

[CASE REPORT]

Bilateral Inflammatory Breast Cancer That Developed Two Years after Treatment for Triple-negative Breast Cancer

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Abstract:

A 66-year-old woman underwent partial mastectomy and a sentinel lymph node biopsy for left breast cancer; the pathological diagnosis was invasive ductal carcinoma (pT1aN0, pStage I, triple-negative subtype). Postoperative radiotherapy was performed. Two years later, she developed redness and induration at both breasts. The diagnosis was bilateral inflammatory breast cancer. After four cycles of dose-dense epirubicin and cyclophosphamide followed by 12 weekly paclitaxel cycles, bilateral total mastectomy and axillary lymph node dissection were performed. At the one-year follow-up after undergoing operation and radiotherapy, she remained alive without recurrence. Dose-dense treatment regimens may help patients achieve complete resection without short-term recurrence.

Key words: bilateral inflammatory breast cancer, dose-dense chemotherapy, triple-negative breast cancer

(Intern Med 61: 2387-2391, 2022)

(DOI: 10.2169/internalmedicine.7786-21)

Introduction

According to the Surveillance, Epidemiology, and End Results (SEER) database, <3% of annual breast cancer diagnoses are inflammatory breast cancer (IBC) (1). However, despite its low incidence rate, IBC reportedly causes 7-10% of breast cancer-associated deaths, and it is often difficult to treat such cases (1).

IBC is associated with tumor emboli in the dermal lymphatics, which are characterized by swelling, redness, heat without a fever, and peau d'orange, and is classified as T4d disease according to the TNM classification. Most women diagnosed with IBC have lymph node involvement, and 30% of them already have metastases at the time of the diagnosis (2). Cases of bilateral IBC are extremely rare.

We herein report a 68-year-old woman diagnosed with bilateral IBC without distant metastasis 2 years after having received early breast cancer treatment.

Case Report

A 66-year-old woman was diagnosed with breast cancer using mammography, ultrasonography, and magnetic resonance imaging (MRI) and underwent partial mastectomy and a sentinel lymph node biopsy for left breast cancer. She had no family history of breast or ovarian cancer. The cancer cells had infiltrated and proliferated in the fibrous stroma showing cord-like structures (Fig. 1A). The tumor was diagnosed as invasive ductal carcinoma, 4 mm in size, with lymphatic invasion 1+, and no vascular invasion. The tumor markers carcinoembryonic antigen (CEA) and cancer antigen (CA) 15-3 were within the normal limits. The nuclear grade was 3, and the tumor was negative for estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor type 2 (HER2) expression. The tumor margin was free of tumor cells.

Postoperative radiation therapy without chemotherapy was administered because the tumor size was <5 mm. She vis-

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Received: April 16, 2021; Accepted: November 23, 2021; Advance Publication by J-STAGE: January 13, 2022

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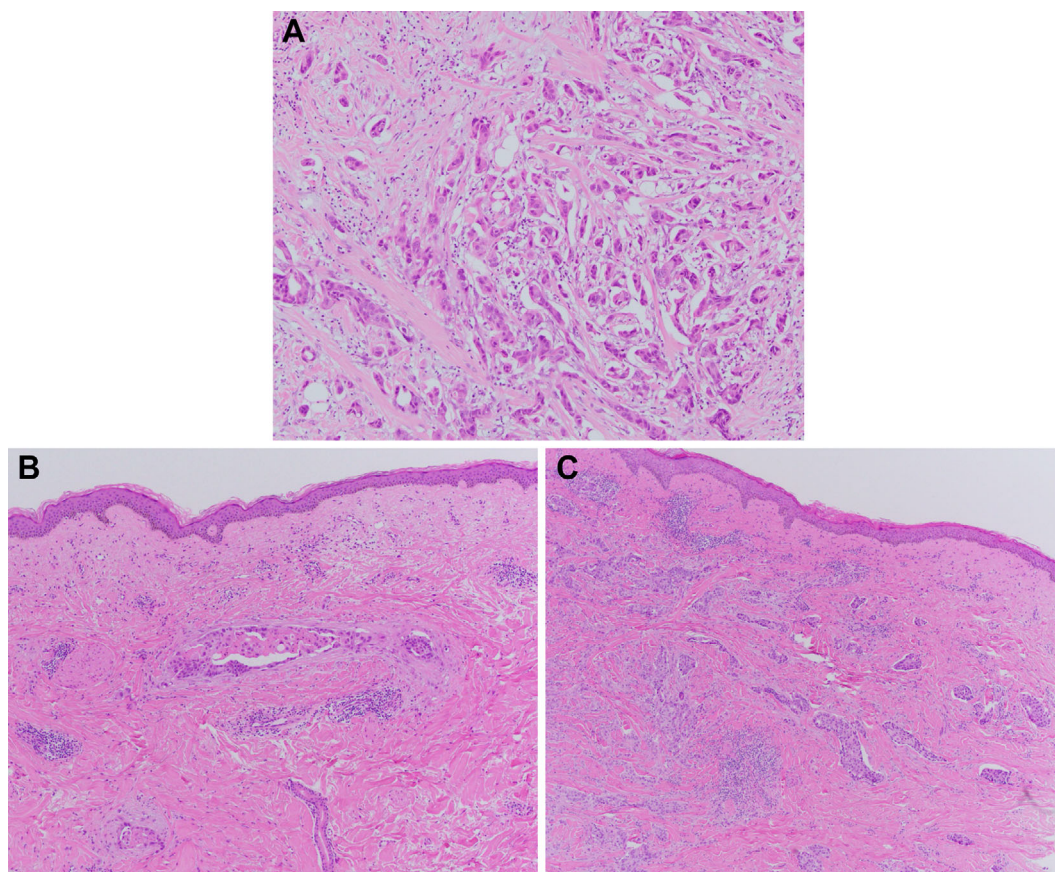


Figure 1. Hematoxylin and Eosin staining. **A:** Cancer cells infiltrated and proliferated in the fibrous stroma showing a cord-like structure. **B:** Skin biopsy specimen from the right breast. Tumor follicles are observed in the dermis layer. **C:** Skin biopsy specimen from the left breast. Numerous tumor embolisms are observed in the lymphatic vessels of the dermis layer.

ited our hospital every six months for follow-up examinations. Slight redness was observed in the left breast one month after radiation treatment, which was unchanged at her six-month, one-year, and one-year and six-month follow-up examinations.

After two years, the patient visited our hospital with a chief complaint of bilateral breast swelling and redness. She presented with erythema, skin edema, and skin tension in both breasts (Fig. 2A). Mammography and ultrasonography findings showed postoperative architectural distortion in the left breast, but no breast mass or lymphadenopathy was observed. Breast MRI findings showed no breast mass but did show hypervascular thickening of the skin and soft-tissue edema in both breasts (Fig. 2B). There were no enlarged axillary lymph nodes. A skin biopsy showed tumor nests in the right breast dermis layer and numerous tumor embolisms in the lymphatic vessels of the left breast dermis layer (Fig. 1B, C). Therefore, the patient was diagnosed with bilateral IBC.

The tumor was negative for ER, PgR, and HER2 expression. The tumor markers CEA and CA15-3 were within the normal limits. Positron emission tomography (PET)/computed tomography (CT) revealed a high fluorodeoxyglucose uptake in the area of non-mass contrast enhancement in the

left breast, mild uptake in the right breast, and no distant metastasis. After 4 cycles of dose-dense epirubicin and cyclophosphamide (EC), followed by 12 cycles of weekly paclitaxel, the erythema disappeared, and MRI showed that the skin thickening and edema had also disappeared. The PET/CT findings showed a decreased uptake in the area of non-mass contrast enhancement in the left breast. We judged that the patient's tumor was operable. Therefore, as complete resection was possible with anthracycline and taxane therapy, examinations for BRCA1/2 and microsatellite instability were not performed.

Bilateral total mastectomy and axillary lymph node dissection were performed. A pathological analysis revealed only three foci of residual lymph vessel invasion in the dermis layer of the left breast and no metastatic lymph nodes. The histopathological response to chemotherapy was Grade 2b.

To investigate the relationship between immune cells, we performed immunohistochemistry for CD3, CD11c, and CD56 markers in the resection specimens from the initial surgery and biopsy specimens from the recurrence (Fig. 3). CD3-positive cells, which reflect T-cells, and CD11c-positive cells, which reflect dendritic cells, were decreased in the biopsy specimens from the recurrence, while CD56-positive

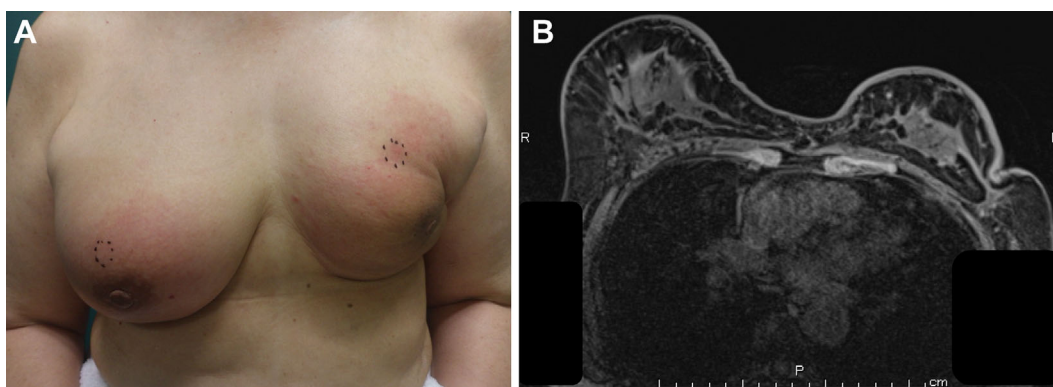


Figure 2. A: The patient presented with erythema, skin edema, and skin tension in both breasts. A skin biopsy was performed in the black-marked area. B: Magnetic resonance imaging findings of the patient showing hypervascular thickening of the skin and soft-tissue edema in both breasts.

cells, which reflect natural killer cells, showed no marked difference. As the patient had already received radiotherapy to the left breast, she also received radiotherapy to the right chest wall. At the one-year follow-up examination, the patient was alive without recurrence.

Discussion

Cases of bilateral IBC are extremely rare. We reported a case of bilateral IBC successfully treated with neoadjuvant dose-dense chemotherapy and bilateral total mastectomy.

A previous study conducted using the SEER database showed that patients with IBC had a poorer overall survival and breast cancer-specific survival rates than those with non-IBC (3). IBC is more often observed in patients with HER2-positive breast cancer and triple-negative breast cancer (TNBC) than non-IBC (3, 4). Among patients with non-metastatic IBC treated with neoadjuvant chemotherapy and surgery, identified from the National Cancer Database, the pathological complete response (pCR) rate was 19.1% in those with TNBC. Furthermore, such patients had a worse 5-year survival rate (44%) than those with other subtypes (4). In our case, a skin biopsy showed that both breast cancers were triple-negative; the tumors were successfully treated with induction dose-dense chemotherapy and bilateral total mastectomy, and pCR was nearly achieved.

Whether or not our case of bilateral IBC constituted recurrence remains unclear. The primary breast cancer was treated at an early stage (pT1aN0), and the skin on the front of the sternum between the bilateral breasts was not red-dened; thus, the redness was not continuous between the two breasts. Comparing primary breast cancer with bilateral IBC revealed that the cancer cells from both tumors were histopathologically similar and of the same subtype (i.e. TNBC). Furthermore, IBC developed a short time after primary breast cancer treatment and might have been a recurrence of the original tumor. There are currently no indicators or predictors for the development of secondary IBC. In contrast, other case studies have reported secondary IBCs wherein the primary breast tumor comprised late-stage can-

cer with lymph node metastasis (5, 6). The time to the secondary IBC onset has been reported to be short, consistent with that observed in our case (5, 6).

IBC is a disease with a poor prognosis; thus, the discovery of biological targets and the development of more effective therapeutics are crucial. Intrinsic characteristics and extrinsic features of the IBC tumor microenvironment have been reported to contribute to the aggressive nature of IBC (7). Regarding stemness, overexpression of the stem cell markers aldehyde dehydrogenase 1 and CD44 was reported to contribute to the alteration of IBC cells (8, 9). Pathways related to inflammation and immune modulation were also reported to play a role in IBC. The presence of tumor emboli obstructs dermal-lymphatic vessels, causing skin inflammation. Preclinical studies on IBC have revealed the importance of tumor-associated macrophages, which contribute to tumor progression and invasion (7). Healthy dendritic cells, natural killer cells, and T-cells are often suppressed in the IBC tumor microenvironment (10, 11). We observed a similar trend in our case. This result suggests that the suppression of anti-tumor immunity was one of the reasons for inflammatory breast cancer recurrence. TNBC is reportedly more responsive to chemotherapy if the tumor-infiltrating lymphocyte count is high (12). However, in this case, the patient was very responsive to chemotherapy, but the tumor-infiltrating lymphocyte count was not high. The tumor microenvironment interacted with IBC cells directly and/or indirectly, promoting stemness, resistance to chemotherapy and/or radiation therapy, and metastatic and invasion potential (7).

The incidence of bilateral breast cancer has been reported to be 4.4% (2.1% synchronous and 2.3% metachronous) (13). Compared to patients with unilateral breast cancer, those with bilateral breast cancer are younger and have smaller and earlier-stage tumors at the diagnosis. A few case reports of bilateral IBC have been published (14-16). Two of these cases involved HER2-positive breast cancer, and one involved TNBC. One case of bilateral IBC with bilateral carcinomatous pleurisy (14) and two cases of metachronous IBC found within one year after the first operation for uni-

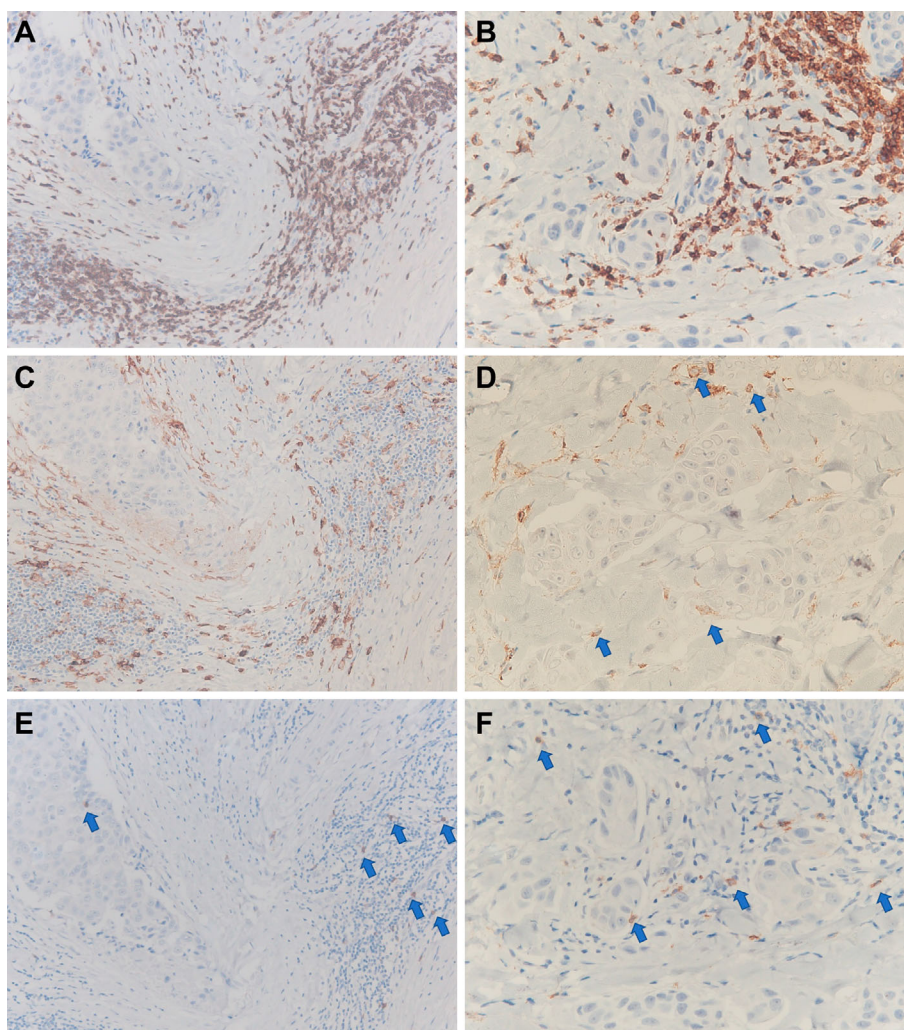


Figure 3. Immunohistochemical staining of A: resection specimen for CD3 marker, B: biopsy specimen for CD3 marker, C: resection specimen for CD11c marker, D: biopsy specimen for CD11c marker, E: resection specimen for CD56 marker, F: biopsy specimen for CD56 marker. CD3-positive cells, which reflect T cells, and CD11c-positive cells, which reflect dendritic cells, were decreased in biopsy specimens from the recurrence site, while CD56-positive cells, which reflect natural killer cells, showed no marked difference between them. Each immunohistochemistry-positive lymphocyte in D through E is indicated by a blue arrow.

lateral IBC have been reported (15, 16). The factors involved in the pathogenesis and progression of bilateral IBC remain unclear. In the present case, the patient underwent partial mastectomy of the left breast before being diagnosed with IBC, and the extent of the tumor of the skin of the left breast was greater than that of the skin of the right breast. We hypothesize that the tumor of the skin of the left breast might have spread to the skin of the right breast. Diagnosing bilateral breast cancer at an early stage is challenging, as it can be misdiagnosed as mastitis (16); however, the early diagnosis of bilateral IBC without distant metastases is important.

Given the rarity of IBC, few prospective randomized clinical trials have included patients with IBC. The current treatment sequence for IBC is systemic chemotherapy and anti-HER2 therapy for patients with HER2-positive cancer, followed by mastectomy and axillary lymph node dissection,

post-mastectomy radiotherapy to the chest wall and regional lymph nodes, and endocrine therapy if applicable (17). A large population-based study comparing multidisciplinary therapy for IBC and non-inflammatory, locally advanced breast cancer found that the application of multidisciplinary therapy improved the survival of patients with IBC (18). Nahleh et al. compared the combination of weekly nab-paclitaxel and bevacizumab followed by dose-dense doxorubicin and cyclophosphamide (AC) to nab-paclitaxel alone followed or preceded by AC as neoadjuvant treatment for HER2-negative locally advanced breast cancer or IBC (19). Among the 24 patients with IBC, the pCR rate was higher in the patients treated with the bevacizumab regimen than in those treated without bevacizumab (30% vs. 14%). However, the difference was not significant in this small patient subset. Bevacizumab may be a useful option for the treatment of IBC. Another study compared intense dose-dense sequen-

tial chemotherapy to conventionally-dosed chemotherapy among women with high-risk primary breast cancer, including a subgroup analysis of patients with IBC (20). Among 101 patients with IBC, no difference was observed in the pCR rate between intense dose-dense sequential chemotherapy (12%) and conventionally-dosed chemotherapy (10%); the disease-free survival and overall survival rates were similar for both treatment arms. Although the efficacy of dose-dense treatment in IBC is not clear, increasing the dose intensity of adjuvant chemotherapy moderately reduces the 10-year risk of recurrence and breast cancer-related mortality for most patients with non-IBC (21). In our case, the patient received dose-dense EC followed by weekly paclitaxel and was able to undergo complete resection and nearly achieve pCR.

In conclusion, a patient with bilateral IBC was successfully treated with induction dose-dense chemotherapy, underwent surgery, and nearly achieved pCR. Although it is difficult to treat IBC, an early diagnosis and multidisciplinary treatment based on the subtype and current treatment recommendations for non-IBC may improve the prognosis of IBC patients.

This case report was approved by the Nagasaki University Hospital Clinical Research Ethical Committee. This study was conducted in accordance with the Declaration of Helsinki (1964).

Written informed consent for the publication of this case report and accompanying images was obtained from the patient. A copy of the written consent form is available for review by the Editor-in-Chief of this journal on request.

The authors state that they have no Conflict of Interest (COI).

Yuta Kawaguchi and Sayaka Kuba contributed equally to this work.

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