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Successful live birth in a patient who underwent cranial radiotherapy and systemic chemotherapy by implantation of a cryopreserved blastocyst on day 7

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Summary

Preservation of fertility has been recommended for cancer-bearing patients of reproductive age before undergoing cancer treatment. However, there are many considerations and it is difficult to preserve fertility for all patients undergoing therapy for malignancies. Female cancer survivors had lower pregnancy and live birth rates compared with others that underwent assisted reproductive technologies (ARTs). We should continue to consider the issue of infertility in patients who underwent therapies for malignancies. This is the first report of a successful live birth in a patient with a cranial tumor who underwent radiotherapy and chemotherapy after implantation of an autologous embryo. The patient was a 27-year-old Japanese woman. She was diagnosed with suprasellar germinoma at 13 years of age, and she developed panhypopituitarism after radiotherapy and chemotherapy. At 27 years of age, she began infertility treatment with in-vitro fertilization (IVF). The level of anti-Müllerian hormone (AMH) was 4.29 ng/ml. After ovarian stimulation by high purified human menopausal gonadotropin (HP-hMG), she obtained two blastocysts and became pregnant by implantation of a cryopreserved blastocyst. At 37 gestational weeks, she delivered a healthy female baby by cesarean section.

Key words: Cranial tumor; Irradiation; Chemotherapy; Infertility; AMH; Live birth.

Introduction

Recently, fertility preservation for cancer patients has become a topical issue. Cancer therapies have developed, and cancer survival rates have greatly improved. Preservation of fertility has been recommended for cancer-bearing patients of reproductive age before undergoing cancer treatment [1]. However, there are many considerations, such as the patient's age, delay of cancer treatment, ovarian hyperstimulation syndrome (OHSS), cost, and low success rate [2]. It is difficult to preserve fertility for all patients undergoing therapy for malignancies.

We should continue to consider the issue of infertility in patients who underwent therapies for malignancies. Ovarian damage and failure are serious and, unfortunately, common long-term side effects of curative chemotherapy [3]. Additionally, hypothalamic and/or pituitary irradiation induces infertility. Female cancer survivors have been reported to have lower pregnancy and live birth rates than non-cancer patients treated with assisted reproductive technologies (ARTs) [4]. This is a rare case report of a successful pregnancy in a patient with a cranial tumor who underwent radiotherapy and chemotherapy. A formal consent form was obtained from the patient, and Institutional Review Board (IRB) approval was obtained before publishing this case report.

Case Report

The patient was a 27-year-old Japanese woman with a gravida of 0 and menarche at 13 years of age. At 13 years of age, she complained of polyuria polydipsia. She was diagnosed with suprasellar germinoma by magnetic resonance imaging (MRI) and based on the finding of high levels of serum beta-human chronic gonadotropin (hCG). She underwent radiotherapy and chemotherapy. The entire brain, focal, and spinal cord radiation doses were 30, 50, and 30 Gy, respectively. The chemotherapy regimen consisted of vinblastine, etoposide, and carboplatin. After radiotherapy and five cycles of chemotherapy, the tumor disappeared, and she developed panhypopituitarism with hypothyroidism, hypogonadotropic ovarian failure, and diabetes insipidus. For panhypopituitarism, she was treated with hormone replacement therapy, including thyroxin, desmopressin acetate, and Kaufmann therapy. At 25 years of age, she married and commenced the ovulation induction treatment with chronic low doses with small incremental rises of high purified human menopausal gonadotropin (HP-hMG) and hCG. This treatment was performed five times and resulted in ovulation, but did not lead to a pregnancy; therefore, the authors decided to perform in-vitro fertilization (IVF). Before the IVF, her serum hormone levels were as follows: luteinizing hormone (LH), < 0.1 mIU/ml; follicular stimulating hormone (FSH), 0.5 mIU/ml; estradiol (E2), < 10 pg/ml; and anti-Müllerian hormone (AMH), 4.29 ng/ml.

For the first round of ovarian stimulation, 150 IU/day HP-hMG was administered at four days after withdrawal of menstruation. When a single follicle obtained a diameter greater than 18 mm, 10,000 IU of hCG was administered. Thirty-five hours

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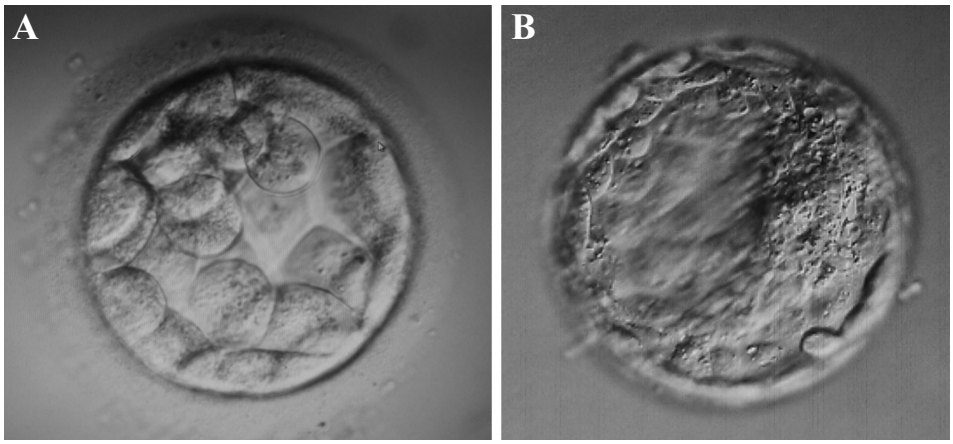

Figure 1. — A: 3BB blastocyst obtained at five days after ICSI. B: 5BA blastocyst obtained at seven days after ICSI.

after hCG injection, transvaginal oocyte pick-up (OPU) was performed. Five cumulus-oocyte complexes (COC) were obtained. The patient's husband had no male infertility factors. The authors performed conventional IVF, but they could not obtain a fertilized ovum in this time.

For the second round of ovarian stimulation, the same protocol was used, but the amount of HP-hMG was higher than that used in the first round. Briefly, 225 IU/day of HP-hMG was administered until a follicle of greater than 18 mm in diameter was obtained; then, 5,000 IU of hCG was injected. Eleven COCs were obtained. The authors performed intracytoplasmic sperm injection (ICSI), and seven fertilized eggs were obtained. At five days after ICSI, only one embryo reached the blastocyst stage. This embryo had the following characteristics: expansion class 3, grade B inner cell mass (ICM), and grade B trophectoderm (TE) (3BB), according to Gardner's classification (Figure 1A). The serum levels of E2 were 4,300 pg/ml at the time of determining OPU. The authors performed cryopreservation of the blastocyst using the vitrification method to avoid OHSS. Four embryos were at the morula stage on day 5. At seven days after ICSI, one embryo reached the blastocyst stage and had the following characteristics: expansion class 5, grade B ICM and grade A TE (5BA) (Figure 1B). This embryo was also cryopreserved by vitrification on day 7.

For the first embryo transfer (ET), the authors selected day 7 blastocyst because of its morphologic superiority. Warmed blastocyst transfer was performed during the hormonal replacement cycle. The patient received oral E2 3 days after withdrawal of menstruation. When the E2 serum level was over 200 pg/ml, administration of progesterone was initiated in the form of 30 mg/day oral dydrogesterone and intramuscular injection of 125 mg hydrogesterone every five days. Five days after the initiation of progesterone treatment, the authors performed ET. Ten days after ET, the serum hCG level was 420 mIU/ml. A gestational sac was detected in the uterus by transvaginal ultrasound at 18 days after ET. At six gestational weeks, an obstetrical sonogram revealed a single viable intrauterine pregnancy. Hormonal replacement was performed until eight gestational weeks. There were no fetal structural abnormalities during the pregnancy. The patient was diagnosed with gestational diabetes at 26 gestational weeks and was placed on insulin therapy until delivery. At 37 gestational weeks, she delivered a healthy female baby (2,450 grams) by cesarean section due to uncontrolled diabetes insipidus.

Discussion

Intracranial germinomas account for 3% of all primary brain tumors and most commonly occur in children or young adults. Radiation is the preferred treatment for this malignant tumor, but there are many complications of radiotherapy, such as intellectual deficits, growth disorders, and endocrine dysfunction. To reduce these complications, combination therapies of radiation and anti-cancer drugs have been attempted for the treatment of intracranial germinomas [5].

This is the first report of a successful live birth in a patient with a cranial tumor who underwent radiotherapy and chemotherapy after implantation of an autologous embryo. The authors performed a Medline search with the following key words: "cranial tumor, chemotherapy, irradiation, and live birth". They found only one article about live birth following IVF in a patient with a cranial tumor who underwent radiotherapy and chemotherapy. Krause *et al.* reported a successful live birth by a woman with a history of cranial radiation and chemotherapy [6]. The uterine volume of their patient was reduced to 40% due to total body irradiation. Therefore, they performed hormone replacement to increase her uterine size. However, in that case, donated oocytes were used for implantation. The uterine size of the present patient was normal. Ito *et al.* also reported a successful live birth in a patient with cranial tumor underwent chemotherapy and irradiation [7]. Their patient achieved pregnancy by ovulation induction treatment by clomiphene citrate. In their case, panhypopituitarism caused by irradiation had been recovered until the time of desire to bear children.

There have been several reports of pregnancies in patients with intracranial tumors who underwent radiotherapy without chemotherapy [8, 9]. The range from 22 to 27 Gy of irradiation for hypothalamic and pituitary induced hypopituitarism and decreased fertility [10]. The patients with hypopituitarism lacked endogenous gonadotropins; therefore, gonadotropin treatment was necessary. For go-

nadotropin treatment, hMG injection is better than recombinant FSH because patients with hypopituitarism require LH [11]. The present patient was also treated with HP-hMG, which contained both LH and FSH.

In the present case, the origin of infertility was not only radiotherapy but also chemotherapy. There are no previous reports of Vinca plant alkaloids, including vinblastine, inducing ovarian failure [12]. With regards to fertility preservation, Vinca plant alkaloids are categorized as low-risk agents [13]. In contrast, carboplatin and etoposide are capable of inducing ovarian failure. A report based on a nationwide survey of cancer survivors in Germany stated that high-dose etoposide treatment in females and carboplatin and/or cisplatin treatment in males and females increases the likelihood of infertility [14]. In regards to fertility preservation, cancer treatment regimens including cisplatin, a platinum agent similar to carboplatin, are categorized as intermediate risk agents [1]. In this case, the levels of AMH were not decreased; therefore, the number of antral follicles was not reduced. Anderson and Wallace revealed that AMH recovered to its pretreatment level in survivors of malignant tumors who were prepubertal at the time of diagnosis and who were judged to be at medium or low risk of infertility [15]. There have been several reports that serum AMH levels are correlated with the number of good quality embryos [16, 17]. To date, the possibility of a correlation between AMH level and oocyte quality in cancer survivors has not been examined, however this case suggested that AMH is also a good tool for the cancer survivors to decide to try pregnancy with an autologous embryo.

Frozen embryo transfer using day 7 blastocysts has been reported by some investigators [18, 19]. Blastocysts cryopreserved on day 7 have lower implantation rates but clinically relevant potential. Kavalevsky *et al.* recommended that embryos that do not achieve blastocyst stage on day 6 should not be discarded and should be observed in culture for one more day [18]. Additionally, Hiraoka *et al.* compared perinatal outcomes of transfers of blastocysts that were cryopreserved on days 5, 6, 7. They found no differences among the three groups in the ratio of male to female embryos, gestational weeks, preterm delivery rate or birth weight [19]. This case report suggests that embryos cultured until day 7 are also useful for ET in cancer survivors when embryos do not achieve the blastocyst stage by day 6.

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