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Contents

Weekly Volume 10 Number 1 January 7, 2022

MINIREVIEWS

ORIGINAL ARTICLE

Case Control Study

Retrospective Study

World Journal of Clinical Cases

Weekly Volume 10 Number 1 January 7, 2022

Contents

World Journal of Clinical Cases

Weekly Volume 10 Number 1 January 7, 2022

Contents

CASE REPORT

World Journal of Clinical Cases

Weekly Volume 10 Number 1 January 7, 2022

Contents

World Journal of Clinical Cases

Weekly Volume 10 Number 1 January 7, 2022

Contents

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CASE REPORT

HER2 changes to positive after neoadjuvant chemotherapy in breast cancer: A case report and literature review

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Abstract

BACKGROUND

As the most common cancer in women, breast cancer is the leading cause of death. Most patients are initially diagnosed as stage I-III. Among those without distant metastases, 64% are local tumors and 27% are regional tumors. Patients in stage IIA-IIIC and those who meet the breast-conserving criterion with the exception of tumor size can consider neoadjuvant chemotherapy (NACT). It is worth noting that the status of tumor cell biomarkers is not consistently static. Endocrine-related estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) encoded by erythroblastic leukemia viral oncogene homolog 2 gene can all alter from positive to negative or *vice versa*, especially in luminal B subtype after NACT. In addition, determination of HER2 status currently mainly relies on immunohistochemistry (IHC) and fluorescence *in situ* hybridization (FISH), but FISH is commonly used when the result of IHC is uncertain. HER2 is regarded as negative when the IHC result is 0/1+ without the addition of FISH. To the best of our knowledge, this is the first report of a case harboring HER2 status transformation and IHC1+ with positive amplification by FISH after NACT.

CASE SUMMARY

A 49-year-old woman discovered a mass in her right breast and underwent diagnostic workup. Biopsies of the right breast lesion and axillary lymph nodes were obtained. The results pointed to invasive ductal carcinoma with the IHC result for ER (80%), PR (60%), Ki-67 (20%) and ambiguous expression of HER2 (IHC 2+) with negative amplification by FISH (HER2/CEP17 ratio of 1.13). She underwent surgery after NACT. The pathological findings of the surgically resected sample supported invasive ductal carcinoma with the tumor measuring 1.1 cm × 0.8 cm × 0.5 cm and had spread to one of fifteen dissected lymph nodes. Retesting of the specimen showed that the tumor was positive for ER (2+, 85%) and PR (2+, 10%) but negative for HER2 by IHC (1+). Also Ki-67 had dropped to

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2%. The patient was regularly monitored every 3 mo without evidence of recurrence.

CONCLUSION
Biomarker status should be reassessed after NACT especially in luminal subtypes.

Key Words: Carcinoma; Ductal; Breast; Neoadjuvant therapy; Biomarkers, Tumor; Case report

Core Tip: The precise molecular subtype of breast cancer is helpful in order to develop individualized strategies for systemic treatment; thus, more attention should be paid to the changes in tumor biomarkers before and after surgery. The conversion probability is fairly low, especially regarding HER2 status; however, it directly affects the formulation of adjuvant treatment. Importantly, anti-HER2 therapy has led to a landmark change in patients with HER2 positive breast cancer.

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INTRODUCTION

As the most common cancer in women, breast cancer is the leading cause of death. Most patients are initially diagnosed as stage I-III. Among those without distant metastases, 64% are local tumors and 27% are regional tumors[1]. Patients in stage IIA-IIIC and those who meet the breast-conserving criterion with the exception of tumor size can consider neoadjuvant chemotherapy (NACT).

It is worth noting that the status of tumor cell biomarkers is not consistently static. Endocrine-related estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) encoded by erythroblastic leukemia viral oncogene homolog 2 gene can all alter from positive to negative or *vice versa*, especially in luminal B subtype after NACT[2]. In addition, determination of HER2 status currently mainly relies on immunohistochemistry (IHC) and fluorescence *in situ* hybridization (FISH), but FISH is commonly used when the result of IHC is uncertain. HER2 is regarded as negative when the IHC result is 0/1+ without the addition of FISH. To the best of our knowledge, this is the first report of a case harboring HER2 status transformation and IHC1+ with positive amplification by FISH after NACT.

CASE PRESENTATION

Chief complaints

A mass was discovered in the right breast of a 49-year-old woman during a routine examination.

History of present illness

The patient discovered a mass in her right breast and underwent diagnostic workup, including a mammogram which showed a nodule and ultrasound that revealed a mass measuring 2.73 cm × 2.13 cm × 2.57 cm, as well as several enlarged axillary lymph nodes with the largest measuring 1.2 cm × 0.9 cm. Biopsies of the right breast lesion and axillary lymph nodes were obtained. The results pointed to invasive ductal carcinoma with the IHC result for ER (80%), PR (60%), Ki-67 (20%) and ambiguous expression of HER2 (IHC 2+) with negative amplification by FISH (HER2/CEP17 ratio of 1.13) (Figure 1). Computed tomography (CT) of the chest, abdomen, and pelvis

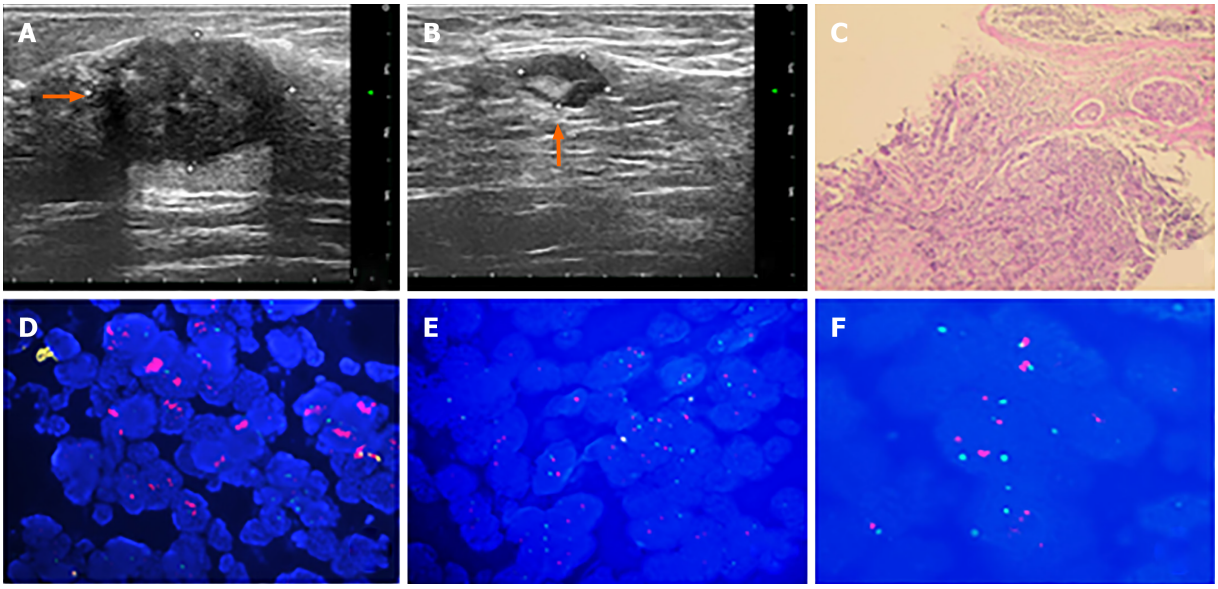

Figure 1 Malignant tumor in the right breast when initially diagnosed. A: Ultrasound showing the mass measuring 2.73 cm × 2.13 cm × 2.57 cm in the 10-o'clock position of the right breast; B: Ultrasound showing the largest right axillary lymph node measuring 1.2 cm × 0.9 cm; C: Hematoxylin-eosin staining indicates an invasive ductal carcinoma (×100); D: Positive control of fluorescence *in situ* hybridization (FISH); E: Negative control of FISH; F: FISH result of the biopsy specimen.

showed no sign of metastatic foci and emission computed tomography (ECT) showed negative results. Accordingly, the patient was classified as stage IIB. The patient received NACT with epirubicin and cyclophosphamide for 4 cycles followed by docetaxel every 3 wk for 4 cycles and she was also supported by long-acting injections to improve the quantity of leukocytes. As a result, the lesion significantly reduced in size and the patient achieved a partial remission according to the RECIST1.1 criteria, and ultrasound showed that the focus had reduced to 0.8 cm × 0.7 cm and no obvious echo of enlarged lymph nodes in the axilla. The patient subsequently underwent lumpectomy of the right breast tumor. Pathological findings of the surgically resected sample supported invasive ductal carcinoma with the tumor measuring 1.1 cm × 0.8 cm × 0.5 cm and had spread to one of fifteen dissected lymph nodes. Retesting of the specimen showed that the tumor was positive for ER (2+, 85%) and PR (2+, 10%) but negative for HER2 by IHC (1+). Also Ki-67 had dropped to 2%. However, HER2 amplified by FISH showed a HER2/CEP17 ratio of 2.46 (Figure 2). The patient completed radiotherapy after surgery. Currently, she is undergoing endocrine treatment with tamoxifen and dual targeted therapy with trastuzumab and pertuzumab. Follow-up which included breast ultrasound, abdominal ultrasound and chest CT were regularly performed every 3 mo without evidence of recurrence.

History of past illness

The patient was healthy without a history of chronic disease or other breast diseases.

Physical examination

A movable mass measuring approximately 2.7 cm × 2.0 cm × 2.5 cm in the right breast and an ipsilateral enlarged axillary lymph node measuring 1.2 cm × 1.0 cm were identified. There was no evidence of disease in the contralateral breast and axillary lymph node.

Laboratory examinations

All laboratory examinations were in the normal range.

Imaging examinations

A mammogram showed a nodule and ultrasound revealed a mass measuring 2.73 cm × 2.13 cm × 2.57 cm, as well as several enlarged axillary lymph nodes with the largest measuring 1.2 cm × 0.9 cm. CT of the chest, abdomen, and pelvis showed no sign of metastatic foci and ECT showed negative results.

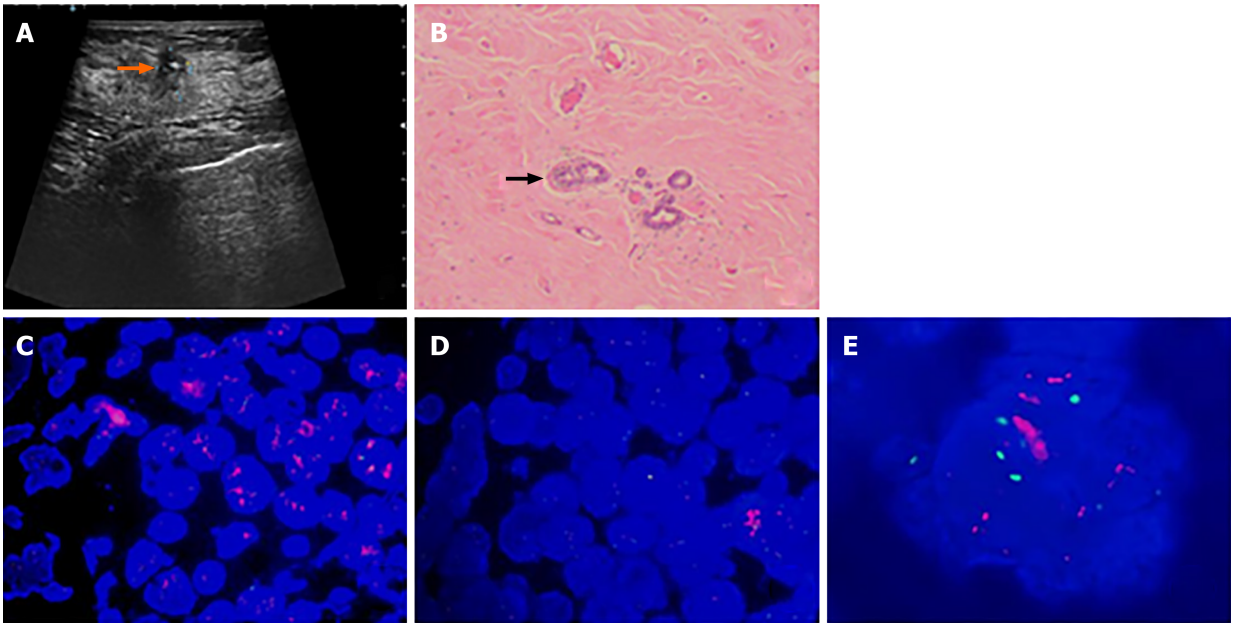

Figure 2 Ultrasound result after neoadjuvant chemotherapy and histopathological and fluorescence *in situ* hybridization findings of the resected tumor. A: Ultrasound demonstrating the tumor measuring 0.8 cm × 0.7 cm after neoadjuvant chemotherapy (arrow); B: Histopathological finding showing the tumor cells tubular arrangement and the development of invasion (H&E staining, × 50) (arrow); C: Positive control of fluorescence in situ hybridization (FISH); D: Negative control of FISH; E: FISH result of the surgically resected tumor.

FINAL DIAGNOSIS

The patient was diagnosed with HER2-positive and hormone receptor-positive invasive ductal carcinoma.

TREATMENT

Epirubicin and cyclophosphamide for 4 cycles followed by docetaxel every 3 wk for 4 cycles and then surgery.

OUTCOME AND FOLLOW-UP

Follow-up including breast ultrasound, abdominal ultrasound and chest CT were regularly performed every 3 mo without evidence of recurrence.

DISCUSSION

It has been several years since NACT was recommended for invasive breast cancer patients by the National Comprehensive Cancer Network guidelines. Compared with postoperative adjuvant chemotherapy, NACT not only has the advantage of downgrading the clinical stage to make lumpectomy available for some patients, it also helps to eliminate micro-metastases. In addition, NACT also provides a novel, rapid and low-cost way to evaluate the effectiveness of systemic treatment. In contrast, observation of the efficacy of postoperative adjuvant therapy requires more time, energy and labor. With the popularization of NACT in locally advanced breast cancer, we have compiled the results over the past ten years (Table 1) and found that, compared with the biomarkers in samples obtained by fine needle aspiration or hollow needle biopsy before surgery, postoperative tissue receptors can occasionally produce completely opposite conclusions. The average conversion rate of ER is 7.3%, PR is 15.0% while HER2 is only 6.8% which is consistent with previous data, that is, the status of PR is most inclined to change while HER2 is relatively more stable[3].

Table 1 Status of biomarkers before neoadjuvant chemotherapy and after neoadjuvant chemotherapy

Ref.	Year	Total patients (*n*)	Frequency of ER alternation, *n* (%)				Frequency of PR alternation, *n* (%)				Frequency of Her-2 alternation, *n* (%)				Frequency of Ki-67 alternation, *n* (%)			
			P × P	P × N	N × P	N × N	P × P	P × N	N × P	N × N	P × P	P × N	N × P	N × N	P × P	P × N	N × P	N × N
Li *et al*[12]	2019	565	229 (40.5)	48 (8.5)	53 (9.4)	235 (41.6)	191 (33.8)	76 (13.5)	53 (9.4)	245 (43.4)	439 (39.7)	117 (10.6)	13 (1.2)	536 (48.5)	NA	NA	NA	NA
Peng *et al*[16]	2019	112	56 (50.0)	18 (16.1)	7 (6.2)	31 (27.7)	32 (28.6)	22 (19.6)	10 (9.0)	48 (42.9)	30 (27.8)	17 (15.2)	6 (5.3)	59 (52.7)	43 (38.4)	42 (37.5)	3 (2.7)	24 (21.4)
Ahn *et al*[2]	2018	442	305 (69.0)	10 (2.3)	8 (1.8)	119 (26.9)	201 (45.5)	65 (14.7)	15 (3.4)	161 (36.4)	109 (24.7)	4 (0.9)	11 (2.5)	318 (71.9)	113 (25.6)	151 (34.2)	12 (2.7)	166 (37.6)
Yang *et al*[17]	2018	231	173 (74.9)	NA	NA	3 (1.3)	158 (68.4)	NA	NA	18 (7.8)	26 (11.3)	NA	NA	150 (64.9)	128 (55.4)	NA	NA	48 (20.8)
De La Cruz *et al*[18]	2018	54	19 (35.2)	2 (3.7)	1 (1.9)	9 (16.7)	NA	NA	NA	NA	5 (9.6)	1 (1.9)	24 (44.4)	NA	NA	NA	NA	NA
Yoshida *et al*[19]	2017	588	NA	NA	NA	NA	NA	NA	NA	NA	66 (11.2)	33 (5.6)	11 (1.9)	478 (81.3)	NA	NA	NA	NA
Xian *et al*[20]	2017	77	NA	NA	2 (3.0)	NA	NA	NA	2 (3.0)	NA	NA	NA	1 (1.0)	NA	NA	NA	NA	NA
Niikura *et al*[21]	2016	16580/16515/16271	10474 (63.2)	499 (3.0)	519 (3.1)	5088 (30.7)	6735 (40.8)	1545 (9.4)	766 (4.6)	7469 (45.9)	2210 (13.6)	601 (3.7)	340 (2.1)	9607 (59.0)	NA	NA	NA	NA
Gahlaut *et al*[22]	2016	133	NA	7 (5.3)	9 (6.8)	NA	NA	13 (9.8)	5 (3.8)	NA	NA	5 (3.8)	2 (1.5)	NA	NA	NA	NA	NA
Lim *et al*[23]	2016	290	189 (65.2)	23 (7.9)	29 (10.0)	49 (16.9)	NA	NA	NA	NA	65 (22.4)	17 (5.9)	0 (0.0)	208 (71.7)	NA	NA	NA	NA
Parinyanitikul *et al*[10]	2015	398	188 (47.2)	23 (5.8)	39 (9.8)	148 (37.2)	105 (26.4)	57 (14.3)	28 (7.0)	207 (52.0)	43 (10.8)	29 (7.3)	11 (2.8)	308 (77.4)	NA	NA	NA	NA
Zhou *et al*[24]	2015	107	66 (61.7)	11 (10.3)	4 (3.7)	31 (29.0)	50 (46.7)	13 (12.1)	13 (12.1)	31 (29.0)	39 (36.4)	3 (2.8)	2 (1.9)	63 (58.9)	NA	NA	NA	NA
Jin *et al*[25]	2015	423	202 (47.8)	55 (13.0)	23 (5.4)	143 (33.8)	NA	NA	NA	NA	55 (13.0)	27 (6.4)	13 (3.1)	328 (77.5)	NA	NA	NA	NA
Tan *et al*[26]	2014	267	87 (32.6)	57 (21.3)	27 (10.1)	123 (46.1)	78 (29.2)	33 (12.4)	21 (7.9)	135 (50.6)	NA	NA	NA	NA	NA	NA	NA	NA
Yang *et al*[27]	2013	113	NA	6 (5.3)	8 (7.1)	NA	NA	8 (7.1)	10 (8.8)	NA	NA	1 (0.9)	1 (0.9)	NA	NA	NA	NA	NA
Cockburn *et al*[28]	2013	133	67 (50.4)	11 (8.3)	1 (0.8)	54 (40.6)	40 (30.1)	16 (12.0)	8 (6.0)	69 (51.9)	24 (18.0)	9 (6.8)	7 (5.3)	93 (69.9)	NA	NA	NA	NA
Lee *et al*[29]	2013	120	58 (48.3)	11 (9.2)	4 (3.3)	47 (39.2)	26 (21.7)	19 (15.8)	3 (2.5)	72 (60.0)	18 (16.8)	6 (5.6)	5 (4.7)	78 (72.9)	NA	NA	NA	NA
Dede *et al*[30]	2013	63	29 (46.0)	2 (3.2)	0 (0.0)	4 (6.3)	17 (27.0)	7 (11.1)	3 (4.8)	6 (9.5)	NA	NA	NA	NA	NA	NA	NA	NA
Kumaki *et al*[31]	2011	53	30 (56.7)	3 (5.7)	2 (3.8)	18 (34.0)	15 (28.3)	4 (7.5)	3 (5.7)	31 (58.5)	9 (18.4)	5 (10.2)	0 (0.0)	35 (71.4)	NA	NA	NA	NA

ER: Estrogen receptor; PR: Progesterone receptor; P: Positive; N: Negative; NA: Not available.

Before 2010, the status of HER2 was only determined by FISH, and since then, the results of IHC analysis have been combined. According to the ASCO/CAP guidelines, if the IHC result is 3+-, it can be diagnosed as HER2 positive, and if the IHC result is 0/1+-, it is regarded as HER2 negative. In an equivocal situation (IHC2+-), that is, the complete membrane staining of > 10% of tumor cells is weak to moderate intensity, *in situ* hybridization (ISH) must be performed to determine whether HER2 is amplified

or not. Therefore, it is not necessary to supplement FISH to further confirm the status of HER2 in cases with an IHC score of 0 or 1+-. However, as luminal subtypes are more likely to reveal biomarker conversion and limited therapeutic efficiency which is attributed to the decreased expression of Ki-67 in luminal cases after NACT, we chose to perform FISH on the postoperative specimens of this patient. The results suggested that although the IHC score was 1+-, HER2 was actually proved to be amplified. When reviewing previous literature, we found that despite the low positive rate of gene amplification in IHC0/1+- cases, there was always a small discrepancy between IHC and FISH. Only 2% of the gene was amplified in negative (0/1+-) expression cases by FISH among Chinese patients in the study by Shui *et al*[4] and was approximately 4% in other populations[5].

At present, there is no concensus on the mechanism of NACT on HER2 status. Some researchers believe that the small tissue samples obtained by fine needle aspiration are insufficient to represent the phenotypic characteristics of the entire tumor as different molecular expressions may be displayed in specimens. Some studies have taken heterogeneity within the tumor into account. It has been speculated that NACT kills cells that are sensitive to chemotherapy and the remaining cells gradually dominate during the treatment process resulting in a different appearance with subsequent unfavorable characteristics and composition[6]. Another group assumed that a low level of estrogen in the body after NACT down-regulates the expression of ERs in tumor cells[7]. The management of HER2 expression is partly dependent on ER and the status transition also affects each of these parameters[8]. Therefore, NACT indirectly affects the status of HER2. One study has recently discovered that HER2 targeted therapy can also result in differential expression of genes[9]; thus, we predict that NACT can induce subtle changes in gene stability. In addition, it is worth noting that drugs that target cell microtubules such as paclitaxel can lead to polyploidization of cells, that is, all chromosomes multiply, including those that carry HER2. This is followed by increased copy number of the HER2 gene and the outcome is not equal to the actual amplification of HER2, which seems to explain why some patients are resistant to drugs even if the copy number of HER2 increases[10]. Although statistical and staining biases are rare and the criteria for defining IHC ambiguity (IHC 2+-) varies among trials, they should not be ignored. On the contrary, Parinyanitikul *et al* [11] analyzed HER2 mRNA level after treatment and the results indicated that the level of HER2 expression in most patients remained stable.

The prognosis of these receptor discordances after NACT are multifarious. For patients with locally advanced breast cancer, HER2 overexpression is an independent risk factor regarding 5-year disease-free survival (DFS). In the multivariate analysis by Tural *et al*[12], clinical stage of the tumor, transformation of HER2 from positive to negative and triple negative receptor status significantly influenced DFS. Li *et al*[13] included 2847 patients from eight studies and found that patients with hormone receptors (HR) which changed from positive to negative had worse DFS. Moreover, compared with patients who maintained negative HR status after NACT, those with negative HR which changed to positive tended to have longer DFS and overall survival. However, there are a variety of cut-off values to define HR positivity including 1%, 5% and 10% with few employing the Allred score, therefore they came to a contradictory conclusion regarding the prognosis of negative conversion of ER and PR status after NACT[2,14]. We cannot simply attribute this to different definitions as the total number of patients and their characteristics may also play a role. Additionally, the level of the protein encoded by the MKI67 gene (Ki67) is another independent predictive factor. A high Ki-67 index before surgery is associated with achieving a complete clinical response to NACT[15], whereas a high Ki-67 proliferation index in post-NACT samples is related to shorter DFS.

Nowadays, the status of HER2 can easily be influenced due to the combination of NACT and HER2-targeted therapy. Therefore, verification procedures should routinely be performed pre- and post-NACT. The decision whether or not to administer HER2-targeted therapy or endocrine therapy is largely based on the result. The estimation of rates of recurrence and outcome can also be affected. We expect the patient in this report to benefit from the use of trastuzumab and pertuzumab in the days to come.

CONCLUSION

The conversion of the status of biomarkers including ER, PR, HER2 and Ki-67 is important. Reassessment of the status of these biomarkers after NACT is

recommended, especially in patients with luminal subtypes.

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