malignancies [1-2] and 0.2 % of cancers among women. The mean age at diagnosis of fallopian tube carcinoma is 58 years, with a range of 26 to 85 years [3]. Many women are asymptomatic; however, the most commonly reported signs and symptoms include abnormal vaginal bleeding or serosanguineous vaginal discharge (35% to 60%), a palpable adnexal mass (10% to 60%), and crampy lower abdominal pain caused by tubal distention and forced peristalsis (20% to 50%) [4].

Classically, two triads of symptoms have been described, and at least one syndrome is considered pathognomonic. Latzko’s triad, described in a 1916 publication, is the combination of pelvic pain, a pelvic mass, and serosanguineous vaginal discharge. A second triad, with a reported frequency of 6% to 38%, involves vaginal bleeding, vaginal discharge, and lower abdominal pain. In addition, the syndrome characterized by colicky lower abdominal pain and a resolving mass after profuse vaginal watery discharge or hydrops tubae profluens, is uncommonly reported (approximately 9%) in large review series, although thought to be diagnostic of fallopian tube carcinoma [5].

Histologically, 80% to 90% of fallopian tube carcinomas are adenocarcinomas. Most of these are serous carcinomas, followed by endometrioid and clear cell adenocarcinomas. Fallopian adenocarcinomas come to attention due to abnormal discharge, bleeding, or occasionally abnormal cells in a Pap smear [6].

The first step in the transformation of fallopian tube epithelium to carcinoma is the evolution of a single-cell TP53 mutant epithelial layer, p53 signature, which includes strong p53 immunopositivity and evidence of DNA damage in otherwise normal secretory fallopian tube cells. This event is then followed by the development of the STIC lesion, characterized by an atypical secretory fallopian tube epithelium with a high proliferative index and accumulation of aberrant p53. The STIC lesions then either invade the tubal stroma locally (developing into primary Fallopian Tube Carcinoma) or exfoliate onto the surface of the ovary or peritoneum (primary ovarian or peritoneal carcinoma) [7]. Other recurrent mutations in are infrequent, but most prominently include BRCA1 and BRCA2, with BRCA germline mutations seen in 13–16% and somatic mutations seen in about 6% of cases [8].

In most studies done worldwide, it is said that a correct diagnosis of PFTC was made preoperatively in only 4.6% of cases in the series of Alvarado-Cabrero et al. [9] Data of this disease in the Philippines is very limited. Based on s search in local publications, there are only a few reported cases on primary fallopian tube carcinoma, there is one with a 50 year old nulligravid who was diagnosed early in the course of disease in an article reported by Angat and Tomacruz [10] and another, a 60 year old multigravid who also presented with rare signs and symptoms in a study done by dela Peña and Tan-Espiritu [11], however there are no reported incidence rates.

This paper aims to present four cases of primary fallopian tube cancer with varied presentation managed in our institution in a 5-year period. Likewise to discuss the managements and prognosis of these patients in the light of recent literature.

Case Series

Case 1.

A 44-year-old, G3P3 (3002) patient with unremarkable past medical, family history and Obstetric and Gynecologic history presented with recurrent vaginal discharge for 3 months. Speculum and internal examination revealed a whitish discharge, an everted cervix with no gross nodularity, no adnexal masses palpated. No significant findings on initial imaging, except a bulky cervix. Cervical punch biopsy was unremarkable. Her vaginal discharge improved but persisted even with extended antibiotics. The plan of colposcopy with possible biopsy was delayed due to the Covid-19 pandemic. A left supraclavicular mass was then noted 6 months later. Excision biopsy disclosed a poorly differentiated carcinoma, metastatic, (+) CK 7, (-) CK 20. Complete surveillance CT scan showed a prominent and enlarged left supraclavicular lymphadenopathy, normal chest findings, unremarkable abdominal organs. Multiple enlarged lymph nodes in clusters seen in the paraaortic and bilateral parailiac spaces. Uterus was normal in size. The cervix appears prominent. The left ovary measures 2.1 x 2.9 cm and shows several thin walled cystic foci. A 2.5 x 2.5 soft tissue nodule is seen posteriorly adjacent to the left ovary and lateral to the uterus, probably an ovarian growth or subserous myoma. An everted cervix with endocervical nodularity was seen on repeat speculum exam, but cervical and endocervical biopsy revealed a benign pathology. Ca125 was elevated at 1090 U/ml. She underwent exploratory laparotomy. The left fallopian tube was thinned out and dilated to 3 cm, filled with granular fleshy tissue at the distal 3rd (Figure 1.1.B). The cervix, uterus, contralateral fallopian tube and bilateral ovaries were grossly unremarkable. (Figures 1.1.A, 1.1.C, 1.1.D). Multiple lymph nodes were palpated at the bilateral pelvic iliac and obturator fossa. A matted aggregate lymph nodes were palpated at the common iliac and paraaortic spaces. Liver, intestines and omentum were grossly normal. She underwent total hysterectomy with bilateral salpingooophorectomy, pelvic lymphadenectomy and omentectomy. Microscopic study of the left fallopian tubes showed high-grade serous carcinoma with tumor noted in the fallopian tube surface (Figure 1.2.A.), tumor size 3.8 cm, lymphovascular invasion was observed (Figures 1.2.B.). All right

lymph nodes were positive for metastasis with perinodal lymphovascular invasion (Figures 1.2.C, 1.2.D.). Uterus, cervix endometrium, ovaries, right fallopian tube , left lymph nodes and omentum were negative for tumor. Her final cancer stage is IVB. Six cycles of chemo carboplatin-Paclitaxel was given. Currently, the patient in ongoing treatment. She just received her 4^{th} cycle chemotherapy with Pegylated Liposomal Doxorubicin.

Case 2.

A 58 years old, G3P3 (3003) consulted for vaginal spotting for the last 4 months. Her past medical, family history and Obstetric and Gynecologic history were unremarkable. Initial examination and ultrasound were unremarkable. 3 months after, there was recurrence of vaginal spotting with associated weight loss of approximately 15-20% of previous body weight, whitish vaginal discharge which was non-foul smelling and generalized body malaise. No associated changes in bowel or bladder habits. CT scan revealed a pelvic mass that may represent new growth of ovarian etiology (Figure 2.1.A). CA-125 was high at 140 U/ ml. Endometrial sampling showed a poorly differentiated carcinoma rule out poorly differentiated squamous cell carcinoma versus adenocarcinoma. She underwent exploratory laparotomy, the right ovary was enlarged to 8 x 10 x 3 cm containing chocolate fluid with no solid papillarities and nodulations. The right fallopian tube cannot be grossly identified but an adnexal mass is noted at the area of the right fallopian tube measuring 10.5 x 7 x 4 cm with cream, purulent surfaces (Figure 2.1.B.). The uterus and the contralateral adnexa were grossly normal. The uterus left ovary and fallopian tube, omentum and appendix appears normal (Figure 2.1.C.). Extrafascial hysterectomy, bilateral salpingooophorectomy, peritoneal fluid cytology, infracolic omentectomy and lymphadenectomy were done. Histopathologic study revealed high grade serous carcinoma, right fallopian tube, positive for omental metastasis (Figures 2.2.A, 2.2.B, 2.2.C.). Her disease is FIGO Stage IIIA2. The patient did not undergo adjuvant therapy but alive after 36 months of follow up.

Case 3.

A 71 years old, G1P1 (1001) presented with a 2 month history of gradually enlarging abdomen with associated dysuria and decreased urine output. This was then followed by vaginal spotting with a foul smelling brownish vaginal discharge one month after the appearance of primary symptoms. Consult was then done where an ultrasound requested reveal ascites and a left lobulated adnexal mass (9.7 x 8.0 cm in size), a follow up CT scan was requested revealing multinocular left adnexal cystic mass measuring 9.7x 10.4 x 8 cm. Preoperative CA 125 was elevated at 500 U/ml. Patient is a known diabetic and hypertensive, her family history and Obstetric and Gynecologic history were unremarkable. Patient then underwent exploratory laparotomy. There was 5L serous ascites drained. Multiple nodularities were noted on the omentum and on the liver surface. The left fallopian tube was converted to a 20 x 25 cm multiloculated mass with friable tissues within (Figure 3.1.C.). Appendix grossly normal. No palpable pelvic and paraaortic nodes. The uterus when cut open had a 2.5x2.0x1.0 endometrial polyp arising from the fundus and bilateral ovaries were normal (Figure 3.1.A, 3.1.B.). Total hysterectomy with bilateral salpingooophorectomy, omentectomy and tumor debulking were performed. A tumor residual on the bladder and liver surface with a total diameter of 7cm. Histopathologic study revealed high grade serous carcinoma, left fallopian tube with formation of omental tumor nodules (Figure 3.2.A, 3.2.B, 3.2.C). No tumor identified in uterus, cervix and contralateral ovary and tube. Her final stage is Stage IIIC. She did not consent for standard adjuvant chemotherapy, instead opted oral Capecitabine. She had nine months of capecitabine but unfortunately expired after a year from the diagnosis.

Case 4.

A 66 year old, G1P1 (1000) patient known diabetic with an unremarkable family history and

Obstetric and Gynecologic history presented with a 3 month history of gradually enlarging abdominal mass with associated changes in bowel movement. No vaginal discharge or bleeding noted. Due to persistence, consult in a local institution at their locality was done where ultrasound reveal the presence of massive ascites and possible ovarian mass, irregularly shaped mass measuring measuring 4.4x3.7x3.2cm in the right adnexa. CA 125 was also done revealing an increased result at 480.80 U/ml. Colonoscopy was also done which was unremarkable. Patient is a known diabetic with a family history and Obstetric and Gynecologic history that is unremarkable. Patient was then advised surgery and hence underwent emergency exploratory laparotomy where 7L of serous ascitic fluid was drained. There were multiple implants noted on the mesentery and peritoneum. The left fallopian tube was converted to a 6 x 6 friable mass (Figure 4.1.B.) with tumor implants on bilateral adnexa. The uterus, right adnexa was unremarkable. (Figure 4.1.A.)Total abdominal hysterectomy with bilateral salpingooophorectomy was then done. Histopathologic study revealed high grade serous carcinoma, left fallopian tube extending to the left ovarian surface and tumor implants on the peritoneum and omentum (Figure 4.2.A., 4.2.B, 4.2.C., 4.2.D.). Her final stage is Stage IIIC. Patient was then advised for chemotherapy with Carboplatin-Paclitaxel however was lost to follow up. Patient then expired two months after the operation.

Discussion

Primary adenocarcinoma of the fallopian tube was first described by Renand in 1897, and it is one of the rarest malignancy of the female genital tract [12]. Due to its rarity, preoperative diagnosis of primary fallopian tube carcinoma is infrequently made. It is usually misdiagnosed as ovarian carcinoma, tuboovarian abscess or ectopic pregnancy [13]. In this study, all of the cases were originally diagnosed as a probable ovarian new growth.

There are two triads of symptoms that was described for fallopian tube carcinoma. Latzko’s triad, the combination of pelvic pain, a pelvic mass, and serosanguineous vaginal discharge. And another triad, with a reported frequency of 6% to 38%, involves vaginal bleeding, vaginal discharge, and lower abdominal pain. Hydrops tubae profluens, although uncommonly reported is thought to be diagnostic of fallopian tube carcinoma [5]. The patients at this case series however all presented differently. There is no specific symptom leading to the diagnosis of fallopian tube carcinoma. Latzko’s triad or hydrops tubae profluens which is said to be pathognomonic for the disease was not present in any of the patient. The first case presented with persistent vaginal discharge that resolved after 3 months and the occurrence of an adnexal mass was evident during work up of the supraclavicular node. In a study made by Healy et al, it is stated that presentation with extra-abdominal lymphadenopathy in fallopian tube carcinoma, especially in the absence of widespread pelvic and intraabdominal disease, is a rare occurrence [14]. The second case initially presented with vaginal spotting that was unremarkable after work-up and the re-occurrence of spotting now with vaginal discharge prompted another work up revealing a probable ovarian new growth. The third and fourth case presented with a gradual enlargement of the abdomen where ascites was noted and upon further work up, an adnexal mass was seen on imaging. A presenting symptom of abdominal distention, and pelvic pressure, are less commonly reported and nonspecific for fallopian tube carcinoma [5]. Due to the lack of specific symptoms for fallopian tube carcinoma in any of the cases, it was not primarily considered as the diagnosis.

The mean age at diagnosis of fallopian tube carcinoma is 58 years, with a range of 26 to 85 years [3]. In the case series presented, the age range of 44-71years was seen with an average of 59 years. According to a review made by Stein et al however, neither age, nor weight, education level, pelvic inflammatory disease, infertility, previous hysterectomy or endometriosis show significant correlations especially with fallopian tube carcinomas [15].

The serum marker, CA-125, a glycoprotein that is a specific tumor marker for ovarian carcinoma is said to be elevated in more than 80% of women with fallopian tube and peritoneal cancer [3]. In this case series it was noted that all women had elevated levels of CA-125 preoperatively. Though

CA-125 is more helpful in monitoring response to treatment, it is still a useful diagnostic tool in women suspected with fallopian tube carcinoma.

All of the patient underwent imaging via ultrasound and/or CT scan. Most of the findings pointed out to a possible ovarian new growth. In a study by Segedi et al [13], it reported that the sonographic features of fallopian tube carcinoma are also non-specific and include the presence of a fluid-filled adnexal structure with a significant solid component, a sausage-shaped mass, a cystic mass with papillary projections within, a cystic mass with cog wheel appearance and an ovoid-shaped structure containing an incomplete separation and a highly vascular solid nodule [13]. These findings were not seen in any of the patients and again a contributary factor to the potential delay of its preoperative diagnosis.

Due to the absence of specific symptomatology and what was seen on preoperative imaging, the cases presented in this study were all initially diagnosed to be of probable ovarian origin. Fallopian tube, ovarian and peritoneal carcinoma are all surgically staged using the 2014 International Federation of Gynecology and Obstetrics (FIGO) Surgical Staging Classification (Appendix F) [16]. All of the cases presented were initially staged as stage IIIA2, IIIC and IV B. The advanced stages seen in our patients may be secondary to non-specific symptomatology which caused potential delay in diagnosis.

The treatment of fallopian tube is similar to that of ovarian carcinoma and in most cases, it includes a combination of surgery and chemotherapy. Based on the SGOP Guidelines, complete surgical staging as primary treatment and resection of any suspicious lesions, masses and adhesions is recommended. [17] In the patients presented, even if they were originally managed as a case ovarian carcinoma, a proper course of management similar as to the treatment of fallopian tube carcinoma was still followed. All of the patients underwent exploratory laparotomy, peritoneal fluid cytology, total abdominal hysterectomy with bilateral salpingo-oophorectomy; with omentectomy and lymphadenectomy. In some cases, given the limitations preoperatively of existing imaging modalities to adequately assess the extent of disease of fallopian tube carcinomoa, diagnostic laparoscopy is often used to determine resectability and decide whether primary surgery or neoadjuvant chemotherapy is more appropriate [3]. Also, according to the SGOP guidelines, for advanced stages, neoadjuvant chemotherapy using paclitaxel-carboplatin should be offered to patients [18]. In a study by Ma & Duan, it is concluded that the earlier the surgery, the more radical the results can be. Thus, an early diagnosis and early treatment are important key factors to improving prognosis of the disease [19].

The most important prognostic factors for survival appear to be the final stage of disease [20]. Patients' five-year survival rate based on The International Federation of Gynaecology and Obstetrics (FIGO) staging were the following: stage I 95%, stage II 75%, stage III 69% and stage IV 45% [21]. The cases presented were all in the advanced stage of the disease. At present, 2 out of the 4 cases have already expired. One did not go further treatment after surgery and the other received oral chemotherapy.

This article presented 4 cases of primary fallopian tube in a 5-year period. In one study from Finland reported that the incidence of PFTC is increasing, with an age-adjusted incidence of 1.2/million for 1953–1957 to 5.4/million for 1993–1997. Furthermore, from 1993 to 1997, an average of 21.6 cases of PFTC/year were newly registered in the Finnish Cancer Registry while during the year 2000, 46 cases were registered [22]. Although rare, there is an increasing incidence of fallopian tube carcinoma due to a likely multifactorial cause: change in diagnostic practices, increased early detection, and improved pathology processing [7].

In conclusion, this paper shows that the preoperative diagnosis of fallopian tube carcinoma is indeed a diagnostic challenge and is oftentimes missed. Clinical presentation of primary fallopian tube carcinoma is non-specific and may be misinterpreted for another gynecologic cancer. Malignancy of fallopian tube origin shall be considered in patients with vague signs and symptoms

such as abnormal vaginal discharge and/or bleeding and also with patients with sudden abdominal enlargement. Although, a mass of ovarian origin is seen on imaging, fallopian tube carcinoma should not be removed as a differential.

Management of adnexal mass due to fallopian tube and ovarian cancer may be similar but high suspicion of fallopian tube carcinoma may initiate earlier investigation and management even without a large or obvious adnexal mass. Therefore, this should encourage gynecologists to remember fallopian tube carcinoma as a differential diagnosis when presented with patients of similar course of disease progression.

A delay in diagnosis and treatment poses an impact on disease progression and prognosis. The extent or stage of the disease is the biggest factor in its prognosis and prognosis respects no age. Although the symptomatology of fallopian tube carcinoma is non specific and varies from patient to patient, a consideration of this disease should always be considered especially in women within the reproductive age group.

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