—Case Report—

A case of mature teratoma in the residual ovary after fertility-sparing therapy for ovarian yolk sac tumor managed with oocyte cryopreservation followed by cystectomy

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Abstract: Some young women with gynecological diseases undergo salpingo-oophorectomy. However, new ovarian tumors may develop in the remaining ovary at a young age after such treatment. Cystectomy is considered to be effective for fertility preservation. However, if the ovarian tumor is large, the normal ovarian parenchyma cannot be clearly detected in some cases. A 10 year-old patient with yolk sac tumor in the right ovary underwent fertility-sparing therapy. Seven years later, a large mature teratoma in her left ovary was detected. Furthermore, the ovarian parenchyma was not clearly detected by ultrasonography. Cystectomy was decided as the treatment, and the patient hoped for oocyte cryopreservation before laparotomy, in case of iatrogenic ovarian failure after surgery. The patient underwent random-start ovarian hyperstimulation in the luteal phase with dual a dual trigger 2 days prior to surgery. On the scheduled operative day, 10 metapase II oocytes were retrieved under direct observation and cryopreserved. Even though the ovarian parenchyma could not be clearly detected before ovarian stimulation, oocytes could be retrieved under direct observation on the operative day. This approach made it possible to safely retrieve enough metaphase II oocytes for cryopreservation.
Key words: Cystectomy, Oocyte cryopreservation, Ovarian yolk sac tumor, Teratoma

Introduction

Some young women with gynecological diseases undergo salpingo-oophorectomy. However, new ovarian tumors may develop in the remaining ovary at a young age after such treatment. Hence, in many cases of juvenile-onset gynecological conditions, fertility-sparing therapy is desired, and cystectomy is considered to be effective for fertility preservation. However, if the ovarian tumor is large, the normal ovarian parenchyma cannot clearly be detected in some cases, and iatrogenic ovarian failure may occur after surgery. Therefore, in cases of juvenile benign ovarian tumor in which fertility is particularly endangered, preoperative oocyte cryopreservation is an option as a fertility-sparing therapy [1].

Here, we present the case of a patient diagnosed with a left ovarian tumor (mature teratoma) at 17 years of age. The patient had been diagnosed at 10 years of age with a yolk sac tumor stage IIIC and she was subsequently treated using fertility-sparing therapy with right salpingo-oophorectomy (RSO) and postoperative chemotherapy.

The patient's left ovarian tumor was large (16 cm in diameter), and her normal ovarian parenchyma could not be clearly detected. Preoperative oocyte cryopreservation was discussed because of the possibility of iatrogenic ovarian failure after ovarian tumor cystectomy.

In the present case, because left ovarian tumor cystectomy was scheduled in collaboration with the pediatric surgery department of our hospital, it was necessary to retrieve the oocytes on the scheduled operative day itself. Therefore, ovulation was induced in the luteal phase

due to the fixed oocyte retrieval date.

Oocyte retrieval is usually performed under transvaginal ultrasound guidance. However, our patient had no experience in sexual intercourse, and it was possible that the normal ovary site was located deep within her pelvis. Hence, oocyte retrieval was performed under direct observation as the same time as cystectomy.

We believe that the clinical course of this case is exceedingly rare. Thus, we report the case with reference**s** to previous literature.

Case Presentation

A 17 year-old girl (with no experience of sexual intercourse, unmarried, gravida 0) with a left ovarian tumor, which was suspected to be a mature teratoma cyst, was referred to the Department of Obstetrics and Gynecology of Niigata University Graduate School Medical and Dental Science, Niigata, Japan, for future preservation of fertility before laparotomy.

Her menarche was at 13 years of age. At her first visit, her height was 161 cm, her body weight was 58 kg, and her BMI was 22.2. Her menstrual cycle was regular with a 28-day cycle.

1. Medical history

When the patient was 10 years of age, a right ovarian tumor and para-aortic lymph node swelling were detected by computerized tomography (CT). The patient underwent RSO and para-aortic and mesenteric lymph node resection. Subsequently, the patient was diagnosed with ovarian yolk sac tumor (stage IIIC). After fertility-sparing surgery, the patient underwent a total of six cycles of bleomycin, etoposide, and cisplatin (BEP) chemotherapy. The patient showed no evidence of disease after the initial treatment.

2. Clinical course

The patient visited the pediatrics department of our hospital once a year for routine follow-up of the yolk sac tumor by pelvic examination and transabdominal ultrasonography. At 17 years of age, the patient was asymptomatic; however, a 16-cm-diameter left ovarian tumor was detected by routine ultrasonography. The patient underwent a CT scan for further evaluation, and the same left ovarian tumor was detected. Left ovarian tumor cystectomy was decided as the treatment; however, the possibility of postoperative iatrogenic ovarian dysfunction was remained a concern. Thus, the patient was referred to our department for the purpose of preoperative fertility preservation.
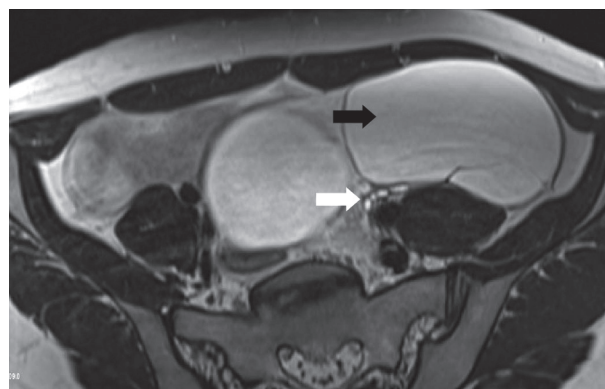
Fig. 1   Magnetic resonance image (T2-weighted) showing a multilocular cystic tumor (black arrow) in the pelvis. The tumor was suspected to be derived from the left ovary. A region of microcystic accumulation can be seen on the margin of the tumor (white arrow), which was speculated to be the normal ovarian parenchyma.

3. Laboratory findings

A blood test revealed a serum anti-Müllerian hormone (AMH) level of 2.13 ng/ml. Magnetic resonance imaging (MRI) revealed low and high T1- and T2-weighted signal intensities, respectively. The MRI findings indicated that the tumor was a mature teratoma composed of fat, as determined through fat suppression. They also showed a region of microcystic accumulation, which was thought to be the normal ovarian parenchyma (Fig. 1). Serum tumor marker levels were tested. The α-fetoprotein, carcinoembryonic antigen, cancer antigen 125, and carbohydrate antigen 19–9 levels were 1 ng/ml, 0.9 ng/ml, 8 U/ml, and 22 U/ml, respectively, which were all within the normal range.

It was thought that left ovarian tumor cystectomy would be necessary to prevent rupture and torsion. However, considering the risk of iatrogenic ovarian dysfunction due to ovarian tumor cystectomy, we explained the option of oocyte cryopreservation to preserve fertility before left ovarian tumor cystectomy to the patient, to which she agreed. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from the patient and her guardians for the publication of this report and the accompanying images. Oocyte cryopreservation for this patient was approved by the Clinical Ethical Committee of Niigata University Medical and Dental Hospital, Niigata, Japan. As the patient was a minor, consent was also obtained from her guardians. The operative day

was decided by consensus between our department and the pediatric surgery department of our hospital. Oocyte retrieval was also planned for the same day as that for surgery.

The patient underwent ovarian hyperstimulation with human menopausal gonadotropin (hMG) (HMG FERRING, Ferring Pharmaceuticals) injection on menstrual cycle day 22 (12 days before laparotomy) when the menstrual cycle was in the luteal phase, as determined by elevated progesterone levels (3.36 ng/ml on menstrual cycle day 20). At 6 days after the hMG injection, some antral follicles inside the left ovarian tumor were detected by transabdominal ultrasonography (Fig. 2), and the hMG dosage was increased from 150 to 300 units. However, due to the low increase in follicle count and low estradiol (E2) level at 7 days after the hMG injection, the hMG dose was increased to 450 units. At 3 days before surgery, gonadotropin-releasing hormone (GnRH) antagonist (0.25 mg) was injected subcutaneously to prevent unexpected ovulation. At 2 days before surgery, the largest follicle size was 17 mm in diameter (Fig. 3).

After ovarian stimulation was started, blood hormone levels were monitored on days 6, 9, and 11. The follicle-stimulating hormone, luteinizing hormone, and E2 levels were 16.3 mIU/ml, 1.0 mIU/ml, and 198 pg/ml, respectively, on day 6 after ovarian stimulation; 26.0 mIU/ml, 0.4 mIU/ml, and 1,278 pg/ml, respectively, on day 9 after ovarian stimulation; and 32.1 mIU/ml, <0.2 mIU/ml, and 2,608 pg/ml, respectively, on day 11 after ovarian stimulation. On day 11 after ovarian stimulation, human chorionic gonadotropin (hCG) (10,000 units; HCG, Mochida Pharma) and gonadotropin-releasing hormone (GnRH) agonist (600 μg; Suprecur, Mochida Pharma) were administered as triggers at 34 h prior to oocyte retrieval. Cystectomy by laparotomy was selected because the ovarian tumor was large, and safe oocyte pick-up was also being implemented. During left ovarian tumor cystectomy by laparotomy, swollen follicles were confirmed by direct observation of the ovary (Fig. 4). We punctured 12 follicles that were more than 15 mm in diameter with a 19-gauge needle under direct observation (Fig. 5), performed a follicular flushing, according to our standard protocol, and retrieved ten metaphase stage II (MII) oocytes and one metaphase stage oocyte. MII was confirmed by the presence of the first polar body under the microscope. On the same day, we cryopreserved the ten MII oocytes and single MI oocyte using the ultra-rapid vitrification method (Cryotop Safety Kit Protocol, Cryotop Method for VT505-TOP-KIT; Kitazato Corporation, Shizuoka, Japan).

After oocyte pick up, there was no worsening of severe
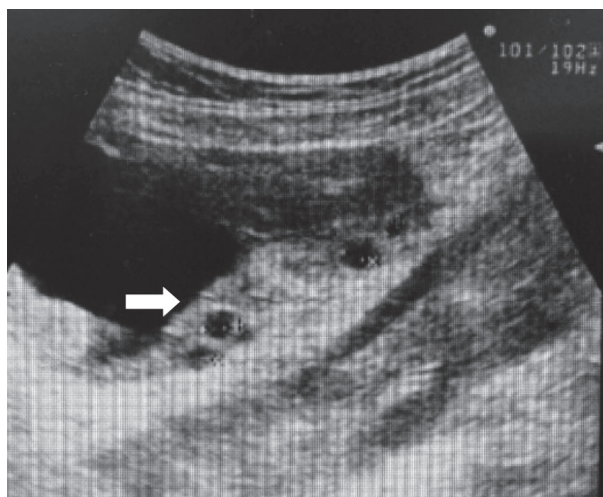
Fig. 2 Transabdominal ultrasonography showing the antral follicles (white arrow) on day 6 after initiation of ovulation induction.
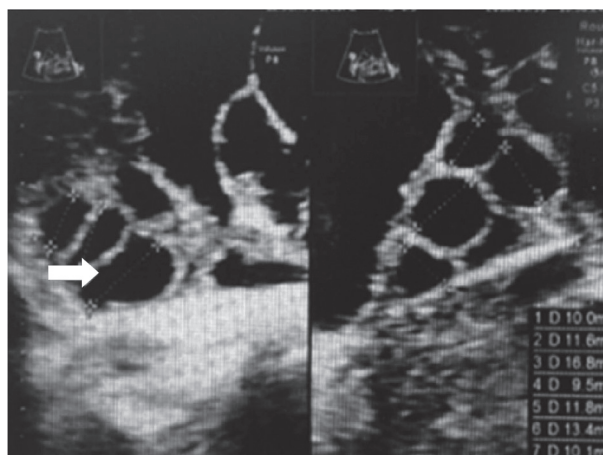

Fig. 3 Transabdominal ultrasonography showing the diameter of the dominant follicle (17 mm; white arrow) and both large and small follicles on day 11 after initiation of ovulation induction (2 days before oocyte retrieval and laparotomy).

ovarian hyperstimulation syndrome (OHSS).

The final histopathological diagnosis of the tumor was a mature teratoma, with no findings of malignancy. One month after surgery, the patient's menstruation resumed. Three months postoperatively, her serum AMH level was 0.49 ng/ml.

The patient's LH and FSH levels were also measured post-surgery. At 2 months postoperatively, they were 3.3 mIU/ml and 7.8 mIU/ml, respectively, after 4 months, 2.8 mIU/ml and 4.1 mIU/ml, respectively; and after 10 months, 3.1 mIU/ml and 9.3 mIU/ml, respectively.
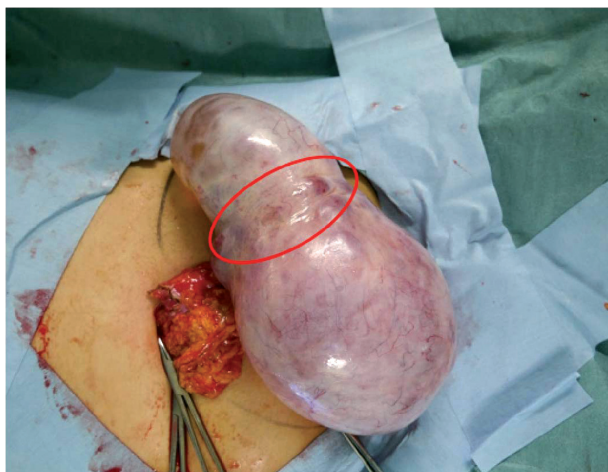
Fig. 4   The normal ovary site (red circle) could easily be identified by placing an echo probe directly on the ovarian tumor.

Fig. 5   Retrieval of oocytes in the operative room. Twenty-five large and small follicles were punctured with a 19-gauge needle under direct ovarian observation.

Currently, the patient is attending regular follow-up every 3 months at the pediatric surgery department, with no recurrence. One year has passed since the operation, her menstruation is regular, and LH and FSH continue to be monitored for consistent levels.

Discussion

We herein present the case of a 17 year-old girl who successfully underwent cystectomy after a fertility- sparing procedure (oocyte cryopreservation). The patient had previously undergone six cycles of BEP chemotherapy. In general, chemotherapy is thought to affect ovarian function, but it has been reported that the BEP regimen does not seem to impair ovarian function [2].

The patient's ovarian reserve was estimated using the serum AMH level. When she presented at our department, her menstrual cycle was at day 10. Since that was within 5 days of menstruation and ovarian stimulation was implemented immediately, there wasn't an opportunity to check her basal hormone levels (FSH, LH, E2). In addition, it was difficult to confirm the existence of antral follicles in the normal parenchyma of the remaining ovary by ultrasonography because of the presence of the large ovarian tumor. Kesley et al. reported AMH levels from conception to menopause. According to their report, a peak AMH occurs at 24.5 years, log10 (AMH+1)(ng/ml) at the age of 17 is nearly the same as the level seen in the early twenties [3]. Therefore, we judged that AMH was useful for predicting our patient's ovarian reserve.

In the present case, when the left ovarian tumor was detected at 17 years of age, the AMH level was 2.13 ng/ml. The mean AMH level of 1,009 Chinese women (mean age, 35.4 years; range, 26–44 years) was 4.18 ng/ml [4], and Chang et al. [5] reported that the mean AMH level of patients with a mean age of 33.75 years was 2.75ng/ml. Thus, we did not judge our patient's AMH levels to be abnormally low.

In the present case, the ovarian tumor was large (16 cm in diameter) and identification of normal ovary sites within the tumor by transabdominal ultrasonography was difficult. There have been several reports regarding ovarian tumor cystectomy and postoperative ovarian function [5, 6]. Although current data indicate that the risk of iatrogenic premature ovarian dysfunction is only 2.4% in cases with chocolate cysts after bilateral chocolate cystectomy [6], it was considered necessary to explain the risk of iatrogenic premature ovarian dysfunction to our patient prior to the performance of left ovarian tumor cystectomy. Moreover, the serum AMH level at postoperative week 1 is lower in cases with endometrioma than in those without a history of endometrioma (33.9% vs. 69.2% of the preoperative level) and in the bilateral group compared with the unilateral group (16.9% vs. 62.0%) [5]. Non-endometriotic cysts are considered to be associated with a lower risk of premature menopause after cystectomy than endometriotic cysts; nonetheless, careful attention to spare the normal ovary site during the operation is important.

In the present case, prior to ovarian hyperstimulation, the normal ovarian parenchyma was not detected clearly by diagnostic imaging. However, following ovulation induction, follicles gradually developed in the normal ovary site. Subsequently, the area surrounded by the tumor could be confirmed clearly by transabdominal ultrasonography. Moreover, when the ovarian tumor was being removed during laparotomy, it was easy to identify

the normal ovarian parenchyma, which was enlarged by ovarian hyperstimulation, under direct observation. As a result, the normal ovarian parenchyma was spared.

In some situations, fertility is especially endangered: for example, in cases of ovarian tumor recurrence (endometriomas), bilateral ovarian cysts, age >35 years, and poor ovarian reserve (previous chemotherapy or radiotherapy, premature ovarian failure, and so on). In these situations, cryopreservation of mature oocytes and ovarian tissue are options for fertility preservation [1].

Several studies have reported on ovarian tissue freezing in addition to ovum cryopreservation for the preservation of fertility in cases of malignant tumors [7]. There is substantial evidence of the restoration of ovarian function and spontaneous pregnancies after assisted reproductive technology following orthotopic transplantation of cryopreserved ovarian tissue. This evidence supports its future consideration as an open clinical application, and embryo and oocyte cryopreservations are first-line fertility preservation methods in post-pubertal women [8].

As the present case was of an ovarian tumor, and it was predicted that the remaining normal ovary parenchyma was very small, we did not select ovarian tissue cryopreservation as the fertility-sparing technique.

We previously reported a case wherein oocytes were cryopreserved before ovarian tumorectomy [9]. However, in that case, the normal ovary could easily be detected by transvaginal ultrasound, and the tumor component was suspected to be a fibroma; thus, transvaginal ultrasonography-guided oocyte retrieval was possible. However, in the present case, the tumor was large, and the normal ovary site was difficult to detect even under transabdominal ultrasonography–guided observation. Moreover, although the normal ovary site could be observed by MRI, tumor components surrounded the normal ovarian parenchyma. In addition, in the imaging studies, the ovarian tumor was suspected to be a mature teratoma, and a case of chemical peritonitis and pleuritis caused by teratoma rupture during ultrasonographically guided transvaginal oocyte retrieval has been reported [10]. Thus, it was considered that oocyte retrieval under ultrasonography guidance should be avoided in the present case, and we decided to retrieve the oocytes under direct visualization during ovarian tumor cystectomy via laparotomy.

This case required collaboration between the pediatric surgery department and our department. and because of manpower and surgical frame constraints, the operation date had already been decided. Therefore it was necessary to retrieve the oocytes on the scheduled date. Furthermore, ovulation in this case occurred approximately 2 weeks before the scheduled date of surgery; thus, it was necessary to implement a random-start ovarian stimulation in the luteal phase. According to Qin et al. [11], the number of MII oocytes retrieved after random-start ovarian stimulation is comparable to that after ovulation induction from the early stage of the follicular phase. However, it takes longer to induce ovulation in the random-start method. In addition, when the ovulation induction start time is in the luteal phase, the average ovarian stimulation period until oocyte retrieval is 10.9 ± 3.4 days [11]. Based on these considerations, we initiated ovarian hyperstimulation 12 days before the scheduled oocyte retrieval day. Subsequently, during the stimulation cycle, the emergence of follicles from the normal ovary was observed in the central part of the tumor.

At 2 days before oocyte collection, the patient's estradiol level was 2,608 pg/ml, relatively high, but the dominant follicle diameter was only 17 mm; thus, a further 450 units of hMG were injected intramuscularly on the same day. Dual trigger with a GnRH agonist and standard dose hCG has been reported to improve oocyte maturity rates in patients with a low percentage of mature oocytes retrieved [12]. Although it was possible that OHSS would more likely occur, the patient consented to the administration of a dual trigger in order to increase the probability of the retrieval of a sufficient number of MII oocytes.

In 2013, the American Society for Reproductive Medicine (ASRM) reported there was no increase in the incidence of chromosomal abnormalities or developmental disorders based on examinations of frozen egg-derived infants, and issued a statement that oocyte vitrification and warming were no longer experimental procedures [13]. Moreover, the clinical pregnancy rate per thawed oocyte has been reported to be from 4.5% to 12% [13]. Thus, a approximately 10 oocytes are thought to be necessary to obtain one child. Hence, we believe that we were able to cryopreserve enough MII eggs for the fertility preservation of our patient.

In the present case, we did not select ovarian tissue cryopreservation as discussed above. In ovarian tissue cryopreservation, ovarian tissue is cut into fragments of approximately 5 × 5 × 1 mm that are frozen in individual ampoules. Subsequently, the number of cortex pieces transplanted varies from 6 to 12 [14]. In the present case, it was thought that we would not be able to secure enough ovarian tissue because we had difficulty in identifying the normal ovary in preoperative imaging diagnose. In the future, if a method which can engraft even smaller slices of tissues were developed, it may become a possible option as a fertility-sparing method before subsequent ovarian tumor cystectomy.

Conclusions

Because cystectomy for a large ovarian tumor in the remaining ovary has a small but non-negligible associated risk of iatrogenic ovarian dysfunction, in cases of unilateral salpingo-oophorectomy, the management of such cases should be decided upon after careful deliberation and analysis of the clinical course and laboratory findings.

Cryopreserving oocytes before ovarian tumor cystectomy may be an option as an advanced fertility-sparing treatment.

Even though the ovarian parenchyma could not clearly be detected before ovarian stimulation, we could detect the normal ovarian parenchyma after ovarian hyperstimulation and could perform safe oocyte pick-up under direct observation on the operative day.

Furthermore, even when the oocyte retrieval date has been fixed and a random-start ovarian stimulation method has been adopted, it is still possible to retrieve enough MII oocytes for fertility preservation by careful ovulation induction and adoption of the dual-trigger method.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding Statement

Acknowledgements

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