Multiple-Focused Analysis of Breast Cancer Late Recurrence –
A Case Report and Literature Review

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Abstract

Breast cancer, given its high incidence rate and morbidity, is one of the most extensively studied malignancies in contemporary medical research. Despite rapid advancements in screening protocols, targeted therapies, and surgical techniques, some aspects of its natural history are still unexplored, particularly the issue of dormancy and late recurrence. In this case report, we present a patient who experienced a relapse 35 years after the curative treatment for invasive breast carcinoma. The diagnostic procedure, therapeutic management, and outcome are thoroughly described. In addition we performed a brief literature review regarding this issue.

Keywords: breast cancer, late recurrence, pleural metastasis, lifelong surveillance

1. Introduction

Breast cancer, the most commonly diagnosed cancer in women worldwide, is notorious for its potential for late recurrences, particularly in Luminal B tumors, and least commonly in the TNBC subtype (1). It predominantly affects women over 50 years old (2). Most literature reports breast cancer relapses occurring within 5 to 15 years after the primary tumor, with only a few studies documenting disease-free survival (DFS) of over 20 years (3). Regarding age distribution, only 6% of newly diagnosed breast cancer cases occur in women under 40 years old (4). Consequently, primary screening is recommended starting at this age and becomes imperative for women over 45, according to the 2023 American Cancer Society (ACS) recommendations.

Given the low curability of distant metastatic breast cancer, with a median survival of just over three years (5), therapeutic management can be particularly challenging. A personalized approach is recommended, adapted to the patient's clinical status and tumoral characteristics.

Here, we present a case of breast cancer in a woman who experienced a late recurrence 35 years post-treatment, involving uncommon metastatic sites beyond the bones and liver. We will present the diagnostic procedures and the various regimens used during more than five years of continuous treatment.
2. Case Report

In 2018, a 76-year-old woman was admitted due to progressive dyspnea for seven days. Clinical examination revealed massive lymphedema in the right arm and absent breath sounds in the lower right lung. Her past oncological history included an invasive breast cancer, luminal A (ER+, PR+, HER2-), diagnosed when she was 35 years old and treated with a curative intent in 1983. The treatment plan at that time included surgery (left modified radical mastectomy with axillary lymphadenectomy) followed by adjuvant radiotherapy. Other significant past medical history included a myocardial infarction followed by a stent placement in 2010 and a cholecystectomy. Her family history was not significant.

A chest computed tomography (CT) revealed a pleural effusion measuring 6.3 cm in thickness and nodular lesions in the right lung (Figure 1).

![Figure 1. CT scan showing right pleural effusion](image1)

Figure 1. CT scan showing right pleural effusion

A bronchial fibroscopy showed a free bilateral tracheobronchial tree with mucosal aspects, suggesting an acute exacerbation of chronic bronchitis. This was followed by diagnostic thoracocentesis with cytoblock histopathological examination, which described pleural metastases from a breast cancer. Investigations concerning local relapse included a mammary ultrasound, which showed only right axillary adenopathy with benign features and significant lymphedema in the left arm, with no focal opacities in the parenchyma, with a BI-RADS score of 2. CA 15-3 was 76.44 U/ml.

The patient was subsequently referred to the Cluj-Napoca Oncologic Institute. Reassessment of the cytoblock using immunohistochemistry confirmed the previous diagnosis and provided a molecular profile of the tumor tissue. The findings described a Luminal A type of mammary carcinoma with ER=95%, PR=95%, Ki67=20%, hER2=0, and positive e-cadherin. The exact immunohistochemical similarity with

![Figure 2. Pleural liquid biopsy – immunohistochemistry showing a PR+, ER+ tumor (Luminal A) (right picture); e-cadherin positive (left picture)](image2)
the primary tumor suggested that this may represent a late relapse.

In theory, per current international guidelines, the standard first-line treatment would have been a combination of endocrine therapy (ET) and a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor. Given the advanced stage of the disease, the patient's age, comorbidities, and prior treatment with anthracycline and taxanes, chemotherapy with Capecitabine 2500 mg/m² daily was chosen. Management of the pleural involvement included pleural liquid drainage and pleurodesis with Bleomycin.

Two months after initiating treatment, the patient underwent a PET-CT to evaluate treatment response. The results showed stationary pleural effusion and a hypercaptant lesion in the left abdomen, indicating the need for a more detailed abdominal work-up. A thoraco-abdominopelvic CT scan revealed micronodular infiltration of the peritoneal fat, highly suggestive of peritoneal carcinomatosis. Echo-guided biopsies were performed, and histopathological results identified the lesions as peritoneal metastases of mammary carcinoma with molecular profiling showing CK7+, CK20+, PR+, ER-, and mammaglobin+.

Due to progressive disease, peritoneal involvement, and hormonal receptor status, the therapeutic regimen was changed in February 2019 to Vinorelbine 30 mg/m² on days 1 and 8 of a 21-day cycle, in combination with Anastrozole 1 mg daily. The patient's clinical status improved, with the CA 15-3 marker levels decreasing until April 2023. At that point, disease progression was evident through imaging (demonstrating peritoneal and pulmonary progression) and serological assessments (with CA 15-3 increasing to 103 U/ml). Consequently, the treatment regimen was switched to Palbociclib and Fulvestrant. Subsequent imaging and serological evaluations indicated disease stability. During treatment, the patient developed mild anemia, leukopenia, thrombocytopenia, first-grade hepatic cytolysis, and altered basal glycemia, and a mild degree of fatigue.

### 3. Discussion

We presented a remarkable case of a very late recurrence of breast cancer, occurring 35 years after the initial diagnosis, with metastases in uncommon sites different from the usual typical bone and liver metastases. Despite the widespread disease affecting both pleura and peritoneum, the patient achieved almost four years of progression-free survival on second-line chemotherapy.

In order to identify similar cases, we conducted a comprehensive search in PubMed Central and Elsevier databases using terms like "late relapse," "metachronous metastases," and "breast cancer" or "mammary carcinoma." Our goal was to identify other instances of breast cancer with relapse intervals exceeding 10 years. We carefully analyzed each case for specifics such as the patient's age at initial tumor occurrence, disease-free survival (DFS), and the metastatic sites involved. We focused on cases similar to our own in terms of pleura involvement or a DFS greater than 30 years, ultimately selecting seven case reports and case series published between 2009 and 2022.

From our review, we identified several critical issues discussed in the literature, including risk factors, biological mechanisms of late breast cancer recurrence, and the most frequently observed sites of relapse.

Factors independently associated with a higher risk of late recurrence include a diagnosis before age 40, ER-positive tumors, breast-conserving surgery, four or more positive lymph nodes, and a primary tumor with a diameter of 20 mm or greater (6). Therefore, patients exhibiting at least one of these characteristics warrant vigilant monitoring, for both local and distal recurrence. Genetic profiling of breast tumors offers a promising predictive tool for relapsing patterns, and further research in this domain is highly needed.

Kamata et al. (7) reported late relapses (13 to 20 years) in four female patients with ER-positive invasive ductal carcinoma who underwent chemotherapy and mastectomy. The study references the ATLAS randomized clinical trial (8), which compares recurrence and mortality rates between patients with ER+ tumors treated with Tamoxifen for 5 years versus 10 years. The 15-year relapse rates were 25.1% for the 5-year treatment group and 21.4% for the 10-year group, indicating a
potential benefit of extended estrogenic treatment in reducing relapse risk.

Rawindraraj et al. (9) presented two cases of pleural relapses after 14 and 21 years, emphasizing the high mortality associated with malignant pleural effusions secondary to breast cancer metastasis, with median survival estimated at 15 months post-fluid accumulation in the lungs.

The case with the longest relapse window was described by Takebayashi et al. (10), involving a 78-year-old patient who developed intestinal obstruction from ileum and peritoneal metastasis of breast cancer 42 years after the initial diagnosis. Metastasis to the peritoneum is exceedingly rare and sparsely documented, making this case particularly noteworthy.

Overall, our findings underscore the importance of prolonged follow-up for breast cancer patients, especially those with risk factors for late recurrence. By remaining vigilant and employing tailored surveillance strategies, we can better manage and potentially mitigate the impacts of these rare but significant late recurrences.

Figure 3. Summarization of the cases included in the review

<table>
<thead>
<tr>
<th>Articles</th>
<th>Age at diagnosis (years old)</th>
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<tr>
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<tr>
<td>Case 1</td>
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<td>32</td>
<td>lymph nodes</td>
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Breast cancer presents a challenge due to its potential for late recurrence, with approximately 20% of cases recurring 10 years after adjuvant therapy (11). The precise mechanism behind this phenomenon remains unclear, though it is believed to involve dormant cancer cells or micrometastases that evade immune surveillance, subsequently reactivating and proliferating (12).

Tumor dormancy encompasses various scenarios. First, quiescent tumor cells enter a reversible G0-G1 arrest, escaping apoptosis and evade immune system recognition (13). A second scenario involves micrometastases or angiogenic dormancy, where the balance of pro- and anti-angiogenic factors regulates proliferation counteracted by limited nutrient availability, inducing a state of autophagy and cellular shrinkage (14). Immunoologic dormancy, the third subtype, is represented by breast tumors exhibiting a higher number of memory T cells compared to controls, suggesting prior exposure to tumor-associated antigens (16). However, dormant cancer cells reduce the expression of these antigens, evading immunologic surveillance (15).
The Danish Breast Cancer Group conducted a population-based cohort study (17), suggesting that patients experiencing late recurrence generally have a more favorable prognosis than those with early recurrence. Particularly, estrogen receptor (ER)-positive and low-risk ER-negative cancers may exhibit prolonged periods of dormancy, resulting in slower disease progression post-recurrence. With an increasing body of evidence showcasing breast cancer recurrence beyond the 10-year mark, there is a growing necessity for mandatory long-term follow-up for such patients.

4. Conclusion
Our case highlights several critical aspects of late relapses in breast cancer. Diagnosing these relatively rare conditions requires extensive long-term surveillance and close patient contact, as patient compliance tends to wane over time. Enhanced attention should be directed towards patients with identified risk factors for late relapse. Given the generally unfavorable prognosis for late recurrences, treatment must be meticulously tailored for each patient, and genetic testing is recommended.

Abbreviations
TNBC – triple-negative breast cancer
ACS -American Cancer Society
NST – no special type
CK – cytokeratin
PR – progesterone receptor
CA15-3 – cancer antigen 15-3
ER – estrogen receptors
HER2 – human epidermal growth factor receptor 2
CT – computed tomography
PET – positron emission tomography
ET – endocrine therapy
CDK4/6 – cyclin-dependent kinase 4 and 6

Statements
Authors' contributions: AOT and TMV conceived the analysis and collected the data from the literature. BOT and BCV contributed data or analysis tools. AOT, TMV, and BOT wrote the paper. CCB made the final approval. All authors provided critical feedback and helped shape the research, analysis, and manuscript.

Consent for publication: As the corresponding author, I confirm that the manuscript has been read and approved for submission by all named authors.

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References


