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Case Report

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Synchronous Bilateral Breast Cancer With Discordant Receptor Status: Treating One Patient but Two Diseases

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Abstract

The expression of hormone receptors (estrogen and progesterone) and human epidermal growth factor receptor-2 (HER2) has been used for both therapeutic and prognostic purposes in the management of breast cancer. The presence of a discordant receptor status complicates the approach to treatment in patients with synchronous bilateral breast cancer. We describe the case of a 45-year-old female with synchronous bilateral breast cancer with a triple-negative tumor and a contralateral HER2-positive tumor and discussed the impact of this on the approach to therapeutic management.

Keywords: Human epidermal growth factor receptor; Estrogen receptor; Progesterone receptor; Breast cancer

Introduction

Synchronous bilateral breast cancer (SBBC) has been defined in the literature as bilateral breast cancer foci diagnosed simultaneously with a cut-off of within 3 and 6 months [1]. It represents 0.2-3% of all newly diagnosed breast cancer cases and is associated with higher mortality compared to unilateral breast cancer [1, 2]. Similar genetic predisposition, environmental exposure, or unrelated genetic or epigenetic alterations underlie the development of SBBC [3]. Tumor heterogeneity, regarded as the hallmark of malignancies, occurs in SBBC with a significant impact on therapeutic management [4]. This heterogeneity is clinically assessed by various modalities including genetic profiling of tumors and assessment of receptor expression status [5].

The expression of hormone receptors (estrogen and progesterone) and human epidermal growth factor receptor-2 (HER2) has been used for both therapeutic and prognostic purposes in the management of breast cancer. We present a case of SBBC with heterogenous receptor expression and explore its impact on therapeutic management.

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Case Report

Investigations

This case details a 45-year-old Hispanic woman who was referred to our clinic by her primary care physician after she discovered a lump in her left breast. The patient reported that the lump was painless, about the size of a pea but denied any nipple discharge or breast skin changes. Her past medical history included type 2 diabetes for which she takes metformin. Her family history is significant for breast cancer in her mother in her early 50s and three other maternal cousins.

On physical examination, she had a palpable, freely movable, non-tender mass in the left breast upper outer quadrant with no skin, nipple, or areolar changes. There was no palpable mass in the right breast and no palpable axillary lymphadenopathy bilaterally.

Diagnosis

Bilateral diagnostic mammography showed a 1.2 × 1.9 cm right breast mass (upper inner quadrant) and a 1.9 × 2.1 cm left breast mass (upper outer quadrant). Breast ultrasound revealed a 1.3 × 1.6 cm heterogenous mass in the right breast with normal appearing right axillary nodes and a 1.8 × 2.1 cm solid mass in the left breast with an abnormal appearing left axillary node. Ultrasound-guided biopsy of the breast lesions showed invasive, poorly differentiated, high-grade ductal carcinoma with medullary features in the right breast, and poorly differentiated invasive ductal carcinoma in the left breast (Figs. 1, 2). The right breast lesion was negative for estrogen receptor (ER-) and progesterone receptor (PR-); the HER2/*neu* immunohistochemistry (IHC) score was 2+ but was positive by fluorescence *in situ* hybridisation (FISH) (percentage of positive

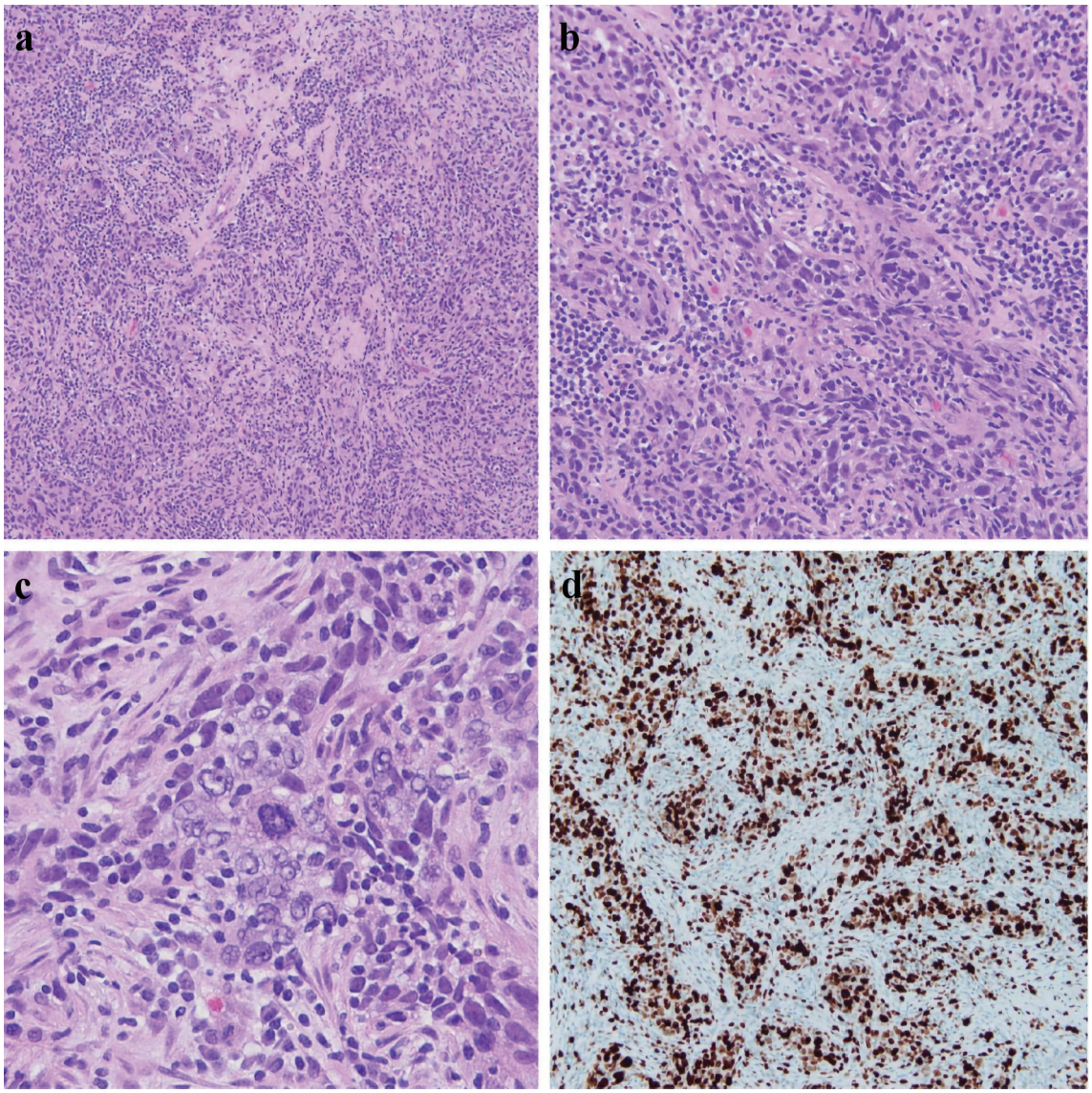

Figure 1. Right core breast biopsy (a, × 10), (b, × 20), (c, × 40) showing infiltrating tumor cells with large and atypical nuclei, a syncytial growth pattern, and a background of lymphocytes. An atypical mitotic figure is present in the center of (c). Ki67 IHC stain showing > 90% nuclear staining of tumor cells, reflecting increased proliferation (d). IHC: immunohistochemistry.

nuclei > 90%). The left breast lesion was negative for ER, PR, and HER2 expression (triple-negative breast cancer (TNBC)). Staging workup with positron emission tomography/computed tomography (PET/CT) confirmed the lesions with a maximum standardized uptake value (SUV) of 6.2 in the right breast lesion and a left breast lesion with a maximum SUV of 17.6 in addition to a hypermetabolic left axillary lymph node with an SUV of 6.0 (Fig. 3). Genetic testing showed the presence of mutation in *BRCA1* gene.

Treatment

She received neoadjuvant therapy with docetaxel/carboplatin/trastuzumab/pertuzumab (TCHP) every 3 weeks for six cycles followed by adriamycin/cyclophosphamide/pembrolizumab every 3 weeks for four cycles.

Follow-up and outcomes

Follow-up imaging showed a complete response to neoadjuvant therapy with no residual mass in the breasts or axillary lymph node abnormalities. She subsequently underwent a bilateral total mastectomy with sentinel lymph node biopsy and immediate tissue expander reconstruction. Histopathology of resected specimens showed a complete response with no evidence of primary tumor in the breasts or axillary node metastasis (ypT0ypN0 in both left and right breast). Pembrolizumab was resumed postoperatively. Although the patient did

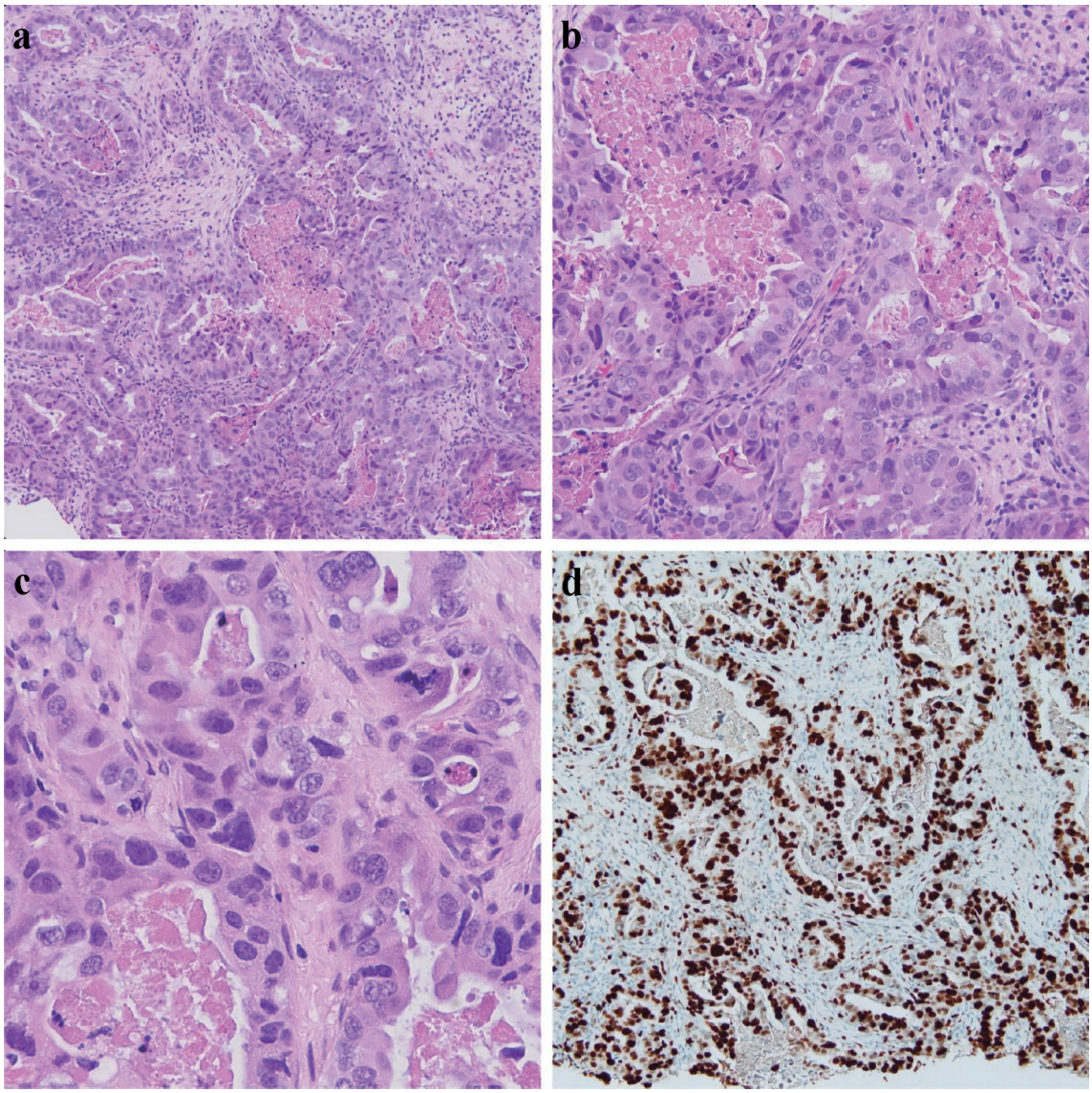

Figure 2. Left breast core biopsy (a, × 10), (b, × 20), (c, × 40) showing infiltrating tumor cells with large, pleomorphic nuclei, with a glandular/tubule formation and associated necrosis within the tubules. An atypical mitotic figure can be seen in (c). Ki67 IHC stain showing > 90% nuclear staining of tumor cells, reflecting increased proliferation (d). IHC: immunohistochemistry.

not immediately meet the criteria for post-mastectomy radiation treatment (PMRT), she was scheduled for evaluation for possible radiation treatment after the completion of breast reconstruction with the removal of tissue expanders. She was referred for gynecologic evaluation for possible prophylactic oophorectomy given her *BRCA1* gene mutation. She is 15 months post-diagnosis and remains disease free.

Discussion

Here, we present a case of SBBC with heterogeneity in receptor expression. Although this patient initially presented with a left breast lump, the presence of bilateral lesions was confirmed on imaging studies with biopsy establishing the diagnosis of a left TNBC and a right breast HER2-positive disease. Most second synchronous tumors are detected by imaging studies in patients who presented with a unilateral breast lesion, and they usually share similar histological features [6]. Some of the factors associated with the development of bilateral tumors include *BRCA* mutations, younger individuals, family history of bilateral breast cancer, and lobular histology subtype [7]. Although these tumors are often similar histologically, heterogeneity can occur between different tumors (intertumor heterogeneity) [8]. These differences in the genomic and phenotypic properties exhibited by different tumors in the same individual often arise from diverse metabolic, immunological, and trophic factors that work to create different neoplastic microenvironments [8, 9].

The *BRCA1* mutation found in our patient is a tumor suppressor gene located on chromosome 17 that plays a role in

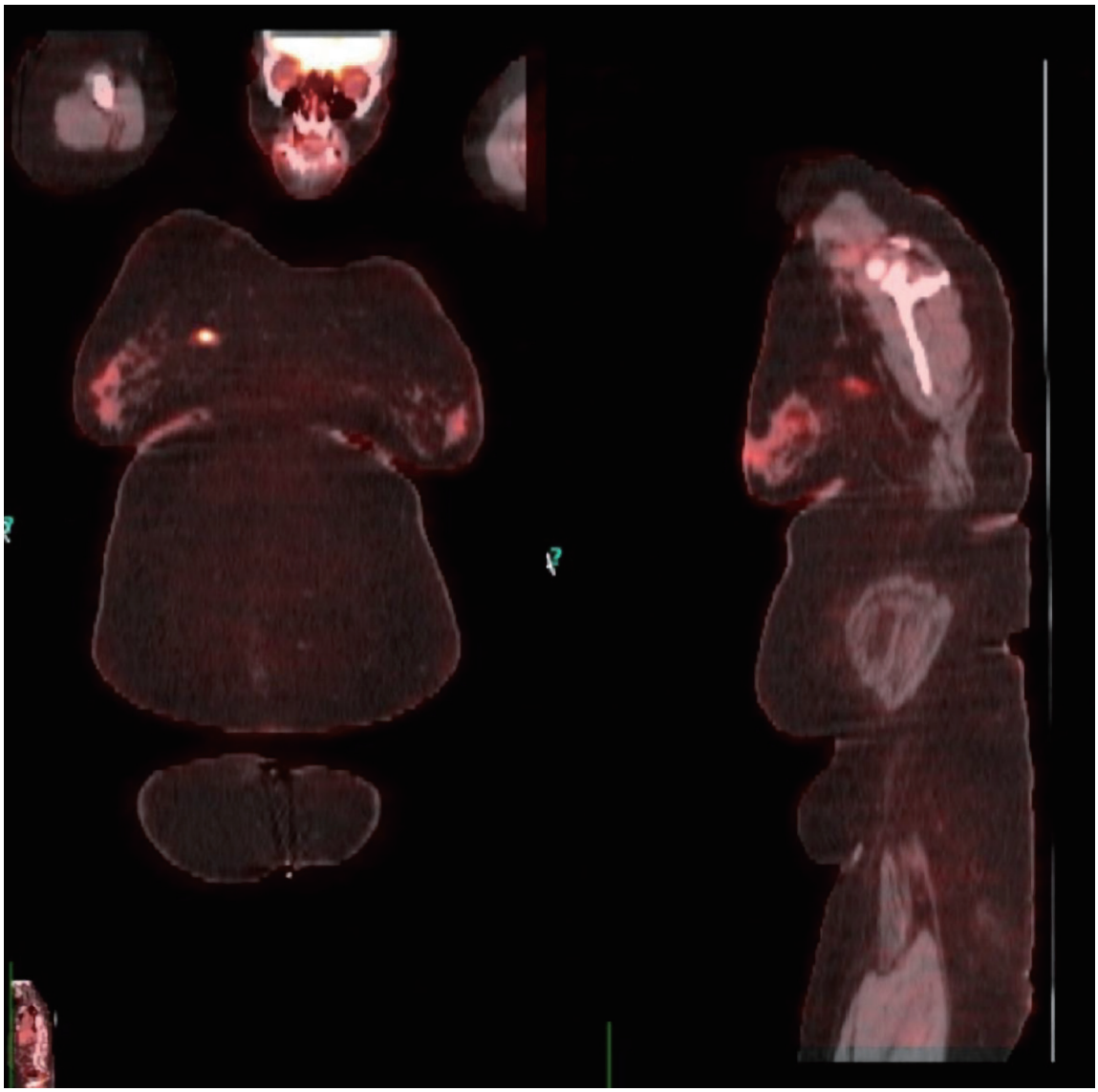

Figure 3. PET/CT scan for staging confirming the lesions in both breasts. PET/CT: positron emission tomography/computed tomography.

DNA damage repair [10]. The lifetime risk of breast cancer in these individuals is high, up to 72% [11]. *BRCA1* mutation is associated with the development of TNBC [12]. Our patient has a TNBC in addition to a contralateral HER2-positive tumor. Individuals with *BRCA* mutations who develop TNBC are sensitive to DNA-damaging chemotherapeutic agents, although this does not translate to improved survival [13, 14].

Although our patient had an early-stage disease bilaterally, she was treated with neoadjuvant therapy before undergoing bilateral mastectomy. Neoadjuvant therapy was traditionally used to downstage locally advanced or inoperable tumors to improve surgical outcomes. However, neoadjuvant therapy is being increasingly used in early-stage disease to assess tumor response and to guide future adjuvant therapies [15]. In addition, it creates a time window for planning breast reconstruction if a patient chooses to undergo a mastectomy. In patients with TNBC and HER2-positive breast cancer, response to chemotherapy is a strong predictor of recurrence [16, 17]. As such, response to neoadjuvant chemotherapy provides a real-life validation model for predicting the long-term effect of treatment [18]. Although the clinical utility of neoadjuvant chemotherapy has been demonstrated in studies, in terms of long-term outcomes, there is insufficient evidence from clinical trials on the superiority of pre- versus post-mastectomy chemotherapy [19, 20].

Our approach to neoadjuvant therapy was the use of two lines of chemo-/targeted therapy. The initial regimen was the TCHP, which not only provided HER2-directed therapy but also contained an anthracycline-free platinum plus taxane regimen for her TNBC. This was followed by a neoadjuvant pembrolizumab-chemotherapy (doxorubicin-cyclophosphamide) regimen specifically directed at the TNBC. One major consideration for this approach was the risk of cardiotoxicity

from trastuzumab and adriamycin. Administering trastuzumab first allows patient to receive a full complement of HER2-directed therapy prior to initiation of adriamycin for TNBC. Trastuzumab cardiotoxicity is largely reversible and non-progressive, while adriamycin toxicity is progressive, cumulative dose-dependent and irreversible [21, 22]. In the KEYNOTE 522 trial, neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab demonstrated a superior event-free survival than chemotherapy alone in TNBC [23]. Although immune checkpoint inhibitors have demonstrated success in the treatment of melanoma, lung cancer and microsatellite unstable colon cancer, the efficacy in breast cancer is somewhat limited [24]. This is likely due to the low expression of programmed cell death-ligand 1 (PD-L1) in breast cancer (10-30%), although this varies by tumor stage and subtype, with the highest expression in TNBC (30-60%) [25, 26]. Our patient had a pathological complete response (pCR) bilaterally. A pCR has been shown to be associated with prolonged event-free survival and overall survival in TNBC [27].

PMRT has been shown to reduce the rate of locoregional recurrence and improve long-term outcomes in selected patient populations [28, 29]. However, the choice of who receives adjuvant radiation treatment after mastectomy depends on the risk of disease recurrence. In patients who received neoadjuvant therapy, the presence of macroscopic nodal disease after treatment is a strong predictor of a higher rate of recurrence after mastectomy [30]. Such individuals in addition to those who have residual breast disease after mastectomy are candidates for PMRT. Although data from prospective studies on the benefit of adjuvant PMRT in patients who achieved a complete response to neoadjuvant chemotherapy are lacking, evidence from retrospective studies is conflicting. For instance, a retrospective study of PMRT in patients with stage III and IV disease found a lower 10-year rate of locoregional recurrence in those who achieved pCR with neoadjuvant chemotherapy compared to those who did not [31]. In contrast, another retrospective study of 3,000 women did not find a significant difference in recurrence rate with or without PMRT [32]. In that study, the predictors of recurrence were pre-treatment nodal involvement, tumor size > 5 cm, and the presence of residual disease after neoadjuvant chemotherapy. As such, an individualized approach to PMRT is warranted, which should take into consideration the risk of disease recurrence, radiation-related morbidities, and the patient's wishes.

Learning points

A heterogeneity of receptor status adds a layer of complexity to the therapeutic management of SBBC. Each of the tumors should be treated as a distinct entity and the therapeutic approach should be guided by the optimal chance of achieving a pCR in both tumors and improving long-term outcomes.

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None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Informed consent was obtained from the patient for publication of this case report and the accompanying images.

Author Contributions

AO, AS, SA, and RS conceived and designed the study. AO, SA, DJ, MG and AA collected and interpreted all relevant clinical and laboratory data. AO, AA and RS prepared the manuscript. All authors read and approved the final manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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