

Premature ovarian insufficiency caused by the treatment of an ovarian malignant mixed germ cell tumor: A case report

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ABSTRACT

This is the case of a 17-year old female patient to whom a left ovariectomy and chemotherapy was carried out because of a left ovarian malignant mixed germ cell tumor when she was 6 years old, who now visited our clinic for fertility preservation. After examination she was diagnosed with premature ovarian insufficiency (POI) and had lost the chance of fertility preservation. We preferred and finally decided to optimize the sequential hormone replacement therapy by using estradiol (14 days) in the first phase and estradiol + dydrogesterone (14 days) in the second phase. This patient was a child when she incurred in an iatrogenic POI. For this situation the only possible fertility preservation method would have been ovarian tissue cryopreservation; however, she and her family were not informed about this option, which should have been performed before chemotherapy. If she would have come to our center of tissue preservation, maybe she still would have had the chance to preserve her fertility. Before proceeding with treatments that may lead to POI, doctors should inform patients of the possible reproductive consequences; and in her case, inform the family of the possible fertility preservation methods.

KEYWORDS

Premature ovarian insufficiency, iatrogenic, fertility preservation, ovarian tissue cryopreservation and transplantation, hormone replacement therapy.

Introduction

Premature ovarian insufficiency (POI) refers to the development of diminished ovarian function in women before the age of 40, mainly in the form of abnormal menstruation (amenorrhea, scanty or frequent periods), elevated gonadotropin levels (FSH >25 IU/L) and fluctuating decreases in estrogen levels ^[1]. The etiology of POI is complex, with medical factors being one of the recognized factors. Common medical factors include surgery, chemotherapy and radiotherapy ^[2]. In recent years, the prevalence of iatrogenic POI has risen due to improved survival rates after treatment for many types of cancer ^[3-5]. Adverse consequences of POI include menopausal symptoms (i.e. hot flashes and sweats, insomnia, etc.); reduced bone density and the increased risk of fracture, infertility and chronic conditions such as cardiovascular disease and dementia ^[6]. Therefore, it is necessary to inform women, who are about to undergo treatment that may lead to POI, regarding pre-treatment methods of fertility and ovarian function preservation. We report the case of a patient with primary amenorrhea and POI due to the treatment of a left ovarian malignant mixed germ cell tumor at the age of 6.

Case report

At the age of 6 years the patient presented with abdominal pain of no apparent cause. She then was taken to a children's hospital to seek medical treatment. Ultrasound revealed a left

Article history

Received 27 Sep 2023 - Accepted 5 Oct 2023

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ovarian mass, 10 cm in diameter and these lab values: alpha fetoprotein (AFP) 4,511 $\mu\text{g/L}$, HCG 325 IU/L, and neuron-specific enolase (NSE) 56.46 ng/mL. No significant abnormalities were seen on chest radiographs. The left ovarian mass was 11.2 x 8 x 8.4 cm, tough and movable, with no adhesions to the surrounding tissues. Left ovariectomy and partial omentectomy were performed. Postoperative pathology reported a left ovarian mixed germ cell tumor, with a predominantly yolk sac with embryonal carcinoma component and most of the tumor degenerated and necrotic. Repeat blood test reported AFP 90.03 $\mu\text{g/L}$, HCG 7,743 IU/L, NSE 19.43 ng/mL. She was then treated with seven courses of chemotherapy with EMA/CO regimen [etoposide (VP-16), methotrexate (MTX), actinomycin D (KSM)/cyclophosphamide (CTX), vincristine (VCR)] and then changed to three courses of PEB regimen [cisplatin (DDP) + etoposide (VP-16) + bleomycin (BLM)] at another hospital.

At the age of 17, she went to the children's hospital where she had the left ovariectomy and partial omentectomy in order to seek medical treatment because of primary amenorrhea and delayed development of secondary sexual characteristics. The examination revealed FSH 27.43 IU/L, E2 12.68 pg/mL (lab) and a uterine size: 2.5 x 4.9 x 1.0 cm, linear endometrium, right ovary size 2.5 x 1.0 cm with the largest follicle being 0.8 x 0.8 cm (ultrasound). Breast ultrasound suggested bilateral gland thickness of 2.1 cm. The diagnosis of POI was made at the follow-up examination one month later, time at which FSH 59.74 IU/L and E2 32.21 pg/mL. She then started taking estradiol valerate tablets, 1/4 tablet day for the first half of the month and a 1/2 tablet day for the second half. Two months later she had the following findings: FSH 61.26 IU/L, E2 20.76 pg/mL (lab) and uterine size 1.8 x 1.0 x 4.9 cm, linear endometrium, right ovary size 2.7 x 1.2 cm, with two follicles 0.4 x 0.4 cm, and three follicles 0.3 x 0.3 cm (ultrasound). Ultrasound of the breast reported bilateral breast echogenicity of the nucleus pulposus: 4.8 x 1.6 x 4.3 cm (left), 4.1 x 1.7 x 4.0 cm (right), and no specific nodule or occupancy observed. Uterine development was unremarkable, breast development was Tanner stage II and pubic hair Tanner stage IV. Estradiol valerate tablets 1/2 tablet per day were then started. The patient then underwent regular follow-ups in the clinic and was not found to be in any discomfort. One year later, she was rechecked for FSH 53.65 IU/L and E2 48.34 pg/mL. Abdominal ultrasound showed: uterus size: 2.5 x 1.5 x 2.9 cm, linear endometrium, right ovary size: 1.9 x 0.5 cm, no follicle echo, and little changes in the uterine size. Subsequently, she started taking one oral estradiol valerate tablet daily. Her menarche occurred on 10 September 2022, with two days of menses when she was eighteen years old.

On October 22, 2022, she visited the clinic because she still had no menstrual flow. The examination showed that FSH was 48.85 IU/L and E2 34.14 pg/mL; transabdominal ultrasound: uterus size: 2.6 x 1.3 x 3.8 cm, endometrium 0.5 cm, right ovary 2.7 x 1.2 cm, and the largest follicle: 0.9 x 0.8 cm. She then was treated with dydrogesterone 20 mg/day for 10 days, which induced a withdrawal bleeding on November 2, and then started a sequential hormone replacement therapy (HRT) regimen: in the first phase (11 days) using estradiol-valerate alone and in the second phase (10 days) estradiol valerate combined with the progestogen cyproterone acetate, followed by 7 days without hormonal treatment.

On December 9, 2022 she first came to our clinic to consult further treatment and whether she had the chance to undergo ovarian tissue cryopreservation (OTC). Lab test results at this point were: FSH 39.50 IU/L, E2 46.81 pg/mL, and AMH 0.14 ng/mL. Upon anal ultrasound: uterus size was 4.7 x 3.66 x 2.48 cm, endometrial thickness 0.4 cm, left ovary not present, and the right ovary: 1.64 x 1.08 cm. Unfortunately, in her case it was too late to undergo OTC. Due to the fact that the endometrium was still thin and menstrual bleedings missing, it was decided to change the HRT to estradiol/estradiol plus dydrogesterone, again a sequential regimen, but in the first phase estradiol for 14 days (instead of 11) and in the second phase the addition of dydrogesterone to estradiol for 14 days (i.e. the combined estrogen/

progestogen phase longer than the first treatment and with the use of dydrogesterone a progestogen which has stronger endometrial efficacy compared to cyproterone acetate). With this HRT regimen the patient presented regular menstrual bleedings, did not have any climacteric symptoms and should also be protected to the long-term consequences of estrogen deficiency due to her POI such as osteoporosis and cardiovascular diseases.

Discussion

In our "Menopause Clinic", the first official in China, there is a large experience with different HRT regimens and treats up to 250 menopausal women every day. In difficult cases, endometrial monitoring is also performed in our "Outpatient Hysteroscopy Center", which to our knowledge has been the first to be established in China. We have been able to demonstrate the strong endometrial efficacy of dydrogesterone, regularly used to induce progestogen withdrawal bleedings like in this case, to avoid endometrial hyperproliferation caused by estrogen treatment. This progestogen in sequential combination with estradiol enables valid secretory transformation of the endometrium, thus providing regular menstrual bleedings at or after the end of the estrogen/progestogen phase of the sequential HRT regimen, as it was evidenced in the present case. However, the choice of HRT and later monitoring is only a secondary aspect of what we want to highlight with this case. The important message is that the patient did not primarily receive the best choice of management. Indeed, as a 6-year-old child she underwent surgery and chemotherapy due to a left ovarian mixed germ cell tumor, resulting in POI and primary amenorrhea with delayed development of secondary sexual characteristics. Because the patient and her family were not aware of fertility protection before treatment, this was not performed. Thus, the severe impact of iatrogenic POI on her fertility could not be reversed, and all we could do was to choose the most appropriate HRT regimen to alleviate symptoms and reduce the risks associated with POI. Contrary to this case, there may be hope for other patients to learn about fertility preservation and OTC and come to our clinic for earlier consultation.

OTC has several advantages in comparison with other methods of fertility preservation^[7]. In particular, it is the only fertility preservation method for prepubertal women such as our patient, and it is also the only option for women for whom radiotherapy cannot be delayed^[8]. More importantly, OTC allows for the preservation and restoration of both female fertility and ovarian endocrine function, reducing the early and long-term adverse effects of POI while preserving patient's fertility^[8]. Other advantages of OTC include the following: a large number of follicles can be preserved in a segment of ovarian tissue; it allows for the stocking of a large number of primordial follicles, which can then be autologously transplanted or isolated and grown *in vitro* to obtain mature oocytes; it is not dependent on the patient's menstrual cycle and controlled ovarian hyperstimulation is not required; the timing of the procedure is flexible and the treatment of the primary disease will not be delayed^[9]; and it can be performed regardless of whether the patient is married or not.

OTC is no longer an experimental technique^[10,11], and it has unique advantages over other methods of fertility preservation and has promising applications. In China, in particular, there are over 4 million new malignancy cases each year^[12]. The first ovarian tissue cryobank in China was established in 2012 by our center, in which nearly 500 cases of cryopreservation and 10 cases of transplantation have been successfully performed^[8]. One of these patients had become spontaneously pregnant and subsequently delivered her child^[13,14]. Furthermore, we are aware of two girls who underwent OTC before puberty and then the transplantation of cryopreserved ovarian tissue^[15,16]. Their ovarian endocrine function was successfully restored and one of them had successfully conceived and delivered a healthy boy^[17]. Hence, for prepubertal women, OTC is also effective. The next step is to make an effort to advertise and promote this technology, which requires not only the actions of fertility protection experts, but also the help of the media and the cooperation of multidisciplinary experts; therefore, more patients will learn about OTC benefits when used before the primary treatment that causes POI, and consult fertility protection specialists in time and keep hope for their future.

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Funding

Supported by Beijing Natural Science Foundation (No. 7202047), Capital's Funds for Health Improvement and Research (No. 2020-2-2112), Beijing Municipal Science & Technology Commission (No. Z161100000516143), and Beijing Municipal Administration of Hospitals' Ascent Plan (No. DFL20181401).

Conflicts of interest

The authors declare having no conflicts of interest.