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LU Yu-Feng *

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Case Report

Endometriosis with Ovarian Cysts and Ovulation Induction Followed by Malignant Transformation into Ovarian Clear Cell Carcinoma: A Case Report

LU Yu-Feng [1]*, Song Xiao-Tong [1], Tian Li [2]

[1]Gynecology and Obstetrics Department of Gansu Provincial People's Hospital, Lanzhou 730000, China.

[2]Peking University People's Hospital Department of Obstetrics and Gynecology Reproductive Center Beijing 100053, China.

***Corresponding Author:** LU Yu-Feng., Gynecology and Obstetrics Department of Gansu Provincial People's Hospital, Lanzhou 730000, China.

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Abstract:

Report a case of ovarian clear cell carcinoma in a patient with endometriosis (EMs) and ovarian cysts who was treated Peking University People's Hospital in May 2018. After the patient was treated, relevant laboratory tests were performed, and assisted reproductive technology (ART) used to help with conception. Ovarian stimulation was performed for 3 cycles, and during the process of ovarian stimulation, it was found that the ovarian cysts undergone solidification, and blood flow signals appeared around the cysts. Considering the possibility of a borderline tumor, conservative surgery was performed to preserve the reproductive function. The operative pathological diagnosis was clear cell carcinoma stage IC and pelvic endometriosis. After the operation, the patient was given 3 courses of chemotherapy with 40 of doxorubicin and 450 mg of cisplatin. The correlation between EMs and ovarian cysts in infertile patients during ovarian stimulation the management of ovarian cysts during ovarian stimulation were analyzed. However, there are few reports of similar cases, and a large number of case data need to be accumulated multiple reproductive centers to verify this.

Key words: endometriosis; ovarian cyst; ovarian clear cell carcinoma; art; infertility

1.Introduction

Endometriosis (endometriosis, EMs)is a common disease caused by the transfer of active endometrial cells to sites other than the endometrium, with an incidence rate of about 10% to 15% [1]. Ovarian cancer (ovarian cancer, OC) caused by EMs is called endometriosis-related ovarian cancer (endometriosis associated ovarian carcinoma, EAOC). OC is the most lethal gynecological malignancy. Among them, ovarian clear cell carcinoma (ovarian clear cell carcinoma, OCCC) and ovarian endometrioid carcinoma (ovarian endometrioid carcinoma, OEC) are the most common [2]. It was found that most of OCCC had EMs precursor lesion [2], and about 1 / 3 were directly originated from EMs lesion [3]. OCCC accounts for about 5% [4] of all ovarian cancers and is a rare malignant type among the five subtypes of ovarian cancer (high grade serous, low grade serous, endometrioid, mucinous cell carcinoma and clear cell carcinoma), with specific genetic and molecular features being a specific histological type in ovarian cancer. This paper presents a case of ovarian clear cell carcinoma in an infertile patient with EMs and ovarian cysts, which is reported as follows.

2.Case Report

The patient, a 38-year-old female, presented to Peking University People's Hospital on June 19,2018 for "left ovarian cyst found for 2 years and 3 years without contraception". Two years ago, B ultrasound in the other hospital: 2.5x1.7x2.0cm left ovarian cyst with clear boundary, poor internal sound transmission and dense punctate echo. Consider ovarian-type endometriosis? The patient had regular menstruation and normal sexual life, and had no contraception for 3 years without pregnancy. Visit to our hospital for reexamination of B ultrasound: multiple cystic echoes could be seen in the left ovary, large 2.4x1.4cm, clear boundary and fine dense dot echo. AMH:1.3ng/ml(2-7.0ng/ml), the underlying sex hormone: FSH:15.33mIU/ml(5-10mIU/mL),LH:3.73mIU/ml(5-10mIU/mL),E2:45.17pg/ml (25-45 pg/mL). Semen routine: semen density: 4.99 million / ml, forward motile sperm rate (PR): 28.38%. The

patient and the family members requested the IVF. Diagnosis: ① Primary infertility; ② ovarian hypofunction (Diminished Ovarian Reserve, DOR); ③ left ovarian chocolate cyst?④ Male oligoasthenospermia. IVF assisted pregnancy (see Table 1). The left ovarian cyst persisted during proinduction. In September 2018, B ultrasound (during the third drainage period): left ovarian cyst 4.6x3.6cm, poor internal sound transmission, strong papillary echo in the cyst wall, maximum 1.1x0.9cm, punctate flow signal, and thin 3.0x2.2cm cyst wall, good sound transmission, and fine segmentation inside. B ultrasound: left ovarian cyst 5.7x4.1x3.0cm, uneven inner wall, multiple papillary processes, maximum diameter of 1.7cm, blood flow signal RI: 0.43, PI: 0.56. On November 23,2018, we performed laparoscopic surgery in Peking Union Medical College Hospital. Microscopically: fine red and purple blue endometriotic lesions were visible in the reverse folding of the bladder, with 2mm purple blue nodules, enlarged left ovary, and a 5cm cyst with thin wall, smooth surface, and no exogenous nipple. Operation method: left ovarian cyst removal + fertility preservation function staging (left accessory resection + right ovarian biopsy + peritoneal biopsy + partial resection of omentum + left pelvic abdominal lymph node dissection). Rapid intraoperative pathology: clear cell carcinoma of the left ovary. Postoperative disease examination: pelvic endometriosis, left ovarian clear cell carcinoma, immunohistochemistry: PAX 8 (+), NapsinA (minimal +), CK7 (+), CK20 (-), GATA 3 (-), SATB (-), CA125 (focal +), ER (-), Ki-67 (index50%), P16 (+), P53 (scattered +), PR (-), WT-1 (-), HNFIB (+). The patient underwent chemotherapy in Peking Union Medical College Hospital for three times. The first chemotherapy was in December 2018. The chemotherapy regimen was doxicin 40mg and bordine 450mg. Chemotherapy was given in January and February 2019, and the chemotherapy regimen was the same as before. From 2019 to 2020, the patients were followed up and reviewed at Peking Union Medical College Hospital on time. Embryo transfer was performed in Peking University People's Hospital in April 2021.4BB and 4 BC embryos were transplanted in HRT-FET protocol and D3 2 (9II 8II) were implanted in January 2022. B ultrasound review in September 2023: two mixed echo sizes 2.1x1.7cm,2.2x1.4cm, regular morphology and clear boundary in the right ovary. CTC and CTEC testing of rare cells of alloploid circulating tumors were performed in May 2024:4 CTC, CTEC 4. After consultation, professor of Obstetrics and Gynecology of Peking University People's Hospital suggested a right ovariectomy. The patient and his family members did not undergo surgery and were still under follow-up.

Table 1 Patients underwent IVF-ET in the reproductive center

Pregnancy cycle	start time	Protocol for ovulation induction	The Gn dose and time	Endometrial thickness in hCG day (mm)）	E2, hCG day (pmol / L）	Day of hCG LH (IU / L)	Day of hCG P (n mol/L)	Number of eggs (individual)	Embryonic results
1	On June 16,2018	Letrezole protocol	225IU for 7 days	4	270	6.94	1.49	3	6II 7II
2	On August 10,2018	microstimulation	150IU for 4 days	6	234	4.8	0.73	2	No embryo
3	On September 17,2018	The luteal stage promotes ovulation	300IU for 9 days	9	2541	2.45	21.63	7	9II 8II
									4BB 4BC
4	In August, 2021	natural period		9	335	14.4	0.58	1	No embryo
5	In December, 2021	natural period		12	148	4.4	2.48	0	

3 Discussion

3.1 Clinical features of endometriosis malignancy

Endometriosis (endometriosis, EMs)is a common disease caused by the transfer of active endometrial cells to locations other than the endometrium, with an incidence rate of about 10% to 15%. There are now about 176 million women with EMs worldwide. The main clinical manifestations of EMs are dysmenorrhea, menstrual volume, menstrual cycle changes and sexual intercourse pain, and most young patients have the confusion of infertility. Ovarian cancer (ovarian cancer, OC) caused by EMs is called endometriosis-related ovarian cancer (endometriosis associated ovarian carcinoma, EAOC). OC is the most lethal gynecological malignancy. Epidemiological studies have shown that EMs cause an increased risk of ovarian cancer in specific tissue types, with ovarian clear cell carcinoma (ovarian clear cell carcinoma, OCCC) and ovarian endometrioid carcinoma (ovarian endometrioid carcinoma, OEC) being the most common.

3.2 Mechanism of ovarian clear cell carcinoma

Ovarian epithelial cancer (epithelial ovarian cancer, EOC), is the most common type of ovarian cancer, accounting for 90% of ovarian cancer cases, is a group of heterogeneous disease with different genomic characteristics, accounting for 3.6% of global female cancer incidence and 4.3% of cancer mortality [3], can be divided into five main subtypes: high grade serous, low grade serous, endometrioid carcinoma, mucous cell carcinoma and clear cell carcinoma [5]. Ovarian clear cell carcinoma (ovarian clear cell carcinoma, OCC) accounts for about 5% [4] of all ovarian cancers. It is a rare malignant type among the five subtypes. It has specific genetic and molecular characteristics and is a specific histological type in ovarian cancer, and its cytoplasm is transparent, so it is named clear cell carcinoma [9-11]. It was found that most of OCCC had precursor lesions of EMs,and about 1 / 3 were directly originating from EMs lesion [3]. Studies have reported that 13% – 15% of ovarian cancer patients carry the BRCA1 or BRCA2 germline mutation [6]. Treatment of PIK3CA and ARID1A mutations, loss of BAF250 protein, promoting sustained IL-6 production, also lead to rapid tumor growth. When PI3K-Akt is activated, it regulates the expression of downstream genes, thereby inhibiting apoptosis and promoting cell proliferation. Furthermore,

PIK3CA mutations enhanced PI3K activity and promoted cell cycle progression, survival and motility [7]. Changes in PI3K / Akt, p53, and HER 2 signaling were found in 87% of OCCC, and chromatin remodeling events occurred in 47% of OCCC.

3.3 ART and ovarian clear cell carcinoma

Currently, there is no clear evidence of a possible correlation between ovulation induction drugs and ovarian cancer due to infertility and combined ovarian endometriosis cysts. In a prospective study of 1.1 million British women, 8719 women developed ovarian cancer during follow-up, Gaitskell[8] et al. Nulliparous individuals had a 24% higher risk of ovarian cancer than women with 1 child, with significant increases in endometrioid and clear cell tumors. In multiparous women, the risk of ovarian cancer decreased overall by 6% per additional child; with the greatest reduction for clear cell tumors, where the overall risk of ovarian cancer in this large prospective study was much higher than the expected impact of singleton births, particularly clear cell and endometrioid tumors, potentially suggesting that infertility is associated to these histotypes. Williams[9] et al, in a British follow-up of 255786 women from 1991 to 2010 showed an increased risk of ovarian cancer after ART. But women receiving ART only for male factors, fallopian factors and unexplained infertility did not have an increased risk of ovarian cancer. Therefore, it also does not explain whether ovarian cancer development in patients receiving ART is due to ART treatment or due to endometriosis itself. In contrast, Frida et al [10] in a 1982 – 2012 study of 13840097 women in Sweden 2,38025 women delivered after receiving ART, 49208 women did not receive ART after diagnosis of infertility and 1252864 women naturally conceived and gave birth. During the follow-up period, 991 women were diagnosed with ovarian cancer. The incidence of ovarian cancer is higher in women who delivered after ART compared to women who did not develop infertility. The incidence of ovarian cancer was also higher in women receiving ART compared with women diagnosed with infertility and who did not undergo ART. Kessous et al. [11], a population-based study comparing the incidence of malignancies in women with and without a history of pregnancy-assisted therapy (including in vitro fertilization (IVF) and induced ovulation (OI)). During the follow-up period, patients with a history of IVF treatment were diagnosed at a significantly increased risk of ovarian cancer compared with patients after OI and those without a history of assisted treatment. The IVF treatment history was independently associated with ovarian cancer. Dariush et al [12] reviews involving more than 70 papers found that high doses of ovulation induction drugs, multiple IVF cycles can increase the risk of ovarian cysts, which leads to ovarian cancer. It was also found that there should be an association between the occurrence of ovarian cancer and drug type, dosage, and continuous ovulation induction for more than 1 year. This case with older, low ovarian function, infertility time is longer, and before ovulation drugs treatment endometriotic cyst, the third ovulation found ovarian cyst consolidation, because this kind of cases belong to rare cases, less sample size, it is difficult to say ovarian cyst evil in the relationship between ovulation and infertility itself. In addition, it is also possible that the ovarian cyst itself may have potential malignant changes, resulting in a reduction of basal follicles, which requires multiple ovulation induction. Therefore, it is not necessarily ovulation induction leading to ovarian cyst malignant change.

3.4 Management of the ovarian cysts included in the ART

About 40%~50% of EMS patients in childbearing age are complicated with infertility, and ART technology is needed to help pregnancy. Studies have shown that [13]. For patients receiving ART, such as ovarian cyst, vaginal ultrasound examination should be performed repeatedly during ART treatment to dynamically monitor the changes of ovarian cyst, such as cyst size, morphology, echo and CDFI. According to the condition, it is feasible to puncture the ovarian cyst, and the puncture fluid can be sent for pathological examination, so as to avoid the patient directly entering the IVF cycle when the ovarian cyst is malignant. However, there are also different opinions. The puncture may cause pelvic infection, tumor dissemination, bleeding and other risks, which will affect the progress of the IVF cycle. At this time, it can enter the IVF cycle normally, and the tumor markers and vaginal ultrasound can be closely monitored. In the process of egg retrieval, ovarian cyst puncture and disease examination can be performed at the same time, so as to achieve early detection and early treatment. Infertility caused by endometriosis is a common cause of infertility. Most patients often help pregnancy through assisted reproduction. In the process of assisted pregnancy, the age, ovarian function, cyst ultrasound performance, tumor markers should be comprehensively evaluated, and whether to conduct assisted reproduction after surgery. Therefore, whether the application of ovulation induction drugs will increase the ovarian endometriosis cyst malignant change, the risk of malignant change, is a clinical research topic. It is necessary to accumulate a large number of case data in multiple reproductive centers to demonstrate, and to extend the follow-up time after the end of the assisted reproductive treatment cycle, so as to monitor the occurrence of ovarian cancer in the process of ovulation induction and after ovulation induction, and guide the egg retrieval interval, and be alert to the occurrence of ovarian cancer.

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