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CASE REPORT

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Fallopian tube cancer– challenging to diagnose but not as infrequent as originally thought

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ABSTRACT

Background: Primary fallopian tube carcinoma (PFTC) is a rare gynecological malignancy though its prevalence may be underestimated given that most 'ovarian' serous cancers originate in the fallopian tube. Its diagnosis is challenging due to its vague signs and symptoms on presentation and it is frequently under-diagnosed pre-operatively.

Case Presentation: We present a case of a pre-menopausal woman who presented with vaginal bleeding. Her laboratory testing and physical examination were grossly unremarkable. Gynecologic ultrasound demonstrated multiple uterine fibroids and a double layer endometrium measuring 4.5 mm. More importantly, the left ovary was seen with a complex cyst with mildly echogenic fluid and a solid excerscence. These findings were suspicious for malignancy. The clinical and radiological findings with elevated CA-125 were consistent with a malignant process. Patient subsequently underwent a diagnostic laparoscopy, which required conversion to exploratory laparotomy, supracervical hysterectomy, bilateral salpingo-oophorectomy, right ureteral lysis, right para-aortic and right pelvic lymph node debulking and omentectomy. Biopsy of left fallopian tube and ovary revealed invasive high-grade serous carcinoma of fallopian tube, with involvement of lymphovascular spaces and with surface involvement. Peritoneal washings were negative for malignancy.

She was diagnosed with a high-grade serous carcinoma of the fallopian tube after undergoing an endometrial biopsy, multiple imaging tests and finally surgical intervention that yielded the diagnosis. She was started on chemotherapy with carboplatin and paclitaxel.

Conclusion: Our aim is to highlight the importance of having PFTC among the differential diagnosis when women present with vaginal bleeding or abdominal pain, as the clinical presentation of PFTC tends to be non-specific, and is often under-diagnosed; reviewing the diagnosis and management, and characterizing the similarities and differences of PFTC with other gynecological malignancies such as ovarian cancer.

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1. Introduction

Primary fallopian tube carcinoma (PFTC) is very rare and accounts for 0.14 to 1.8%[1] of all gynecological cancers. Vaginal bleeding and abdominal pain is the most common presenting symptom in patients with PFTC. Other symptoms are defined by the Latzko triad, which consists of colicky lower abdominal pain, pelvic mass and watery vaginal discharge. This occurs in less than 15% of cases [2]. Vaginal bleeding is a non-specific symptom that could be seen in other gynecological etiologies, the most common being endometrial malignancies. As a result, endometrial biopsies are performed to evaluate for endometrial malignancies and PFTC will often be under diagnosed if further investigations are not performed.

We present a case of a pre-menopausal woman who presented with vaginal bleeding. She was diagnosed with a high-grade serous carcinoma of the fallopian tube after undergoing an endometrial biopsy, multiple imaging tests and finally surgical intervention that yield the diagnosis.

Our aim is to highlight the importance of having PFTC among the differential diagnosis when women present with vaginal bleeding or abdominal pain, as the clinical presentation of PFTC tends to be non-specific, and is often under diagnosed; reviewing the diagnosis and management, and characterizing the similarities and differences of PFTC with other gynecological malignancies such as ovarian cancer.

2. Case presentation

Patient is a 50-year-old woman with tobacco use disorder who presented with abnormal uterine bleeding. Since her menarche, she had had regular menstrual cycles. 15 days into her menstrual cycle, she noticed vaginal bleeding, requiring approximately 3 pads daily. Given that it persisted after a few weeks, she sought medical attention. Vaginal bleeding was

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associated with fatigue, bloating, nausea, loss of urinary control and hot flashes. Her obstetric history included one normal pregnancy and an uncomplicated vaginal delivery. The only relevant family history was breast cancer in her paternal grandmother. Her most recent Pap smear was negative for intraepithelial lesion or malignancy and Human Papilloma Virus (HPV) high risk was negative.

Her laboratory testing and physical examination were grossly unremarkable. An endometrial biopsy was performed with no evidence of endometrial intraepithelial neoplasia (EIN). Subsequent gynecologic ultrasound demonstrated multiple uterine fibroids and a double layer endometrium measuring 4.5 mm. More importantly, the left ovary was seen with a complex cyst with mildly echogenic fluid and a solid excrescence. Increased flow was noted in the septum and the excrescence. These findings were suspicious for malignancy. For staging purposes, a computed tomography (CT) of chest, abdomen and pelvis was obtained. Multiple enlarged retroperitoneal lymph nodes and some enlarged lymph nodes along the iliac chain on the right side were visualized. The patient subsequently underwent a diagnostic laparoscopy, which required conversion to exploratory laparotomy, supracervical hysterectomy, bilateral salpingo-oophorectomy, right ureteral lysis, right para-aortic and right pelvic lymph node debulking and omentectomy. The surgical debulking was suboptimal due to unresectable right periaortic lymphadenopathy. Peritoneal washings were negative for malignant cells.

Biopsy of left fallopian tube and ovary revealed invasive high-grade serous carcinoma of fallopian tube, with involvement of lymphovascular spaces and with surface involvement. All periaortic and pelvic lymph nodes were positive. Patient was ultimately diagnosed with stage IIIA1ii PFTC. Tumor marker CA-125 was elevated and CA 19–9 was within normal range. Tumor cells demonstrated the following immunophenotype: positive with WT-1, ER (80%, 1–2+) and PR (40%, 2–3+); p53 showed aberrant (>95%, intense) staining pattern. Genetic testing was negative for known disease-causing pathogenic mutations in 47 genes, including *APC, ATM, AXIN2, BARD1, BRCA1, BRCA2, BRIP1, BMPR1A, CDH1, CHEK2, CDK4, CDKN2A, CTNNA1, DICER1, EPCAM, GREM1, HOXB13, KIT1, MEN1, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NTHL1, PALB2, PDGFRA, PMS2, POLD1, POLE PTEN, RAD50, RAD51C, RAD51D, SDHA, SDHB, SDHC, SDHD, SMAD4, SMARCA4, STK11,TP53, TSC1, TSC2*, and *VHL., however* a variant of uncertain significance termed c.8531A>G was identified in the BRCA2 gene. Although she has a BRCA 2 variant of uncertain significance, the patient was referred for breast cancer surveillance due to her potential increased risk of developing a malignancy.

She was started on chemotherapy with carboplatin and paclitaxel. After cycle 4, she developed grade III myalgia and therefore, paclitaxel dose was reduced. She also developed grade I peripheral neuropathy and alopecia. Her peripheral neuropathy, though persistent, is medically managed with duloxetine. However, patient received a total of 8 cycles of carboplatin and paclitaxel therapy which was well tolerated. Her tumor marker, CA 125, is being assessed every three months to monitor for re-occurrence. At present, her CA-125 levels continue to be within normal range.

3. Discussion

Primary fallopian tube carcinoma (PFTC) is a rare malignancy. It constitutes less than 1% of all gynecological malignancies [3]. The etiology and cellular precursor of this malignancy is unknown, but it appears to be a combination of hormonal, reproductive and genetic factors [4]. It is often classified under the umbrella of epithelial ovarian cancer – along with primary ovarian and peritoneal carcinomas. However, there is evidence to support that epithelial ovarian cancers originate from a precursor of the fallopian tube [5]. High parity, oral contraceptives and pregnancy are protective factors, whereas nulliparity has been associated with increased risk. Hormonal, reproductive and genetic factors increase the propensity of developing PFTC. Chronic pelvic inflammatory diseases and tubal inflammatory lesions are associated with anaplastic changes [6]. However, data on endometriosis, smoking, obesity, age and race is inconclusive [3,6,7]. Studies demonstrated possible association of BRCA-1, BRCA-2, p52, HER2/Neu and c – myc gene mutations with the tumorigenesis process [6]. Ashkenazi Jewish population is potentially at a higher lifetime risk due to the increased proportion of this population carrying the BRCA gene mutation [3].

PFTC occurs most commonly in fourth to sixth decade of life, with a median age of 55 at the time of diagnosis. The clinical symptoms, such as abdominal colicky pain, vaginal discharge and vaginal bleeding are non-specific and can delay the diagnosis. It is essential to consider PFTC in patients with gynecological or gastrointestinal symptoms with negative pap smears as depicted in this case.

A pathognomonic feature of PFTC is intermittent discharge of clear or blood-tinged vaginal fluid, which leads to the relief of abdominal pain and subsequent shrinkage of the adnexal mass[1]. As this could be the first presentation, it is essential to obtain a detailed gynecological history as an internist in order to triage the urgency of a visit with a gynecologist, which can lead to early diagnosis.

Because of the lack of awareness and screening modalities for PFTC, most diagnosis occurs in advance stages [5]. In fact, PFTC is mostly diagnosed post-operatively. A pre-operative diagnosis has been reported in only 2% of patients [1].

The diagnostic criteria of PFTC were initially set by Hu et al. with further revisions performed by Sedlis et al. The criteria include the main tumor arising from the endosalpinx with the histology showing epithelium of tubal mucosa as well as the transition from benign to malignant tubal epithelium cells with no pathological evidence of endometrial nor ovarian origin [8].

Imaging with ultrasound is usually the first line in the assessment of vaginal bleeding. Other imaging modalities also utilized are computed tomography (CT) and magnetic resonance imaging (MRI) of the abdomen. Trans-vaginal and trans-abdominal ultrasound findings of tubal carcinoma can be non-specific. Some common findings are a cystic mass with spaces and mural nodules, a sausage-shaped mass or a multilobular mass [9]. In this case, the ultrasound findings revealed a non-specific complex cyst, a cyst with mildly echogenic fluid and a solid excrescence, which could easily be misdiagnosed as ovarian malignancy.

CA-125 tumor marker is a useful marker, sometimes aids in the diagnosis but specially to assess response of the treatment as well as recurrence. As evidenced in this case, CA-125 can be elevated in patients with PFTC. The pre-treatment serum levels are an independent marker in determining the extent and response to the treatment. It has been shown that the serum levels of CA-125 increase in concordance to staging as reflected in the median level for stage I to IV is 20.5, 488, 1066, and 2045, respectively, [10].

PFTC depicts similarity to ovarian carcinoma. Some theories indicate that ovarian carcinoma originates from the distal fallopian tubes. The fimbroid ends of the fallopian tubes appear to be the main site of origin, especially in patients with BRCA mutation [4]. Both have a histological as well as clinical resemblance. The serous type is the most common type of PFTC as in our reported case and it is identical to the ovarian serous carcinoma with the pathology-showing invasion in papillary, glandular and solid pattern with high-grade atypical features of nucleus [4]. The other types of PFTC are endometrioid, undifferentiated, mucinous and transitional carcinomas [4].

Because of the similarities between primary epithelial ovarian cancer, fallopian tube and peritoneal carcinomas, there are no studies that have focused exclusively on PFTC treatment. The treatment is based on the staging of the tumor. Surgical excision is the mainstay treatment and it can be a total abdominal hysterectomy, bilateral salpino-ophorectomy, omentectomy, and pelvic and para-aortic lymphadenopathy [9]. Stage I is low-risk disease and resolves with surgical excision. Stage II through IV requires adjuvant chemotherapy with carboplatin and paclitaxel [4]. Recurrent and persistent disease is treated with platinum-free interval and cytoreduction [4]. Radiotherapy was used as adjuvant therapy but with the effective chemotherapy and the complications associated with postoperative radiotherapy, administration of radioisotopes is no longer recommended [1]. The prognosis appears to be better for women with PFTC in comparison to ovarian cancer. 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% [8]. There are ongoing trials with immunotherapy, including combinations of platinum-based chemotherapy, PARP inhibitors, anti-VEGF antibody and programmed cell death-1 (PD-1) inhibitor or cytotoxic T-cell lymphocyte-4 (CTLA-4) inhibitors that may improve overall survival by changing the course of the disease [5].

Genetic testing can also be undertaken to identify any familial genetic mutation or the onset of sporadic mutations. Primary care physicians are recommended to utilize familial risk assessments, such as Ontario Family History Assessment Tool, Manchester Scoring System, Pedigree Assessment Tool, International Breast Cancer Intervention Study Instrument, 7-Question Family History Screening Tool, as screening tools to assess the risk of a BRCA1 and BRCA 2 mutation [11]. However, trained health professionals should perform genetic counseling about mutation testing. According to the American Cancer Society, genetic testing is recommended for women who have a known family history of BRCA mutation, women diagnosed with ovarian cancer, pancreatic cancer, family history of breast cancer at a younger age, more than one family member with breast cancer and breast cancer in a male family member [12].

Breast Cancer gene (BRCA- 2) mutation has been identified in patients diagnosed with PFTC. A study by Cass et. al. evaluated patients with germline BRCA gene mutation in contrast to sporadic cases [13]. Results showed that patients with BRCA gene mutation had a median survival time of 68 months compared to 37 months in sporadic cases[13].

In conclusion, PFTC is a rare gynecological malignancy, though it's prevalence may be underestimated given that most 'ovarian' serous cancers originate in the fallopian tube. Its diagnosis is challenging due to its vague signs and symptoms on presentation and it is frequently under-diagnosed pre-operatively. Internist should have a high suspicion when a patient presents with signs or symptoms that fulfill the Latzko triad, ie intermittent profuse serosanginous vaginal discharge, colicky pain relieved by

discharge, abdominal or pelvic mass [7] Primary care physicians play a vital role in identifying patients who may possibly have a malignancy, as well as identifying patients who are at higher risk of developing a gynecological malignancy such as familial cancer, nuliparity or history of genetic mutations. The PFTC has shown to have up to 95% 5-year survival rate if diagnosed at stage I. Early identification and close collaboration among the internist and oncologist can lead to decreased morbidity and mortality. Therefore, it is essential that it be considered within the differential diagnosis in patients presenting with peri-and post-menopausal abdominal pain, vaginal discharge and/or bleeding.

Disclosure statement

No potential conflict of interest was reported by the authors.

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