CASE REPORT

Challenges of treating incidental synchronous bilateral breast cancer with differing tumour biology

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SUMMARY

A 59-year-old woman with right breast mass was diagnosed with invasive ductal carcinoma (IDC). Workup consisted of bilateral diagnostic mammogram and ultrasound (US); both showed a right breast mass with normal left breast. Core biopsy showed IDC with estrogen receptor negative (ER–)/progesterone receptor negative (PR–) and HER2/neu positive receptor status. The patient underwent carboplatin-based chemotherapy with Herceptin. The mass completely resolved. The patient desired to proceed with bilateral total mastectomy with right sentinel lymph node biopsy (SLNB). Pathology showed complete resolution of the right-sided breast mass without malignancy in right SLN. Incidentally, IDC was found in the left breast specimen, which was ER+/PR+ and HER 2/neu negative. Tumour board consensus was to obtain a left axilla US with MRI in 6 months if the US was unremarkable. Biologically different synchronous bilateral breast cancer poses a difficult clinical challenge for management due to differing responses to treatment. Use of MRI may be a diagnostic option in women who choose contralateral prophylactic mastectomy.

BACKGROUND

Synchronous bilateral breast cancer (SBBC) can be defined as contralateral breast cancer diagnosed within 1 year of previous breast cancer.¹ SBBC is a rare entity occurring 0.2–3.2% in many cases but has been reported to be as high as 12%.^{2–3} Little is known about the rates of SBBC with different hormonal status such as HER2, estrogen receptor (ER) and progesterone receptor (PR), but it is even more infrequent to have bilateral breast cancer with different biological markers, as bilateral tumour biology concordance rates have been found to be between 80% and 100%.^{2–4–5} Coradini *et al*⁶ had suggested that similar clinical management should be given for bilateral breast cancer and unilateral breast cancer based on these particular concordance rates. However, our patient's tumour responded differently to neoadjuvant chemotherapy in each breast. This case provides unique aspects of synchronous breast cancer with differing tumour biology and how certain risk factors of breast cancer may indicate the use of MRI in the workup of SBBC.

CASE PRESENTATION

Our patient is a 59-year-old woman who presented to the clinic after a workup for right-sided mastodynia. An initial mammogram showed a hypoechoic solid-appearing mass at the 10-o'clock

position which was 2.2×2×1.7 cm with irregular lobulated borders concerning for malignancy in her right breast.

Family history was negative for breast cancer, but positive for prostate cancer on the paternal side. On physical examination, a 2 cm mass at the 10-o'clock position 1 cm from the areolar edge was palpable in the right breast with moderate dimpling over the area. The area was tender to palpation. There was minimal redness and oedema in the right hand and arm but was tender to palpation. There was no cervical, supraclavicular or axillary lymphadenopathy.

Bilateral digital mammogram showed a mass in the right breast 11 o'clock in the anterior 1/3 and was 3 cm in diameter. There were no suspicious findings in left breast. Ultrasound (US) of the right breast showed a hypoechoic mass 3.3×2.9×3.2 cm at the 11-o'clock position, 3 cm from the nipple. At the 2-o'clock position, 4 cm from the nipple, US of the right breast showed a circumscribed hypoechoic 0.3×0.3×0.3 cm in mass. Biopsy of the right axillary lymph node showed no malignancy. Biopsy of the right breast at the 11-o'clock position, 3 cm from nipple indicated grade 3 invasive ductal carcinoma (IDC). Biopsy of right breast at 2 o'clock, 4 cm from nipple showed fibrocystic changes with chronic inflammation and ductal ectasia without evidence of malignancy. Receptor report indicated that the tissue was hormone receptor (ER and PR) negative and HER2/neu positive with a high level (67%) of proliferation indicated by Ki-67 marker (table 1). After completion of neoadjuvant chemotherapy, bilateral digital mammogram showed complete resolution of the right breast mass and the left breast was normal.

TREATMENT

After the completion of neoadjuvant chemotherapy (carboplatin-based chemotherapy with Herceptin), bilateral digital mammogram showed complete resolution of the right breast mass and the left breast was normal. Subsequent bilateral total mastectomy, right axillary sentinel lymph node biopsy (SLNB) and immediate bilateral breast reconstruction were performed at patient's request. Pathology showed no evidence of residual tumour in the right breast specimen. The right axillary SLNB showed no malignancy. To our surprise, the specimen from the left breast indicated the presence of grade 2 IDC with lobular features and low-grade focal ductal carcinoma in situ. Receptor report of the left breast indicated ER+/PR+ and HER2/neu negative with low Ki-67, indicating opposite biology to that

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Table 1 Tumour characteristics pre-NAC and post-NAC

Characteristics	Right breast	
	Pre-NAC	Post-NAC
Tumour size (mm)	30	Resolved
ER positivity	0%	–
PR positivity	0%	–
HER2	3+	–
Ki-67 activity	67%	–
Tumour grade (Nottingham)	3	–

ER, estrogen receptor; NAC, neoadjuvant chemotherapy; PR, progesterone receptor.

originally present in the right breast (table 2). Using the Memorial Sloan Kettering Cancer Center SLN Metastasis Nomogram, we found the probability of spread to lymph nodes in this patient was only 8%, so we decided SLNB was unnecessary. Plans were made to begin hormonal treatment as well as left axillary US and MRI in 6 months if any abnormalities were not found.

DISCUSSION

Therapeutic approaches to breast cancer have significantly improved over the past few decades, facilitating better screening and prognostic abilities. Additionally, these specific treatment plans have decreased mortality and improved outcomes of breast cancer.^{7 8} A hot topic of current research is the use of biological markers such as HER2, ERs and PRs, changing the approach to breast cancer from a singular disease to a multifaceted one with a spectrum of clinical, prognostic and therapeutic features. When breast cancer is detected bilaterally, the contralateral tumour must be determined to be either polyclonal or monoclonal in origin, as this will alter the staging and therapeutic approach of the cancer.^{9 10} Reports have shown polyclonal origin in bilateral breast cancer with different biological markers.^{8 11} The receptor status of breast cancers is used to help differentiate polyclonal origin and also to better assess the therapeutic strategy used during treatment.^{9 12 13} This has allowed for the emergence of a new class of drugs selective for tumour cells, such as selective ER modulators, like tamoxifen or medications which induce receptor degradation, such as fulvestrant.

Hormonal treatment plans can be efficacious, but many factors may lower the effectiveness of the medications. For example, tumours which have a mixed receptor status ER–/PR+ or ER+/PR– or those that have an overexpression of HER2 have shown decreased response to treatment due to the mixed

receptor status and intrinsic resistance to hormonal therapy, respectively.^{14 15} Many researchers have shown that even conventional hormone therapy may be hindered by HER2+ tumours, though many studies have shown that treatment with trastuzumab in combination with or after chemotherapy dramatically improves patients with HER2+ survivability.^{16–20}

The use of MRI has been a debated issue in the screening and treatment of cancer. The use of MRI for screening purposes in some cases has been shown to have deleterious effects such as increased incidence of bilateral mastectomies, removal of benign lesions and increased costs of clinical workups.²¹ Nonetheless, MRI has value in detecting neoplasms that are not palpable or seen using traditional mammography.²² This practice could reduce the numbers of missed tumours during clinical workup, and it could prevent the recurrence rate after surgery. MRI screening should always be followed with MRI-guided biopsies to reduce the risks of surgical removal of benign lesions.^{23 24} Misra *et al*²² expressed certain MRI breast screening recommendations including patients having BRCA mutation, BRCA mutation in first-degree relative, lifetime breast cancer risk of 20–25% or radiation to the chest between 10 and 30 years. However, there are no current universally accepted guidelines for the use of MRI in breast cancer screening for patients with a lifetime risk of <15%.^{22 24 25} Without family history or increased risk of breast cancer, our patient had only a 4.3% lifetime risk. Therefore, no MRI screening guidelines exist for our patient. This case illustrates the need for further research to develop guidelines for the use of MRI screening before surgical treatment in certain breast cancer populations.

Hayashi *et al* presented a similar patient also without family history of breast cancer with SBBC with two different biological markers. The patient presented with masses in each breast that were easily diagnosed in clinic. MRI and core needle biopsies were used to diagnose the patient with IDC with the right breast being ER+/PR+ and HER2 negative, while the left breast was ER–/PR– and HER2+. The patient received neoadjuvant chemotherapy, resulting in left mass reduction without any change in the right mass. Bilateral modified radical mastectomies were performed with axillary lymph node dissection and showed no lymph node involvement on the left, but 2 lymph nodes of 12 on the right side were affected. The patient was given adjuvant chemotherapy and had no recurrence at time of death.²⁶ Hayashi *et al*'s²⁶ case differs from ours in that the patient presented with known bilateral breast cancer and workup included MRI prior to surgery. This case further exhibits the use of neoadjuvant chemotherapy and MRI as a valuable diagnostic tool in patient-directed surgical procedures.

Table 2 Tumour characteristics preoperation and postoperation

Characteristics	Right breast		Left breast	
	Preop	Postop	Preop	Postop
Tumour size (mm)	30	–	–	14
ER positivity	0%	–	–	79%
PR positivity	0%	–	–	40%
HER2	3+	–	–	0+
Ki-67 activity	67%	–	–	1%
Tumour grade (Nottingham)	3	–	–	2

ER, estrogen receptor; Postop, postoperation; PR, progesterone receptor; Preop, preoperation.

Learning points

- ▶ Biologically different synchronous bilateral breast cancer poses a difficult clinical challenge for management due to differing responses to treatment.
- ▶ Incidentally found breast cancers further complicate management, especially related to staging.
- ▶ Use of MRI may be a diagnostic option in women who choose contralateral prophylactic mastectomy to assess the breast and axilla prior to surgery.²²
- ▶ Management options should be individualised to each patient depending on tumour biology and patient preference.

Contributors JWE and MP equally contributed to the article as first authors and should be considered as co-first authors for this article.

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