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Case Report
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Neoadjuvant Therapy for Dual Breast Cancer (Triple Positive and Triple Negative): A Case Report and Comprehensive Literature Review

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Abstract

Background: Bilateral primary breast cancer is a rare occurrence. One breast exhibit triple-positive breast cancer, while the other presents with triple-negative breast cancer. Tailoring treatment based on molecular subtyping can enhance the Pathological Complete (PCR) response rate and improve long-term prognosis.

Case Report: The hospital admission of a 56-year-old female patient was prompted by the presence of extensive erythema and edema on the skin of her left breast. Initial diagnostic procedures, including color Doppler ultrasound, mammography, and magnetic resonance imaging, revealed bilateral breast cancer upon admission. Subsequent histopathological examination confirmed triple-negative breast cancer in the left breast and triple-positive breast cancer in the right breast. Biopsy of the left cutaneous tissue and puncture of bilateral axillary lymph nodes demonstrated metastatic carcinoma. After 6 cycles of neoadjuvant therapy, the patient achieved partial remission. Following bilateral modified radical mastectomy, the bilateral postoperative Miller-Payne grade was determined to be grade 3, and subsequent intensive treatment was administered.

Conclusion: Bilateral molecular subtypes should be taken into consideration when determining neoadjuvant therapy for bilateral breast cancer. This particular patient necessitated dual anti-HER-2 targeted therapy in conjunction with treatment for triple-negative disease. In such instances, subsequent therapeutic interventions should be intensified to target both the multitarget (endocrine and HER2 gene) in triple-positive breast cancer and the nonresponsive target in triple-negative breast cancer. Consequently, more sophisticated personalized treatment approaches are imperative.

Keywords: Dual breast cancer; Triple-positive breast cancer; Triple-negative breast cancer; Neoadjuvant Therapy

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Abbreviations

PCR: Pathological Complete Response Rate; TCbHP: T (albumin-bound paclitaxel), Cb (carboplatin), P (pertuzumab), H (trastuzumab); HER-2: The Human Epidermal Growth Factor Receptor 2; NCCN: National Comprehensive Cancer Network; CSCO: Chinese Society of Clinical Oncology

Background

The prevalence of breast cancer is significantly higher among women, with bilateral primary breast cancer being a relatively uncommon occurrence [1,2]. Bilateral primary breast cancer refers to the simultaneous or successive occurrence of independent primary breast cancers in both breasts. The classification of bilateral breast cancer encompasses synchronous bilateral breast cancer and metachronous bilateral breast cancer, which are distinguished based on the temporal interval between the onset of both breasts [3]. The prevalence of synchronous and metachronous breast cancer was 0.73% and 1.4%, respectively. According to most scholars, when the time interval between these occurrences is ≤ 6 months, it is known as synchronous bilateral breast cancer; however, if the interval exceeds 6 months, it is referred to as metachronous bilateral breast cancer [4].

The presence of dual breast malignancies signifies the existence of two distinct clonal neoplasms with a genetic underpinning, necessitating separate therapeutic approaches [5]. Patients harboring

dual breast cancer displaying diverse biological characteristics may encounter heightened difficulties and challenges due to their disparate responses to various therapeutic interventions [6]. The findings of various studies have consistently demonstrated that metachronous breast cancer is associated with a higher tumor stage, reduced expression of Estrogen Receptors (ER), and an increased risk of both local recurrence and distant metastasis compared to synchronous breast cancer [7]. Additionally, in patients diagnosed with synchronous bilateral breast cancer, the presence of discordant estrogen-receptor status between the two tumors has been identified as an independent predictor for survival [8]. In addition, the presence of HER-2 positivity has been consistently associated with an increased risk of bilateral breast cancer, and individuals with HER-2 gene mutation are more prone to developing synchronous bilateral breast cancer [9,10].

With the advancement of research on molecular classification and biological characteristics of breast cancer, triple-positive breast cancer is increasingly recognized as a distinct molecular subtype that relies on both the ER pathway and HER2/EGFR pathway, exhibiting high expression of PIK3CA, low expression of TP53, and low expression of TILs. Clinical and preclinical evidence supports the interplay between HER2 and ER pathways in conferring resistance to endocrine therapy and anti-HER2 therapy [11]. According to the 2021 NCCN guidelines, neoadjuvant chemotherapy combined with anti-HER therapy is recommended for patients with triple-positive breast cancer [12]. The combination of classic drugs such as anthracycline, paclitaxel, or carboplatin is the preferred neoadjuvant therapy for triple negative breast cancer.

The present study presents a unique case of synchronous bilateral breast cancer, characterized by one side exhibiting triple-positive breast cancer (positive for hormone receptors and the human epidermal growth factor receptor 2) and the other side displaying triple-negative breast cancer (negative for hormone receptors and the human epidermal growth factor receptor 2). After neoadjuvant therapy, successful clinical downstaging was achieved. Following the completion of the operation, the subsequent treatment plan was formulated based on the postoperative Miller-Payne grade.

Case Presentation

The fundamental patient data

The patient, a 56-year-old female, was admitted to the hospital due to a large maculopapular rash and erythema on the skin of her left breast. She had previously received treatment for cutaneous maculopapular lesions in the dermatology department but was referred to the breast surgery department due to inadequate response to self-administered dermatological medications. The patient had no underlying medical conditions, no family history of breast cancer, was in the postmenopausal stage, and exhibited no discharge, invagination, or significant pain in both nipples upon physical examination.

Imaging and histopathological assessment

Color Doppler ultrasonography revealed a hypoechoic nodule measuring 55 mm × 29 mm × 45 mm (BI-RADS grade 4C) located approximately 40 mm from the nipple in a 10 o'clock orientation of the right breast (Figure 1A). Additionally, there was an approximately 60 mm × 30 mm × 50 mm hypoechoic nodule (BI-RADS class 5) observed located approximately 30 mm from the nipple in the three o'clock direction of the left breast (Figure 1B). Ultrasound-guided needle biopsy was recommended (The biopsy specimen included masses in both breasts, lymph nodes in both axillae, and a maculopapular rash on the left skin). The biopsy and immunohistochemical findings demonstrated that: The positive expression rates of Estrogen Receptor (ER) and Progesterone Receptor (PR) in the tumor tissue of the right breast were 90% and 0%, respectively, while HER-2 exhibited a positive expression status. However, there was a negative expression observed for estrogen receptor, progesterone receptor, and HER-2 status in the tumor of the left breast. The bilateral axillary lymph nodes and the skin tissue of the left breast exhibited metastatic carcinomas originating from the breast. (Tumor Estrogen Receptor (ER), Progesterone Receptor (PR) status was evaluated by Immunohistochemistry (IHC); Her-2 status was evaluated with IHC, FISH was studied in the presence of score II. ER positivity was evaluated >1%). The patients underwent tattooing on the skin overlying bilateral breast tumors prior to treatment.

Treatment and neoadjuvant efficacy evaluation

According to the guidelines provided by NCCN and CSCO, for patients diagnosed with locally advanced HER-2 positive breast cancer, the recommended treatment approach entails neoadjuvant chemotherapy in conjunction with two targeted medications (trastuzumab combined with pertuzumab). The selected drug regimen comprises T (albumin-bound paclitaxel, 260 mg/m^2), Cb (Carboplatin AUC=6), P (Pertuzumab, initial dose of 840 mg followed by 420 mg), H (trastuzumab, initial dose of 8 mg/kg followed by 6 mg/kg). Corrected sentence: Furthermore, a subcutaneous injection of pegylated recombinant human granulocyte-stimulating factor was administered 48 h after the initiation of treatment. Breast ultrasound,

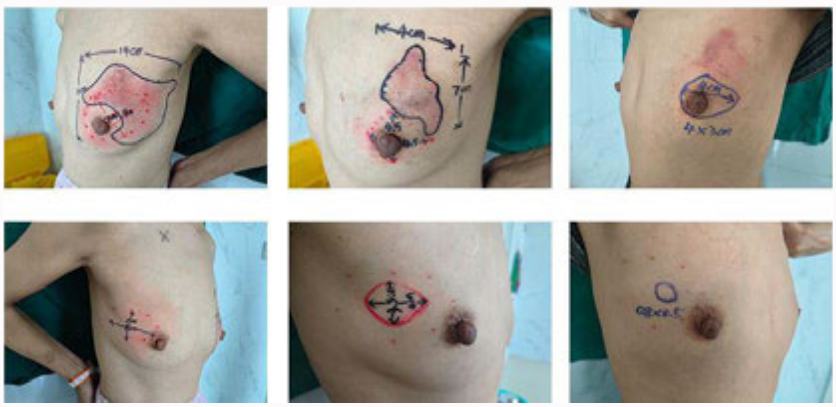

Figure 1: Illustrates the placement of patient tattoo marks and tumor surface markers at intervals of every 2 cycles.

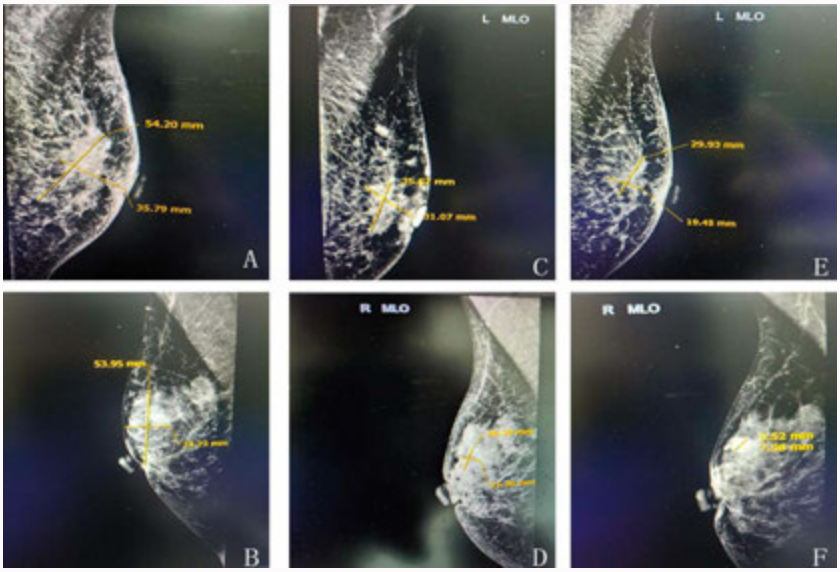

Figure 2: Illustrates the tumor size on mammography of the left (A, C, E) and right (B, D, F) breast.

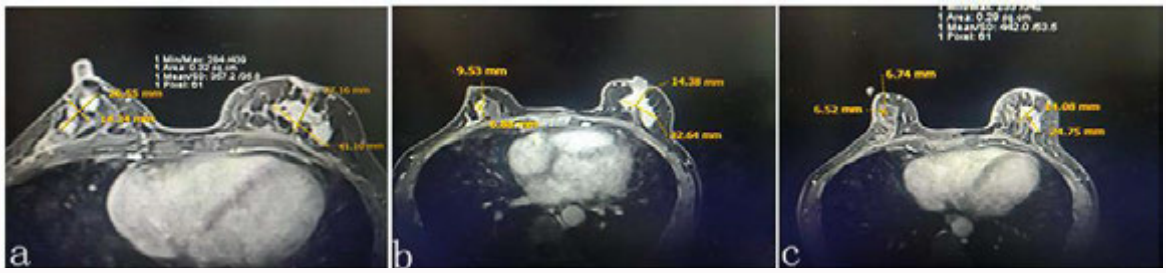

Figure 3: Illustrates the MRI images of both breasts, displaying the respective tumor sizes observed in each of the two cycles (a,b,c).

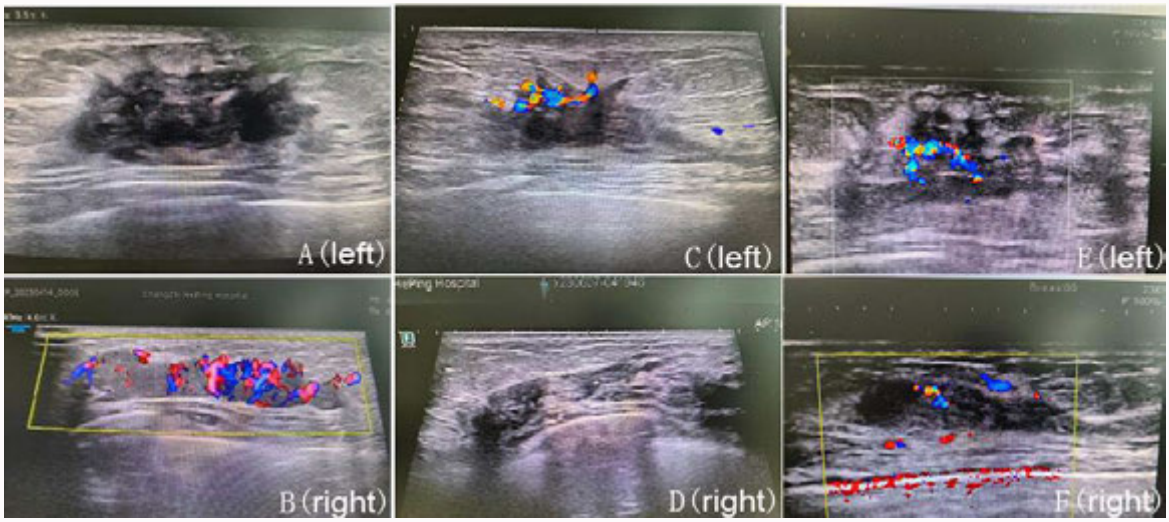

Figure 4: Illustrates the tumor size on ultrasound of the left (A, C, E) and right (B, D, F) breast.

mammography, and breast magnetic resonance imaging were conducted every two cycles for evaluation and measurement based on RECIST 1.1 criteria (Figures 1-4). The Tumor size was checked and the effect was evaluated by complete remission, partial remission or un-remission. The patient experienced partial remission of clinical symptoms in both breasts. After completing six cycles of treatment, bilateral modified radical mastectomy was performed, resulting in a postoperative Miller-Payne grade classification of grade 3 for bilateral breast cancer (Figure 5). The presence of six metastatic lymph nodes was identified in each axilla.

Discussion

According to both domestic and foreign breast cancer guidelines and consensus, preoperative neoadjuvant therapy may be considered

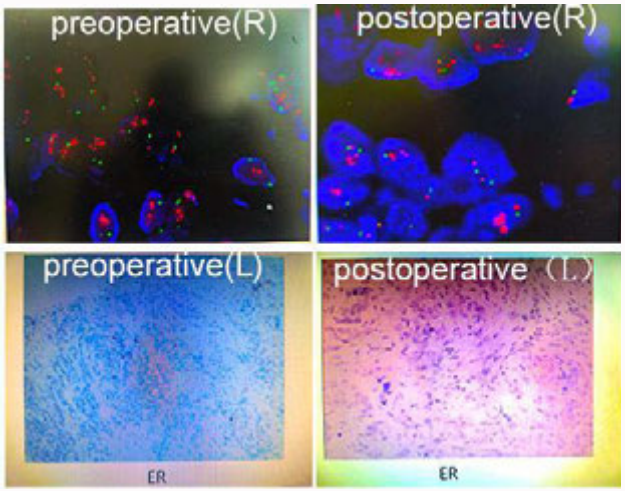

Figure 5: Illustrates the pathological alterations of estrogen receptor in the left breast and human epidermal growth factor receptor 2 in the right breast, both before and after surgery.

in the following situations: When the tumor exceeds 5 cm or presents axillary lymph node metastasis; when the tumor is HER-2 positive or triple negative, and the patient expresses a preference for breast-conserving treatment but faces challenges due to a high ratio of tumor size to breast volume. The available options for drug therapy encompass chemotherapy, targeted therapy, and endocrine therapy. The neoadjuvant therapy is indicated in this case as both breasts are locally advanced tumors.

The right breast tumor in this patient is characterized by being Hormone Receptor-Positive (HR+) and HER-2 positive. When combined with the findings from the NEOSPHERE [13], PEONY [14], and TRAIN-2 [15] studies, the combination of trastuzumab and pertuzumab has shown a Pathologic Complete Response (PCR) rate ranging from 26% to 55% in patients with hormone receptor-positive tumors [13]. Therefore, dual targeted therapy provides significant benefits for patients with HER-2 positive breast cancer during the neoadjuvant phase. TCbHP and THP are recommended as first-line treatments. In this case, the patient was treated with the TCbHP regimen and achieved definite clinical benefit.

The tumor in the patient's left breast was characterized by triple-negative breast cancer, which also meets the indication for neoadjuvant therapy. Both NCCN and CSCO guidelines recommend anthracyclines plus taxanes as the standard neoadjuvant chemotherapy for triple-negative breast cancer. With the continuous development of GeparSixto [16], CALGB40603 [17], and BrighTNess [18] studies, incorporating platinum agents into neoadjuvant therapy has shown potential to further enhance the Pathological Complete Response (PCR) rate in triple-negative breast cancer. The NeoCART [19] study led by Chinese scholars has confirmed that paclitaxel combined with carboplatin is superior to anthracycline combined with taxane. Therefore, a combination of taxane and carboplatin is considered as the preferred neoadjuvant chemotherapy regimen for triple-negative breast cancer. In this case, albumin-bound paclitaxel and carboplatin were administered during the neoadjuvant phase resulting in a favorable PCR rate.

The patient was classified as grade 3 according to the Miller-Payne classification [20] post-surgery, with a higher incidence of axillary lymph node metastasis, which was categorized as non-PCR and required intensive treatment. After surgery, the right breast tumor remained HER-2 positive, while the left breast cancer continued to be triple-negative. Due to the proven benefits of anthracyclines in patients with positive axillary lymph nodes, the patient underwent four cycles of anthracycline therapy after surgery. Upon completion of chemotherapy, T-DM1 intensification therapy should be continued based on findings from the KATHERINE study [21]; meanwhile, capecitabine intensification therapy should be implemented for triple-negative breast cancer following guidelines established by the CREATE - X study [22].

Conclusion

This is a unique case of bilateral breast cancer following neoadjuvant therapy, characterized by the molecular classification of triple-positive breast cancer on one side and triple-negative breast cancer on the other side. The cornerstone of treatment for locally advanced Hormone Receptor Positive/HER-2 positive breast cancer lies in anti-HER-2 therapy. The addition of carboplatin significantly enhanced Progression-Free Survival (PFS) and Pathological Complete Response (PCR) in patients diagnosed with triple-negative breast cancer. Therefore, we opted for anti-HER-2 therapy as the primary approach in initial treatment, supplemented with platinum drugs to improve tumor shrinkage rate in cases of triple-negative breast cancer. Anthracyclines were administered after bilateral modified radical mastectomy to address positive axillary lymph nodes identified through postoperative pathology examination, aiming to improve prognosis. Subsequent treatment involved radiotherapy combined with T-DM1 targeted therapy and endocrine therapy using exemestane. Upon completion of treatment, it is advisable for patients to undergo BRCA testing, which will guide decisions regarding further intensification strategies for managing triple-negative disease. This patient's case highlights the importance of selecting therapeutic targets and formulating an individualized treatment plan based on relevant clinical research findings; thus, making it a noteworthy case that warrants further investigation.

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