Amenorrhea in women with breast cancer who received chemotherapy: a case report

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ABSTRACT

Introduction: Breast cancer is the second most common cancer in premenopausal age, has a better outcome now. Increasing early detection rates and the effectiveness of adjuvant chemotherapy treatments are factors that influence the prognosis and survival rate. However, adjuvant chemotherapy treatment can lead to ovarian dysfunction resulting in decreased quality of life.

Case: A-29-year-old woman with breast cancer received a chemotherapy regimen of Docetaxel, Doxorubicin, and Cyclophosphamide for six cycles and had no menstrual bleeding (amenorrhoea) after chemotherapy finished. Physical examination, gynecology, and ultrasound showed no abnormalities. However, the Anti-Mullerian Hormone (AMH) immunoserology laboratory test showed shallow results.

Conclusion: The gonad toxicity effects of chemotherapy on breast cancer can cause premature ovarian failure, which can manifest as oligomenorrhea, amenorrhea, or known as chemotherapy-induced amenorrhea (CIA), which can lead to induction of premature menopause or chemotherapy-induced menopause (CIM).

Keywords: Chemotherapy-induced amenorrhea, chemotherapy-induced menopause, breast cancer.

INTRODUCTION

Breast cancer is the most common cancer affecting women worldwide. This diagnosis accounts for 28% of the most common causes of cancer death in women. Breast cancer is a disease with invasive malignancy that is most common in women of reproductive age, with 30% in premenopausal and 10% aged 35-45 years.¹⁻³

In the past 50 years, breast cancer has a better outcome because of the higher rate of early detection of the disease and the effective adjuvant treatment it provides. Clinical trials have shown oral hormone treatment (Tamoxifen) taken once daily for five years reduces the risk of recurrence. It improves survival, a recent demonstration of continued therapy with ten years of treatment.⁴⁻⁶

Side effects in women undergoing chemotherapy for breast cancer include ovarian dysfunction and amenorrhoea due to the toxicity of chemotherapy agents. In the future, it may be associated with decreased quality of life and poor health outcomes.⁷⁻⁹

Chemotherapy in premenopausal women with hormone-receptor-positive breast cancer is essential in assessing ovarian function after chemotherapy, especially in primary adjuvant endocrine therapy. More than half of premenopausal women (52.2 to 77.7%) experienced chemotherapy-induced amenorrhea (CIA). It is also possible to develop chemotherapy-induced premature menopause (CIM). Amenorrhea is described as a lack of menstrual cycles that can be primary (e.g., without a previous menstrual cycle) or secondary (e.g., with a previous occurrence of the cycle). In contrast, the term menopause is defined as no menstrual period in the last 12 consecutive months. The CIM incident was the outgrowth of the CIA after a long period. Some individuals report that after 20 years, the menstrual cycle can return.⁷⁻⁹

The primary determinant of the CIA could also be influenced by the age of patients with young premenopausal women (<35 years). It is less likely to achieve amenorrhea with chemotherapy than older premenopausal women's chemotherapy intensity and the dose of tamoxifen.⁹⁻¹⁰

Chemotherapy-induced amenorrhea (CIA) divided into three types, namely: (1) long-term type, defined as the absence of menstruation for 12 months and no recovery; (2) temporary, which can return to menstruation after at least three months of amenorrhea; and (3) menstrual irregularity, any change in menstrual pattern, either in frequency or in the number of menstruations.⁷ Women who achieve chemotherapy-induced amenorrhea have a better prognosis than women who maintain their periods.¹⁰

Pathogenesis of ovarian toxicity induced by chemotherapy involves the loss of ovarian reserve. Therefore, some studies have been associating with primary ovarian failure mechanism in which there is accelerated loss of ovarian reserve.¹¹

CASE REPORT

A-29-year-old woman, parity 2 with complaints of no menstruation for 12 months. She was treated with Cyclophosphamide for six cycles and had no menstrual bleeding (amenorrhoea) after chemotherapy finished. Physical examination, gynecology, and ultrasound showed no abnormalities. However, the Anti-Mullerian Hormone (AMH) immunoserology laboratory test showed shallow results.
The patient initially lumped the right breast with suspicion of malignant. The patient underwent a mastectomy of the right breast and removed lymph nodes in the lower part of the upper arm with the result of the anatomical pathology of an invasive ductal carcinoma infiltration with metastatic lymph nodes. The patient continued with chemotherapy seven months ago. The patient received six cycles of Docetaxel, Doxorubicin, and Cyclophosphamide chemotherapy regimens, and now the patient is continuing with the new oral Tamoxifen therapy started one month ago. History of normal menstrual cycles before getting chemotherapy. The patient did not complain of abdominal pain, enlarged abdomen, blood spots from the birth canal, or vaginal discharge. On general and gynecological examination, the results were within normal limits. The patient underwent a transabdominal ultrasound examination and found no abnormalities (Figure 1). However, the Anti Mullerian Hormone (AMH) immunoserology laboratory test showed <0.01 ng/mL (1.2 - 4.6 ng/mL). Our patient was diagnosed with secondary amenorrhoea at seven months et causa induction chemotherapy for breast cancer indication.

**DISCUSSION**

The incidence of cancer in women under 40 is around 7%, a survival rate of up to 70% with breast cancer patients most often at the reproductive age of 20-39 years. The gonad toxicity effect of chemotherapy causes 42% of young women to experience prematurity of ovarian failure. In young women, the incidence of breast cancer has been relatively stable in recent years. However, the risk of relapse in these patients is still high, so aggressive strategies such as adjuvant chemotherapy have been developed to improve the quality of life.

The main problems affecting the quality of life include the risk of ovarian dysfunction, which can manifest as oligomenorrhea, amenorrhoea induced by chemotherapy (CIA), to infertility leading to premature menopause. Damage to fertility, sexual dysfunction, and osteoporosis are the most significant consequences of the toxicity effects of chemotherapy agents that affect women's physical and psychosocial well-being. However, our study found the CIA effect 41.7% positively impacted survival, but in another study, 58.3% found no benefit.

The National Surgical Adjuvant Breast and Bowel Project Protocol B-30 conducted trials to assess the efficacy of three different adjuvant chemotherapy. The regimens containing doxorubicin, cyclophosphamide, and docetaxel (one regimen does not contain cyclophosphamide) and found that overall survival was significantly improved. In women who achieved at least six months of chemotherapy-induced amenorrhoea, regardless of chemotherapy, and, surprisingly, regardless of hormone receptor status. Ovarian suppression is thought to be an effect of chemotherapy therapy.

The chemotherapy agents that cause the CIA are divided into three divisions, its role as a predictor of pregnancy rates in cancer survivors. Its role as a predictor of pregnancy rates in cancer survivors. In one study found evidence that CIA incidence occurred more frequently at age >40 years and with the use of tamoxifen. In the case that we found events according to the CIA experienced research, the therapeutic effect obtained by the patient is persistently high-risk agents and the risk of moderate to lead the CIA.

Levels of anti-Mullerian hormone (AMH) are routinely used to evaluate ovarian reserve and a more consistent predictor for “ovarian age” than the number of antral follicles in the ultrasonic levels, inhibit B or FSH. The ovaries produce AMH, which is confirmed by the fact that AMH levels are undetectable after surgical removal of the ovaries and menopause. Fertility is associated with the number of primordial follicles in the ovaries and the quality of the oocytes. In the CIA or CIM, the rate of epithelial follicles and theca cells accelerates the aging process due to chemotherapy agents and induces apoptosis of primordial follicles. Follicular epithelial cells produce AMH so that AMH reflects the number of primordial follicles recruited. When receiving chemotherapy, it can be observed that the amount of AMH will decrease significantly compared to oestradiol and inhibit-B, and AMH can be a potential biomarker for ovarian reserve and the most promising. Indeed, serum AMH has been associated with the restoration of ovarian function in young women during and after chemotherapy. Several prospective studies are underway to determine the role of AMH as a marker of the preservation of ovarian reserve and, more importantly, its role as a predictor of pregnancy rates in cancer survivors. In a case, we found deficient AMH levels post-chemotherapy, confirming that the chemotherapy

![Figure 1. Gynecological ultrasound examination within normal limits.](image)
regimen can decrease ovarian reserve.

Diagnostic procedures for the CIA include determination of ovarian reserve and measurement of the perimenopausal hormone. Consequently, a decrease in FSH oestradiol levels and, to a lesser extent, LH levels occur. Checking hormonal levels should be prevented from the start of chemotherapy therapy to estimate the reproductive potential of the ovaries and the risk of ovarian insufficiency. Still, these biomarkers have not been routinely performed. Examination of biomarkers accurately than to predict fun g of the ovaries also provides patient education to be gained from the effects of chemotherapy agents.2, 19 According to the National Cancer Comprehensive Network (NCCN), diagnosing menopause in breast cancer should include one of the following criteria; a history of previous bilateral oophorectomy, age more than 60 years, or younger than 60 years, and amenorrhea during ≥ 12 months without chemotherapy.20

Chemotherapy appears to have a dual action: amenorrhea occurs in a relatively short period. Some studies conclude that post-chemotherapy changes in ovarian function are not permanent and vary according to chemotherapy agents acquired. It has been studied that menstruation can return even after 2 to 3 years of amenorrhea. The long-term effects associated with the destruction of primordial follicles will become apparent later in life. They can lead to irreversible premature menopause, so serial biomarker measurements are highly recommended as evidence to ensure that patients who develop amenorrhea after chemotherapy have had permanent ovarian termination and have gone through menopause.22–24

CONCLUSION
The gonad toxicity effect of chemotherapy causes 42% of young women to experience prematurity of ovarian damage. Which can manifest as oligomenorrhea, amenorrhea induced by chemotherapy therapy (CIA). It causes infertility to premature menopause. Serial biomarker measurements are highly recommended as evidence to ensure that patients who develop amenorrhea after chemotherapy actually experience permanent ovarian discontinuation and thus experience menopause.

ETHICAL CONSIDERATION

The patient had received information and given consent regarding data publication before any data collection.

CONFLICT OF INTEREST

The authors declare no conflicts of interest in this report.

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AUTHOR CONTRIBUTION

All the authors are responsible for the study from the conceptual framework.

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