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Leucopenia Induced by Tamoxifen in a Breast Cancer Patient: A Case Report

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ABSTRACT

Background: The main side effects of Tamoxifen are menopausal symptoms. We report a case of leucopenia induced by Tamoxifen in a 28-year-old woman treated in the adjuvant setting.

Case Presentation: A 28-year-old woman was diagnosed with invasive ductal carcinoma of the left breast. The final tumor stage was pT2 pN3. She received adjuvant chemotherapy with four cycles of Adriamycin and Cyclophosphamide every three weeks, followed by four cycles of Taxol every three weeks. After chemotherapy, she received the standard dose of adjuvant radiotherapy *(RT= 50 Gy/15 fractions)* for three weeks. Then she received Tamoxifen and Zoladex treatment for two years. Zoladex was discontinued, and she received Tamoxifen only for five months. A complete biological assessment showed: anemia *(hemoglobin= 9.5 g/dL)*, leucopenia *(white blood cells= 2.2 x10 ^9/L)*, neutropenia *(granulocytes= 0.9 x10 ^9/L)* and no thrombocytopenia *(platelets= 222 x10 ^9/L)*. Screening for connective tissue disorders was negative as follows antinuclear antibodies (ANA) test was negative, anti-double stranded DNA antibody test was negative, erythrocyte sedimentation rate *(ESR= 7)*, C-Reactive Protein (CRP) test was negative. Bone marrow aspirate and biopsy of bilateral iliac crest was normal. Tamoxifen was discontinued for one month, and we found improvement in leucopenia *(white blood cells= 3.24 x10 ^9/L)*. The patient received Tamoxifen again, and leucopenia *(white blood cells= 2.6 x10 ^9/L)* became more severe. These findings support that Tamoxifen can be responsible for leucopenia.

Conclusion: Tamoxifen can be responsible for leucopenia, a rare adverse event of Tamoxifen.

KEYWORDS: Tamoxifen; Breast Cancer; Ductal Carcinoma; Leucopenia

INTRODUCTION

According to the Centers for Disease Control and Prevention, cancer is the second leading cause of death in women after heart disease, making breast cancer the most common type of cancer regardless of race or ethnicity [1]. Unfortunately, the incidence rates of breast cancer are increasing. Breast cancer is becoming more common, unfortunately. While this could be related to considerable improvements in diagnostics and identification, it also emphasizes better treatment for this cancer. Breast cancer heterogeneity makes diagnosis and

treatment extremely difficult. Breast cancer therapy and detection procedures have steadily advanced over the last few decades [2].

Individualized medicine or personalized therapy regimens intended to treat specific types of cancer would be highly beneficial to breast cancer patients. Surgery, radiation therapy, chemotherapy, hormone therapy, and biological therapy are the five primary intervention methods available to treat breast cancer. These therapy methods are frequently used in conjunction. The treatment option chosen is determined by the cancer type, size, location, and stage. Age, health, and if a woman, menopausal state are all considered [2].

According to their molecular expression characteristics, breast cancers can be divided into several categories. For example, triple-negative breast cancer that lacks the human epidermal growth factor receptor 2 (HER2), progesterone receptor (PR), or estrogen receptor (ER) [3-5]. The effects of hormones, particularly estrogen, on cancer tumor cells determine whether the cancer is estrogen receptive or not. Estrogen promotes the growth of tumor cells in breast cancer, speeding up the disease progression [2]. As a result, breast cancer is a heterogeneous disease with various pathological types and outcomes [3-5]. Breast tumors also include a variety of genetic abnormalities that influence a variety of signaling pathways [6].

Whether or not chemotherapy is provided, endocrine treatment lowers the rates of recurrence and mortality in ER or PR positive early breast cancer [7]. The use of Tamoxifen for at least five years is considered the standard of treatment [8-11].

This case study focuses on Tamoxifen, one of the most widely recommended medications for treating breast cancer, and its impact on premenopausal women with invasive ductal carcinoma of the breast.

CASE PRESENTATION

A 28-year-old woman was diagnosed in 2018 with invasive ductal carcinoma of the left breast. The estrogen receptor was positive *(ER= +5/8)*, progesterone receptor was positive *(PR= +3/8)*, Human Epidermal Growth Factor Receptor 2 was Non-amplified *(HER2= 2+)*, and the FISH test was negative. She had a total left mastectomy with axillary node dissection. The final tumor stage was pT2 pN3.

She received adjuvant chemotherapy with four cycles of Adriamycin and Cyclophosphamide (AC) every three weeks, followed by four cycles of Taxol every three weeks. After two weeks from the first cycle of AC chemotherapy, she had unfit neutropenia. Fluorescence in situ hybridization (FISH) test was done between the third and fourth cycles on breast cancer tissue removed during biopsy to see if the cells have extra copies of the HER2 gene. The result of the test was negative [12].

After chemotherapy, the ultrasound (US) of the right breast, left mastectomy bed, axilla, and abdomen were normal. Chest X-ray was normal. We also obtained the value of breast cancer antigen 15-3 *(CA15-3= 11.5)*.

After chemotherapy, she started receiving the standard dose of adjuvant radiotherapy *(RT= 50 Gy/15 fractions)* [13] for three weeks. Then she received Tamoxifen and Zoladex treatment every three weeks for two years. During receiving Tamoxifen and Zoladex, the US of the right breast, left mastectomy bed, axilla, and abdomen were normal. Chest X-ray was normal. Magnetic resonance imaging (MRI) was normal. We obtained CA15-3 every three months, and it was *(9.1) (9.5) (9.5) (8.6)*, respectively. The alkaline phosphatase (ALP) test was normal, but its value was *(ALP= 185)* by the end of the year.

Zoladex was discontinued, and she received Tamoxifen only for five months. A complete biological assessment showed: anemia *(hemoglobin= 9.5 g/dL)*, leucopenia *(white blood cells= 2.2 x10 ^9/L)*, neutropenia *(granulocytes= 0.9 x10 ^9/L),* and no thrombocytopenia *(platelets= 222 x10 ^9/L)*. Laboratory tests showed: thyroid-stimulating hormone *(TSH > 100 UI/L), (CA15-3= 6.39).* At this stage, we expected hypothyroidism to be associated with connective tissue disorders [14], resulting in leucopenia [15]. However, screening for connective tissue disorders was negative as follows: IgG/IgM antinuclear antibodies (ANA) test was negative, anti-double stranded DNA antibody test was negative, erythrocyte sedimentation rate *(ESR= 7)*, C-Reactive Protein (CRP) test was negative. Bone marrow aspirate and biopsy of bilateral iliac crest was normal. Hence, we excluded leucopenia induced by connective tissue disorders probability.

Left mastectomy bed US showed: a clean bed with a hypoechoic area at the lateral aspect *(4 × 9 mm)*, a single axillary node of benign criteria *(7 × 3 mm)*, and normal skin thickness. Right breast US showed: fibrogranular tissue, few axillary nodes of benign criteria, and normal skin thickness. The neck US was normal.

Tamoxifen was discontinued for one month, and we found improvement in leucopenia *(white blood cells= 3.24 x10 ^9/L)*. The patient received Tamoxifen again, and leucopenia *(white blood cells= 2.6 x10 ^9/L)* became more severe. These findings support that Tamoxifen can be responsible for leucopenia.

DISCUSSION

Hematological toxicity is common with cytotoxic medications, however, agranulocytosis caused by non-chemotherapy treatments is a rare side effect [16,17]. Tamoxifen hematological toxicity has been recorded in only a few cases. Extended usage of Tamoxifen was linked to worldwide bone marrow suppression in two studies [18]. Agranulocytosis was reported in conjunction with fatal acute hepatic failure in one case. According to the Gell-Coombs classification, the agranulocytosis in other instances was most likely

caused by a type II immune-mediated hypersensitivity reaction. Tamoxifen and trastuzumab were used in a similar study as a hormonal treatment for invasive ductal carcinoma of the breast. Hypocellularity was found with pseudoblockade of the granulocyte line at the promyelocyte stage and no mature granulocytes in a bone marrow biopsy [19].

In our case, the blood film had no immature cells, and bone marrow aspiration was normal. When Tamoxifen was discontinued for one month, we found improvement in leucopenia *(white blood cells= 3.24 x10 ^9/L)*. The patient received Tamoxifen again, and leucopenia *(white blood cells= 2.6 x10 ^9/L)* became more severe. These findings support that Tamoxifen can be responsible for leucopenia.

Tamoxifen is a major endocrine treatment option, particularly for women who still have a significant ovarian oestrogenic activity that cannot be controlled by aromatase inhibitors [10, 11, 20-25]. In pre-and perimenopausal women with advanced breast cancer, Zoladex plus Tamoxifen was evaluated. There has been no evidence of a negative endocrinological interaction between the medicines. Although the combination of medications resulted in a higher proportion of static illness, possibly at the price of partial remissions, the time to disease progression was prolonged in women who got Zoladex plus Tamoxifen. Patients with ER-positive tumors were more likely to achieve remission [26]. FSH circulating concentrations are suppressed more effectively with combination medication [27]. We used this combination in our case, and the FSH level decreased from 100 UI/L to 16.27 UI/L. The partial estrogen agonist characteristics of Tamoxifen may explain the effective suppressive impact of Zoladex and Tamoxifen on serum FSH concentrations [28].

Adjuvant therapy for premenopausal breast cancer patients has enhanced survival [29]. As adjuvant chemotherapy, we used AC and Taxol. One of the most often used and effective chemotherapy medications for breast cancer is this combination [30].

The most often utilized serum marker in breast cancer is CA 15-3. It is a big transmembrane glycoprotein that's typically overexpressed and glycosylated abnormally in cancer cells. It appears to play a role in cell adhesion physiologically, and its elevated levels in cancer may be causally related to metastasis. CA 15-3 may thus be the first independent predictive serum marker in breast cancer, as rising CA 15-3 levels over time may suggest that a patient is not responding to treatment or that the cancer is reoccurring [31]. The combination of ALP and CA153 has the highest sensitivity and positive predictive value for breast cancer bone metastases [32]. We used that combination to detect any metastasis, and we noted that our patient's CA 15-3 level was decreasing during hormonal treatment. In 20 to 30 percent of advanced and metastatic breast cancer patients, the HER-2 gene is overproduced, making it a significant contributor to poorer survival chances. As a result, we followed the HER-2 gene in our case, which was amplified [33].

CONCLUSION

Tamoxifen can be responsible for leucopenia, a rare adverse event of Tamoxifen when used as a hormonal treatment in breast cancer in premenopausal women. Tamoxifen has been proven to be a safe, effective, and simple therapy technique in most trials. More research is needed to determine the optimum treatment protocols and long-term outcomes. To confirm the current findings, bigger size longitudinal studies for extended periods are required.

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