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Her-2 Transformation in Lung Metastasis of Breast Cancer: A Case Report and Literature Review

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Abstract: To investigate the significance of Her-2 transformation in breast cancer after treatment. A case of breast cancer with lung metastasis was reported. The second biopsy showed Her2 transformation, and anti Her2 treatment was performed and the literature was reviewed. Before treatment, the primary lesion of the patient was Luminal B type, Her2 was negative, and after comprehensive treatment, the needle biopsy of pulmonary metastatic lesions was Her2 positive. Her2 status of patients with breast cancer may change after comprehensive treatment, and re biopsy can be considered to provide more treatment opportunities for patients.

1. Case

The patient is a 67 year old female. In December 2018, the CT findings of the tumor surgery in our hospital showed that the right breast occupied space, so we performed a modified radical operation for right breast cancer under general anesthesia. Postoperative pathology showed that (right side) non-specific diffuse breast cancer was Grade II, no cancer tissue was found in residual cavity, no cancer tissue was found in nipple and base, and metastatic cancer was found in lymph node (right armpit) (1/15). Immunohistochemistry: ER95% (+) PR71% (+) Her-2 (-) E-cadherin membrane (+) P120 membrane (+) Ki-67 about 40% (+) EGFR (-) GST - π (-) TOP0 Ⅱ about 20% (-). After operation, patients were treated with 4 cycles of "EC sequential T regimen chemotherapy for 8 cycles, followed by letrozole endocrine therapy.In August 2019, PET-CT showed right lung metastasis, and NX chemotherapy was performed for 6 cycles. In January 2020, CT reexamination showed that the lung metastatic tumor was enlarged, and the patient was changed to receive 6 cycles of albumin bound paclitaxel plus cisplatin chemotherapy. In December 2020, CT examination showed that the lung metastatic tumor was enlarged, and the progress of the disease was evaluated. Gemcitabine chemotherapy+bevacizumab targeted therapy was adopted for 2 cycles.

In March 2021, CT examination showed that some metastatic tumors in the upper lobe of both lungs were slightly enlarged than before, and the progress of the disease was evaluated. Fluvastatin combined with anastrozole was adopted for endocrine therapy.In April 2021, CT guided lung biopsy was performed. Pathology showed that (lung) metastatic adenocarcinoma, combined with the history and immunohistochemistry, indicated the origin of the breast. Immunohistochemistry: ER about 80% (medium+) PR small focus (+) GATA3 (+) TTF-1 (-) NapsinA (-) Ki-67 about 40% (+) HER-2 (++, positive). According to the lung puncture biopsy results of the patients, after informing the patients and their families of the situation and obtaining consent, they changed to trastuzumab targeted therapy+docetaxel chemotherapy. The efficacy of 2 cycles was evaluated as partial remission, and the efficacy of 4 cycles was evaluated as maintaining partial remission. At present, trastuzumab maintenance therapy is in progress.

2. Discussion

Breast cancer is the most common female malignant tumor. GLOBOCAN data in 2018 shows that China's incidence rate and mortality of breast cancer are relatively low in the world, but based on China's large population base, China's breast cancer morbidity and mortality ranks first in the world. At present, in addition to surgery, chemotherapy and radiotherapy, endocrine therapy and targeted therapy play an important role in the treatment of breast cancer. According to the expression of ER, PR and HER2, breast cancer can be divided into Luminal A type, Luminal B type, HER2 overexpression type and triple negative type. The strength of gene expression is not only used to guide treatment, but also to evaluate the prognosis of patients [1].

Table 1. Epidemiology of breast cancer

Epidemiology of breast cancer in 2020	Number of patients	Incidence rate of breast cancer in the world	Deaths
Global	2300 thousand	100%	680 thousand
China	410 thousand	18.4%	120 thousand

Table 2. Molecular typing of breast cancer

Intrinsic subtype	Clinic pathological significance	
Luminal-A type	ER and PR positive HER2 negative Ki-67<14% Low risk of recurrence	
Luminal-B type	HER2 negative	ER positive B type HER2 negative Meet any of the following indicators Ki-67≥14% PR Negative or low expression has a high risk of recurrence
	HER2 positive	ER positive HER2 positive Whatever Ki-67 Whatever PR
Her2 overexpression Type	Her2 positive Er and pr negative	
Base type	ER, PR (-) HER2 (-)	

Table 3. Prognosis and treatment of breast cance

Classification of breast cancer		Treatment	Proportion
Luminal-A type		Most patients only need endocrine therapy	60%-70%
Luminal-B type	HER2 Negative	Some patients need endocrine therapy, and some patients need chemotherapy when necessary	10%-20%
	HER2 positive	Chemotherapy+resist HER2+Endocrine therapy	
Her2 Overexpression type		Chemotherapy+resist-her2treatment	13%-15%
Base type		Chemotherapy	10%-15%

Recurrence and metastasis are the leading causes of death in breast cancer patients [2]. Studies have shown that the expression of re-biopsy genes may change after relapse and metastasis in breast cancer patients, mainly in ER, PR and HER2 status .Andreas[3] retrospectively analyzed the data of 27 patients with cervical lymph node metastasis with breast cancer and found that there were differences in the expression of ER, PR and Her2 in the primary lesion and metastasis, the positive rate of ER, PR and Her2 in metastatic lesions was lower than that of the primary lesion, and the loss of ER and PR was higher than that of Her2 Lang et al. [4] detected all lesions of 156 cases of invasive multi-lesion breast cancer and found that the inconsistency rates of ER, PR, Ki-67 and HER-2 expression between different lesions were 3.8%, 2.6%, 5.8% and 1.3%, respectively. Another study [5] counted the expression of HER2 in the primary lesion and metastasis of 48 patients with breast cancer bone metastasis, and the researchers found that the new positive rates of HER2 were 18.75% and 10.5%, respectively. Studies have shown that when breast cancer patients relapse and distant metastasis, the ER, PR and HER2 status of some patients will change. In 2019, the expert consensus of the Chinese Anti-Cancer Association pointed out [6]: patients with recurrent and metastatic breast cancer should undergo pathological biopsy again, and at the same time combine their imaging to formulate a new treatment plan. Other studies have shown that when breast cancer patients are resistant to endocrine therapy or anti-HER-2 targeted therapy, it is also necessary to perform a re-biopsy to provide patients with more appropriate treatment options to improve prognosis.

Breast cancer is a typical disease treated according to biological molecular typing decisions, and it has been found in clinical work that its molecular typing cannot absolutely explain the difference in prognosis of clinical patients. This can be explained by tumor heterogeneity, which means that different subtypes of tumors exist in the same space, and their molecular typing can change during tumor development, which is explained by tumor temporal heterogeneity. Wang Ruoxi [7] et al. retrospectively studied 273 breast cancer patients and found that the expression of ER, PR and Her2 in the margins, regional lymph nodes, local recurrence or distant metastasis of the primary lesion and the primary lesion were different. The inconsistency rates of ER, PR and HER-2 in different parts of the primary lesion were 28.3%, 34.0% and 15.1%, respectively. The inconsistency rates of ER, PR and HER-2 in primary lesions and regional lymph nodes were 18.4%, 24.5% and 14.6%, respectively. The inconsistency rates of ER, PR and HER2 between primary lesions and local recurrence/distant metastases were 36.0%, 31.2% and 16.4%, respectively, and the results found that the three molecular typing changes were unstable, and ER and PR changes were the most significant, followed by HER2, ER and PR changes were mainly lost. Shen Zengli [8] studied the expression of ER, PR and HER2 in 53 cases of primary lymph node lesions and metastases in breast cancer and found that ER, PR and HER2 were expressed differently before and after treatment due to tumor heterogeneity, and if the primary lesion (lymph node metastasis) before treatment and the primary lesion (lymph node metastasis) were homogeneous before and after treatment, if the

heterogeneity was reversed, according to their homogeneity and heterogeneity, the changes of primary lesions and lymph node metastases before and after treatment were divided into 4 types. The primary lesion is heterogeneous and lymph node homogeneity, the primary lesion is homogeneous and the metastatic lesion is heterogeneous, the primary lesion and the metastatic lesion are heterogeneous, and the primary lesion and metastatic lesion are homogeneous. Among them, ER and PR had high homogeneity in primary lesions and metastases, 66% and 67.9%, respectively, and HER2 had poor homogeneity between the two, accounting for 92.3%. The proportions of ER, PR and HER2 in primary and metastatic lesions were 3.8%, 5.7% and 1.9%, respectively. In this study, the same as Wang Ruoxi's study, the expression of ER, PR and HER2 molecular typing is inconsistent, and the HER2 stability is good. The reasons for the change of molecular typing are, on the one hand, the difference between the material and pathological reading techniques, on the other hand, the impact of treatment on the tumor, and on the other hand, based on the consideration of tumor heterogeneity. When performing pathological examination in patients with breast cancer based on this, multi-needle aspiration or pathological biopsy should be performed to accurately exclude factors affecting the filming. Data analysis, breast cancer patients after comprehensive treatment, compared with HR receptor, HER2 receptor is more stable, which may be based on pathologists IHC for HER2 detection, when HER2 genotype expression is uncertain, further use FISH technology for determination, and FISH detection technology is more stable.

Table 4. HER2 test method: FISH and IHC difference

Test method	Detection object	Advantage	Shortcoming
IHC	protein	Low laboratory requirements Easy to operate The experimental data is obtained quickly cheapness	Poor data accuracy
FISH	gene	Data accuracy	High laboratory requirements High technical requirements The experimental data is obtained slowly Expensive

Breast cancer anti-HER2 has been widely used, for the determination of HER2 detection methods there are two methods, IHC (immunohistochemistry) and FISH (in situ fluorescence hybridization technology), accurate determination of HER2 level can be used to guide the rational use of trastuzumab, so the measurement method and judgment standards are particularly important. Oldham et al. [9] compared the HER2 changes in breast cancer patients with HER2 overexpression in the primary lesion after neoadjuvant therapy, and found that 21.4% of breast cancer patients experienced loss of HER2 gene after neoadjuvant therapy. Zheng Yuhui et al. compared IHC (immunohistochemistry) and FISH (in situ fluorescence hybridization) to determine the HER2 gene status of 1448 breast cancer patients, and the results showed that: when IHC detection showed 1+ and 3+, IHC and FISH determination were parallel, based on the accuracy of FISH detection, if IHC showed 2+, FISH detection must be performed to guide medication; Another case report found [10]: the use of IHC to detect the primary lesion and metastatic lymph node HER2 are negative, the application of FISH test, the primary lesion and metastatic lymph node are inconsistent, indicating that the detection of protein level is not parallel to the detection of gene level, the researchers speculate that the application of trastuzumab inhibits the expression of HER2 protein, but HER2

gene amplification still exists. According to the guidelines and norms for the diagnosis and treatment of breast cancer of the Chinese Anti-Cancer Association, breast cancer specimens are generally directly judged by IHC detection of 3(+) and trastuzumab targeted therapy can be used, and if the patient's IHC test is 2(+), FISH detection is performed to determine whether gene amplification is used to guide the use of targeted drugs.

The use of trastuzumab targeted therapy has become one of the main means of treatment of breast cancer patients, and some patients benefit from the anti-HER2 treatment process is limited, the reason is the formation of drug resistance, so the study of drug resistance mechanism has become a hot spot. Peifeng Li [11] through a retrospective study of 124 breast cancer patients found that: after receiving neoadjuvant therapy, IHC (immunohistochemistry) was used again to measure HER2/neu protein expression, and it was found that there was a difference in HER2 protein expression before and after treatment, 23.4% (29 out of 124 cases) of tumors showed IHC down-regulating HER2/neu expression, however, using FISH (in situ fluorescence hybridization) to determine the lesions of breast cancer patients, HER2/ NEU amplification is stable or unamplified, and this study data found that HER2 has a change in molecular typing under the influence of neoadjuvant therapy, and does not clearly indicate the specific regimen of neoadjuvant therapy. The study found that the expression of HER2 before and after different neoadjuvant (chemotherapy alone, chemotherapy + targeted, and dual target) treatment in breast cancer patients was different, and the results were not uniform due to the lack of research data. Guarneri [12] found that HER2 loss rates were higher with chemotherapy alone than chemotherapy combined with targeted therapy, and lower HER2 loss rates with chemotherapy combined with targeted therapy. The study [13] found that chemotherapy will cause HER2 loss, and targeted therapy will not affect HER2 expression. Ignatov et al. [14] found that HER2 loss was associated with anti-HER2 therapy, not chemotherapy, and that dual-targeted therapy could improve HER2 loss, which was very different from the Niikura study data.A Japanese study on gastric cancer found that more than one-third of patients with gastric cancer based on anti-HER2 therapy experienced HER2 loss. Therefore, chemotherapy, chemotherapy combined with targeted therapy, and dual-target therapy all affect the expression of HER2, and the loss of HER2 is positively correlated with the use of anti-HER2 drugs. Changes in HER2 expression on breast cancer reneedle biopsy are not only associated with therapeutic interventions, but also with heterogeneity of the tumor itself. Liu Jianlan et al. [15] studied the expression of HER2 after neoadjuvant therapy in 110 patients with breast cancer HER2-positive, IHC detected 91 cases of breast cancer diffuse 3 (+), 20 cases of heterogeneity 3 (+) and FISH detected 9 cases of 2 (+) in a total of 3 groups, and re-puncture biopsy after neoadjuvant therapy, a total of 7 patients had HER2 loss, of which 1 patient was diffuse 3 (+), and the rest were heterogeneous 3 (+) HER2 from positive to negative. Studies have found [16] HER2 gene amplification or overexpression has a certain predictive value for the prognosis of breast cancer patients, and the stronger the HER2 gene expression, the greater the benefit from anti-HER2 therapy, and the better the prognosis. However, anti-HER2 therapy is not always effective for HER2 overexpression patients, some patients can only benefit from anti-HER2 therapy for less than 1 year, in order to prolong survival, recent research on anti-HER2 resistance mechanism has become a research hotspot, research data found that Some breast cancer patients may have HER2 gene loss after comprehensive treatment, based on modern molecular level considerations, the anti-HER2 resistance mechanism can be studied from gene loss, block their HER2 loss pathway, and accurately formulate treatment plans that meet individual patients, in order to improve the prognosis of patients[17].

Table 5. Summary of re biopsy studies on recurrent and metastatic breast cancer

Author	Particular year	Num-ber of cases	Repunct-Ure site	Inspection Method	Er pr her2 of expression
Li Lili[18]	2010-2014	149 cases	Transfer Position	Uncertain	Er20.6% undergo changes Pr39.3% undergo changes Her2 12.3% undergo changes
Zhang Shuo[19]	2009-2010	92 Cases	Before and after neoadjuvant therapy	Ihc	Er23.9%% undergo changes Pr31.5% undergo changes Her2 13% undergo changes
Jiang Nanyu [20]	2013-2016	96 Cases	Transfer Position	Ihc	Er 20%% undergo changes Pr 34% undergo changes Her2 13% undergo changes
Wang Yingzhe [21]	1999-2013	175 Cases	Transfer Position	Ihc Fish	Er 35.4%% undergo changes Pr 39.4% undergo changes Her2 14.8% undergo changes
Pan Chao[22]	2014-2015	30 Cases	Before and after operation	Ihc	Er 93.3%% undergo changes Pr 90% undergo changes Her2 83.3% undergo changes

It is reported that a 67 year old female patient with malignant tumor originally occurred in the right breast underwent a right breast puncture biopsy in April 2018, which showed that: ER+, PR+, Ki67 was greater than 40%, HER2 ,surgery, endocrine and chemotherapy were performed (the chemotherapy program was adjusted timely due to the progress of the disease). It will progress to pulmonary metastasis in April 2021. Lung biopsy shows that ER+, PR+, Ki67 are greater than 40%, HER2++. Then targeted chemotherapy and radiotherapy were performed.

The "precision treatment" of tumors is deeply rooted in people's hearts, and more and more studies have shown that there are changes in the expression of relevant genes during the development of breast cancer. Therefore, whattimepoint to detect and what detection method to use is of great significance for the determination of treatment options for breast cancer patients. According to the literature summary, in addition to the first biopsy puncture, if the patient has recurrent metastasis or develops drug resistance, biopsy aspiration can be performed again to improve prognosis. Based on the spatial and temporal heterogeneity of breast cancer, the rules of molecular typing changes were sought, and then individual treatment plans were formulated to prolong the survival of patie-nts and improve their prognosis.

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Data Availability

The datasets used during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

The author states that this article has no conflict of interest.

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