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Association between spontaneous ovulation and serum anti-Müllerian hormone levels in a premature ovarian insufficiency patient after a multimodal treatment for breast cancer

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Abstract

The high toxicity of chemotherapy can damage a patient's gonadal function, leading to premature ovarian insufficiency (POI). Here, we report the case of a patient suffering from POI after chemotherapy for breast cancer, who 3 years later ovulated spontaneously and became pregnant. The patient, a 31-year-old infertile women, nulligravida, was diagnosed with breast cancer. The Anti-Müllerian Hormone (AMH) level in her serum was 1.85 ng/mL before multimodal treatment for cancer. She later visited our hospital for amenorrhea and 2 years after cancer treatment, she was diagnosed with POI. Her AMH level at that point was less than 0.1 ng/mL. One year after the diagnosis of POI, the patient's AMH level increased slightly to 0.14 ng/mL and she ovulated spontaneously. The patient later became pregnant using Assisted Reproductive Technology on the fourth attempt.During the course of treatment for infertility at our hospital, the AMH levels in her serum changed along with the recovery of ovarian function. These findings suggest the possibility that ovulation and pregnancy could be predicted by the chronological changes of the AMH levels in the patient's serum.

Key words: anti-Müllerian hormone, breast cancer survivor, fertility preservation, ovarian reserve, premature ovarian insufficiency.

Introduction

It is common during the different types of cancer treatments that female adolescents and young adult (AYA) patients with cancer experience premature ovarian insufficiency (POI) due to the high toxicity of chemotherapy damaging the patient's gonadal function.[1,2] However, there are several case reports in the literature involving POI patients who conceived during long-term follow-ups.[3,4] Here, we report the case of an AYA patient suffering from POI after multimodal breast cancer treatment.

Three years after treatment, the patient ovulated spontaneously and became pregnant. Upon further investigation, we found that follicle development had restarted in the patient despite undergoing chemotherapy only several years prior. During and after the patient's cancer treatment, serum Anti-Müllerian Hormone (AMH) levels were measured and it was found that the patient's AMH levels increased right before she became pregnant. We therefore found it reasonable to believe that AMH could be a possible predictor of a woman's ability to conceive after receiving chemotherapy. This case report is, as far as we know, the first to present the correlation between recovering

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AMH levels and pregnancy after treatment with Cyclophosphamide (CPA) and Tamoxifen for breast cancer.

Case Report

In 2010, at 28 years of age, the patient got married. After 1 year of marriage, the couple underwent infertility treatment for male factor infertility at a neighborhood clinic. Semen analysis was performed and revealed that the patient's husband had asthenozoospermia. The husband was referred to an urologist where he received varicocele surgery. During this time, AMH level in the patient's serum, which was measured by using a commercial assay kit (AMH GenII ELISA; Beckman Coulter Company) from SRL Inc, was 1.85 ng/mL. Once the husband recovered from surgery, the couple resumed infertility treatment using timed intercourse, but this was unsuccessful. In 2013, at 31 years of age, the patient presented with a palpable mass in her left breast and was diagnosed with breast cancer (stageI, T1N0M0 infiltrating ductal carcinoma, ER+, PR+, HER2-, KI67: 48.6%). At that time, a regional oncofertility network in Japan for providing information related to oncofertility counseling had not yet been established. Therefore, the oncologist who treated the patient's cancer did not provide the patient with adequate information about fertility preservation and the patient did not use ovary cryopreservation before chemotherapy.

The patient's cancer treatment included a left breast conserving mastectomy and chemotherapy using Docetaxel and CPA, both of which are known for being particularly damaging to a woman's gonads. Following this, the patient was simultaneously treated with Tamoxifen and radiation therapy (50Gy/25Fr) for 2 years and was subsequently treated with a gonadotropin-releasing hormone agonist for 3 months. The standard duration of hormonal therapy is 5 years; however, the patient decided to interrupt the hormone treatment because she felt her age along with chemotherapy greatly reduced her chances of becoming pregnant.

At 33 years of age, the patient went into remission and she was referred to our hospital with the desire to become pregnant. Once the patient was admitted, she was diagnosed with POI due to amenorrhea with raised gonadotrophins and low estradiol. At this point, her serum AMH level was found to be less than 0.1 ng/mL. We also tested the patient's serum for follicle stimulating hormone (FSH), luteinizing hormone

Table 1 Fertility treatment at our hospital

	iCOS	Gn or CC	Total of Gn (IU)	E2 level (pg/ml)	Day of E2 measurement	OPU	ICSI	ET	Pregnancy	Frozen
2016. 2	Short	450 IU × 18 day	8100	<10	Day 8, Day 11 Day14, Day17	Cancel				
5	CC	150 mg × 5 days		<10	Day 23, Day 33	Cancel				
7	CC	150 mg × 5 days		<10	Day 21, Day 28	Cancel				
8–10		(No visit to our hospital, BBT was bipase at this point: Ovarian function was recovered)								
11	Natural			241	Day 16	(IUI)			Failed	
12	CC			342	Day13 (2 days before OPU)	1	1/1	6 cell (III)	Failed	
2017. 2	CC	150 mg × 5 day		333	Day7 (2 days before OPU)	1	0/1			
4	Short	450 IU × 3 + 300 IU × 11	4650	1278	Day16 (2 days before OPU)	4	3/4	8 cell (II)	Failed	1 (4BB) (preserved)
6	Short	450 IU × 3 + 300 IU × 9 + retrozol 5 mg/day	4050	125	Day 14 (2 days before OPU)	2	1/2	4 cell (I)	Succeed	

CC, clomiphene citrate; ET, embryo transfer; Gn, gonadotropin; iCOS, individualized controlled ovarian stimulation; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; OPU, oocyte pick-up.

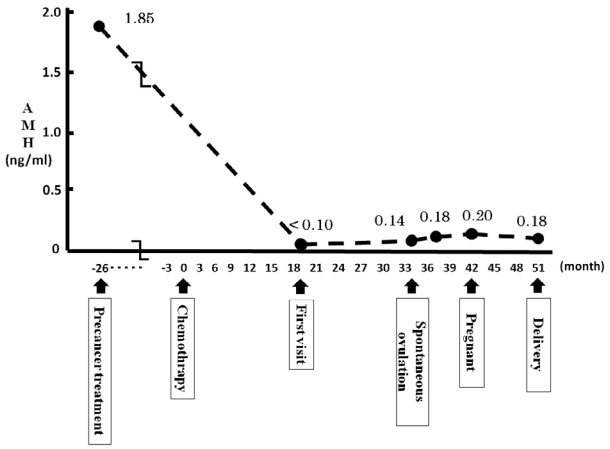

Figure 1 The change in the levels of Anti-Müllerian Hormone (AMH) during the course of the treatment. AMH in the patient's serum was 1.85 ng/mL before chemotherapy. When the patient first visited our hospital, serum AMH level was found to be less than 0.1 ng/mL. When we confirmed a spontaneous recovery of ovulation, AMH level was found to be 0.14 ng/mL. During pregnancy, AMH level in the patient's serum increased to 0.2 ng/mL and dropped slightly to 0.18 ng/mL a month after delivery.

and E2 and found their levels to be 18.83 IU/L, 8.95 IU/L and less than 10 pg/mL, respectively. We treated her with various treatment regimens, which are outlined in Table 1. However, despite our efforts, there was no recovery of an ovulatory cycle. The patient continued infertility treatment, and a year after she was diagnosed with POI. Her basal body temperature and estradiol level confirmed the spontaneous recovery of ovulation. We evaluated her serum AMH level and found that it increased to 0.14 ng/mL. At this point, we began infertility treatment using Assisted Reproductive Technology. After two unsuccessful embryo transfer attempts, the patient became pregnant on the third attempt using a four cell embryo. The stimulation protocol used short gonadotropin-releasing hormone agonist with 4050 IU of FSH plus retrozol. When we found the patient to be pregnant, we retested her serum AMH levels and found that it increased to 0.18 ng/mL. During her pregnancy, we continued to monitor her serum AMH level. It remained mostly stable until about a month after her Cesarean delivery (due to a breech presentation), which at that point, her serum AMH level dropped slightly to 0.18 ng/mL. Figure 1 shows the change of AMH levels in relation to breast cancer treatment, pregnancy and delivery.

Discussion

AMH is produced by the granulosa cells of the preantral and small antral follicles during the early stages of follicular recruitment. The number of these follicles is associated with the size of the primordial follicle pool. Thus, AMH represents a marker of ovarian reserve and the ovarian response.[2] Furthermore, it is reported that serum AMH concentration could be a clinically useful marker for the size of the remaining primordial follicle pool after cancer therapy.[2] However, AMH level immediately after the cancer therapy was reported to be inappropriate for the evaluation of the ovarian reserve.[4] Brougham *et al*.[2] reported that AMH decreased progressively during chemotherapy becoming undetectable in 50% of the patients in recovery in the low to medium risk groups after completion of the treatment. With patients in the high-risk group, AMH became undetectable and they showed no recovery.[2] In the current case, the patient received CPA for her chemotherapy, which is classified as an intermediate risk medicine for patients developing permanent amenorrhea.[5] This was the case with our patient as the high toxicity of CPA damaged her gonadal function leading to POI. As a result, AMH level in the patient's serum was found to be less than 0.1 ng/mL 2 years after chemotherapy.

Three years after chemotherapy, AMH level in the patient's serum increased to 0.14 ng/mL and the patient ovulated spontaneously. It is reported that CPA administration induces more severe oocyte damage and follicular closure to the developing follicle than to the primordial follicle.[6] It suggests that remaining primordial follicles began developing once the patient went into remission and the developing follicle produced AMH. The recovery in AMH after chemotherapy suggests the recovery of the pool of small growing follicles, which in turn reflects the size of the non-growing primordial pool.[2] Folliculogenesis is the process in which a recruited primordial follicle grows into a mature ovarian follicle ready to either ovulate its egg into the oviduct for fertilization or to atresia. This process is long, requiring almost 1 year for a primordial follicle to grow to the ovulatory stage.[7] However, the dynamics and regulatory mechanisms of follicular development in the ovary are not fully understood.[8] In this case, 3 years might have been the required time for a primordial follicle to restart follicle development, moving from a primordial follicle after chemotherapy to the development of the ovulatory stage.

It is well known that many women become amenorrheic during chemotherapy, but some show resumption of menses.[9] Morarji *et al.*[1] reported that young breast cancer survivors often show significant damage to the ovarian function in spite of having normal menstrual cycles after cancer treatment. The number of ovarian follicles decreases with age, and therefore, age is a surrogate for the number of pretreatment follicles. It was reported that serum AMH in cancer survivors was roughly equivalent to that measured in control patients 12 years older.[9] Along with this, Anderson and Cameron reported that the women with a pretreatment AMH serum level of less than 1.9 ng/mL became amenorrheic after chemotherapy.[9] Therefore, AMH levels before administration of chemotherapy can predict later amenorrhea. In the current case, AMH level in the patient's serum before chemotherapy was 1.85 ng/mL. Interestingly, a study was done about the association between AMH levels and the probability of pregnancy in systemic lupus erythematosus patients exposed to cyclophosphamide. The authors found that the likelihood of becoming pregnant was not predicted by AMH levels, but by cyclophosphamide exposure and age. However, AMH levels decreased significantly with increasing age and cyclophosphamide exposure.[10]

AMH in the patient's serum was mostly stable during the course of her pregnancy. However, a previous study found that the AMH levels normally decrease during the course of pregnancy since folliculogenesis is inhibited.[11] Most of the primordial follicles are in a resting state and hence, a down-regulation in AMH production is observed. On the other hand, according to another report, a significant change was not observed in the AMH levels during pregnancy.[12] In our case, AMH levels in the patient's serum were beyond the healthy limits reported by recent studies both before and during pregnancy. Taken together, it is clear that more research needs to be done about AMH levels during pregnancy before a conclusion can be stated.

In our case report, fertility preservation of the patient's oocytes or ovaries was not performed before cancer therapy. Cryopreservation of sperm, embryos, unfertilized mature oocytes and ovarian tissues is performed for fertility preservation before AYA patients with cancer irreversibly lose fertility due to cancer therapy.[13,14] Guidelines from the American Society of Clinical Oncology state that the possibility of cancer treatment-induced infertility should be discussed with all cancer patients of reproductive age before adjuvant chemotherapy.[5,15] Thus, all healthcare providers should pay attention to fertility preservation guidelines to make it possible for AYA patients to conceive in the future before they are treated with chemotherapy, radiation therapy, or surgery.[16] In order to provide information related to onco-fertility counseling, as of December 2017, a regional onco-fertility network was established in Gifu, Shiga, Saitama and 18 other prefectures in Japan.[3,13] This network makes it easier for oncologists and reproduction specialists to exchange information about fertility preservation and cancer treatment in Japan.

This case study has some limitations. First, the levels of AMH were measured on random days during the patient's menstrual cycle and variability in AMH has been shown to be associated to the day of the menstrual cycle. Hadlow *et al.*[17] reported that although the absolute changes in low AMH levels were less pronounced, the percent change could be high and therefore, especially in case AMH, can push the result closer to a clinical cutoff. Given this, clinicians should consider variability in a patient's serum AMH level during their menstrual cycle when assessing a patient for the possibility of becoming pregnant.

Second, the patient described in this report was diagnosed with POI due to amenorrhea with raised gonadotrophins and low estradiol at 33 years of age. However, the ESHRE Guideline Group on POI recommends the following diagnostic criteria for POI: oligo/amenorrhea for at least 4 months and an elevated FSH level of more than 25 IU/L on two occasions more than 4 weeks apart.[18] FSH levels in this patient was 18.83 IU/L during her first visit and we did not follow up with subsequent tests.

In conclusion, during the course of treatments at our hospital, AMH levels in the patient's serum changed along with her ability to ovulate. It suggests that even if the AMH level immediately after the cancer therapy is low, there is a chance that dormant primordial follicles in the ovary begin to develop after an extended period. Therefore, ovulation and the ability to conceive could be predicted by a change in the serum AMH levels after a successful cancer treatment.

Disclosure

None declared.

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