MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
SUMY STATE UNIVERSITY
ACADEMIC AND RESEARCH MEDICAL INSTITUTE

Eastern Ukrainian Medical Journal

116, Kharkivska st., Sumy 40007, Ukraine eumj.med.sumdu.edu.ua
e-mail: eumj@med.sumdu.edu.ua ISSN: 2663-5909 (print)/2664-4231 (online)

How to cite: Rozhkovska N, Sumtsov D, Sumtsov H, Smiyan S, Savenko T, Gladchuk I. An unusual case of primary fallopian tube cancer. *East Ukr Med J*. 2025;13(3):647-653

DOI: https://doi.org/10.21272/eumj.2025;13(3):647-653

ABSTRACT

AN UNUSUAL CASE OF PRIMARY FALLOPIAN TUBE CANCER

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Introduction. Cases with an open ampullary opening among primary fallopian tube cancer (PFTC) are extremely rare, highly malignant, and difficult to diagnose. Primary fallopian tube cancer accounts for 1.8% of female genital cancers and about 4-6% of cancers of the uterine appendages. According to available data, the incidence of this tumour has increased up to 4 times in recent decades. Preoperative diagnosis of the PFTC has been and remains an unresolved problem for cervical cancer, which leads to untimely treatment or treatment in non-oncological institutions. Even during surgeries, errors reach 50%, which provokes inadequate surgeries and treatment methods and delays the recovery of patients.

Objective: to demonstrate a case of misdiagnosis during surgery, the need for oncological care and a detailed study of the macro preparation in the operating room.

Material and Methods: the results of clinical, morphological and immunohistochemical examination of the case of primary fallopian tube tract and analysis of publications in the relevant literature.

Results and Discussion: The clinical, morphological and immunohistochemical analysis of an unusual case of primary fallopian tube cancer was performed. The diagnosis was made only after a routine histological and immunohistochemical examination. A broader review of this clinical case will improve cancer screening and diagnosis. Primary fallopian tube cancer remains a rare but challenging problem in terms of diagnosis and treatment. Improving diagnostic accuracy is based on a thorough preoperative examination of patients with any pathological changes in the uterine appendages, including the study of tumour markers of epithelial tumours (CA-125, HE-4, etc.). In recent years, the prevention of cancer of the fallopian tubes, ovaries, pelvic peritoneum and mammary glands by opportunistic salpingectomy has been actively implemented, with cases of primary and metastatic

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tumours in the fallopian tubes being reported.

There have been some reports of malignant tumours developing after 'preventive' surgeries, although the cause of such outcomes is unknown, and the question of whether they can be avoided remains open.

Conclusion: Only cancer awareness and careful examination of the removed material in the operating room and the use of suboperative morphological diagnostics will allow avoiding such errors during surgery. Abnormal uterine bleeding cannot be the result of a tumour microsite.

Key words: *primary fallopian tube cancer, abnormal uterine bleeding, uterine fibroids, adenomyosis, endometrial hyperplasia, pathology, morphological diagnosis*.

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НЕЗВИЧАЙНИЙ ВИПАДОК ПЕРВИННОГО РАКУ МАТКОВОЇ ТРУБИ

Вступ. Випадки з відкритим ампулярним отвором серед первинного раку маткових труб (ПРМТ) є надзвичайно рідкісним, дуже злоякісним та складним для діагностики захворюванням. Первинний рак маткових труб становить 1,8% раку жіночих статевих органів і біля 4-6% раку додатків матки. За наявними даними, останні десятиліття відбувається ріст захворюваності цією пухлиною до 4 разів. Невирішеною проблемою для ПРМТ була та залишається передопераційна діагностика захворювання, що призводить до несвоєчасного лікування або лікування не в онкологічних закладах. Навіть під час операцій помилки досягають 50%, що провокує неадекватні операції, методи лікування та затримує оздоровлення хворих.

Мета дослідження: продемонструвати випадок помилкового діагнозу під час операції, необхідність онконастороженості та детального вивчення макропрепарату в операційній.

Матеріал і методи: результати клінічного, морфологічного та імуногістохімічного дослідження випадку первинного траку маткових труб та аналіз публікацій тематичної літератури.

Результати та обговорення: Проведений клінічний, морфологічний та імуногістохімічний аналіз незвичайного випадку первинного раку маткових труб. Діагноз виставлений тільки після планового гістологічного та імуногістохімічного дослідження. Широке ознайомлення з цим клінічним випадком покращить онконастороженість і діагностику. Первинний рак маткової труби залишається рідкісною, але складною проблемою в діагностичному та лікувальному відношенні. Покращення точності діагностики полягає у ретельному доопераційному обстеженні хворих з будь-якими патологічними змінами додатків матки, включаючи дослідження онкомаркерів епітеліальних пухлин (CA-125, HE-4 тощо). В останні роки активно впроваджується профілактика раку маткових труб, яєчників, тазової очеревини та молочних залоз шляхом опортуністичних сальпінгектомій, при цьому описані випадки виявлення первинних та метастатичних пухлин в маткових трубах. Зустрічаються окремі повідомлення щодо розвитку

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злоякісних пухлин після «профілактичних» операцій, хоча причина таких результатів невідома, так само відкритим залишається питання, чи можна їх уникнути.

Висновок: Тільки онконастороженість і ретельне вивчення видаленого препарату в операційній та застосування субопераційної морфологічної діагностики дозволить уникнути таких помилок під час операцій. Аномальна маткова кровотеча не може бути результатом появи мікроосередка пухлини.

***Ключові слова**: первинний рак маткових труб, аномальні маткові кровотечі, міома матки, аденоміоз. гіперплазія ендометрія, патологія, морфологічний діагноз.*

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INTRODUCTION

Primary fallopian tube cancer (PFTC) is a rare, highly malignant and difficult disease to diagnose. For a long time, gynaecologists and morphologists considered the occurrence of cancer in the fallopian tube to be impossible. The first to describe and histologically confirm the PFTC was K. Orthman in 1888. He proved that the previously described cases of PFTC were not primary, but arose secondary to tumours in the ovary or uterus. In the same year, 1888, Dr N.P. Fedorov presented a report on a fallopian tube tumour that had arisen in the hydrosalpinx at a meeting of the Kharkiv Medical Association. Nowadays, there is no doubt about the possibility of cervical cancer, as it is known that cervical cancer accounts for up to 1.8% of female genital cancers and 4–6% of uterine appendage cancers, and the overall incidence of cervical cancer is 3.72 to 4.1 per million women [1–4]. In addition, since the beginning of the XXI century, there has been an increase in the incidence of PFTC. For example, Liao CI and co-authors (USA, California) report a 4-fold increase in the incidence of PFTC from 2001 to 2014 [5]. The same trend was recorded by Korean authors after analysing the national database, where from 1999 to 2016 the incidence of PFTC per 100,000 women increased from 1.06% to 4.46% [6].

Recent ecological and biomedical studies also emphasize that the stability of host–parasite systems and their adaptation to environmental stressors illustrate how hidden biological risks can persist and manifest unexpectedly, which provides a broader perspective for understanding the increasing incidence of rare tumours [18].

Diagnostics has been and remains an unsolved problem for PFTC. Both at the beginning of the twentieth century and today, according to publications in the literature, reliable preoperative diagnosis of PFTC remains in the range of 0 to 10–12% (about 4% on average), and diagnostic errors even during surgery reach 50% [7, 8, 9]. As a result, the results of 5-year survival rates of patients with PFTC are still below 50%. According to [10], diagnostic difficulties lead to 5.8 and 15-year survival rates of 44.7%, 23.0% and 18.0%, respectively, and the absence of signs of tumour activation occurs only in 27.2%, 17.0% and 14.0% of patients with breast cancer, respectively.

The reason for the difficulty of diagnosis is the clinical features of the disease. Unlike ovarian cancer, PFTC occurs in the fallopian tube cavity and remains ‘closed’ for a long time, does not penetrate the wall, does not spread to the abdominal cavity and does not cause additional symptoms in patients. There have been observations of patients with PST with minor periodic pain and constant pathological discharge from the genital tract (lymphoma) not agreeing to surgical treatment for several months to a year [11, 12].

Cases of PFTC with an open fimbrial foramen, when there is a high probability of tumour cells spreading through the abdominal cavity with the occurrence of peritoneal metastases and possibly ascites, are rare. For example, in our 50-year practice, we have not encountered any cases of PFTC with an open fimbrial foramen, and in the analysis of more than 3.5 hundred literature sources covering at least a thousand observations of PFTC only two authors reported the development of a tumour with an open fimbrial foramen [13, 14]. Of course, it is possible that some authors did not pay attention to this characteristic feature of the tumour, which is very rare, when describing the removed macro specimen. The closed nature of the development of PFTC is one of the reasons for the absence of peritoneal metastases in the abdominal cavity and ascites in most patients with PFTC [15].

MATERIALS AND METHODS

We present our clinical observation of PPT, which was detected only during a routine morphological examination. Patient S., 52 years old, was admitted to the Department of Invasive Diagnostic and Treatment Methods of the Multidisciplinary Medical Centre of ONMedU with complaints of uterine bleeding that lasted more than two weeks. She had been menstruating since the age of 13 without any peculiarities. In the anamnesis – 2 births, 1 medical abortion. She has known about the presence of uterine fibroids for 4 years, but has not come for a routine examination. Over the past year, her menstrual periods became irregular, heavy, with clots and lasted more than 8 days. She sought medical care due to abnormal uterine bleeding (heavy menstrual bleeding lasting more than 10 days with clots) and lack of effect from symptomatic therapy (tranexamic acid, ethamsylate).

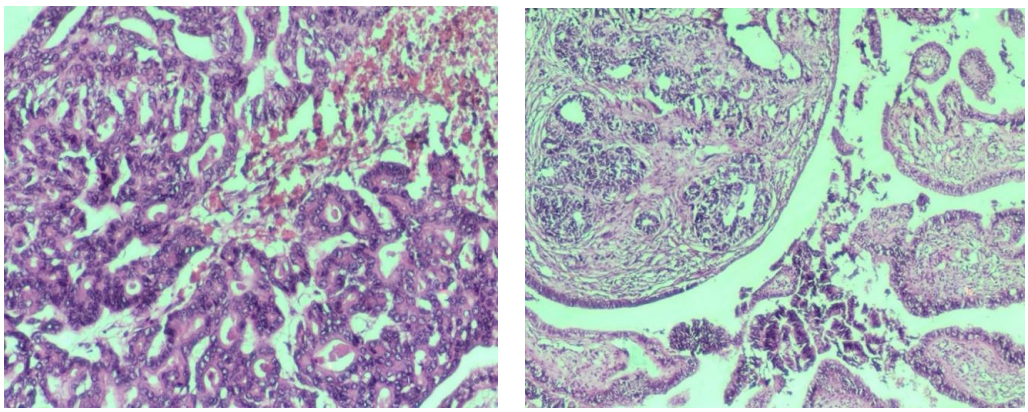
Ultrasound examination of the pelvic organs revealed: a spherical uterus measuring 118x103x130 mm, with multiple myomatous and adenomyotic nodes and a double submucous myomatous node measuring 66.1x31.7 mm (FIGO type 2–5). M-echo – 33 mm. The cervical canal is homogeneous, with nabotic cysts. The right ovary measures 36x16 mm, contains 3 follicles, the largest with a diameter of 12.8 mm. The left ovary is 39.5×21.5 mm, it has a fluid structure of 42×22.8 mm with a parietal component (ORADS 2). Preliminary diagnosis: Large multiple nodular leiomyoma of the uterus with submucous nodes. Adenomyosis. Endometrial hyperplasia. Left ovarian cyst (functional?). Abnormal uterine bleeding.

The data of clinical and laboratory examinations are within the normal range, except for a decrease in haemoglobin level to 115 g/l. Cervical cytology: inflammatory type of smear with squamous epithelium hyperkeratosis and moderate dysplasia of the cylindrical epithelium in the transformation zone. Pipeline biopsy of the endometrium showed inactive glandular hyperplasia. Diagnosis: Abnormal uterine bleeding on the background of multiple uterine leiomyoma, adenomyosis, endometrial hyperplasia.

In connection with acute abnormal uterine bleeding on the background of adenomyosis, and multiple myomatous nodes, including submucous, endometrial hyperplasia, the patient underwent an urgent operation – laparoscopic hysterectomy with appendages. During the laparoscopic revision, the fallopian tubes were of normal appearance with single transparent peritubal unions. Small follicular cysts in the right ovary, a smooth-walled cystic mass in the left ovary with a diameter of 4 cm. The uterus is large, deformed by leiomyomatous nodes. No other pathological changes or effusions were detected. The operation and postoperative period were uneventful, she was discharged on day 3.

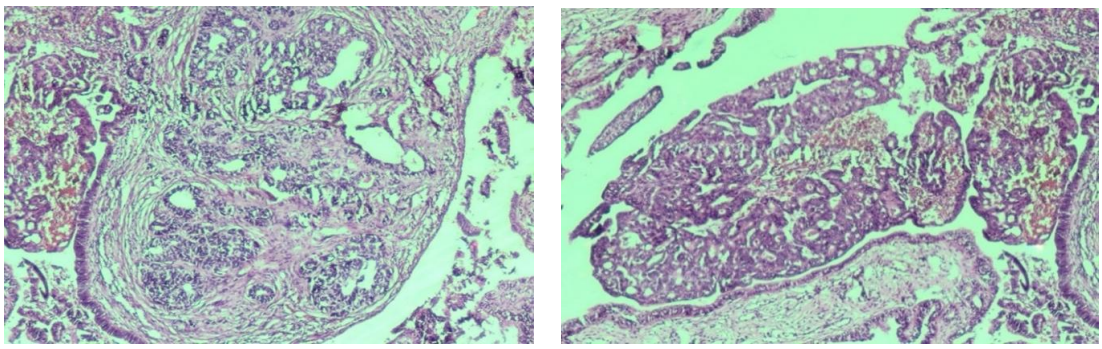
RESULTS

During the routine histological examination of the postoperative material, in addition to atypical glandular endometrial hyperplasia, adenomyosis, multiple leiomyomas and adenomyomas, serous cystadenoma of the left ovary with a diameter of 4 cm, a morphologist detected a 0.3 x 0.3 cm invasive growth of high-grade serous carcinoma in the fimbrial region of the left fallopian tube against the background of serous tubal intraepithelial neoplasia and chronic non-acute salpingitis, small paratubal cysts. On examination, several invasive cystic tumor complexes of similar structure were found in one of the villi in the stroma. Foci of tubal intraepithelial neoplasia were also found in the right fallopian tube (Fig. 1–2).



A B

Fig. 1. Patient S., 52 years old. Serous carcinoma of the fallopian tube, moderately differentiated. Hematoxylin-eosin staining, x250. A – papillary-alveolar structure, B – tumour complexes invade the fimbrial stroma



A B

Fig. 2. Patient S., 52 years old. Serous carcinoma of the fallopian tube, moderately differentiated. Hematoxylin-eosin staining, x100. A – intramural invasive complexes of serous carcinoma of the fallopian tube, B – Tumour elements in the fallopian tube cavity

Upon re-evaluation of histological preparations of primary specimens in one of the fallopian tubes, there is a small focus of growth of serous carcinoma of the fallopian tube with a high degree of malignancy. When cutting the material from the blocks, the tumor focus is absent, and there are no signs of serous neoplasia in situ in other areas of the fallopian tube. When performing sections from this block for immunohistochemical examination, this tumor tissue is already absent. When performing immunohistochemical examination on this block, the tubal epithelial cells are positive for cytokeratins (DAKO, clone AE1/AE3), PAX-8 (Cell Marque, клон MRQ-50), estrogen receptor alpha (DAKO, clone EP1), Wilms tumor antigen (WT-1) (DAKO, clone 6F-H2), negative for p16INK4a (DB Biotech, clone R15-A). Expression of p53 (DAKO, clone DO-7) is of the “wild” type – heterogeneous positive reaction in tubal epithelial cells. In all sections of the fallopian tubes, the staining pattern for p53 is “wild”. Thus, the primary slides reveal a small focus of high-grade serous carcinoma of the fallopian tube. When additional sections are taken from this block, the tumour tissue is no longer detected. In all sections of the fallopian tubes, no signs of serous neoplasia in situ are detected.

Diagnosis after surgery and postoperative examination: Serous carcinoma of the left fallopian tube G3 T1a N0Mo on the background of bilateral tubal serous intraepithelial neoplasia. After a consultation with a chemotherapist, the patient received 6 cycles of adjuvant cisplatin polychemotherapy with paclitaxel and was recommended to undergo continuous monitoring every 3–6 months. Unfortunately, the patient has moved to another country, but reports by phone that she has been feeling satisfactory for a year and will come for a routine check-up if possible.

DISCUSSION OF RESULTS

To this day, the treatment of the first stage of breast cancer remains a subject of debate, as some oncologists perform adjuvant polychemotherapy, while others deny its necessity. Even in modern clinical protocols, there are no clear recommendations on this issue. Starting the discussion on the choice of treatment method in our patient, we consider it appropriate to demonstrate a similar case from the literature, described in 2015 by Nomura H et al. from Japan. The patient was 39 years old, with abnormal uterine bleeding, and tumour cells were found among normal endometrial cells. According to the results of a comprehensive examination, no pathology was detected, but fallopian tube cancer was suspected, and after the patient's consent, a pangysterectomy with removal of the uterine appendages was performed. No pathology was detected during the operation and only a thorough histological examination of the left fimbriae revealed a pre-invasive carcinoma ≤ 0.5 mm in size. No adjuvant treatment was performed.

Nine months later, a routine transabdominal ultrasound revealed an enlarged para-aortic lymph node (LN). A PET/CT scan confirmed pathological activity only in the para-aortic lymph node (SUV max , 2.42), and no other metastases were found. The patient's CA-125 level was 42.7 IU/ml. Recurrent metastatic carcinoma (MCC) was suspected. During the laparotomy, the diagnosis of metastatic adenocarcinoma was made on the basis of histological suboperative examination by freezing. The pathological diagnosis for the recurrent tumour was adenocarcinoma. Histologically, adenocarcinoma metastases were detected in 3 of 69 removed LUs. No cancer cells were found in the omentum. Peritoneal lavage cytology was negative for cancer. The patient was prescribed

polychemotherapy (paclitaxel: 175 mg/m2, carboplatin: AUC 6) [16].

In contrast to the demonstrated case, our patient had not pre-invasive but invasive high-grade cancer. Moreover, it was a special, "open" cancer with a high probability of microimplantation in the peritoneum. Therefore, the 6 cycles of adjuvant polychemotherapy performed after consultation with a chemotherapist are well justified. Moreover, as a result of an erroneous diagnosis, the patient underwent an insufficiently radical operation and did not undergo a cytological examination of the abdominal cavity. In our opinion, with an open ampullary orifice, even in the absence of tumor cells in the abdominal cavity, this is not stage 1A, but at least 1C2 with all the necessary changes in treatment and follow-up.

In recent years, the prevention of fallopian tube, ovarian, pelvic peritoneal and breast cancer through opportunistic salpingectomies has been actively implemented everywhere. At the same time, depending on the patient population, asymptomatic latent neoplasms are detected in 3.5 to 12% of cases, namely pre-invasive and initial invasive fallopian tube cancer, ovarian and even breast cancer metastases. Of course, in these cases, a significant proportion of tumours are 'open', and the tactics of postoperative management are not defined. There have been some reports of malignant tumours developing after 'preventive' surgeries, although the cause of such outcomes is unknown, and the question of whether they can be avoided remains open [10, 15, 17].

CONCLUSIONS

Only oncological awareness and careful examination of the removed specimen in the operating room and the use of suboperative morphological diagnostics will allow avoiding such errors during surgery. Abnormal uterine bleeding cannot be the result of a tumor microsite.

AUTHOR CONTRIBUTIONS

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Received 29.03.2025 ***Accepted 20.05.2025***

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