ACCSCIENCE PUBLISHING

Tumor Discovery

CASE REPORT

Efficacy of pyrotinib and capecitabine in recurrent breast cancer with a HER2-negative genetic switch following systemic therapy: A case report and literature review

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Abstract

Despite the demonstrated safety and efficacy of pyrotinib and capecitabine in treating human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer, their efficacy in recurrent breast cancer in which the HER2 status has changed to negative remains unexplored. Here, we report a case of a 38-year-old female diagnosed with invasive ductal adenocarcinoma of the left breast, staged as mcT2N0M0. Fluorescence *in situ* hybridization (FISH) confirmed that the tumor was hormone receptor (HR) positive with low HER2 expression (2+) and a HER2/CEP17 ratio of 3.56. Following neoadjuvant targeted therapy and chemotherapy, she underwent a modified radical mastectomy. Post-surgical histopathological examination revealed a non-pathological complete response, classified as ypT1cypN1M0. The tumor remained HR positive with low HER2 expression (2+), but the FISH result was negative (HER2/CEP17 ratio of 1.65). For 1 year, she was administered dual-targeted therapy with goserelin and exemestane. Sequential therapy with neratinib was initiated; however, it was discontinued due to grade IV diarrhea. Despite ongoing endocrine therapy, she experienced tumor recurrence on the left chest wall. A biopsy of the recurrent lesion revealed it to be HR positive with low HER2 expression (2+) and a negative FISH result (HER2/CEP17 ratio of 1.33). The recurrent lesion responded to combination therapy consisting of pyrotinib and capecitabine, with tolerable adverse events. This case highlights the potential advantages of combining pyrotinib and capecitabine when the HER2 status changes to negative following systemic therapy.

Keywords: Breast cancer; Human epidermal growth factor receptor 2 change; Low human epidermal growth factor receptor 2 expression; Pyrotinib; Case report

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1. Background

Human epidermal growth factor receptor 2 (HER2) status discordance is prevalent in breast cancer, reflecting its heterogeneity. Approximately 15% – 22% of patients exhibit

HER2 status alterations post-neoadjuvant therapy.[1-3] After chemotherapy, HER2-positive patients typically become HER2 negative, whereas the reverse is less frequent. A meta-analysis reported a 21.3% conversion rate from HER2 positive to negative and a 9.5% conversion rate from negative to positive.[4] Intratumoral HER2 heterogeneity, linked to ambiguous expression and minor gene amplification,[5] is associated with increased recurrence and metastasis[6] and poor response to HER2-targeted therapy,[7] impacting prognosis in metastatic cases.[8] Despite the efficacy of combination chemotherapy in treating HER2-positive cancer, residual disease may cause loss of HER2 amplification, increasing the risk of recurrence and metastasis.[9-11]

Tyrosine kinase inhibitors (TKIs) have become pivotal in treating HER2-positive metastatic breast cancer. By inhibiting tyrosine kinases, enzymes that activate proteins through signal transduction, TKIs can limit cancer cell growth and proliferation.[12] HER2 is the target of several notable TKIs, including afatinib, lapatinib, neratinib, tucatinib, and pyrotinib.[13] In particular, pyrotinib, when paired with capecitabine, significantly increases patient survival.[14] The PERMEATE trial revealed the efficacy of pyrotinib and capecitabine against brain metastases in HER2-positive cases.[15] Pyrotinib also appears to be more potent than lapatinib in countering T-DM1 resistance.[16]

This case report presents a breast cancer patient who transitioned from a HER2-positive status to HER2-negative status following systemic anticancer therapy. Upon experiencing recurrence with a HER2-negative lesion, the patient demonstrated a favorable response to the combination therapy of pyrotinib and capecitabine, suggesting potential therapeutic benefits in such scenarios.

2. Case presentation

In November 2021, a 38-year-old female noted a mass in her left breast that persisted for 3 months. Physical examination and imaging revealed two irregular, firm, mobile, non-tender lumps in the left breast: one located 1 cm from the nipple in the inner upper quadrant (5.0 × 4.0 cm) and another 2 cm from the nipple in the outer upper quadrant (3.5 × 2.5 cm). In addition, a 2.0 × 1.0 cm firm, mobile, painless lymph node was identified in the left axilla. Breast cancer was confirmed through imaging modalities, such as mammography, magnetic resonance imaging (MRI), and ultrasonography. Head MRI; neck, chest, and abdominal computed tomography; and bone scan did not reveal any distant metastases. A core biopsy of two lesions in the left breast and axillary lymph node revealed invasive ductal adenocarcinoma of non-specific type (Figures 1A and B) with two primary tumors and a negative axillary node (Figure 1C). Immunohistochemistry (IHC) of the inner upper quadrant lesion demonstrated estrogen receptor (ER) positivity (90%, moderate to strong) (Figure 1D), progesterone receptor (PR) positivity (5%, weak to moderate), low HER2 expression (2+) (Figure 1E), and Ki67 positivity (10%). IHC of the outer upper quadrant lesion revealed low HER2 expression (2+) and positive results for ER (90%, moderate to strong), PR (90%, weak to moderate), and Ki67 (25%). HER2 amplification was verified using fluorescence *in situ* hybridization (FISH) (HER2/CEP17 ratio of 3.56) (Figure 1F). Consequently, she was diagnosed with hormone receptor (HR)- and HER2-positive breast cancer (mcT2N0M0).

The patient received six cycles of neoadjuvant therapy, which included docetaxel (75 mg/m^2), carboplatin (area under the curve 6), trastuzumab (initial dose, 8 mg; subsequent doses, 6 mg), and pertuzumab (initial dose, 840 mg; subsequent doses, 420 mg). She underwent total mastectomy of the left breast and axillary lymph node dissection in May 2022 after showing a partial response to neoadjuvant therapy, as determined by the response evaluation criteria in solid tumors.[17] Both the intraoperative frozen sections and post-operative skin margins exhibited negative results (Figure 2A). The surgical specimen revealed a moderately differentiated invasive ductal adenocarcinoma of non-specific type measuring 1.5 × 1.5 cm in the inner upper quadrant (Figure 2B), with high-grade ductal carcinoma *in situ*, comedo type, and no vascular or perineural invasion. One of the 10 dissected lymph nodes demonstrated metastases, including extranodal fibrous tissue. Of the remaining nodes, one exhibited micrometastasis (Figure 2C), and two contained isolated tumor cells (Figure 2D). The IHC results demonstrated low HER2 expression (2+) (Figure 2E), PR negativity, and positive results for ER (70%, weak to moderate) and Ki67 (3%), with a negative HER2 status on FISH (HER2/CEP17 ratio of 1.65) (Figure 2F). Financial constraints prevented the patient from receiving T-DM1 therapy. Post-operative adjuvant radiotherapy included computer tomography-guided volumetric modulated arc therapy with 6MV-X external beam radiation, targeting the left chest wall and supra/infra-clavicular areas. The planned target volume was formed by expanding the clinical target volume by 5 mm with a cumulative dose of 50 Gy in 25 fractions. The patient received goserelin and exemestane between May 2022 and February 2023. Sequential neratinib therapy was initiated but discontinued due to the onset of grade IV diarrhea. The patient persisted with goserelin and exemestane endocrine therapy. Two subsequent follow-up visits revealed no abnormalities. The patient discovered a chest wall lesion in November 2023 (Figure 3A). A biopsy of this lesion revealed invasive carcinoma (Figure 3B).

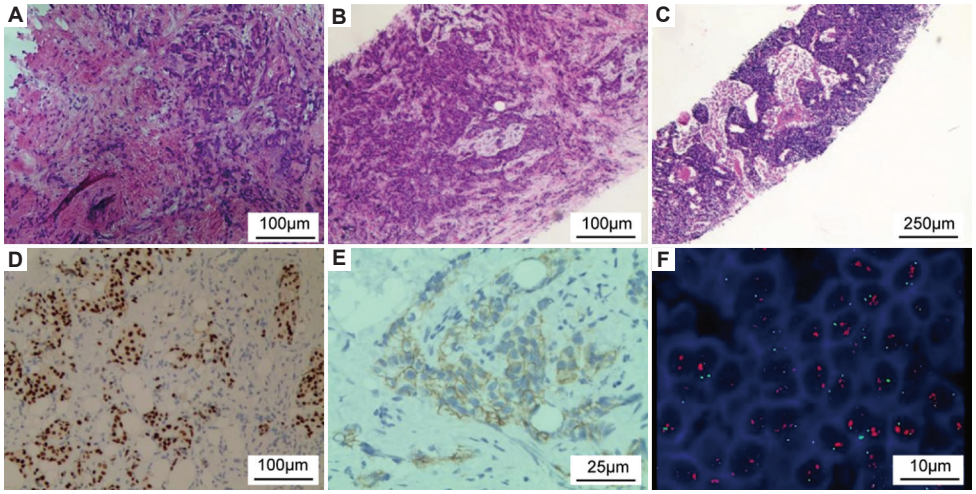


Figure 1. Initial diagnostic histopathologic findings. (A) Hematoxylin-eosin (H&E)-stained core needle biopsy specimen from the inner upper quadrant of the left breast, demonstrating invasive ductal carcinoma (×100 magnification). (B) H&E-stained core needle biopsy specimen from the outer upper quadrant of the left breast, suggesting invasive ductal carcinoma (×100 magnification). (C) H&E-stained core needle biopsy specimen of the left axillary lymph node, wherein no tumor cells were observed (×40 magnification). (D) Immunohistochemistry findings were positive for estrogen receptors in the primary tumor (×100 magnification). (E) HER2 immunohistochemistry scored 2+ in the primary tumor (×400 magnification). (F) Fluorescence *in situ* hybridization revealed HER2 gene amplification (HER2/CEP17 ratio: 3.56) in the primary tumor's core needle biopsy specimen (×1000 magnification).
Abbreviation: HER2: Human epidermal growth factor receptor 2.

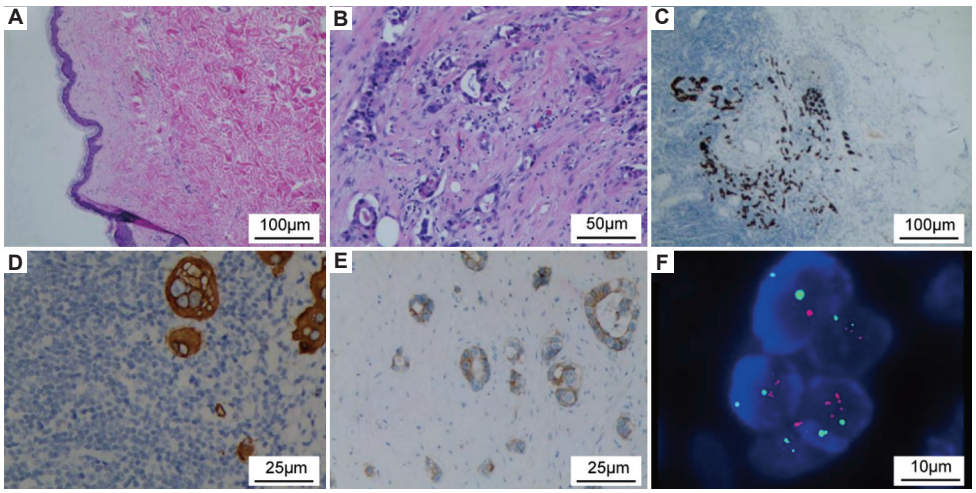


Figure 2. Surgical specimen histopathology. (A) hematoxylin–eosin (H&E) stain reveals negative skin margins (×100 magnification). (B) H&E stain of the excised primary tumor lesion (×200 magnification). (C) Immunohistochemistry-based findings of post-operative axillary lymph nodes exhibited micrometastasis (×100 magnification). (D) Immunohistochemistry-based findings of post-operative axillary lymph nodes reveal isolated tumor cells (×400 magnification). (E) Immunohistochemistry-based findings of the post-operative lesion demonstrated a HER2 score of 2+ (×400 magnification). (F) Fluorescence *in situ* hybridization revealed HER2 gene-negative (HER2/CEP17 ratio: 1.65) post-operative lesion ×1000 magnification).
Abbreviation: HER2: Human epidermal growth factor receptor 2.

IHC of the lesion revealed low HER2 expression (2+) (Figure 3D) and positive results for ER (95%, strong) (Figure 3C), PR (1% weak), and Ki67 (25%), with a negative FISH result (HER2/CEP17 ratio of 1.33) (Figure 3E). No distant metastases were detected on head, neck, chest, and abdominal computed tomography or bone scans.

A multidisciplinary team (MDT) proposed four treatment options, including T-DXd, pyrotinib and capecitabine, T-DM1, and a CDK4/6 inhibitor with fulvestrant. Due to cost constraints, the patient chose the pyrotinib and capecitabine and experienced manageable grade II diarrhea treated with loperamide. After one cycle, the tumor exhibited necrosis and reduced size (Figure 3F). At present, the patient's condition is stable on medication. Figure 4 summarizes the patient's diagnosis and treatment process.

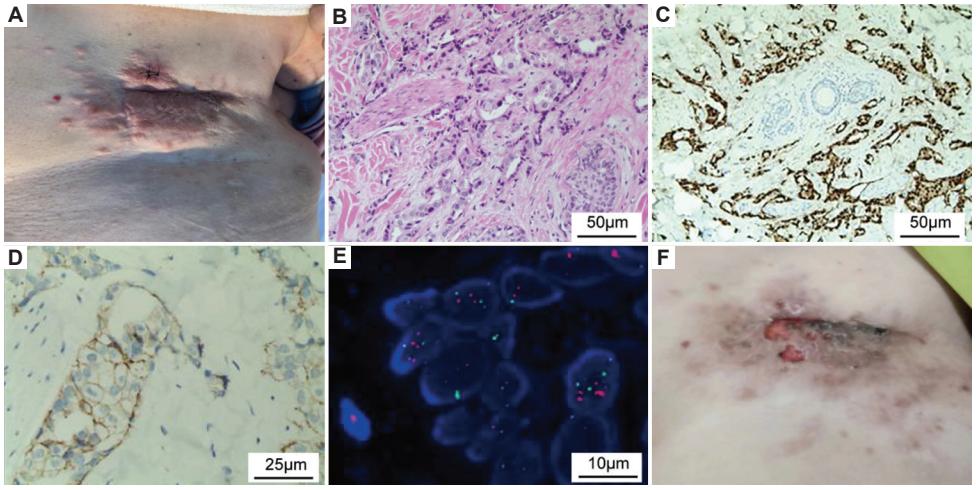


Figure 3. Recurrent lesion image and histopathology. (A) Image of the recurrent lesion on the left chest wall. (B) Hematoxylin–eosin (H&E) staining of the excised recurrent lesion revealed invasive ductal carcinoma (×200 magnification). (C) Positive estrogen receptor immunohistochemistry findings in the recurrent lesion (×200 magnification). (D) Immunohistochemistry examination of the recurrent lesion revealed a HER2 score of 2+ (×400 magnification). (E) Fluorescence *in situ* hybridization revealed HER2 gene negative (HER2/CEP17 ratio: 1.33) recurrent lesion (×1000 magnification). (F) Post-treatment image of the left chest wall lesion after one cycle of pyrotinib plus capecitabine.
Abbreviation: HER2: Human epidermal growth factor receptor 2.

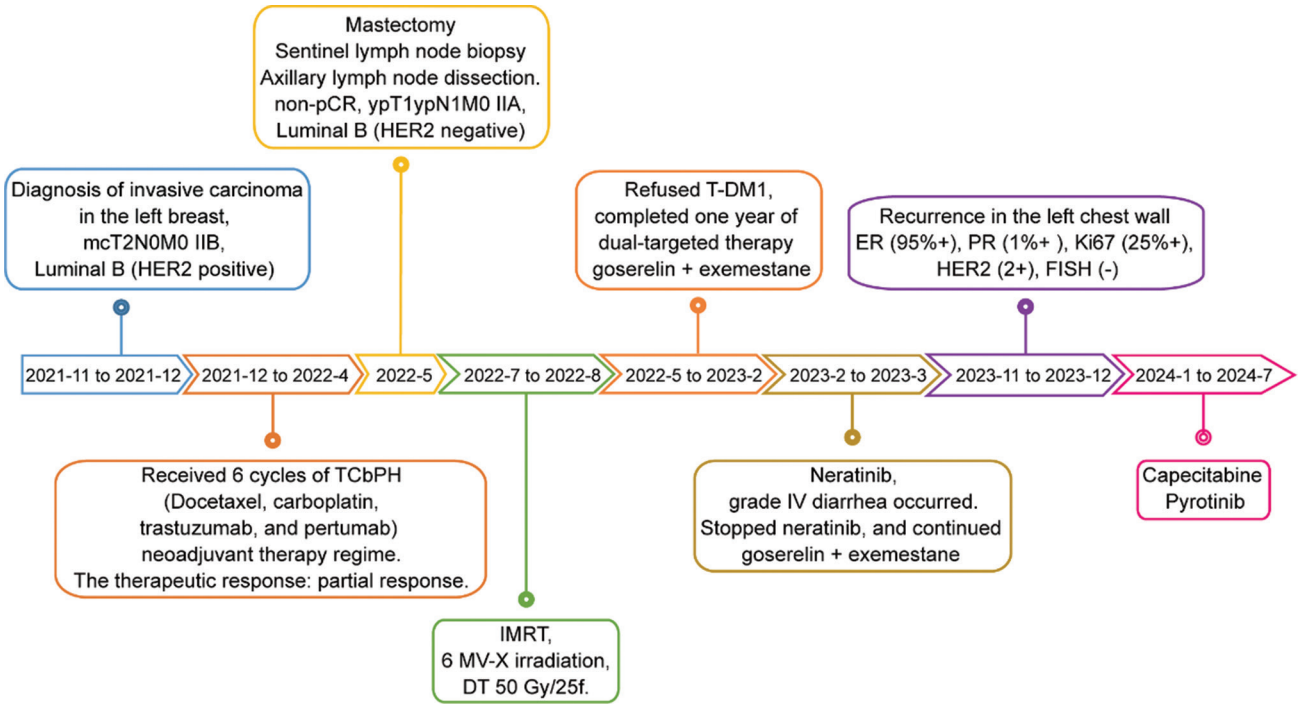


Figure 4. Diagnosis and treatment summary of the present case

3. Discussion

Tumor heterogeneity often leads to therapeutic refractoriness, posing significant challenges in cancer treatment.[18] Considering the dynamic and diverse nature of cancer, periodic evaluation of individual patients, specific lesions, and distinct sites is imperative. These assessments enable tailored disease treatments at the molecular level. The patient in the presented case was initially diagnosed with left breast cancer. The primary lesion, post-operative specimen, and recurrent lesion were all found to consistently exhibit high ER expression. PR expression declined to near absence, whereas HER2 expression remained low. FISH test results for HER2

were negative in post-operative and recurrent samples, confirming tumor heterogeneity.

MDT involves a comprehensive approach that aims to maximize therapeutic efficacy, improve survival through multimodal therapy, and ensure adherence to guidelines.[19] It is especially recommended for locoregional recurrent breast cancer management.[20] It promotes patient autonomy and collective decision-making for effectively treating locoregional recurrence. MDT was consistently employed in this patient's care, encompassing pre-neoadjuvant therapy, post-operative therapy, and post-locoregional recurrent therapy plans. Following a single salvage therapy course, the patient exhibited a partial response with notable lesion reduction. Ultimately, MDT involves a customized, synergistic strategy to enhance breast cancer outcomes.

Both positive-to-negative and negative-to-positive conversions of HER2 status were observed, with no clear predominance.[1] Typically, the transition from HER2-negative or HER2-equivocal primary to HER2-positive metastatic disease is more prevalent, especially in HR-positive patients. This may be the result of excluding patients with HER2-negative metastatic lesions and could be influenced by subclonal expansion and treatment-specific selective pressures in early breast cancer. Non-centralized testing may also contribute. These findings suggest reassessing HER2 status during disease recurrence or progression to determine therapeutic strategies. Studies have detected HER2-positive circulating tumor cells in a significant subset of patients with HER2-negative primary tumors.[21] While metastatic lesion biopsy may not always be possible or informative, circulating tumor biomarkers may be a non-invasive alternative for tissue-based HER2 status biomarkers.[22]

According to the fifth international consensus guidelines for advanced breast cancer by the European School of Oncology and the European Society for Medical Oncology, optimal treatment strategies following the loss of HER2 amplification remain undefined.[23] The current recommendations advocate continuing therapies targeting the HER2 signaling pathway.[24,25] Another strategy is to switch to alternative HER2-targeted therapies, such as ADCs (T-DM1 and T-DXd), and combine other TKIs with chemotherapy to overcome resistance to initial therapy and enhance patient outcomes.[24,26,27] The KATHERINE study detected HER2-negative residual disease in 70 out of 845 (8.3%) patients upon retesting at surgery. Among these, 11 invasive disease-free survival events occurred in the 42 trastuzumab-treated patients (26.2%), whereas none were observed in the 28 T-DM1-treated patients. This suggests that patients with HER2 status conversion may continue to benefit from HER2-targeted therapy.[28] The DESTINY-Breast04 study found that T-DXd significantly improved progression-free survival and overall survival with manageable safety compared to the physician's choice of treatment in low-HER2 metastatic breast cancer patients who had received 1 – 2 prior lines of chemotherapy.[29] Subgroup analysis revealed that the median treatment duration was 8.4 months with T-DXd and 3.5 months with the physician's choice in 213 Asian patients.[30] Further clinical trials are needed to find the best treatments and understand their long-term effects on patients with a HER2-negative switch.

Pyrotinib efficacy in treating HER2-positive metastatic breast cancer is well established.[31,32] A Chinese phase II trial involving patients previously treated with taxanes, anthracyclines, and/or trastuzumab demonstrated that pyrotinib with capecitabine exhibited a higher response rate (78.5%) and longer median progression-free survival (18.1 months) than lapatinib.[33] The phase III PHOEBE trial corroborated these benefits, with pyrotinib demonstrating improved overall survival and progression-free survival across various subgroups, regardless of trastuzumab resistance or prior chemotherapy.[14] Xu *et al.* advocate pyrotinib as a viable second-line treatment for trastuzumab-resistant cases, especially where access to newer therapies is limited.[32] Pyrotinib and capecitabine significantly decreased lesion size in the current patient.

4. Conclusions

Our case emphasizes that the pyrotinib and capecitabine combination may be beneficial in patients experiencing a HER2-negative switch following systemic therapy. This finding may lead to promising breast cancer research and the development of therapeutic strategies.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Chunfa Chen, Jundong Wu
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Investigation: Yuling Zhang, Bingfeng Chen
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Writing–original draft: Yuling Zhang
Writing–review & editing: Chunfa Chen, Jundong Wu

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Cancer Hospital of Shantou University Medical College (approval no.: 2022139).

Consent for publication

Written informed consent was obtained from the patient for publication of the details of her medical case and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal upon request.

Availability of data

Not applicable.

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