Case Report

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대한영상의학회지

Bilateral Triple Negative Invasive Ductal Breast Carcinoma in a *BRCA1* Mutation Carrier with Discrepant Pathologic Response to Neoadjuvant Chemotherapy

BRCA 유전자 변형 환자의 양측 삼중음성 유방암의 선행화학요법에 대한 상이한 반응

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Herein, we report a case of synchronous bilateral triple negative invasive ductal breast carcinoma in a patient with discrepant pathologic response to neoadjuvant chemotherapy. Right and left breast cancer stages at the initial diagnosis were T1cN0M0 and T4dN3aM0, respectively. The patient was identified as a *BRCA1* mutation carrier and treated with four cycles of adriamycin and cyclophosphamide, followed by four cycles of docetaxel. Bilateral breast cancer stages decreased with the first regimen. However, the bilateral breast cancers showed discrepant responses to chemotherapy with docetaxel. The right breast cancer showed a continuous tumor volume reduction while the left breast cancer showed marked progression. Finally, the tumor size was 0.3 cm and 12 cm in the right and left mastectomy specimens, respectively. As bilateral breast cancers of the same subtype may show discrepant responses to neoadjuvant chemotherapy, close monitoring and follow-up imaging are required to avoid delayed surgery.

Index terms Breast Neoplasm; Carcinoma; Neoadjuvant Therapy; Triple Negative Breast Neoplasm

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INTRODUCTION

Triple-negative breast cancer (TNBC) is defined by the lack of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (Her2) expression. It accounts for 12–17% of total invasive breast cancers and occurs at a higher rate in young women (< 50 years) than in older women (1). It has a poor prognosis due to the aggressive tumor biology and early recurrence after standard treatment (2). TNBC subtypes are associated with different clinical outcomes. It is most frequently observed in *BRCA1* mutation carriers; *BRCA1* loss-of-function mutations are associated with a high-histological grade and a basal-like gene expression profile (3).

We report a 38-year-old female patient with synchronous bilateral invasive ductal breast carcinomas (IDC) with the triple negative, basal-like subtype. The patient was identified as a *BRCA1* mutation carrier and exhibited discrepant pathologic responses after undergoing neoadjuvant chemotherapy (NAC).

CASE REPORT

A 38-year-old women visited our institution due to a palpable lump in the left breast for 10 days with erythema. She had an intellectual disability due to head trauma and a family history of breast cancer in two aunts. A *BRCA1* germline mutation was later identified.

Mammograms revealed global asymmetry involving nearly the entire left breast with diffuse skin and trabecular thickening and suspicious lymphadenopathy in the left axilla (Fig. 1A-a). Right mammogram revealed negative finding. Ultrasonograms (Fig. 1A-b) revealed a 6.9-cm irregular shaped, hypoechoic infiltrative mass involving the upper outer quadrant of the left breast with a diffuse edematous change of the skin. Suspicious lymphadenopathies were noted in the left axillary area along level I–III. Incidentally, a 1.7-cm-sized oval, well-circumscribed hypoechoic mass was detected in the upper outer quadrant of the right breast (Fig. 1A-c). No pathologic lymph node was detected in the right axillary area. Both tumors were examined by ultrasound-guided core needle biopsy and were diagnosed as triple negative, basal-like IDC. Metastasis in the left axillary lymph node was confirmed by fine needle aspiration cytology.

On dynamic contrast-enhanced MRI (DCE-MRI, Fig. 1A-d), axial T1 subtraction image indicated a 7.5-cm-sized non-mass enhancement showing a segmental distribution, heterogeneous enhancement involving the upper outer quadrant of the left breast. And 2.7-cm-sized, oval shaped, and circumscribed marginated mass with rim enhancement in the upper outer quadrant of the right breast on sagittal T1 subtraction image (Fig. 1A-e). Bilateral breast tumors showed initially fast and delayed washout kinetics, typical of malignancy. Staging work-up by whole body PET-CT showed no distant metastatic lesions. The clinical stages were identified as T4dN3aM0 for the left breast cancer and T1cN0M0 for the right cancer.

The patient underwent treatment with adriamycin and cyclophosphamide (AC) followed by docetaxel as follows: adriamycin (60 mg/m^2 intravenous injection) plus cyclophosphamide (600 mg/m2 intravenous injection) on day 1, every 21 days for 4 cycles, followed by docetaxel (75 mg/m2 intravenous injection) on day 1, every 21 days for 4 cycles. The volumes of bilater-

Fig. 1. Imaging and pathologic features of bilateral triple-negative breast cancer in a patient with *BRCA1* mutation.
A. The initial mammogram reveals global asymmetry involving the left breast with diffuse skin and trabecular thickening. Suspicious left axillary lymphadenopathy is also noted (arrow, a). Ultrasonography reveals an irregular, hypoechoic infiltrative mass, measuring 6.9 cm, involving the left breast (b) and a well-circumscribed oval hypoechoic mass, measuring 1.7 cm, in the right breast (c). The axial T1-weighted subtraction image reveals a segmental, heterogeneous non-mass enhancement lesion, measuring 7.5 cm, involving the left breast (d) and a well-circumscribed oval rim-enhancing mass, measuring 2.7 cm, involving the right breast (arrow, e).
B. Follow-up mammogram of left breast after the first and second NAC regimens reveal newly noted fine pleomorphic microcalcifications (arrow, a) with an increased extent of the skin and trabecular thickening. Follow-up ultrasonography after the second NAC regimen reveals regrowth of the left breast tumor with newly noted microcalcifications (arrows, b), and in contrast, decrease in the right breast tumor size (arrow, c). The follow-up axial T1-weighted subtraction image after the second NAC regimen reveals a markedly increased extent of the left breast tumor (d), and in contrast, a marked decrease in volume of the right breast tumor (arrow, e).
NAC = neoadjuvant chemotherapy

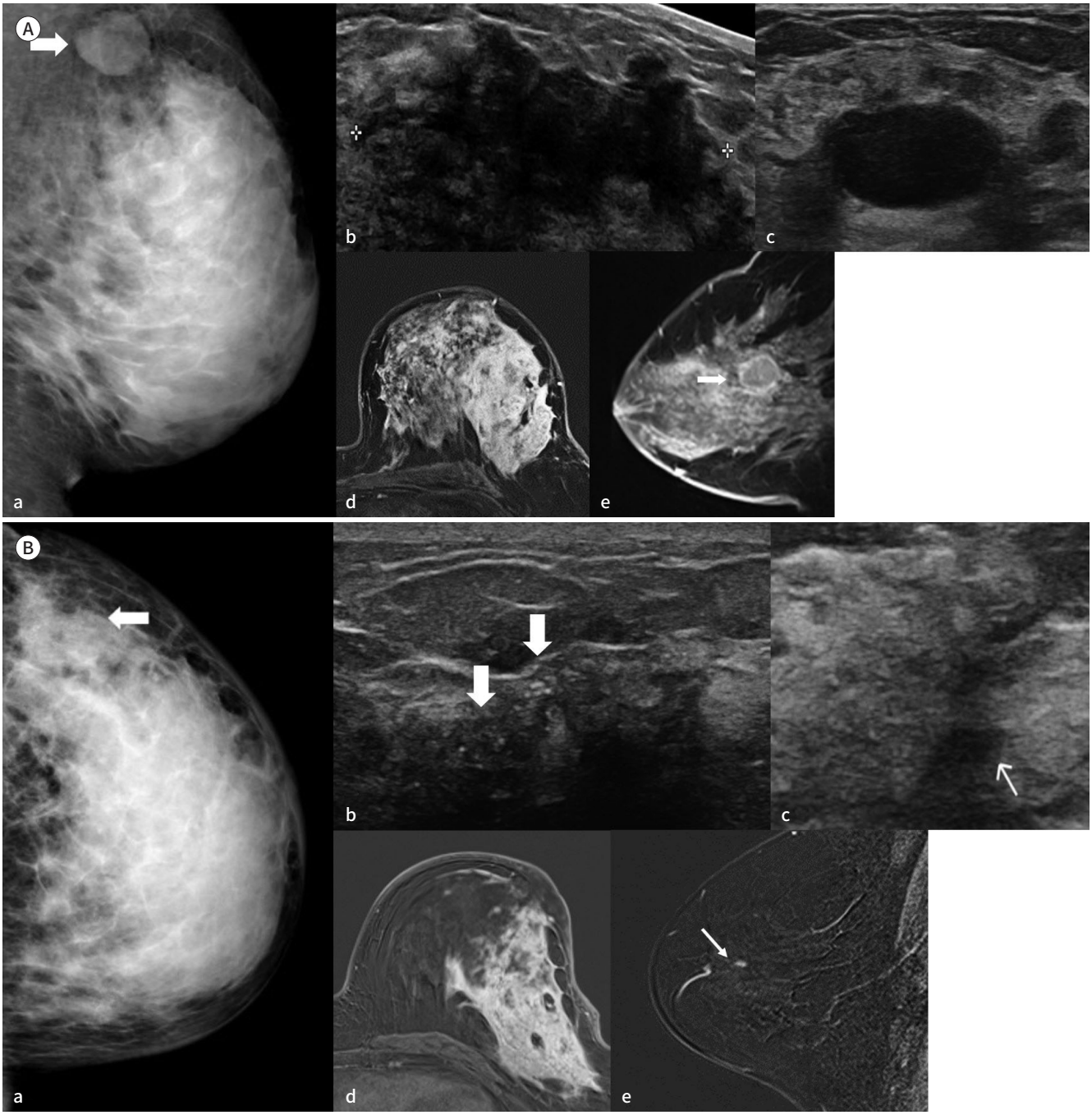
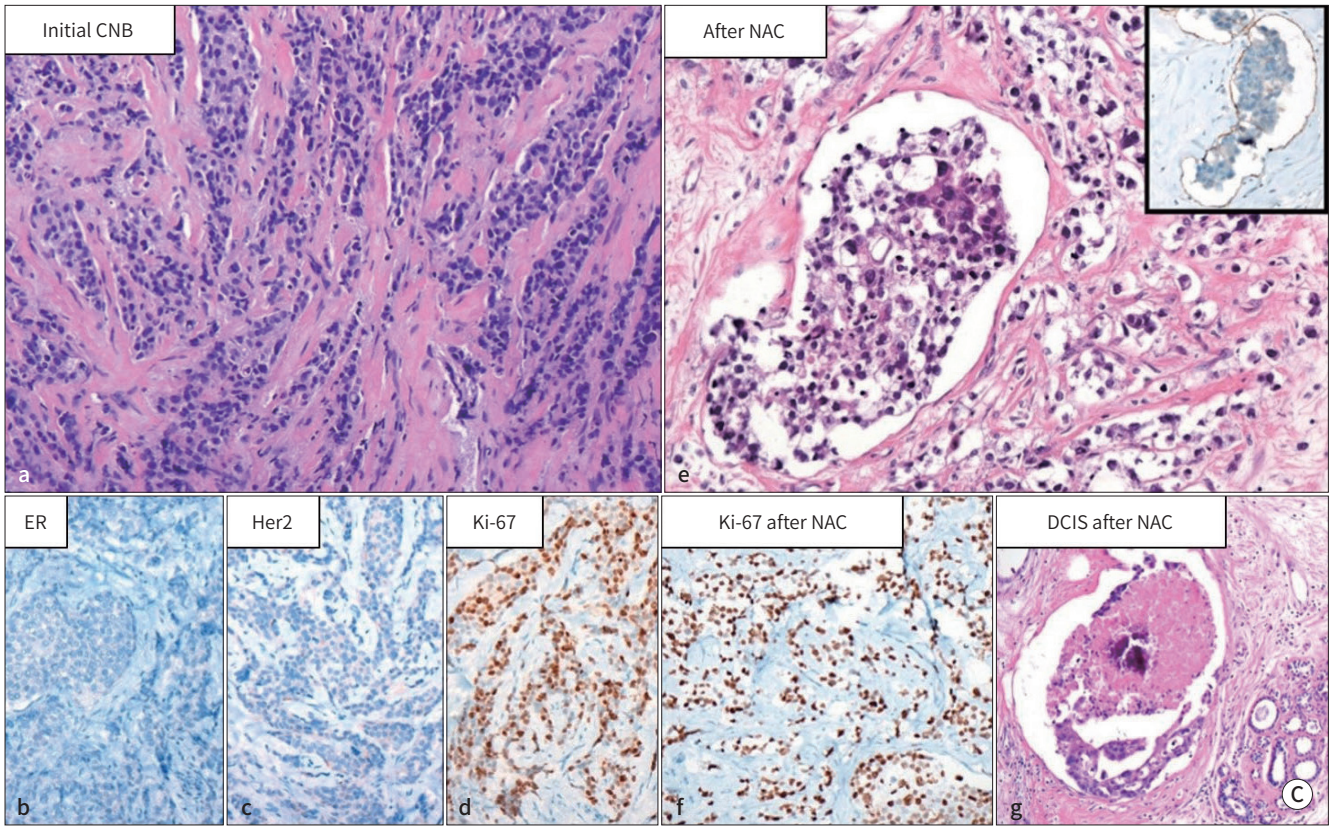


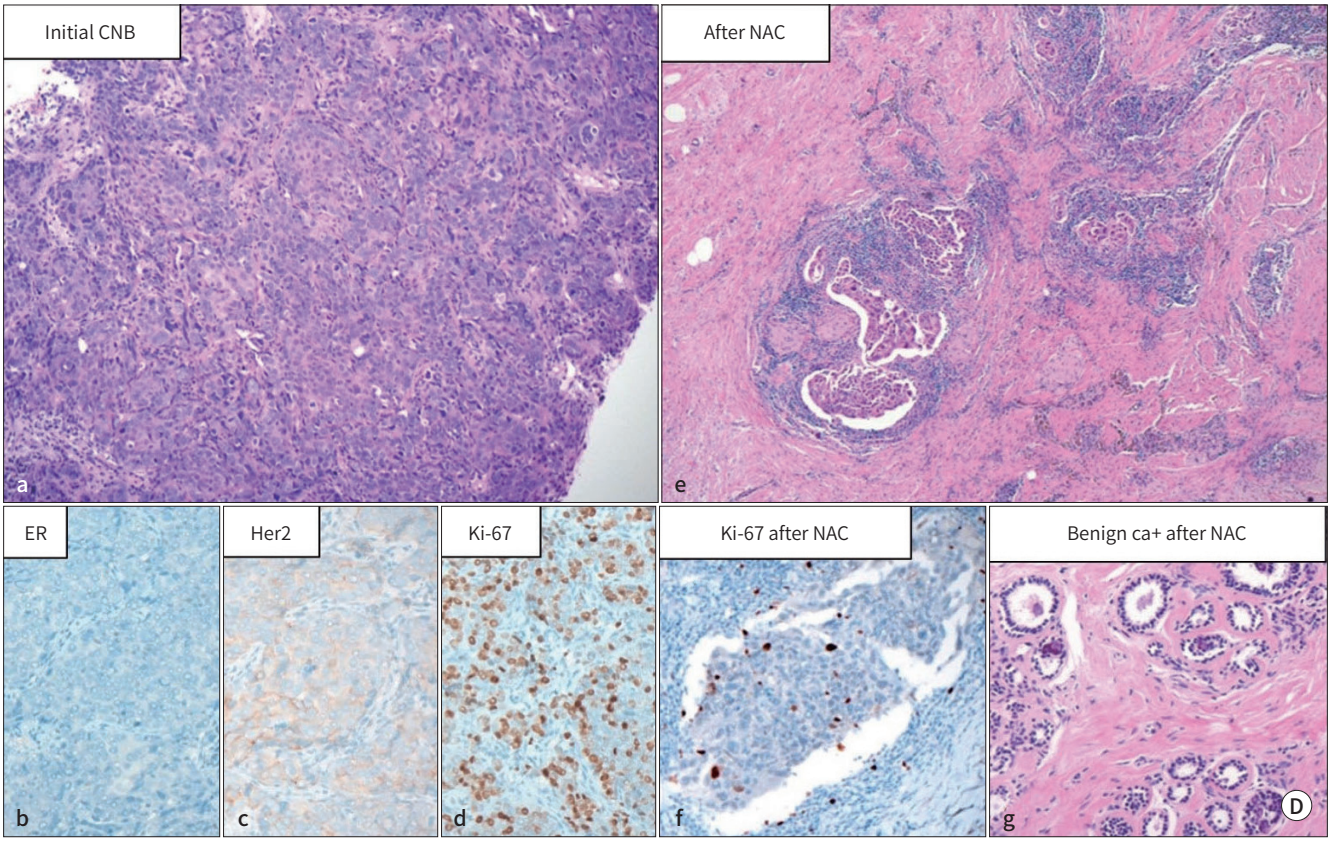
Fig. 1. Imaging and pathologic features of bilateral triple-negative breast cancer in a patient with *BRCA1* mutation.
C. Pathologic features obtained from a needle biopsy of the left breast reveals invasive ductal breast carcinoma with high cellularity (a, H&E stain, × 200). In the mastectomy specimen obtained after NAC (e, H&E stain, × 200), the tumor shows marked nuclear pleomorphism and minor loss in cellularity with extensive lymphovascular invasion (e, inset, D2-40 stain, × 200), and the triple-negative phenotype expression [ER/Her2-negative (b, ER stain, × 200 and c, Her2 stain, × 200) and high Ki-67 level (d, 78.20%, Ki-67 stain, × 200)] and Ki-67 level are consistently high (f, 84.41%, Ki-67 stain, × 200). Furthermore, the in-situ component with comedo necrosis and central calcifications are noted after NAC (g, H&E stain, ×200).
CNB = core needle biopsy, DCIS = ductal carcinoma in situ, ER = estrogen receptor, H&E = hematoxylin and eosin, Her2 = human epidermal growth factor receptor 2, NAC = neoadjuvant chemotherapy



al breast cancers and left metastatic axillary lymph nodes decreased remarkably in follow-up ultrasonograms after 4 cycles of AC.

However, bilateral breast cancers showed discrepant responses to docetaxel. After the completion of 3 cycles of docetaxel, the patient showed diffuse enlargement of the left breast with erythema. The left breast cancer regrew markedly during docetaxel treatment, while the size of right breast cancer decreased continuously during the full cycles of chemotherapy. Fine pleomorphic and amorphous microcalcifications were newly noted in the upper outer quadrant of the left breast with aggravation of the skin and trabecular thickening in a follow-up mammogram (Fig. 1B-a). Follow-up ultrasonogram revealed an increase of the irregular, infiltrative mass of the left breast with diffuse edematous change and skin thickening (Fig. 1B-b). On follow-up DCE-MRI, axial T1 subtraction image revealed an increase of diffuse heterogeneous nonmass enhancement in the left breast (Fig. 1B-d). The metastatic left axillary lymph node exhibited enlargement. The size of right breast cancer decreased (Fig. 1B-c, d, e).

Fig. 1. Imaging and pathologic features of bilateral triple-negative breast cancer in a patient with *BRCA1* mutation.
D. Pathologic features observed through a needle biopsy of the right breast cancer reveal invasive ductal breast carcinoma with high cellularity (a, H&E stain, × 100). In the mastectomy specimen obtained after NAC, the tumor shows marked loss of cellularity without lymphovascular invasion (e, H&E stain, × 100), and the triple-negative phenotype expression [ER/Her2-negative (b, ER stain, × 200 and c, Her2 stain, × 200) and high Ki-67 level (d, 68.59%, Ki-67 stain, × 200)] and Ki-67 level are low (f, 8.25%, Ki-67 stain, × 200). Furthermore, microcalcifications are identified in the benign duct after NAC (g, H&E stain, × 200).
CNB = core needle biopsy, ER = estrogen receptor, H&E = hematoxylin and eosin, Her2 = human epidermal growth factor receptor 2, NAC = neoadjuvant chemotherapy



The patient underwent a nipple-sparing mastectomy for the right breast cancer and modified radical mastectomy for the left-sided cancer and simultaneous reconstruction with a transverse rectus myocutaneous flap for both breasts. Both tumors showed a high level of Ki-67 [78% (left), 68% (right)] on initial core needle biopsy specimens (Fig. 1C-d, D-d). The left breast cancer still shows a high level of Ki-67 (84%) without a loss of tumor cellularity on mastectomy specimen pathology (Fig. 1C-d, f). The right breast cancer showed a low Ki-67 level (8%) with a marked loss of tumor cellularity (Fig. 1D-d, f). Bilateral axillary lymph node dissection revealed four metastases in the left axillary lymph nodes and no metastasis on the right side. The final postoperative stages were ypT3N2aM0 (left) and ypT1aN0M0 (right).

DISCUSSION

Bilateral breast cancer is rare, accounting for 2–5% of all breast malignancies, and bilateral TNBC is even rarer. Synchronous bilateral cancers are identified within 6 months of the primary tumor with an incidence of 0.2–2% (4). TNBC is associated with a high recurrence rate

and short survival. It has a heterogeneous and aggressive nature and an effective molecular targeted therapy has not been established.

We characterized a patient with synchronous bilateral breast cancers, both classified as the triple negative, basal-like subtype, showing discrepant pathologic responses during treatment with AC followed by docetaxel. Both breast cancers showed a good response to AC; however, only the right breast cancer exhibited a continued response to docetaxel, while the left breast cancer exhibited marked regrowth. This can be explained by three theories: heterogeneity of tumor biology in TNBC, subtype conversion during NAC, and change of Ki-67 level during NAC.

First, TNBC shows various responses to chemotherapy in the neoadjuvant setting owing to the heterogeneity in tumor biology (5). Lehmann et al. (6) classified TNBC into the following 7 subtypes based on gene expression microarray data: basal-like 1 (BL1), basal-like 2 (BL2), immunomodulatory, mesenchymal, mesenchymal stem-like, luminal androgen receptor, and unstable. A previous report (7) has suggested that TNBC subtype predicts the pathologic complete response (pCR) rate. In particular, the BL1 type shows the highest pCR rate and BL2 type shows the lowest pCR rate. Both types have high Ki-67 expression levels and show enrichment for proliferation genes but they differ in growth factor signaling. In our case, TNBC subtype analysis was not available.

Second, the molecular subtype of breast cancer may change after NAC (8). This conversion of subtypes may explain the discrepancy in the response to another chemotherapy agent after the favorable response to NAC. Subtype conversion may alter prognosis. In our case, subtype conversion was not revealed on specimen of mastectomy after NAC.

Third, in our case, bilateral TNBC was classified as basal-like. TNBC with high Ki-67 expression shows poorer survival than that of TNBC with low Ki-67, despite a higher pCR rate (9). TNBC with high Ki-67 shows rapid recurrence within 3 years. A change in Ki-67 or the postoperative level of Ki-67 has an important role in predicting the treatment response (6). One study (9) has shown that the post-therapy Ki-67 level is a significant independent predictor for relapse-free survival and overall survival. In our case, bilateral breast cancers showed high levels of Ki-67 before chemotherapy in initial core needle biopsy specimens. Interestingly, the Ki-67 level in the left breast cancer remained high in the surgical specimen after NAC, while the Ki-67 level in the right breast cancer decreased after treatment. The response to chemotherapy was partial in right breast and progression was observed in the left breast, as evidenced by the difference in pre-chemotherapy and post-chemotherapy Ki-67 levels. The change in Ki-67 level after chemotherapy could reflect a change in tumor biology.

TNBC is strongly associated with BRCA-1-related hereditary breast cancers. About 56–87% of *BRCA1* mutation carriers have TNBC. Additionally, 10.5% of patients diagnosed with breast cancer at or before the age of 50 years are *BRCA1* mutation carriers. Among patients with TNBC, *BRCA1* carriers have a more favorable pCR rate to neoadjuvant anthracycline-based regimens than that of non-carriers. There are no significant differences in recurrence-free survival and distant metastasis-free survival between *BRCA1* carriers and non-carriers (2).

Our patient had a *BRCA1* mutation. She showed a good response to the anthracycline-based regimen but a poor response to taxane. Platinum agents, like cisplatin and carboplatin, are DNA-damaging agents and may be beneficial in patients with TNBC (10). Platinum

agents, in addition to a standard NAC regimen, might be beneficial in our patient.

In conclusion, we present a patient with bilateral synchronous TNBC showing discrepant responses to NAC, i.e., progression after a good response in the left breast cancer and a favorable response throughout the treatment course on the right side. This case report highlights that breast cancers of the same subtype can exhibit diverse responses to NAC, intertumorally and even intratumorally. Careful clinical monitoring with imaging follow-up should be performed throughout the whole period of NAC to avoid delays in the appropriate surgical intervention.

Author Contributions

Conceptualization, S.G.W., P.Y.M., K.T.H., L.A.; investigation, S.G.W., P.H.Y.; supervision, P.Y.M., Y.H.K., K.T.H., L.A., P.H.Y.; writing—original draft, S.G.W., P.H.Y.; and writing—review & editing, P.Y.M., Y.H.K., K.T.H., L.A., L.Y.J., B.J.W., H.Y.J.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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저자들은 *BRCA* 유전자 변형 환자의 양측 삼중음성 유방암의 선행화학요법에 대한 상이한 반응에 대한 증례를 보고한다. 우측은 T1cN0M0, 좌측은 T4dN3aM0으로 각각 진단되었다. 환자는 Adriamycin, cyclophosphamide 항암요법 4차, docetaxel 4차를 시행 받았다. 양측 유방암은 첫 번째 항암요법 4차 이후에 부분 관해를 보였다. Docetaxel 항암요법 중 양측 유방암은 상이한 반응을 보였다. 우측 유방암은 지속적인 관해를 보였으나, 좌측 유방암은 진행되는 양상을 보였다. 전절제술 결과, 우측 유방암은 0.3 cm, 좌측은 12 cm로 측정되었다. 동일한 삼중음성 유방암에서도 항암요법에 대하여 좌우가 상이한 반응을 보일 수 있으므로, 면밀한 추적 관찰이 고려되어야 할 것이다.

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