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Case reports in breast cancer 2022

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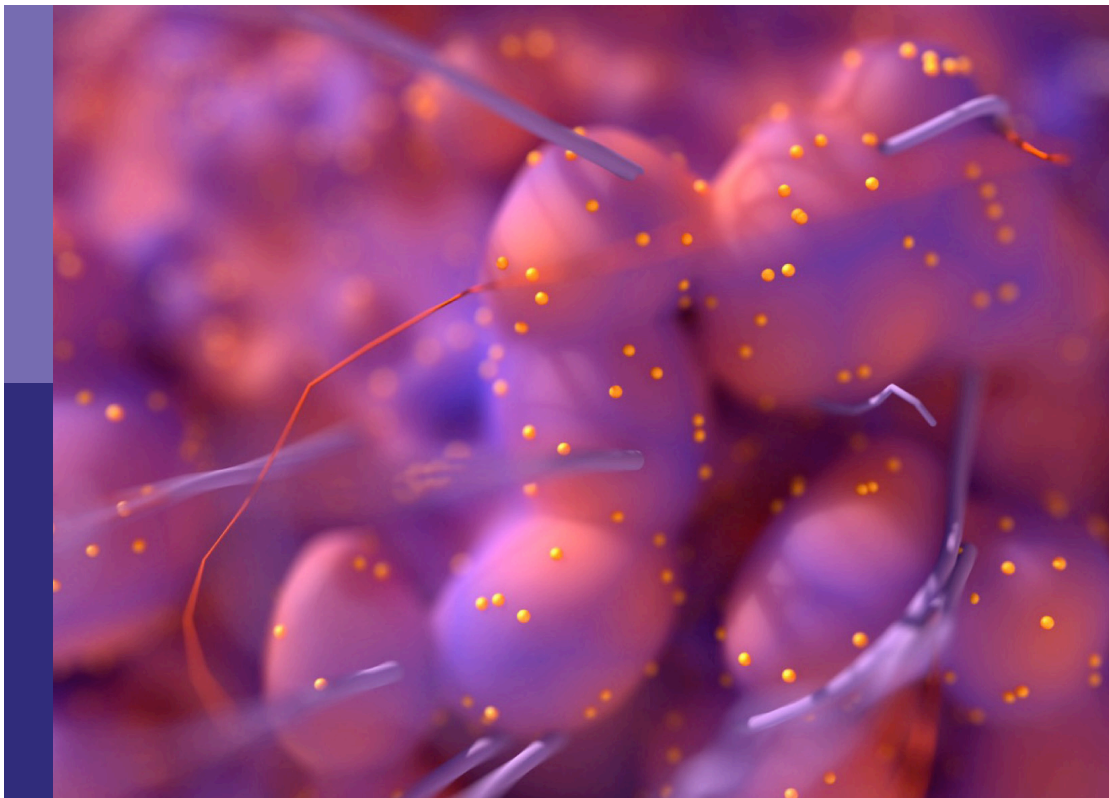

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Case reports in breast cancer : 2022

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Editorial: Case reports in breast cancer : 2022

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KEYWORDS

Pseudo-Meigs' syndrome, tamoxifen-associated acute pancreatitis, pseudoprogression, PET/CT, Sacituzumab-govitecan, PARP inhibitors, IORT, ultrasound-guided microwave ablation

Editorial on the Research Topic
Case reports in breast cancer : 2022

1 Introduction

Although case reports are considered to be at a lower level of evidence compared with systematic reviews, randomized controlled trials, and meta-analyses, in the history of medical development, the importance of clinical case reports cannot be ignored. Case reports also play an important role in the era of evidence-based medicine and have served as the building blocks of medical knowledge. These succinct narratives, grounded in real-world patient experiences, offer a rich tapestry of evidence that provided valuable insights into rare or atypical clinical scenarios, novel therapeutic approaches, and unexpected side effects. They have a special place in advancing the field of breast cancer (BC) care by shedding light on the nuances of diagnosis, treatment, and patient management. As guest editor for the Research Topic, "*Case Reports in Breast Cancer: 2022*," I am delighted to present a summary of the nine insightful case reports that have contributed to our understanding of BC over the past year. In the pages that follow, we traverse the landscapes of clinical intricacies, therapeutic challenges, and diagnostic innovations presented by these case reports. Each narrative, a testament to the invaluable role of case reports in the fabric of evidence-based medicine, adds to the collective wisdom of our field.

2 Summary of case reports

Within this compendium, we embark on a journey through diverse clinical landscapes, offering glimpses into the complexity of BC. Two case reports delve into the clinical diagnosis and treatment of BC. The first report unravels the intriguing case of ovarian metastasis of BC, unveiling the clinical manifestation of pseudo-Meigs' syndrome (Lin et al.). In contrast, the second report narrates the clinical intricacies of post-operative BC patients facing severe hyperlipidemia-induced acute pancreatitis following the administration of tamoxifen (Zhai et al.).

The cause of ascites in pseudo-Meigs' syndrome remains unclear. It may be related to the stimulation of the peritoneum by hard solid ovarian tumors (1), or it may be

related to the leakage caused by the pressure difference between the arterial supply of large tumors and the accompanying venous and lymphatic drainage (2), it may also be related to increased capillary permeability due to elevated intraperitoneal inflammatory cytokines and vascular endothelial growth factor (VEGF) (3). Cases of ovarian metastasis of BC with pseudo-Meigs' syndrome is extremely rare. Among the reported cases of pseudo-Meigs' syndrome caused by ovarian metastasis of BC, this report in our Research Topic is the fifth case (1). In the previous 4 cases and this case report, all patients with ovarian metastasis from BC complicated by pseudo-Meigs syndrome had estrogen receptor-positive (ER+) BC (4–7). I think this is very interesting and may be useful for studying BC metastasis to the ovary. Basic research on the relevant factors is suggestive, and I support and encourage clinicians to report such cases, which will make it easier for us to look for the same factors in different cases.

Tamoxifen is a medication commonly used in the treatment of hormone receptor-positive (HR+) BC, and it is known to have several potential side effects. One of the less common but significant side effects associated with long-term use of tamoxifen is an increase in triglyceride (TG) levels (8, 9), which, in rare cases, can lead to the development of acute pancreatitis (10–12). Acute pancreatitis is a serious and potentially life-threatening condition characterized by inflammation of the pancreas. The exact mechanism by which tamoxifen affects lipid metabolism is not fully understood, but it may involve alterations in the liver's synthesis and secretion of TG, as well as changes in lipid clearance from the bloodstream. If a patient on tamoxifen develops hypertriglyceridemia or acute pancreatitis (13), treatment typically involves discontinuation of tamoxifen and management of the underlying condition (14). In this case report of tamoxifen-induced hypertriglyceridemia and acute pancreatitis (Zhai et al.), the authors used a comprehensive treatment plan including fasting, strict non-fat total parenteral nutrition, insulin combined with subcutaneous injection of low molecular weight heparin, etc. The plasma total TG of the two patients was quickly and effectively reduced to normal within 3 to 6 days after admission, thereby avoiding hemodialysis and plasma exchange. The method adopted by the authors is simple, cheap, safe, effective, easy to promote clinically, and is worth learning from.

Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST Ver1.1) has been widely adopted in clinical trials and clinical practice to evaluate the treatment effect of solid tumors, including BC (15). RECIST V1.1 is mainly based on computed tomography (CT) to evaluate the patient's condition. Although the European Organization for Research and Treatment of Cancer (EORTC) developed recommendations for ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) (16) and PET response criteria for solid tumors (17) ^{18}F-FDG PET has failed to become a standard for response assessment in solid tumors (18). F-fluoroestradiol (^{18}F-FES) is a specific ER-targeting molecular probe used for PET assessment of ER expression in cancer (18) ^{18}F-FES uptake is closely related to human estrogen receptor-α (ERα) immunohistochemistry (IHC) score, clinical studies have shown that ^{18}F-FES PET can reliably detect ER+ BC lesions (19, 20). Research findings have demonstrated that ^{18}F-FES PET is capable of assessing the extent of metastatic heterogeneity and furnishing valuable prognostic information regarding overall survival (OS) when evaluating bone lesions in patients with ER+BC at the time of their initial diagnosis (21). A retrospective head-to-head study comparing the efficacy of 18F-FES and 18F-FDG PET/CT in the context of metastatic invasive lobular BC revealed that 18F-FES PET demonstrated effectiveness in pinpointing metastatic sites, with a particular advantage observed in identifying bone metastases over 18F-FDG PET (22).

In this Research Topic, we have collected three interesting case reports related to PET/CT. Two of these reports underscore the remarkable sensitivity of ^{18}F-FDG PET in assessing treatment response in patients with advanced BC, reaffirming the importance of this imaging modality in monitoring therapeutic efficacy. In a case report, a patient with advanced metastatic breast cancer (MBC) and multiple bone metastases had relief of bone pain symptoms after treatment, but the efficacy evaluation of conventional imaging (CT and SPECT) suggested that her disease had progressed. Fortunately, she finally confirmed the remission of her disease through ^{18}F-FDG PET/CT examination (Tian et al.). In another case report, when evaluating the response of liver metastases to treatment in a patient with human growth factor receptor 2 (HER2) positive MBC, the efficacy assessment based on ^{18}F-FDG PET examination reflected the treatment response more accurately than the efficacy assessment based on CT examination (Suto et al.). In the third case report ^{18}F-FES PET non-invasive demonstrated the ER heterogeneity of tumors in a ER+/HER2-MBC patient and predicted the efficacy of using second and third line cyclin-dependent kinase 4/6 (CDK4/6) inhibitors after treatment failure with first-line CDK4/6 inhibitor (Pan et al.).

Triple-negative breast cancer (TNBC) is the most aggressive subtype of BC, and is known to be associated with a poor prognosis and limited therapeutic options. The breast cancer susceptibility genes (BRCA), specifically BRCA1 and BRCA2, play a crucial role in the occurrence and development of BC (23). These genes are involved in deoxyribonucleic acid (DNA) repair and help maintain genomic stability (24). Poly (ADP-ribose) polymerase (PARP) inhibitors are targeted therapeutics that have demonstrated efficacy as monotherapy in metastatic BRCA-mutant (BRCA-MUT) TNBC patients (25). We had incorporated two case reports that pertain to the systemic treatment of MBC in individuals with BRCA gene mutations in this Research Topic. These reports individually chronicle the treatment strategies employed—one involving the utilization of antibody-conjugated drugs and the other involving the administration of PARP inhibitors—and both achieved notable therapeutic outcomes (Mauro et al., Albarran et al.).

One of the case reports included in this Research Topic focuses on the treatment of a patient with active brain metastases (BMS) due to BRCA-mutant triple-negative MBC using a combination of Sacituzumab-govitecan (SG) and radiotherapy. In Italy, the use of PARP inhibitors for the treatment of MBC is allowed only after platinum-based chemotherapy failure. The MBC patient with a BRCA2 germline mutation experienced rapid brain metastases after only 3 months of first-line treatment. Since the major clinical trials of PARP inhibitors excluded platinum-refractory disease and their intracranial activity remained uncertain, the authors ultimately

opted for SG combined with whole-brain radiotherapy as a second-line treatment for this patient. This patient's progression free survival (PFS) (10 months) was significantly better than the median PFS (2.8months) for TNBC patients with brain metastases in the pivotal trial (26, 27). This case report provides support for the potential role of SG in treating active BMS in patients with BRCA-mutant TNBCand offers reference data regarding the safety of combining SG with whole-brain radiation therapy (WBRT). In another case report, a BC patient with a pathogenic germline BRCA2 mutation experienced early disease relapse while receiving adjuvant therapy with tamoxifen. She refused to use endocrine therapy alone or in combination with CDK4/6 inhibitors as a first-line treatment after recurrence due to disappointment with endocrine therapy and opted for a treatment regimen of talazoparib, at a dosage of 1 mg/24 hours. The patient achieved a complete disease remission (CR) after two cycles and her condition remained stable until the last follow-up time before the publication (November 2022). This case report represents the longest reported response to a PARP inhibitor to date and the first long-term response reported with talazoparib. This case report highlights the potential of using PARP inhibitors as a first-line treatment option for patients with HR-positive/HER2-negative BC who have disease recurrence and carry a pathogenic germline BRCA2 mutation. It suggests the potential of PARP inhibitors in this specific patient population.

Additionally, two other reports within this Research Topic center on local treatment strategies for breast tumors. One report underscores the significance of intraoperative radiotherapy (IORT) as a standard approach for BC patients with disabilities or compromised health (Omosule et al.). The other presents a case report on ultrasound-guided microwave ablation of a benign giant breast leiomyoma. While the latter does not directly address malignant tumors, the data it provides can inform local treatment strategies for BC and holds potential significance in this regard (Zhang et al.).

Intraoperative radiotherapy offers a potential solution for older patients with BC who may have debilitating health conditions or impairments (28). This technique delivers a targeted dose of radiation directly to the tumor bed during surgery, reducing the need for prolonged external beam radiotherapy sessions. The case report on IORT for BC in an elderly patient holds significant importance in the context of BC treatment. This case report emphasizes the successful application of intraoperative radiotherapy in an older patient, demonstrating the feasibility and efficacy of this treatment modality (Omosule et al.). By shedding light on the benefits and outcomes of intraoperative radiotherapy in this specific patient population, this case report contributes to the expanding knowledge and understanding of personalized treatment options for older adults with breast cancer. It underscores the significance of tailoring therapeutic approaches to meet the unique needs and characteristics of elderly patients, ultimately improving their quality of life and treatment outcomes. Therefore, the insights gained from this case report are instrumental in guiding clinicians and researchers towards more patient-centered and evidence-based care for elderly BC patients, fostering advancements in the field of geriatric oncology.

In addition to these 8 BC-specific case reports, we also present a case report addressing ultrasound-guided microwave ablation (US-MWA) for a benign giant breast leiomyoma (Zhang et al.). US-MWA is a minimally invasive technique used for the treatment of various types of tumors, including malignant phyllodes tumors and soft tissue sarcomas of the breast. It is a thermal ablation method that uses microwave energy to heat and destroy cancerous tissues. When combined with ultrasound guidance, US-MWA becomes a precise and effective approach for treating these tumors. The authors used US-MWA in the treatment of a breast mass located in close proximity to the pectoralis major muscle, measuring in excess of 7 cm in diameter—a dimension unprecedented in the existing literature on ablation (29–31). To enhance the efficacy of the ablation procedure, the authors innovatively employed refrigerated sterile saline to create a protective barrier, isolating the tumor from adjacent tissues. This approach effectively mitigated the thermal effects of the ablation, resulting in reduced patient discomfort and improved surgical field visibility for the operating surgeon. Moreover, the surgical methodology incorporated strategic interventions, including the implementation of short-term and long-term intervals, as well as multiple ablations. These measures were meticulously executed during the procedure to optimize the safeguarding of surrounding tissues and muscle structures against thermal damage, thus further elevating the quality of care provided. While not directly focused on malignant tumors, this report offers reference data that could have implications for local treatment strategies in BC.

3 Conclusion

In this Research Topic, the cases we collected emphasized the significant sensitivity of ^{18}F-FDG PET in evaluating the therapeutic response of late-stage BC patients, the predictive value of ^{18}F-FES PET in ER+/HER2- MBC for CDK4/6 inhibitor treatment response, the clinical manifestations of pseudo-Meigs syndrome caused by BC ovarian metastasis, the clinical complexity of severe hyperlipidemia and acute pancreatitis in BC patients receiving tamoxifen treatment, and the remarkable therapeutic effects of antibody-drug conjugates and PARP inhibitors in the systemic treatment of BC patients with BRCA mutations. In terms of local treatment strategies for breast tumors, the cases we collected highlighted the importance of IORT as a standard approach for BC patients with disabilities or comorbidities, and the surgical experience of using US-MWA for the treatment of large breast tumors. Each of these case reports is a valuable piece of the BC puzzle, contributing to our evolving understanding of this complex disease.

Author contributions

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Case report: ^{18}F-FES PET/CT predicted treatment responses of second-line and third-line CDK4/6 inhibitors after disease progression on first-line CDK4/6 inhibitor in a HR+/HER2- metastatic breast cancer patient

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Background: Cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) has become the commonest first-line treatment of hormonal receptor positive and human epidermal growth factor receptor 2 negative (HR+/HER2-) metastatic breast cancer (MBC). However, therapy is quite individualized after progression of disease (PD) when CDK4/6i fails. Estrogen receptor (ER) status of metastatic lesions of bone, lung or liver might be different from the primary tumor and biopsy of metastatic lesions was invasive and not always available. Prediction of treatment response after PD of CDK4/6i remains unsolved. ^{18}F-fluoroestradiol (FES) PET/CT could non-invasively reveal ER expression both in primary and metastatic breast cancer and recognize heterogeneity of ER status.

Case presentation: A 70-year-old woman with Parkinson's disease, osteoporosis and cardiovascular co-morbidity was diagnosed with HR+/HER2- breast cancer (pT2N2M0, stage IIIa). Three years later, she developed metastases in right lung and pleura with pleural effusion and received palbociclib + letrozole. After 8 months the disease progressed, and ^{18}F-FES PET/CT revealed multiple ER-positive pleural lesions and ER-negative pulmonary nodules after PD and the progression-free survival (PFS) of first-line CDK4/6i was 8 months. Since most of the metastatic lesions were ER-positive, abemaciclib + fulvestrant were chosen as the second-line CDK4/6i treatment and the PFS was 15 months. Another ^{18}F-FES PET/CT showed a new ER-positive pleural mass with multiple ER-negative

pulmonary nodules. Since ^{18}F-FES PET/CT revealed that the dominant lesions were still ER-positive, dalpiciclib + exemestane + fulvestrant were prescribed as the third-line CDK4/6i treatment. Currently the patient's disease had been stable for 2 months.

Conclusion: This case demonstrated that ^{18}F-FES PET/CT could show ER heterogeneity non-invasively and reveal the treatment responses a predictive imaging tool of serial second- and third-line of CDK4/6i treatments when first-line CDK4/6i failed in HR+/HER2- MBC. So long as the dominant or newly-developed metastatic lesion was ER-positive on ^{18}F-FES PET after first-line CDK4/6i, the patient might show certain therapeutic response towards endocrine-based treatment including second- and third-line of CDK4/6i, and thus increased the time to chemotherapy (TTC).

KEYWORDS

metastatic breast cancer, FES PET/CT, estrogen receptor (ER), CDK4/6 inhibitor, treatment response

1 Introduction

Breast cancer (BC) is the commonest malignancy worldwide and the leading cause of cancer death in Chinese women younger than 45 years (1–3). Cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) has become the standard first-line treatment of hormonal receptor positive and human epidermal growth factor receptor 2 negative (HR+/HER2-) metastatic breast cancer (MBC) (4, 5). However, the treatment for the progression of disease (PD) after CDK4/6i fails would be quite diversified and individualized (6). ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is the most commonly used PET tracer for metastatic examination, management response, and suspected recurrence of BC (7). However, based on increased glycolysis and glucose transporters of tumor cells, ^{18}F-FDG is not a cancer-specific tracer. Estrogen receptor (ER) is over-expressed in approximately 70% of breast malignancies and an important target for endocrine therapy (8). ^{18}F-fluoroestradiol (^{18}F-FES) is a radiotracer binding to ER, and allows non-invasive, whole-body evaluation of ER expression in BC (9).With its potential to serve as a prognostic and predictive biomarker for hormonal therapy of BC, ^{18}F-FES PET has gained growing interest in research (10). Here we report a case of HR+/HER2- MBC patient whose serial ^{18}F-FES PET/CT revealed treatment responses of second-line and third-line CDK4/6i + endocrine therapy after PD on first-line CDK4/6i + endocrine therapy. ^{18}F-FES PET/CT may act as a non-invasively predictive imaging tool to guide subsequent treatments when first-line CDK4/6i failed in MBC patients.

2 Case presentation

2.1 Surgery and postoperative adjuvant therapy of the primary tumor

A 70-year-old woman noticed a palpable mass in her left breast for three months and came to the hospital in December 2016. Her past medical history included Parkinson's disease, osteoporosis, and cardiovascular co-morbidities such as mild ischemic heart disease and lacunar infarctions of brain, and she took medications accordingly. She has no family history of BC. On physical examination, she could walk and talk slowly with continuous tremor in left arm and hand and decreased facial expression which was typical as 'masked face' of Parkinson's disease. There was a 2.5cm round hard lump in the left upper outer quadrant of the left breast without nipple discharge and palpated movable lymph nodes (LN) about 1.5cm in size in the left axilla. Ultrasound revealed a left breast solitary mass measuring 3.1×2.7cm^2 and abnormal enlarged LN in the left axilla, infra- and supra-clavicular fossa, considering LN metastasis. The mammogram did not find clusters of micro-calcifications. Multi-disciplinary consultation indicated that the risk of general anesthesia for the patient was relatively high. Both the patient and her relatives preferred procedures under local anesthesia to ensure safety. Considering the abnormally enlarged supra-clavicular LN, the surgical procedure might be palliative instead of radical.

The patient underwent left breast extended lumpectomy under local anesthesia (LA) in January 2017. Intraoperative fast frozen biopsy revealed left BC so patient subsequently received sentinel and targeted axillary lymph node biopsy under LA on the same day. Post-operative pathology showed invasive breast carcinoma, not otherwise specified (NOS), measuring 2.3×1.5×1.5cm^3, and LN metastasis (6/6). Immunohistochemistry (IHC) was ER (++, 95%), PR (++, 40%), HER2 (2+), fluorescence *in situ* hybridization (FISH) (-), and Ki-67 index 30%. The stage was pT2N2M0, IIIa, and molecular subtype was luminal B. With awareness of the risk of insufficient treatment and lack of evidence, the patient and her relatives refused intravenous chemotherapy and chose oral chemotherapy. Therefore she was put on adjuvant capecitabine (1.5g BID, 2 weeks on/1 week off) for 8 cycles. Concurrently, the patient underwent whole breast radiotherapy (WBRT) plus tumor bed boost, with the left axilla included. After the oral chemotherapy was finished, she received tamoxifen as endocrine therapy instead of aromatase inhibitor (AI) due to osteoporosis.

2.2 First-line CDK4/6i (palbociclib) treatment for metastasis

The patient was followed every half-year post-operatively and the results were normal. However, in January 2020, her chest CT showed multiple pulmonary nodules in right lung (the largest measuring 12.2 mm) andmasses in right pleura (the largest measuring 5.0 × 1.4 cm^2) (Figure 1A). She developed mild cough and dyspnea in July 2020, and followed-up chest CT showed the progression of the pulmonary nodules and masses in the right pleura (Figure 1B), suggesting pulmonary and pleural metastases. ^{18}F-FDG PET/CT showed multiple FDG avid pleural masses with maximum standardized uptake value (SUVmax) 9.4, and multiple pulmonary nodules with mild FDG uptake (SUVmax1.6), demonstrating pulmonary and pleural metastases (Figure 2A). The metabolic tumor volume (MTV) of the largest pleural mass was 27.7 cm^3. There were no metastases in bone, liver, or brain on ^{18}F-FDG PET/CT. The imaging evaluation of the patient was summarized in Table 1. In August 2020, the patient received first-line CDK4/6i palbociclib (125mg QD, 3 weeks on/1 week off) + letrozole (2.5mgQD) and intravenous bisphosphonate (Q6M) with 1, 25-dihydroxyvitamin D3 to intensify the treatment of osteoporosis.

She suffered from mild delirium, delusion, progressive tremor of left upper extremity and grade 4 neutropenia after the first cycle of palbociclib, so the dose of palbociclib was reduced to 100mg QD (3 weeks on/1 week off) from the second cycle. All the above-mentioned adverse effects recovered partially yet remained. In December 2020, her discomfort had relieved, and the chest CT showed both the pulmonary nodules and pleural masses were smaller (the largest pulmonary nodule measuring 9.4 mm, and the largest pleural mass measuring 4.3 × 1.3 cm^2), achieving partial remission (PR). However, her cough and dyspnea got worse in April 2021, and her chest CT revealed that pulmonary nodules and masses in pleura were larger than before (the largest pulmonary nodule measuring 10.1 mm, and the largest pleural mass measuring 4.4 × 1.2 cm^2), and there was increasing pleural effusion, suggesting PD. The progression free survival (PFS) of first-line CDK4/6i was 8 months.

2.3 Second-line CDK4/6i (abemaciclib) treatment for metastasis and ^{18}F-FES PET/CT

In May 2021, the patient started second-line CDK4/6i abemaciclib (150mg, BID) + fulvestrant (500mg, im, Q2W×3,

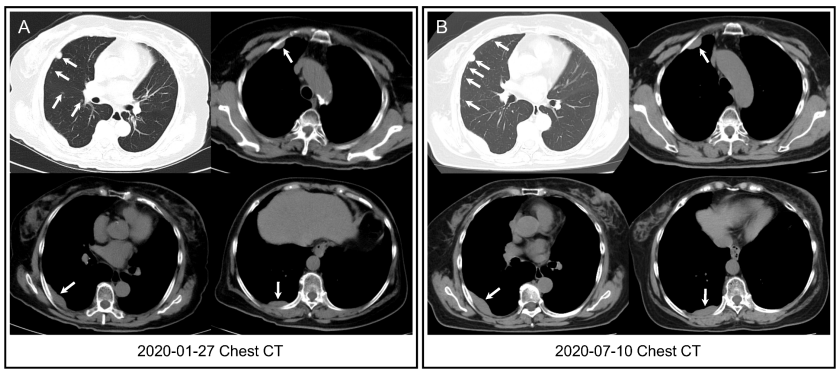

FIGURE 1
Chest CT. **(A)** Chest CT showed multiple pulmonary nodules in right lung and masses in right pleura (arrows) three years after surgery. **(B)** Followed-up chest CT revealed that pulmonary nodules increased in number, and pleural masses increased in size (arrows) when first-line CDK4/6i + endocrine therapy was started.

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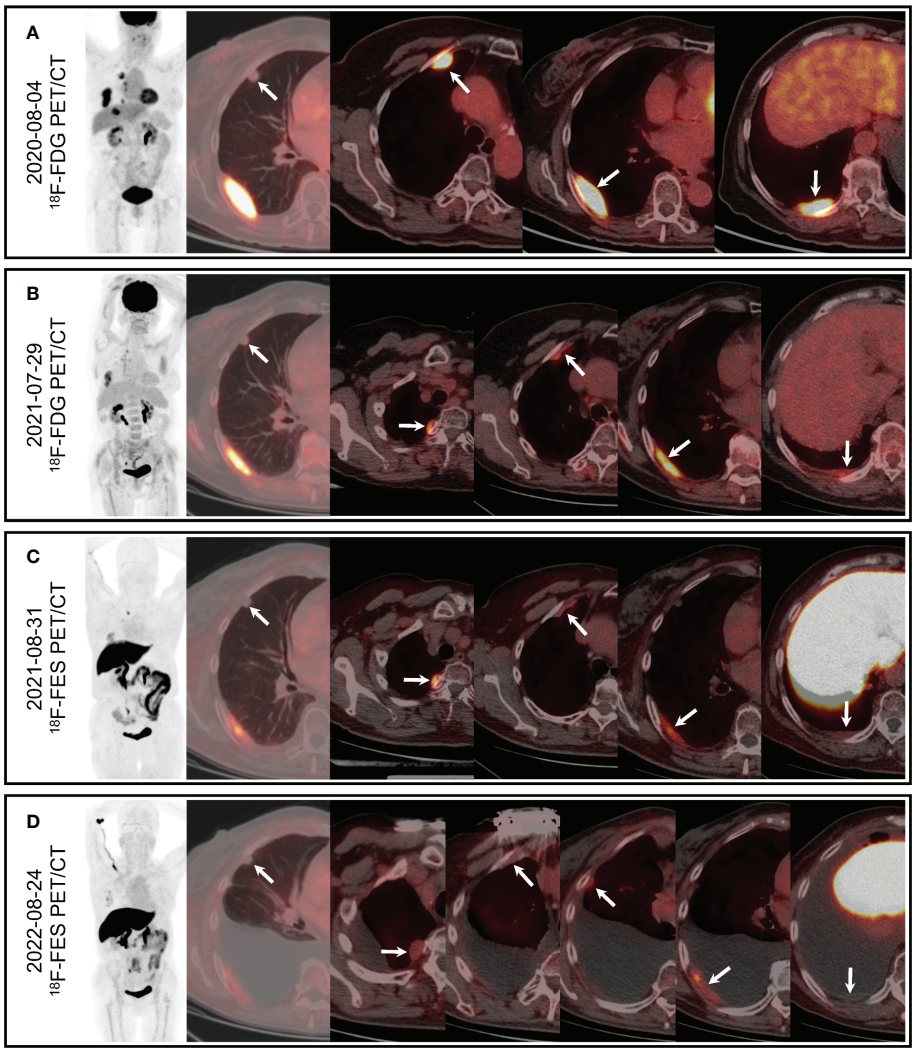

FIGURE 2
PET/CT. **(A)** ^{18}F-FDG PET/CT showed mild FDG uptake of the largest pulmonary nodule (arrow, SUVmax 1.6) and increased FDG uptake of the multiple pleural masses (arrows, SUVmax 9.4). **(B)** Followed-up ^{18}F-FDG PET/CT showed mild FDG uptake of the largest pulmonary nodule (arrow, SUVmax 1.2) and increased FDG uptake of the multiple pleural masses (arrows, SUVmax7.0). **(C)** Pulmonary nodule was negative on ^{18}F-FES PET/CT (arrow), and multiple pleural masses showed obvious FES uptake (arrows, SUVmax 5.0). **(D)** Pulmonary nodule was negative on followed-up ^{18}F-FESPET/CT (arrow), and multiple pleural masses showed different levels of FES uptake (arrows, SUVmax3.8).

then Q4W) after palbociclib + letrozole had failed. Two months later, ^{18}F-FDG PET/CT was performed to evaluate the treatment response (Figure 2B), which revealed that both the pulmonary nodules and the pleural masses were smaller than that of chest CT in April 2021 (the largest pulmonary nodule measuring 9.6 mm, and the largest pleural mass measuring 4.0 × 1.2 cm^2), and pleural effusion was decreased. SUVmax of the lesions as well as MTV of the largest pleural mass (13.9 cm^3) were decreased than those of previous FDG PET/CT (Table 1)

To evaluate the ER status of metastatic lesions, ^{18}F-FES PET/CT was performed subsequently (Figure 2C). The study was approved by the institutional ethics review board of the Peking Union Medical College (PUMC) Hospital (IRB protocol #JS-2959), and written informed consent was obtained. The ^{18}F-FES PET/CT showed multiple ER-positive pleural masses with obvious FES uptake and multiple ER-negative pulmonary nodules, which implied ER heterogeneity of metastases. The ER expression volume (EEV) of the largest pleural mass was 17.2 cm^3. The condition of the disease was partial remission (PR). Hence the treatment (abemaciclib + fulvestrant) was continued, and the tolerance was acceptable. She suffered adverse effects including grade 2 neutropenia and grade 1/2 diarrhea, without delirium or delusion, and the tremor was mitigated. Medications including bisphosphonate (iv, Q6M), 1, 25-dihydroxyvitamin D3 were also continued.

TABLE 1 Imaging evaluation of the patient.

Variables	Chest CT2020-01-27	Chest CT2020-07-10	^{18}F-FDG PET/CT2020-08-04	Chest CT2020-12-24	Chest CT2021-04-27	^{18}F-FDG PET/CT2021-07-29	^{18}F-FES PET/CT2021-08-31	^{18}F-FES PET/CT2022-08-24
Diameter of the maximum pulmonary nodule (mm)	12.2	11.0	11.3	9.4	10.1	9.6	9.5	9.7
SUVmax of the maximum pulmonary nodule	NA	NA	1.6	NA	NA	1.2	0.8	1.2
Size of the targeted pleural lesion (cm^2)	5.0 × 1.4	5.3 × 1.3	5.2 × 1.5	4.3 × 1.3	4.4 × 1.2	4.0 × 1.2	3.8 × 1.0	4.8 × 1.1
SUVmaxof the targeted pleural lesion	NA	NA	9.4	NA	NA	7.0	3.6	3.8
MTV of the targeted pleural lesion (cm^3)	NA	NA	27.7	NA	NA	13.9	NA	NA
EEV of the targeted pleural lesion (cm^3)	NA	NA	NA	NA	NA	NA	17.2	5.3

CT, computed tomography; FDG, fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography; FES, fluoroestradiol; SUVmax, maximum standardized uptake value; MTV, metabolic tumor volume; EEV, estrogen receptor expression volume; NA, not available.

In August 2022, she felt uncomfortable and the dyspnea recurred. The second ^{18}F-FES PET/CT was performed and there was a new ER-positive pleural mass with SUVmax 2.7 and EEV 5.3 cm^3 (Figure 2D), and the other pleural metastases decreased both in size and uptake of FES. Multiple pulmonary nodules were still ER-negative, and the pleural effusion increased notably. The imaging evaluation suggested PD, and PFS of second-line CDK4/6i was 15 months.

2.4 Third-line CDK4/6i (dalpiciclib) treatment for metastasis

Since ^{18}F-FES PET/CT revealed that the most of the metastatic lesions were still positive, the patient and her relatives turned down the option of intravenous or oral chemotherapy and were willing to try another line of endocrine-based therapy. In September 2022, the patient was put on dalpiciclib (125mg, QD, 3 weeks on/1 week off) + fulvestrant (500mg, im, Q4W) + exemestane (25mg, QD), and underwent the drainage of pleural effusion. She felt improved appetite, relieved fatigue afterwards, and laboratory test revealed grade 2/3 neutropenia. Currently her disease had been stable for 2 months after the third-line CDK4/6i. The timeline of the patient's disease progression was summarized in Figure 3.

3 Discussion

Breast cancer (BC) is one the leading cause of cancer-related death in women worldwide and the five-year cancer-specific survival of MBC is no more than 40% (2, 3, 5, 11–13). HR

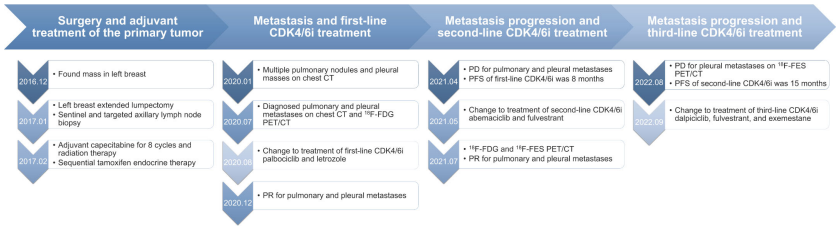

FIGURE 3
Timeline of the patient's disease progression.

+/HER2- subtype comprises approximately 60% of all BC, and hyperactivity of CDK4/6 pathway is a common characteristic of HR+/HER2- BC, leading to resistance to endocrine therapy (14, 15). CDK4/6i in combination with endocrine therapy as both first-line and second-line treatment have shown to improve survival outcomes in patients with HR+/HER2- MBC with accumulating evidence of clinical trials including the MONARCH (6, 16, 17), PALOMA (18, 19), MONALESSA (20–22) and DAWNA series (23, 24). Meta-analysis and pooled-analysis also confirmed the survival benefits of all CDK4/6i in combination with endocrine therapy for HR +/HER2- MBC patients (25, 26).

ER status of BC could be assessed by PET/CT with ^{18}F-FES (9, 11, 27), which binds to ER *in vivo* and enables imaging of ER expression both in primary and metastatic tumors non-invasively (11, 28). Based on the recommendations of ^{18}F-FES PET to image the ER *in vivo* and clinical studies that correlated 18F-FES PET with IHC, a lesion with SUVmax >1.5 should be considered ER positive (8). A prospective study has shown high agreement between ^{18}F-FES PET/CT result and ER status by IHC (11). Another large prospective trial also demonstrated high diagnostic accuracy of ^{18}F-FES PET/CT, with a sensitivity of 95%, a specificity of 80%, a positive predictive value of 93%, and a negative predictive value of 85% (28). Therefore, ^{18}F-FES PET/CT is a valid non-invasive imaging modality to determine ER status in MBC patients.

Furthermore, multiple potential clinical applications for ^{18}F-FES PET have been proposed, including selecting patients for hormonal therapy, solving clinical dilemmas and systemic staging of tumors with low metabolic activity (10). In terms of prediction of therapeutic response, study had shown that patients with ER heterogeneity or uncertainty tumors on ^{18}F-FES PET showed better sensitivity to chemotherapy rather than endocrine therapy (29). In another trial evaluating tumor heterogeneity by ^{18}F-FES PET as a predictive marker in MBC patients receiving palbociclib combined endocrine therapy, nine out of ten patients with an FES-negative site developed PD, with a median PFS of only 2.4 months. Among 46 patients with only FES-positive lesions, only four patients developed PD, with a median PFS of 23.6 months. Hence ^{18}F-FES-PET may provide a promising method for identifying and selecting candidate ER+/HER2- MBC patients who would most likely benefit from CDK4/6i combined with endocrine treatment (30).

However, detection of hepatic metastases is known to be difficult on ^{18}F-FES PET because of physiologic excretion of ^{18}F-FES by the liver (8, 31). For this reason, patients need to be evaluated by contrast-enhanced CT, MRI, or ^{18}F-FDG PET to detect hepatic lesions and ^{18}F-FES PET is used to evaluate ER status of detected hepatic lesions. Homogeneous uptake suggests the absence of lesions, but ER-positive lesions with similar uptake as the liver cannot be excluded; “hot spots” indicate ER-positive lesions; and “cold spots” indicate benign cysts, ER-negative lesions, but also lesions with low ER expression or even high expression (8, 31).

Our patient suffered from metastases three years after surgery, partly due to the insufficient post-operative adjuvant therapy. In addition to chemotherapy, she might also potentially benefit from intensified adjuvant treatment of abemaciclib, which was not available until April 2021. In consideration of the ER-positive pleural masses and ER-negative pulmonary nodules, the metastases of the lady showed ER heterogeneity. Notably, she showed the acceptable therapeutic effect of second-line CDK4/6i + fulvestrant after the first-line CDK4/6i + aromatase inhibitor (AI). The mechanism leading to CDK4/6i resistance included the loss of drug target genes such as RB and FZR1, the over-expression of genes which are involved in the progression of cell cycle, the over-expression of factors which are upstream of the cell cycle such as FGFR, PI3K/AKT/mTOR, and the TGF-β induced expression of several transcription factors involved in epithelial-mesenchymal transition (EMT) *via* Smad and the PI3K/AKT/mTOR pathways (32). Accordingly, the treatment choice after CDK4/6i fails included endocrine therapy in combination with mTOR inhibitor (e.g. everolimus) (33, 34), PI3K inhibitor (e.g. alpelisib) (35), another CDK4/6i (e.g. ribociclib, as in MAITAIN trial) (36) and HDAC (e.g. chidamide) (34). Antibody-drug conjugates (ADC) and chemotherapy would also be reasonable options under certain circumstances. Particularly, our patient was very reluctant to receive chemotherapy. She refused intravenous chemotherapy directly. We chose CDK4/6i as second- and third-line treatment to save other treatment methods with certain PFS for later use and to increase the time to chemotherapy (TTC). Therefore, so long as the dominant or newly-developed metastatic lesion was ER-positive on ^{18}F-FES PET, the patient would show certain therapeutic response towards endocrine-based treatment including second- and third-line of CDK4/6i.

4 Conclusion

This case demonstrated that ^{18}F-FES PET/CT could non-invasively show ER heterogeneity and predict the treatment response of second- and third-line CDK4/6i treatment in HR +/HER2- MBC after the first-line CDK4/6i failed. So long as the dominant metastatic lesion was ER-positive on ^{18}F-FES PET, the patient would show certain therapeutic response towards endocrine-based treatment and the time to chemotherapy (TTC) might be increased.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics review board of the Peking Union Medical College (PUMC) Hospital (IRB protocol #JS-2959). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

BP, ZH, and YX designed the study and wrote the first draft of the manuscript. ZW, RY, and XW made contributions to the acquisition of the clinical data. YZ, QS, and LH made critical revisions and approved final version. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Publisher's note

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Pseudoprogression after advanced first-line endocrine therapy in metastatic breast cancer with bone metastasis: A case report

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Approximately 75% of patients with advanced breast cancer develop bone metastasis, which significantly affects both the quality of life and the survival rate of patients. Accurate determination of the status of bone metastases is important for developing treatment strategies and the prognosis of the disease. Here, we report the case of a 33-year-old patient with advanced metastatic breast cancer (MBC) and multiple bone metastases, in which advanced first-line endocrine therapy and second-line chemotherapy were both considered unsuccessful according to the efficacy evaluation by conventional imaging. Considering the possibility of bone pseudoprogression, the original endocrine scheme was reapplied, and bone metastases achieved a great response of non-complete response (CR)/non-progressive disease (PD). This case showed that, in the course of therapy for the disease, if bone scintigraphy (BS) shows increased lesion density or new lesions, this probably indicates a favorable response (osteoblastic repair of osteolytic lesions) to therapy, and not the worsening of metastatic lesions, called bone pseudoprogression. This paper will provide new insights into strategies for the treatment of bone metastasis and shows the significance of distinguishing osteoblastic bone repair from real bone lesion progression in clinical settings.

KEYWORDS

pseudoprogression, flare, efficacy evaluation, bone metastasis, breast cancer

Introduction

Although the 5-year survival rate for early-stage breast cancer is around 80%, recurrence and metastasis nevertheless occur in 30%–40% of cases (1). Approximately 65%–75% of patients with metastatic breast cancer (MBC) develop bone metastasis. Bone is also the first site of metastasis for 27%–50% of patients with MBC (2). Skeletal complications of bone metastasis include bone pain, hypercalcemia, pathologic fractures, and spinal cord compression, all of which can greatly impair quality of life (3). However, although breast cancer with bone metastasis remains a virtually incurable disease, eliminating complications can improve quality of life and lead to better overall survival (OS). Standard treatments for bone metastasis are anticancer agents, such as chemotherapy and endocrine therapy, radiotherapy, and surgery. Bisphosphonates are generally used to prevent skeleton-related events.

Response to bone metastasis treatment is considered "unmeasurable" and is periodically estimated by using a combination of methods, including multiple kinds of imaging examinations, measurement of serum biochemical markers, and evaluation of patients' symptoms (4, 5). Efficacy evaluation by imaging techniques is an essential part of the management of bone metastasis in breast cancer and is significant in the formulation of treatment plans and the clinical prognosis of patients. Imaging by single-photon emission computed tomography/computed tomography (SPECT/CT), computed tomography (CT), or magnetic resonance imaging (MRI) is a conventional part of evaluating bone metastases. CT scans, especially bone window scans, play a significant role in the evaluation of bone metastases response (6), and are superior to SPECT and MRI for showing clearly any changes in bone structure. Whole-body bone scans (WBSs) may identify metastases at an earlier stage and provide more information than radiography, CT, or MRI. Fluorodeoxyglucose F 18 ([^{18}F]FDG) positron emission tomography/computed tomography(^{18}F-FDG PET/CT) has potential advantages over anatomical imaging in displaying changes in metabolic activity. By organically combining the functional phenomena of PET and the anatomical imaging of CT, it can show changes in metabolic activity before and after treatment for bone metastases, and it is more sensitive and specific than conventional imaging in detecting and evaluating bone metastases. The efficacy evaluation of bone metastases is of great importance in determining the appropriate treatment plan and clinical prognosis of patients. Although the diagnosis and treatment of bone metastases have been comprehensively improved, the efficacy evaluation of bone metastases is still less clear and controversial, and no consensus has been reached on the optimal imaging modality for this purpose. There is as yet no fully recognized standard for efficacy evaluation of bone metastases in breast cancer. Consistent, reproducible, and validated methods of assessing response to therapy have become even more important (7).

Fluorodeoxyglucose F 18 ([^{18}F]FDG) is the most popular agent in tumor imaging and [^{18}F]FDG PET/CT has become routine in clinical examination in recent years. It has played an important role in diagnosis, evaluation of tumor stage, and evaluation of efficacy. In terms of efficacy in bone metastases in breast cancer, it was found that some lesions with abnormally increased bone density had significantly lower glucose metabolism rates than osteolytic lesions and mixed lesions, demonstrating that local tumor cell proliferation is not actually active (8). This suggests that the enlargement or increase of osteogenic lesions indicated by CT or SPECT may be responsible for osteoblast repair rather than lesion progression, known as bone pseudoprogression.

The comprehensive use of various imaging methods to correctly determine the pseudoprogression of bone is important in the evaluation of the efficacy of bone metastasis in breast cancer; a diagnostic error may lead to a premature change in systemic drug scheme in clinics, which not only affects the choice of treatment plan and OS rate of patients but also shortens the application period of effective drugs. Herein, the case is reported of a premenopausal woman with advanced breast cancer with bone pseudoprogression that appeared after first-line therapy by CDK4/6 (cyclin-dependent kinase 4/6) inhibitors with aromatase inhibitors. We described the process of diagnosis, therapy, and efficacy assessment of skeletal lesions in detail, which should inform future clinical work.

Case report

In March 2020, a 33-year-old woman was admitted to the Second Hospital of Dalian Medical University with the principal complaint of having a painless lump in her right breast, which she found accidentally. The breast ultrasonography showed a 2.8 cm × 2.7 cm × 1.2 cm mass in the right breast, which was classified as 4C by the breast imaging reporting and data system (BI-RADS). A core needle biopsy was performed on 23 March 2020, and the subsequent pathology revealed adenocarcinoma (from the punctured tissue of the right breast mass)—non-specific invasive breast cancer grade 2—part of which was a high-nuclear-grade ductal carcinoma *in situ*. The immunohistochemical (IHC) report revealed ER (70%+), PR (50%+), HER-2 (1+), Ki-67 (about 30%+) and BRCA1 (−). At the same time, the CT scan showed no obvious abnormalities in the liver, brain, or lung; however, WBS suggested the possibility of bone involvement in malignant lesions. To be more accurate and for comprehensive staging, the patient underwent [^{18}F]FDG PET/CT examination on 31 March 2020, which showed multiple lymph nodes metastases (in the right axilla) and bone metastases (in the anterior coracoid process of the right scapula, 1st thoracic vertebra, first, second and fourth lumbar vertebrae, and right ilium) (Supplementary Figure 1). All bone metastases showed osteolysis and increased glucose metabolism, suggesting that tumor cells proliferated actively at

the lesion. The patient had no family history or genetic history of cancer. She was in good health and had no medical history of hypertension or diabetes or smoking, drinking, or other bad habits. In the end, the patient was diagnosed with grade 2 invasive breast cancer with lymph node metastasis in the right axillary and bone metastasis, cT2N3M1, stage IV.

The patient was administered advanced first-line endocrine therapy with palbociclib [125 mg po (per os, orally) qd (quaque die, daily) d1–d21, q28d] combined with exemestane (25 mg po qd) for six cycles from 30 March to 16 September 2020. During the same period, goserelin was used to suppress ovarian function and ibandronate monosodium was used to treat bone metastasis. During endocrine therapy, laboratory findings showed levels of tumor markers, and related biochemical indicators showed a slight decrease or a stable trend. The patient underwent CT and WBS on 16 September 2020 to assess efficacy. The CT showed that the primary lesion of the right breast reduced (59%), shrinking to 1.3 cm × 0.8 cm. WBS showed that the bone metabolism of the lumbar vertebra, right sacroiliac joint, and first thoracic vertebra decreased or even disappeared with increased bone density on CT (Figure 1A). The bone metabolism of the right scapula was similar, but its bone density on a CT scan showed an increase first and then a decline, suggesting that bone metastasis was progressing (Figure 1B, left). In addition, new nuclide-concentrated foci appeared in the right ninth rib, as shown by WBS, and the bone density of the lesion increased after endocrine therapy, so this was identified as a new lesion (Figure 1B, center and right). Based on the examination results at that time for the bone metastases and efficacy, the disease was categorized tentatively as progressive disease (PD). This meant that first-line endocrine therapy was not effective and the treatment plan should be changed.

From 22 September 2020, albumin-bound paclitaxel [200 mg intravenous glucose tolerance test (IVGTT) d1, d8, q21d] combined with capecitabine [1,500 mg po qd d1–d14, q21d] was administered as the second-line chemotherapy for six cycles, with ibandronate monosodium continuing. After four cycles of combined therapy, the CT scan showed that, despite most of the bone metastases being similar to before, the edge of the right iliac lesion had begun to blur (Figure 2A). Moreover, the level of alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) as well as CA125 had increased at the end of third cycle. All of these indicated the progression of the disease, and that the current treatment efficacy was poor. We switched to maintenance treatment with capecitabine alone for eight cycles and the patient continued to receive ibandronate monosodium injections every month. On 6 May 2021, the CT examination after the first two cycles of capecitabine alone showed different degrees of osteolytic changes in the right scapula (Figure 2B). Because the patient complained that the oral painkillers contributed nothing to the pain relief, overloaded doses of ibandronate monosodium were administered. At the end of second-line chemotherapy, an examination with CT and SPECT/CT scans was conducted on 26 July 2021, which indicated that the skeletal lesion had progressed again. The size of the right breast tumor continued to reduce; however, in comparison with the CT and SPECT/CT images before chemotherapy, most metastatic bone lesions showed osteolytic changes. The new osteolytic lesions were also found in the

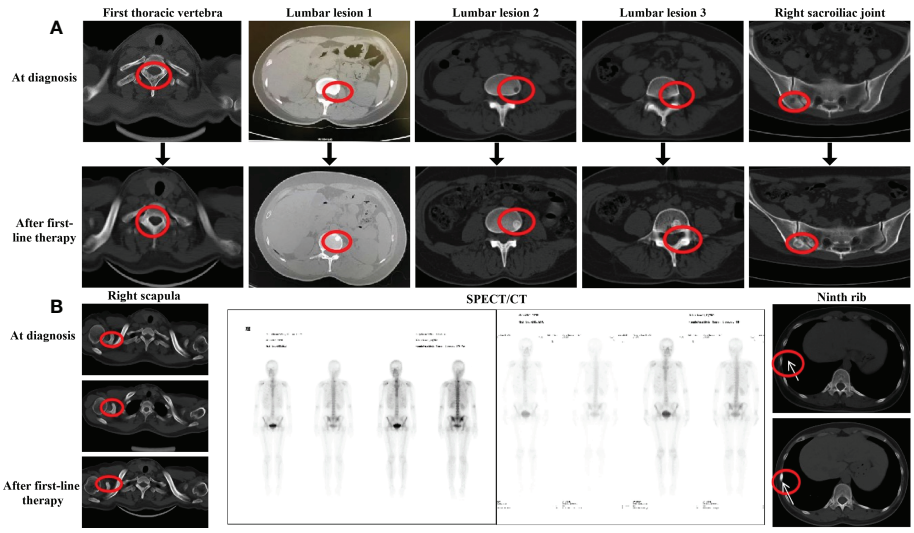

FIGURE 1
Evaluation after first-line endocrine therapy **(A)** CT evaluation of the bons lesion after first-line endocrine therapy in September 2020. **(B)** CT evaluation of right scapula the ninth rib and SPECT evaluation after first-line endocrine therapy in September 2020.

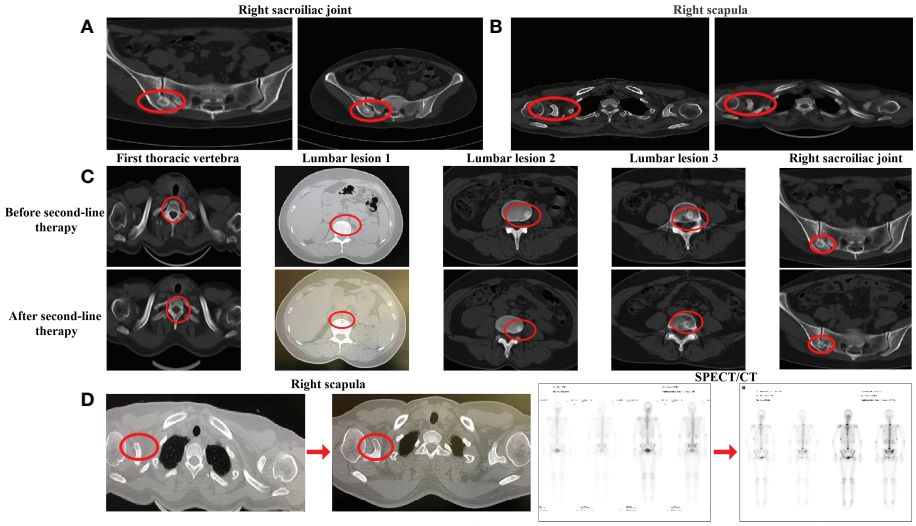

FIGURE 2
Evaluation after second-line chemotherapy. **(A)** CT evaluation of the right sacroiliac joint before chemotherapy and after cycles in December 2020. **(B)** CT evaluation of the right scapula before chemotherapy and after chemotherapy in May 2021 **(C)** CT evaluation of the bone lesion after second-line therapy in July 2021, **(D)** CT evaluation of the right scapula and SPECT evaluation after second-line therapy in July 2021.

thoracic vertebra, the first and third lumbar vertebrae, and the right sacroiliac joint (Figure 2C), and the original osteolytic lesion in the coracoid process of the right scapula was enlarged (Figure 2D, left). In addition, WBS demonstrated that there were multiple new nuclide-concentrated foci. Combined with the decreased density of bone lesions, increased tumor markers, and the exacerbation of bone pain symptoms, after efficacy evaluation the disease was categorized as PD again (Figure 2D, right); the advanced second-line chemotherapy was declared a failure.

With the failure of advanced first-line and second-line therapy, we reviewed the patient's previous imaging outputs and found that the changes in bone lesions after first-line endocrine therapy may be similar to bone pseudoprogression and considered that the first-line efficacy evaluation may be wrong. Despite the lack of evidence-based medical evidence and guidelines, after multidisciplinary treatment (MDT), we changed the treatment regimen to the original endocrine regimen. During 3 months of the re-administration, the patient's clinical manifestations and other indicators generally improved, the CT scan revealed that the scope of osteogenic lesions expanded, and the density increased (Figure 3A). In October 2021, approximately three cycles after endocrine therapy administration, the patient received radiotherapy as a synergistic treatment. [^{18}F]FDG PET/CT in the same month demonstrated that the FDG uptake in multiple original bone lesions (thoracic vertebrae, lumbar vertebrae, and right sacroiliac joints) decreased significantly or disappeared, and lesion density changed from osteolysis into osteogenesis (Figure 3B). All the above conditions were considered to be a sign of reactive osteogenesis after treatment for the metastatic tumor. Because of the results of [^{18}F]FDG PET/CT scans and the improvement of clinical manifestations, we believed that tumor proliferation of bone metastases was inhibited. The increased osteogenesis phenomenon was considered to be osteoblastic repair; this suggested that the current treatment options were effective.

After seven cycles, a breast CT scan showed a significant reduction in the lesion size in the right breast (the maximum measurement diameter was about 0.6 cm); and after 15 cycles (October 2022) the lesion size remained stable. After 10 cycles, the osteoblastic range of each bone metastasis lesion continued to increase, and osteolytic lesions of the right scapular acoid began to show osteogenic changes (Figures 4A–D). SPECT/CT scan indicated increased bone density and a decrease in the number of bone-concentrated foci and the degree of nuclide concentration (Figure 4E). Those changes were considered for reactive osteogenesis after multiple bone metastases therapy. The results of relevant laboratory findings are also very important and support the efficacy evaluation. We systematically reviewed tumor markers such as CEA, CA153, and CA125 during the whole treatment, which were all within the normal range, although there were changes during different therapy stages. The values of ALP and LDH showed obvious variation at different stages of the treatment. The levels of both enzymes fluctuated within the normal range during endocrine therapy, both increased to varying degrees during the advanced second-line chemotherapy, and both decreased to within the normal range after the original endocrine therapy was applied

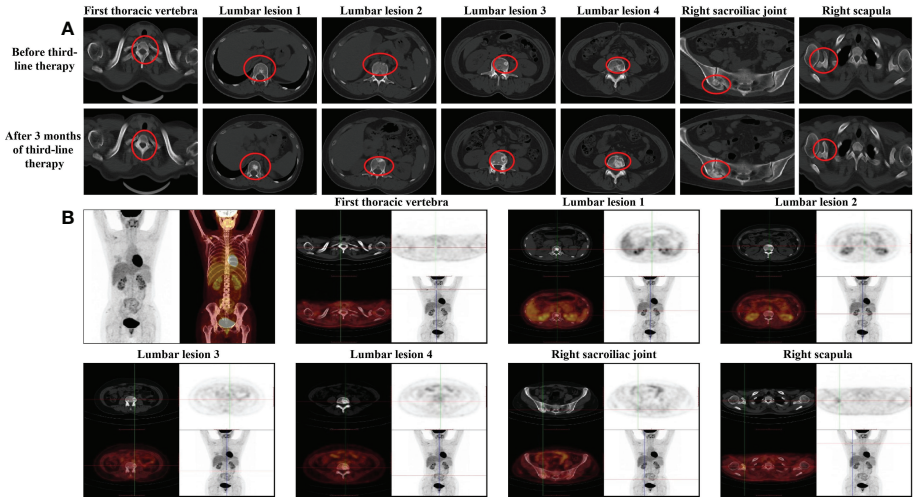

FIGURE 3
Imaging examinations during the third-line endocrine therapy **(A)** CT evaluation of the bone lesion after 3 months of third-line endocrme therapy in October 2021. **(B)** PET/CT evaluation of each bone lesion after 3 months of third-line endocrine therapy in October 2021.

(Supplementary Figures 2, 3). In addition, the latest treatment relieved pain and improved the patient's health-related quality of life. Above all, the efficacy evaluation achieved a great response of non-CR/non-PD, and the original endocrine therapy was a hard-won success. At the time of writing, the patient had been receiving endocrine therapy for 15 months and remained progression free, showing good tolerability and a high quality of life.

Discussion

As far as breast cancer is concerned, the incidence of bone metastasis is high, patient quality of life is poor, and there are many changes after therapy. Diagnosis, treatment, and efficacy evaluation are challenges that need to be addressed in clinical practice. Internationally, there are four main criteria for the efficacy evaluation in bone metastases: those of the International Union Against Cancer (UICC) (9), the World Health Organization (WHO) (10), the MD Anderson Cancer Center USA (MDA) (2), and the Positron Emission Tomography Response Criteria in Solid Tumor (PERCIST) (11). The WHO's efficacy evaluation criteria for bone metastases of 1981 declares that partial response (PR) includes "decreased density of blastic lesions for at least four weeks", and progressive disease (PD) is defined as an "increase in the size of existent lesions or appearance of new lesions" (10), which is not universally accepted by clinical experts around the world because it is not consistent with clinical cases.

In 2018, a Chinese professor, Song Santai, proposed that the increase and enlargement of osteoblastic lesions should not be understood to automatically indicate the progression of bone metastasis and may instead be a sign of effective treatment in certain circumstances. Decreased bone density and osteolytic changes that occurred in osteoblastic lesions were the symptoms of deterioration when the next-line therapeutic scheme should be initiated (12). Although in complete contradiction with the WHO's guidance, Song's view has already been verified in clinical settings successfully, and more and more clinicians around the world raise doubts about the WHO's criteria. In recent years, new bony lesions that may represent osteoblastic bone healing have been studied extensively and defined as bone pseudoprogression. In 2021, Professor Zhang Jian and his team launched a clinical trial that used WBS to monitor disease progression in bone in 48 patients with hormone receptor-positive MBC. It was found that osteoblastic new bony lesions detected on follow-up may represent bone pseudoprogression (13). Huang et al. reported that a woman with MBC had pseudoprogression after first-line therapy that included palbociclib combined with exemestane (14). At the time of writing, all published articles about bone pseudoprogression in breast cancer have involved HR-positive patients who developed bone pseudoprogression during or after endocrine therapy. However, no studies have proved a direct connection between bone pseudoprogression and endocrine therapy. A large number of scholars attribute this to the fact that HR-positive patients account for the largest proportion of breast cancer patients, and bone metastasis is a common occurrence in MBC.

The presence of metastatic lesions in breast cancer can influence bone homeostasis to favor bone resorption or bone formation by affecting the activity of osteoclasts or osteoblasts, thereby resulting in osteolytic, osteoblastic, or mixed lesions (15,

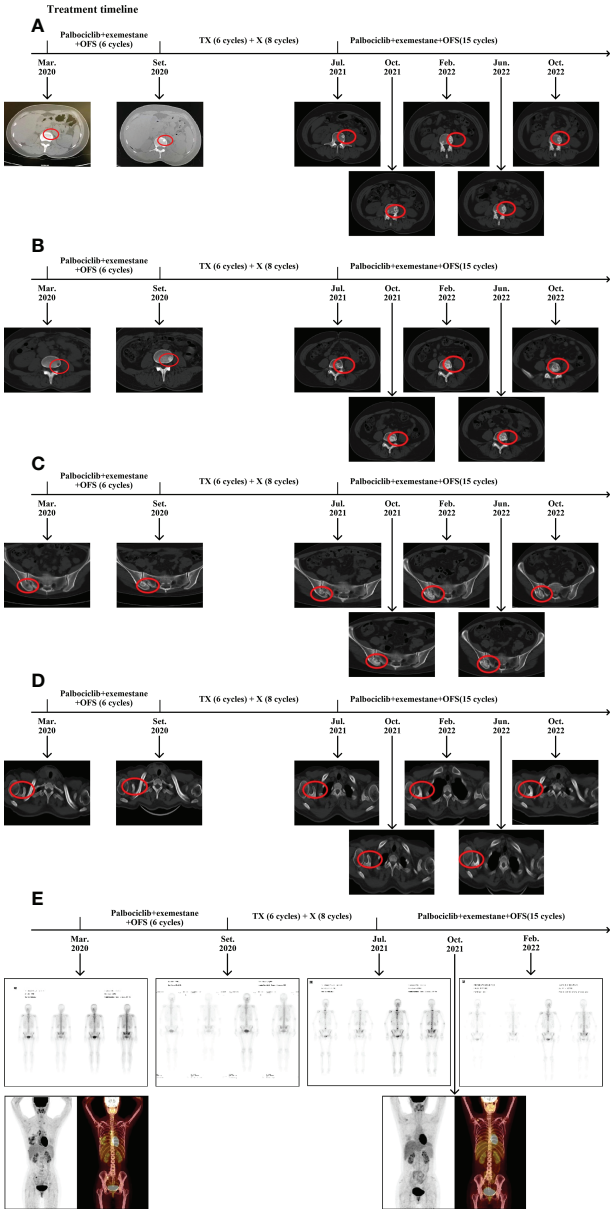

FIGURE 4
Changes in bone lesions during the treatment. **(A)** CT evaluation of the lumbar lesion 1 during the treatment. **(B)** CT evaluation of lumbar the lesion 2 during the treatment. **(C)** CT evalution of the right sacroiliac joint during the treatment. **(D)** CT evaluation of the coracoid process of the right scapula during the treatment. **(E)** SPECT/CT evaluation during the treatment. T: Albumin paclitaxel; X: Albumin paclitaxel.

16). It is known that most bone metastases in breast cancer are osteolytic (17). Although osteoblastic metastases in breast cancer are relatively rare, it is easy to misdiagnose and initiate the wrong treatment. It should be noted that not all newly emerging skeletal lesions, increases in skeletal lesion density, and expanded ranges of skeletal lesions are indicative of progression; this may be osteogenic repair after treatment of osteolytic lesions and a manifestation of effective therapy (13, 14). Therefore, we need to explore the combination of multiple imaging methods to accurately evaluate the response of bone metastases to treatment. Effective treatment should be continued if patients' clinical manifestations are relieved, and osteogenesis is observed.

In this case, the efficacy evaluation of advanced first-line endocrine therapy was not completely correct. Reviewing the course of the disease, initial imaging seemed to indicate bone flare, and the increased and enlarged lesions after first-line endocrine therapy were mistaken for progression, which misled the clinical evaluation of endocrine resistance, thus a

premature switch to chemotherapy that was harmful to the patient. Scintigraphic bone flare sign is characterized by an increase in the intensity of tracer uptake at the sites of bone metastases and/or the appearance of "new" lesions shortly after the commencement of treatment (18, 19). The phenomenon referred to as new or more prominent osteoblastic bony lesions arises in the tumor lesions because of effective therapy. Osteoblasts mediate bone healing, and an early increase in osteoblast activity following successful systemic therapy has been observed, as evidenced by increased radiotracer uptake on WBS. Some serial biochemical measurements of osteoblast function also confirmed the flare response (20). As a result, bone flares can be considered a sign of therapeutic efficacy. However, the osteolytic lesion that has been overlooked on WBS before therapy might also present a new site of radiotracer uptake. Therefore, the patient may be misinterpreted as indicating possible PD (21). In our case, all bone metastases were osteolytic lesions when they were diagnosed, and glucose metabolism of all lesions increased, suggesting tumor cells proliferate vigorously. After first-line endocrine therapy, a CT scan showed that the possibility of the osteoblastic bone repair of osteolytic lesions was considered. In addition, the re-examination of WBS revealed that a new lesion had appeared. The above situations suggest that, through effective treatment, not only does osteolytic bone destruction turn into osteoblastic bone repair, but those tiny osteolytic lesions that cannot be detected by conventional imaging also show osteogenic repair. As a result, both new lesions and enlarged lesions observed on later imaging were actually the results of osteoblastic bone repair, and the number of bone repair lesions after treatment is often greater than the number of original sites of osteolytic destruction (22).

Therefore, when the progression was defined after second-line chemotherapy, we re-analyzed images carefully and finally defined relevant evidence of increased bone lesion density on bone window CT during endocrine therapy through repeated comparison. There was a great possibility that the osteoblastic flare phenomenon had occurred; the progression during this period was considered to be bone pseudoprogression. The appearance of these lesions as a result of osteoblastic repair proved that the patient was sensitive to endocrine therapy, so the original endocrine scheme was resumed. This choice was based on an adequate analysis of the previous images and knowledge of pseudoprogression, although it was without support from evidence-based medicine and guidelines. During the treatment of the original endocrine scheme, results of periodic bone window CT scans demonstrated that all bone metastases had successively exhibited osteoblastic changes, and the osteoblastic range was continuously expanding. SPECT/CT tomographic fusion imaging also confirmed that increased bone density and decreased degree of concentration were osteoblastic repair changes after treatment. The efficacy of bone metastases was evaluated as non-CR/non-PD, and, combined with the reduction of the primary lesion, the improvement of clinical symptoms, and the decrease of tumor markers, the original endocrine therapy was considered effective.

There were still two limitations during the treatment. We did not perform a needle biopsy to confirm the pathological diagnosis of multiple bone metastases, and we did not incorporate the corresponding biochemical markers to evaluate efficacy. Needle biopsy is an invasive procedure; it is not ethical to perform a needle biopsy on every bone metastasis. Clinically, we usually make a judgment through imaging and other non-invasive methods. Besides, when local small lesions or a small number of lesions change, the corresponding biochemical markers often do not increase enough to show the change sensitively. At this time, the most effective method is to evaluate by imaging and patient symptoms, which also highlights the significance of imaging methods in evaluating the efficacy of bone metastases.

With immunotherapy becoming a more popular practice, pseudoprogression is a common phenomenon. The possibility of osteoblastic flare should be considered to avoid a misinterpretation of radiological findings, emphasizing that accurate efficacy evaluation of imaging plays a pivotal role throughout the treatment. Our case report points out that timely follow-up imaging and a critical analysis of both clinical and iconography evolution are vital for making the right therapeutic decisions (23). With the findings assessed by WBS, CT, SPECT/CT, and [^{18}F]FDG PET/CT in this case, and in conjunction with other studies on the progression of pseudobone, it is not clear which imaging modality can be isolated to assess accurate response in bone metastasis. From our point of view, the best imaging modality to assess accurate response in bone metastasis is a combination of various imaging methods, and it is significant to compare the density change of the same bone metastasis site before and after treatment. When different imaging results are contradictory, [^{18}F]FDG PET/CT is recommended to clarify the efficacy evaluation. In future clinical research, we will continue to work to build a diagnosis and treatment model for early detection and diagnosis of bone pseudoprogression to make progress in the study of bone metastasis pseudoprogression of breast cancer.

Conclusion

This is the first clinical case of pseudoprogression in a patient who changed to the original endocrine therapy scheme after pseudoprogression was found. Although the imaging progression, the patient's clinical manifestations improved during endocrine therapy. Clinicians should be aware of the

possibility of bone pseudoprogression in an MBC patient with bone metastasis. We must analyze and observe the changes carefully, and pharmacotherapy should not be hastily discontinued. On the basis of improvement of clinical symptoms, we must analyze and observe the changes carefully, and should not change the treatment plan hastily.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.1099164/full#supplementary-material

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Ultrasound-guided microwave ablation for giant breast leiomyoma: A case report

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Rationale: Breast leiomyoma is the rarest non-epithelial tumor of the breast. As a benign tumor, its main treatment is regular follow-up. Surgical treatment is often used in clinical practice when patients have symptoms or strongly require treatment. However, if the tumor is large or located around the nipple or areola, the cosmetic effect of surgery is not good, so it is urgent to find new treatment methods. We pioneered the use of microwave ablation in the treatment of giant breast leiomyoma and achieved good results.

Patient concerns: A 37-year-old female was admitted to hospital because she found a breast mass of approximately 8 cm. She had no obvious clinical symptoms, but had great psychological pressure.

Diagnosis: Pathological biopsy showed leiomyoma followingly the surgical operation of giant breast leiomyoma was planned. However, the breast mass was large, and the postoperative scar would affect the breast appearance.

Interventions: The consent was obtained from the patient and her family. The Ultrasound-guided microwave ablation was successfully performed.

Outcomes: The patient was followed up for 10 months, and the tumor volume ablation rate was 69.8%. The cosmetic effect of breast was excellent.

Lessons: To our knowledge, this is the first case to using microwave ablation (MWA) for the treatment of breast leiomyoma. Ultrasound-guided MWA can be used for the treatment of breast leiomyoma, especially when the mass is large and requires traditional surgical resection. It can effectively improve the breast aesthetics and further improve the quality of life of patients. However, it is only a case report, and needs more research to verify MWA in breast leiomyoma.

KEYWORDS

ultrasound$_1$, breast$_2$, leiomyoma$_3$, microwave ablation$_4$, therapy$_5$

Abbreviations: MWA, microwave ablation.

1 Introduction

Breast leiomyoma is considered as the rarest non-epithelial tumor of the breast, accounting for less than 1% of all breast neoplasms (1, 2), and it usually occurs in middle-aged women. At present, the clinical manifestations, imaging features and differential diagnosis of breast leiomyoma have been reported in the related studies (3–5), but the treatment of breast leiomyoma is rare. In clinical practice, traditional surgical resection is often chosen for the treatment of large breast leiomyomas. However, postoperative scars can affect the appearance of the breast, or cause nipple traction and tilt or damage to the breast ducts. It's urgent to find new treatments to improve the prognosis of patients with large breast masses. We reported a case of giant breast leiomyoma treated by ultrasound-guided microwave ablation (US-MWA) and followed up for 10 months.

2 Case report

A 37-year-old woman complained with a mass in the left breast and visited our hospital. One month ago, the patient accidentally found a goose-egg-sized mass in the lower inner quadrant of the left breast, which was hard but removable. The patient did not have any clinical symptoms, no breast skin change or ipsilateral axillary lymph node enlargement, etc. The patient had been in good health and had no family history of breast cancer. In the inner and lower quadrant gland of the left breast, enhanced MRI revealed a hypoechoic oval mass measuring 7.6*6.6*7.5cm mass that showed progressive enhancement in the arterial phase and diffuse enhancement in the delayed phase. The dynamic enhancement curve (TIC type) of this mass was characterized as plateau type (type II). The mass was classified as being in Breast Imaging-Reporting and Data System (BI-RADS) category 4. It had morphological rules and circumscribed margins, and was coincident with the location described through US (Figures 1A, B). The patient was diagnosed as breast leiomyoma by pathological examination *via* sonography guide core needle biopsy (Figure 2). Because of the large size of the tumor, the surgeon recommended that the patient undergo traditional surgical resection, but the incision should be at least 4cm. The patient is a young woman who has a strong desire to keep a good-looking appearance of the left breast. Finally, the patient chose to undergo US-MWA to treat the giant leiomyoma of the left breast.

2.1 Preoperative examination

No abnormality was found in blood routine, coagulation and pre transfusion examinations. The 2D-Ultrasound Contrast-enhanced ultrasound (CEUS) was performed using Mindry Resona 7 ultrasound system to discover the optimal ablation puncture path (Figures 1C, D).

2.2 Ablation process

The surgeon was a radiologist with more than 10 years of experience in interventional therapy. Instruments used during the

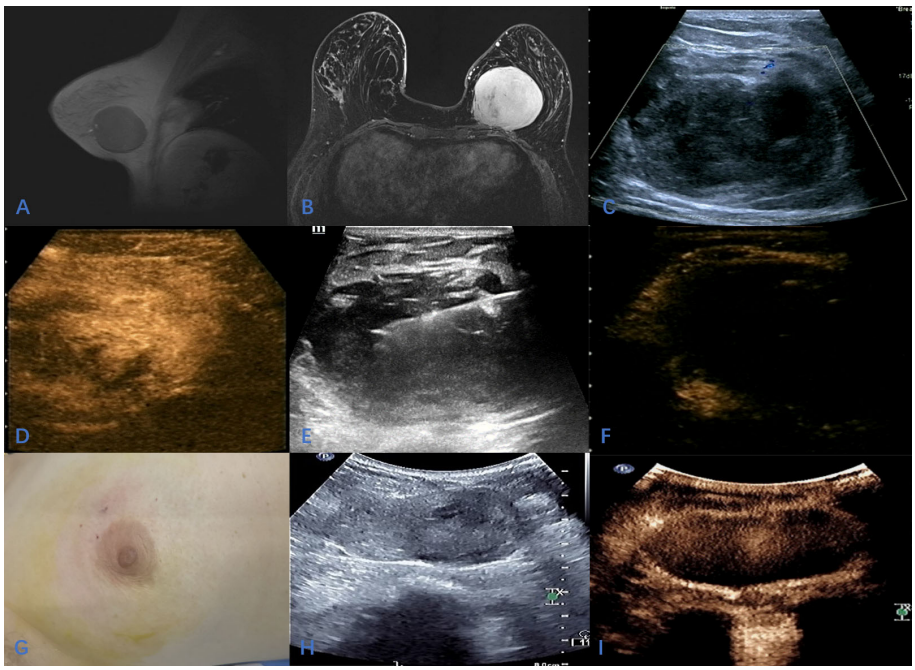

FIGURE 1
A 37-year-old female with huge mass in the left breast; **(A, B)** The location of the tumor on enhanced MRI; **(C)**; Sonographic appearance of the tumor on 2D-Ultrasound; **(D)** Contrast-enhanced ultrasound showed homogeneous hyperenhancement of the tumor during the arterial phase; **(E)** During ultrasound-guided microwave ablation; **(F)** The area of ablation showed no enhancement in arterial phase and venous phase after ablation; **(G)**; The skin of the breast was slightly ecchymosis after ablation, and the appearance of the breast was intact; **(H, I)** After 10 months of follow-up, two-dimensional ultrasound showed that the mass was significantly reduced, and CEUS showed that there was no enhancement in the arterial phase and venous phase of the ablation area.

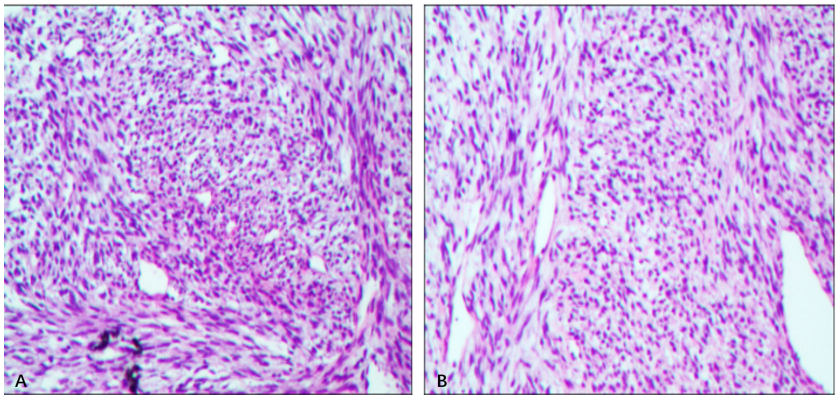

FIGURE 2
Histological sections revealing monotonous spindle cell proliferation, necrosis or mitotic figures found. **(A, B)** Histologic image of leiomyoma. (H&E, × 400).

operation include Mindry Resona 7 ultrasound system, microwave ablation instrument (Nanjing Kangyou, 2000KY), sterile disposable microwave ablation needle (3mm in diameter). The operative region was disinfected and shopped towels routinely. The operative procedure was started under local anesthesia. The use of refrigerated saline (3-5°C) to isolate and protect the breast tissue and pectoralis muscle around the tumor before ablation could reduce the high temperature caused by thermal ablation and avoided thermal damage to the surrounding tissues during ablation. The intraoperative ablation power was 20-40W. During the operation, short time, long time interval and multiple ablations were performed. When the hyperechoic area was completely covered by ablation, CEUS examination was performed, and there was no enhancement in the ablation area, indicating that the ablation was completed. (Figures 1E, F). Patients were instructed to apply ice at an interval of 24 hours after ablation.

2.3 Postoperative follow-up

The patient had postoperative pain in the operation area, and the VAS score was 4. After cold compress, the swelling and pain in the operation area decreased significantly after about 3 days, and returned to normal in about 3 weeks. There was slight ecchymosis, redness and swelling on the skin of the operation area after operation (Figure 1G), which disappeared completely after 4 weeks. Patients were reexamined after 10 months of follow-up using Philips EPIQ 7 ultrasound system. CEUS showed no enhancement in the ablation area of the left breast, and the size of the ablation area was 6.0*3.5*5.4cm. The ablation area was completely ablated without recurrence, and the lesion was significantly smaller than before (Figures 1H, I). The tumor volume ablation rate was 69.8%.

3 Discussion

Breast leiomyoma is a rare benign mesenchymal tumor that presents as an isolated, slow-growing tumor with features similar to those of the most common benign tumors (3, 6). At present, the cell origin of breast parenchymal leiomyoma is not fully understood (7). Several hypotheses have been proposed, including theories of embryonic transposition of smooth muscle cells from smooth muscle hemangioma cells or pluripotent mesenchymal cells and smooth muscle cells in the areola (8–11).

Treatment of breast leiomyomas is controversial. One study reported that the patient had no malignant transformation during a 9-year follow-up period (12). Breast leiomyoma without obvious clinical symptoms can also be similar to other benign breast tumors and regularly followed up. However, it has been reported that in order to avoid local recurrence, the standard recommended treatment is local resection with free margins (13). The patient in this case report underwent microwave ablation for minimally invasive treatment due to high pressure on breast appearance and concerns about excessive tumor volume.

It was our first attempt to ablate such a large breast mass, which was close to the pectoralis major muscle. During the operation, we adopted some ablation technology reforms to reduce the patients' pain during the operation and improve postoperative prognosis. In this report, the limited experience with ultrasound-guided giant breast leiomyomas is summarized as follows: Firstly, we used refrigerated sterile saline to isolate the tumor from the surrounding tissue, which neutralized the heat generated by thermal ablation, reduced the patient's pain, and increased the operator's visibility of the surgical area. Secondly, short time ablation, long time interval and multiple ablations during the operation could maximize the protection of surrounding tissues and adjacent muscle tissues and avoid thermal damage.

To the best of our knowledge, this is the first treatment of breast leiomyoma using MWA. Moreover, this was a case report, and the follow-up period was short and only 10 months. Additional follow-up MRI should have been performed, but the patient declined to undergo MRI because of mild claustrophobia after the initial preoperative MRI, and we used contrast-enhanced ultrasonography for postoperative follow-up. The application of MWA in the treatment of breast leiomyoma still needs multi-center and large sample studies to confirm its efficacy and safety. Patients after ablation should be followed up for a longer period of time to observe whether the absorption pattern of the ablation area after ablation is similar to other benign breast tumors.

4 Conclusion

Ultrasound-guided MWA may be used for breast leiomyoma which can completely ablate tumor and retains the integrity of the breast shape, especially when the tumor volume is large, minimally invasive surgery cannot be performed. However, it is only a case report, and needs more research to verify MWA in breast leiomyoma.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Cancer Hospital affiliate to School of Medicine, University of Electronic Science and Technology of China (UESTC) Medical Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication. SZ, LW, ML designed the study and drafted the manuscript. SZ, LW, and JY performed data collection and data analysis. SZ wrote the manuscript, and ML supervised the study and critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Sacituzumab govitecan and radiotherapy in metastatic, triple-negative, and BRCA-mutant breast cancer patient with active brain metastases: A case report

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Background: Triple-negative breast cancer (TNBC) is an aggressive cancer subtype, owing to its high metastatic potential: Patients who develop brain metastases (BMs) have a poor prognosis due to the lack of effective systemic treatments. Surgery and radiation therapy are valid options, while pharmacotherapy still relies on systemic chemotherapy, which has limited efficacy. Among the new treatment strategies available, the antibody-drug conjugate (ADC) sacituzumab govitecan has shown an encouraging activity in metastatic TNBC, even in the presence of BMs.

Case presentation: A 59-year-old woman was diagnosed with early TNBC and underwent surgery and subsequent adjuvant chemotherapy. A germline pathogenic variant in BReast CAncer gene 2 (BRCA2) was revealed after genetic testing. After 11 months from the completion of adjuvant treatment, she had pulmonary and hilar nodal relapse and began first-line chemotherapy with carboplatin and paclitaxel. However, after only 3 months from starting the treatment, she experienced relevant disease progression, due to the appearance of numerous and symptomatic BMs. Sacituzumab govitecan (10 mg/kg) was started as second-line treatment as part of the Expanded Access Program (EAP). She reported symptomatic relief after the first cycle and received whole-brain radiotherapy (WBRT) concomitantly to sacituzumab govitecan treatment. The subsequent CT scan showed an extracranial partial response and a near-to-complete intracranial response; no grade 3 adverse events were reported, even if sacituzumab govitecan was reduced to 7.5 mg/kg due to persistent G2 asthenia. After 10 months from starting sacituzumab govitecan, a systemic disease progression was documented, while intracranial response was maintained.

Conclusions: This case report supports the potential efficacy and safety of sacituzumab govitecan in the treatment of early recurrent and BRCA-mutant TNBC. Despite the presence of active BMs, our patient had a progression-free survival (PFS) of 10 months in the second-line setting and sacituzumab govitecan

was safe when administered together with radiation therapy. Further real-world data are warranted to confirm sacituzumab govitecan efficacy in this patient population.

KEYWORDS

sacituzumab govitecan, triple-negative breast cancer, brain metastases, BRCA2, antibody-drug conjugate

Introduction

Triple-negative breast cancer (TNBC), characterized by the lack of expression of the estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2), accounts for approximately 12–15% of breast cancers diagnosed worldwide (1–3). Despite extensive studies that have led to a better understanding of its clinical and biological heterogeneity (4–6), TNBC remains the most aggressive breast cancer subtype, owing to its high visceral metastatic potential, especially to the lungs and brain (7): The median overall survival (OS) is 10–13 months in the metastatic setting (1).

A recent meta-analysis highlighted that approximately one-third of patients with metastatic TNBC will eventually develop brain metastases (BMs) (8). The main current therapeutic options for BMs in TNBC are surgery and radiation therapy, either stereotactic radiosurgery (SRS) or whole-brain radiotherapy (WBRT) (9, 10): In particular, WBRT should be the favored choice for multiple BMs not amenable to SRS, due to neurological symptoms, size, number, and/or location (10).

BM pharmacotherapy of patients with TNBC remains challenging due to the lack of targeted therapies and the difficulties associated with drug delivery to the brain. Moreover, few data are available on the role of systemic treatments because patients with BMs have been generally excluded from clinical trials for several reasons, such as limited penetration of agents through the blood–brain barrier, difficulties in monitoring the response, and typically poor prognosis (11). Cytotoxic chemotherapy remains the mainstay of systemic treatment for BMs in TNBC, with an objective response rate (ORR) of about 30% (9, 10, 12), and different chemotherapy agents have been employed, such as taxanes, anthracyclines, etoposide, platinum compounds, capecitabine, and temozolomide (12–14).

For this reason, various efforts have been made to develop new therapeutic options and to identify molecular biomarkers, with the purpose of improving the clinical outcomes of patients with TNBC (15). From the expression of the programmed death-ligand 1 (PD-L1), patients who are more likely to benefit from the association between an immune checkpoint inhibitor (ICI) and chemotherapy in the metastatic setting may be selected (16, 17). However, the benefit for patients with BMs is uncertain.

Additionally, nearly 15% of patients with TNBC harbor a germline mutation of BRCA1 and/or BRCA2 (18). Although these patients may receive benefit from poly(ADP-ribose) polymerase (PARP) inhibitors, such as olaparib and talazoparib (19, 20), no data are available on the efficacy of PARP inhibitors in TNBC patients with BMs and new agents able to cross the blood–brain barrier are under development (21).

Sacituzumab govitecan is a first-in-class antibody-drug conjugate (ADC) that targets the human trophoblast cell-surface antigen (Trop-2), which is expressed on approximately 90% of TNBCs, and delivers its payload based on SN-38, the active metabolite of irinotecan (22, 23). The phase III ASCENT trial demonstrated a significant improvement over standard chemotherapy with respect to median progression-free survival (PFS) and median OS in TNBC patients who had received at least two chemotherapy regimens for advanced disease (24). TNBC patients with stable BMs were eligible to enter the trial, but they were a small cohort (61 patients) and excluded from the primary analysis; patients with active BMs were not eligible. Furthermore, in this trial, only 7% of patients had BRCA1/2 mutations and information on BRCA status was lacking in 38% of study population (24).

In this report, we present the clinical course and outcomes of a metastatic, early recurrent, TNBC patient, with a BRCA2 mutation and active BMs, who showed a remarkable response to radiotherapy combined with sacituzumab govitecan as second-line treatment.

Case presentation

In December 2019, a 59-year-old woman presented with a left breast mass measuring 13 mm. Twenty-seven years before presentation, when she was 32 years old, she was diagnosed with stage II triple-negative left breast cancer and was treated with surgery, adjuvant chemotherapy, and radiotherapy; after 12 years (15 years before presentation), she was diagnosed with contralateral stage II TNBC and was treated similarly with surgery, adjuvant anthracycline-based chemotherapy, and radiotherapy. Her family history was notable for breast cancer in her maternal aunt.

An ultrasound-guided core biopsy showed grade 3, invasive TNBC, and a Ki-67 expression of 90%. Preoperative staging with CT scan did not show other metastatic lesions. She underwent a left-sided skin-sparing mastectomy and subsequently completed adjuvant chemotherapy with epirubicin and cyclophosphamide followed by weekly paclitaxel. A germline genetic testing was performed, which revealed the presence of a pathogenic variant in

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BRCA2 (8765delAG); however, no adjuvant PARP inhibitor therapy was available at that time. Due to the BRCA2 germline pathogenic variant, she underwent risk-reducing bilateral salpingo-oophorectomy 10.5 months after completing adjuvant treatment. A routinary chest CT scan after surgery revealed the appearance of two right pulmonary nodules (5 and 9 mm) and a subsequent 18F-FDG PET confirmed their high metabolic activity and demonstrated pathological uptake in the right hilar lymph nodes. A bronchoscopy with fine-needle aspiration cytology of the lymph nodes assessed the presence of neoplastic cells, whose morphology was attributed to breast carcinoma. Immunohistochemical studies confirmed TNBC and the PD-L1 expression (Ventana SP142) was < 1%. Brain CT scan was negative. The disease-free survival (DFS) in the adjuvant setting was 18.5 months.

With her score being '0' on the Eastern Cooperative Oncology Group performance status (ECOG PS) scale, in August 2021, the patient began first-line chemotherapy with carboplatin AUC 2 and paclitaxel at 90 mg/m^2 on days 1, 8, 15 every 28 days. After 3 months from starting chemotherapy, the patient reported a progressive onset of headache: Brain CT scan showed the appearance of numerous lesions, both in the cerebellum (10-mm diameter in the right hemisphere) and in the supratentorial region (5 mm in the parietal and frontal lobes, bilaterally). The radiological evaluation also documented pulmonary, hilar nodal, bone, and bilateral adrenal disease progression, resulting in a PFS of 3.5 months after the first-line treatment.

Her ECOG PS score then became '1' as she did not complain further symptoms, apart from the headache. Considering the unavailability of clinical trials in our hospital at that time and the patient's preference to continue systemic therapy, sacituzumab govitecan was requested as part of the Expanded Access Program (EAP). Treatment was approved by the local ethics committee and the patient provided written informed consent prior to the initiation of treatment.

Sacituzumab govitecan, at 10 mg/kg (on days 1 and 8 every 21 days), was started as second-line treatment in January 2022. After the completion of the first cycle, the patient described a rapid clinical benefit and reported a reduction both of the headache intensity and of the need for corticosteroids. Nonetheless, due to the extensive central nervous system (CNS) involvement and the uncertainty with respect to the depth and the duration of intracranial clinical response, the patient also received WBRT (30 Gy in 10 fractions), starting 2 days after day 8 of the first cycle. Treatment with sacituzumab govitecan was restarted 8 days after the end of WBRT upon patient's request. The CT scan restaging after three cycles of sacituzumab govitecan showed a significant partial response on all disease sites and a near-to-complete intracranial response. Considering the absence of new lesions and/or edema after WBRT, treatment with corticosteroids was gradually tapered and stopped 21 days after the end of radiotherapy. Her PS remained good and treatment tolerance was globally acceptable, with the prevalent side effects of grade 1 (G1) or 2 (G2): G2 asthenia, G1 diarrhea, G2 neutropenia, and G1 dry skin. However, after the completion of four cycles of treatment, G2 asthenia persisted despite supportive treatment (reintroduction of low-dose corticosteroids and ginseng supplements) and made a significant impact on the patient's quality of life; therefore, in agreement with the patient, sacituzumab govitecan was reduced to 7.5 mg/kg and was continued at this dose. No further relevant adverse events emerged during treatment; after 10 months from starting sacituzumab govitecan, a CT scan documented systemic disease progression, while intracranial response was maintained.

Our patient's timeline is reported in Figure 1 and the radiological evaluations of extracranial (lung) and intracranial response during sacituzumab govitecan treatment are reported in Figures 2, 3.

Discussion

This case report outlines the efficacy of sacituzumab govitecan as a second-line treatment in a patient with metastatic TNBC, who harbors a BRCA2 mutation and active BMs.

Patients with BRCA-mutant TNBC have an increased susceptibility to DNA-damaging drugs, such as platinum compounds (25); indeed, the TNT trial demonstrated a double ORR with carboplatin *versus* docetaxel in subjects with BRCA-mutant metastatic TNBC (68% *vs.* 33%, respectively) (26).

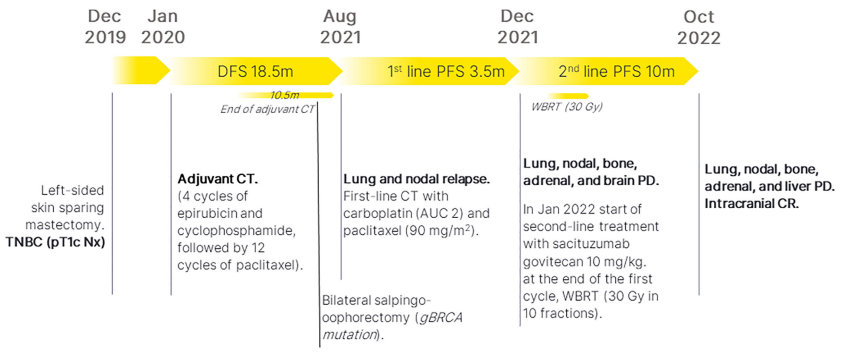

FIGURE 1
Patient's timeline. TNBC, triple-negative breast cancer; CT, chemotherapy; DFS, disease-free survival; PFS, progression-free survival; PD, progressive disease; CR, complete response; WBRT, whole-brain radiotherapy; m, months.

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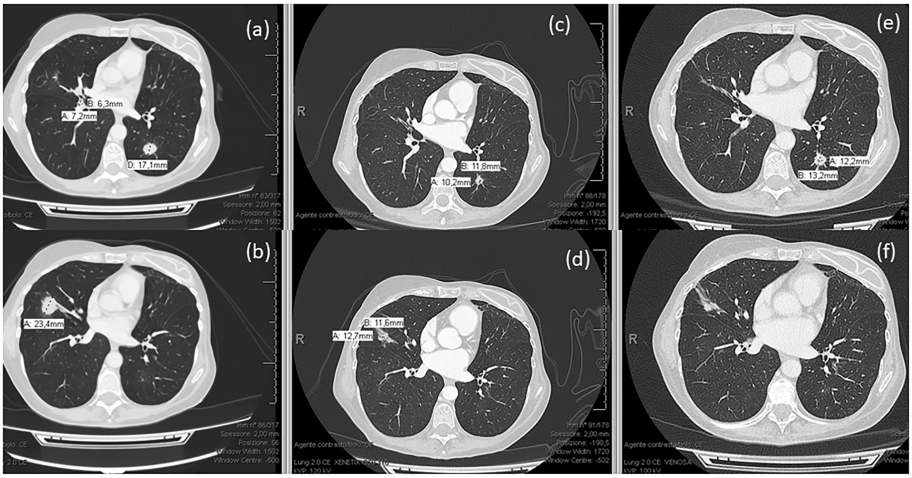

FIGURE 2
Radiological evaluation of the patient's lung metastases **(A, B)** before, **(C, D)** after 3.5 months, and **(E, F)** after 7 months of treatment with sacituzumab govitecan.

However, the European Society for Medical Oncology (ESMO) guidelines recommend a PARP inhibitor as first-line treatment in this patient population (12): In fact, subjects who received first-line olaparib had a greater OS benefit compared with standard chemotherapy in the OlympiAD trial (27) and PARP inhibitor therapy has confirmed its broad efficacy in a recent meta-analysis, either as a single agent or combined with other drug classes (28). Nevertheless, in Italy, treatment with PARP inhibitor for metastatic breast cancer is allowed only after failure of platinum-based chemotherapy; therefore, our patient who relapsed after 11 months from adjuvant anthracycline- and taxane-based chemotherapy, started first-line treatment with carboplatin and paclitaxel.

Our patient developed rapid, symptomatic, and diffuse BMs after only 3 months from starting chemotherapy. It is well known that one-third of patients with metastatic TNBC will eventually develop BMs (8): As opposed to the HER2-positive breast cancer counterpart, for which several target therapies exist (29), drugs with potential intracranial efficacy are not available for TNBC and are under investigation (9, 15).

Our patient experienced a quick disease progression and had a high brain tumor burden: Since platinum-refractory diseases were excluded from the main PARP inhibitor clinical trials and their intracranial activity is uncertain, we preferred to start sacituzumab govitecan as a second-line treatment in the EAP. The phase III ASCENT trial enrolled TNBC patients who had received two or more lines of chemotherapy in the metastatic setting (24). Patients were randomized to receive sacituzumab govitecan *versus* chemotherapy of the physician's choice (eribulin, vinorelbine, capecitabine, or gemcitabine): The control arm did not employ platinum-based compounds and only a minority of patients were BRCA-mutant (7%). Even if patients with BMs at baseline were accepted, the primary endpoint analysis did not include this patient population. The study showed a significant benefit of sacituzumab govitecan *versus* chemotherapy with respect to the median PFS (5.7 *vs.* 1.7 months; hazard ratio, (HR) 0.41; $p < 0.001$) and median OS (12.1 *vs.* 6.7 months; HR, 0.48; $p < 0.001$) (24).

An exploratory sub-analysis of the ASCENT study assessed the efficacy of sacituzumab govitecan as second-line treatment, namely, patients who received one line of therapy in the metastatic setting and recurred ≤ 12 months after (neo)adjuvant chemotherapy prior to study enrollment. The benefit in PFS and OS was consistent with the results of the ASCENT trial (30). Our patient, who could be part of this cohort, experienced an excellent PFS of 10 months, despite having active BMs at the start of the treatment.

Moreover, a recent network meta-analysis showed the superiority of sacituzumab govitecan on all endpoints compared

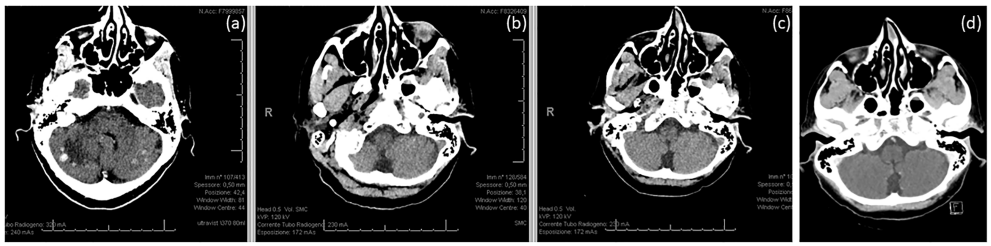

FIGURE 3
Intracranial disease **(A)** before, **(B)** after 3.5 months, and **(C)** after 7 months of treatment with sacituzumab govitecan. **(D)** Intracranial response was maintained after systemic progression.

with other treatments for TNBC in second/further lines (31). Taken together, these data strongly support sacituzumab govitecan being the preferred second-line treatment in metastatic TNBC.

Regarding safety, the most common grade 3 (G3) adverse events in the pivotal trial for sacituzumab govitecan were neutropenia (63%), diarrhea (59%), nausea (57%), alopecia (46%), and asthenia/fatigue (45%) (24). Our patient experienced good treatment tolerance, reporting only G1–G2 treatment–related adverse events; of note, no hematological or gastrointestinal G3 adverse events occurred, but persistent G2 asthenia was the most relevant, due to which sacituzumab govitecan was reduced to 7.5 mg/kg after four cycles.

It is not clear if these symptoms were entirely treatment related or caused by the association between sacituzumab govitecan and WBRT: In fact, our patient continued to receive sacituzumab govitecan and no data exist regarding the safety of this concomitant approach.

However, we hypothesize that this treatment combination allowed our patient to achieve a clinically relevant symptomatic relief and a near-to-complete response on BMs as evidenced by the preliminary data on CNS penetration of sacituzumab govitecan (32) and the enhanced drug concentrations in brain parenchyma after WBRT. BMs from breast cancer remain a therapeutic challenge and new medical strategies are currently under investigation (9, 11): Among these, ADCs have shown encouraging results, even when administered concomitantly with radiotherapy in the context of HER2-positive disease (33). However, medical therapy of BMs specifically from TNBC is lacking in new strategies, as only data from small studies with the addition of bevacizumab to chemotherapy have been reported (34–36). For these reasons, the administration of the ADC sacituzumab govitecan in patients with BMs from TNBC may be worth further investigation. Although intracranial response was not a dedicated endpoint in the ASCENT trial, an exploratory analysis including patients with stable BMs at screening showed a numerically better ORR and PFS for sacituzumab govitecan, but not OS (37).

Finally, Trop-2 expression by immunohistochemistry was not available: Despite patients with high or medium Trop-2 expression having had more favorable outcomes, a recent biomarker analysis of the ASCENT trial suggested that this feature may not be needed to predict patient response (38). Notably, the same analysis emphasized the efficacy of sacituzumab govitecan regardless of germline BRCA mutation status (38).

To summarize, our patient experienced a PFS of 10 months after radiotherapy and sacituzumab govitecan as second-line treatment, which was better compared with the median PFS from the pivotal trial (5.7 months), despite the presence of active BMs. The best overall response was extracranial partial response and near-to-complete intracranial response. She is now a candidate to start a new line of therapy, either with a PARP inhibitor or with a different chemotherapy regimen.

Conclusions

The present case report supports a potential role for sacituzumab govitecan in the treatment of early recurrent and BRCA-mutant TNBC. Moreover, sacituzumab govitecan showed a high activity in active BMs and was globally safe when administered concomitantly with WBRT in our patient. So far, no experiences about radiotherapy and concurrent sacituzumab govitecan are described.

This evidence suggests its indication and use in the early steps of the systemic treatment sequence: However, real-world data are warranted to confirm its efficacy and safety in metastatic TNBC when administered with radiotherapy, either as SRS or WBRT.

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author (p.dimauro001@unibs.it).

Ethics statement

The studies involving human participants were reviewed and approved by Comitato Etico Spedali Civili di Brescia. The patients/participants provided their written informed consent to participate in this study.

Author contributions

PdM, GS, and RP designed the case report and wrote the first draft of the manuscript. LL, AE, and ML gathered the clinical and radiological data. VA, SG, DC, and AB contributed to the critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

RP received consultancy fees from Novartis, Eli Lilly, Amgen, Gilead, Daichi Sankyo, Roche, Eisai, and Seagen. AB reported receiving grants and personal fees from Janssen Cilag and from Astellas, and personal fees from Bayer outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Severe hyperlipidemia pancreatitis induced by taking tamoxifen after breast cancer surgery—Case report

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Introduction: The research investigates the mechanism, diagnosis, treatment, and subsequent endocrine therapy of severe pancreatitis induced by tamoxifen treatment in patients who have undergone breast cancer surgery.

Case presentation: We studied two cases of breast cancer in whom severe acute pancreatitis developed after taking tamoxifen for endocrine therapy in our hospital. A brief literature review was provided to analyze the causes, clinical manifestations, treatment process, and prognosis of severe acute pancreatitis. Both cases involved patients with severe hyperlipidemic pancreatitis. After conservative treatment, none of them died. Pancreatitis did not recur after changing endocrine therapy drugs.

Discussion/conclusion: Endocrine therapy with tamoxifen in breast cancer patients can induce hyperlipidemia, which can subsequently cause severe pancreatitis. The treatment of severe pancreatitis should strengthen the regulation of blood lipids. The application of low-molecular-weight heparin combined with insulin therapy can rapidly lower blood lipids. Involved treatments, including acid suppression, enzyme suppression, and peritoneal dialysis, can accelerate the recovery of pancreatitis and reduce the occurrence of serious complications. Patients with severe pancreatitis should not continue to use tamoxifen for endocrine therapy. To complete follow-up endocrine therapy, switching to a steroidal aromatase inhibitor is better if the situation allows it.

KEYWORDS

hyperlipidemia, severe pancreatitis, tamoxifen, breast cancer, endocrine therapy

Introduction

Premenopausal hormone receptor-positive breast cancer patients taking tamoxifen after surgery have become the standard endocrine treatment regimen, with a treatment course of 5–10 years (1, 2). Patients who take tamoxifen for a long time have more common perimenopausal symptoms; however, it can also cause severe abnormal blood lipid

metabolism, which in turn induces hyperlipidemic acute pancreatitis (HAP). This disease has a sudden onset, is dangerous and complex, and has a high case-fatality rate, thereby seriously endangering the lives and health of patients. This should arouse great caution in a physician. Here, we retrospectively analyze the relevant case data of our cancer center, review the relevant literature, analyze the possible causes of its occurrence, and summarize the relevant experience of its diagnosis, treatment, and follow-up endocrine therapy.

Case presentation

Looking back at our hospital records from January 2010 to May 2020, a total of 1,265 patients (1,250 women and 15 men) who took tamoxifen for endocrine therapy after breast cancer surgery were admitted. The total duration of medication ranged from 3 months to 10 years. There was one male case and one female case of hyperlipidemia in acute pancreatitis, with an incidence rate of 0.15%. After receiving active conservative treatment, both patients were cured. Two patients took tamoxifen regularly for 2–3 years until the onset of hyperlipidemic pancreatitis. Those two patients did not receive additional drug therapy. They had no history of hyperlipidemia, pancreatitis, or biliary system disease, no obesity at the time of onset, and a normal body mass index (BMI).

Case 1

A 46-year-old male patient was admitted to the emergency department on 22 October 2017, due to "persistent left upper abdominal pain for 10 h." Past history: In 2014, a "modified radical mastectomy" was performed for "right-sided breast cancer." Medical examination: right invasive breast cancer invaded the nipple with visible nerve, vascular invasion, and intravascular tumor thrombus. No cancer metastasis was found in 39 axillary lymph nodes. Immunohistochemistry: ER (3+, 90%), PR (3+, 85%), Her-2 (−), Ki-67 (40%). After surgery, eight cycles of chemotherapy were used based on the EC-T regimen. After chemotherapy, the patient continued taking tamoxifen (20 mg/day) for endocrine therapy for a total duration of 36 months. The patient has no history of diabetes, hyperlipidemia, pancreatitis, or biliary system disease. The patient has a regular regimen without binge drinking, alcohol consumption, or other triggers before the onset of the disease. Physical examination on admission: T37.3°C, R30 beats/min, P110 beats/min, BP120/80 mmHg, BMI 23.51. Breath sounds in both lungs were thick, with a small number of moist rales heard in both lower lungs. There is no apparent cardiac abnormality on examination. The abdomen was slightly swollen, giving whole-body positive abdominal tenderness on physical examination. The subxiphoid tenderness and tenderness in the left upper abdomen area were significantly noticed, with no rebound tenderness. The patient was negative for Murphy's sign, with no mobile dullness or weak bowel sounds. Hematological parameters of the patient are listed here: blood amylase 1,541 U/L, lipase 1,574 U/L, triglycerides 91.7 mmol/L, total cholesterol 12.14 mmol/L, blood calcium 1.74 mmol/L, blood sugar 13.6 mmol/L, white blood cells 16.5 × 109/L, neutrophils at 90%, and hematocrit at 50%. Chest and abdomen CT examinations (see Figure 1): bilateral lower lung inflammation and bilateral pleural effusion were observed. Acute necrotizing pancreatitis with massive peripancreatic exudation was diagnosed. The abdominopelvic effusion and fatty liver were found, but there were no abnormalities in the biliary system. Liver function test results showed no abnormalities in bilirubin or transaminases. The patient was considered to have acute severe pancreatitis induced by severe hyperlipidemia, excluding biliary pancreatitis and other factors.

Treatment process: 1. conventional treatment such as dietary suppression, gastrointestinal decompression, infection prevention, fluid replacement, volume expansion, and fluid resuscitation; 2. treatment with acid suppression (proton pump inhibitor), enzyme suppression (growth inhibitor or octreotide), and protease inhibitor (ustekin) to inhibit gastric acid and pancreatic juice secretion and suppress inflammatory response in the body; 3. for severe hyperlipidemia, treatment with insulin combined with low molecular heparin: insulin was continuously micropumped to control blood glucose between 5 and 8 mmol/L, and low molecular heparin 6150u was administered subcutaneously twice a day, after which the patient's triglycerides and total cholesterol decreased to normal on the sixth day after admission. 4. A peritoneal dialysis tube was placed under local anesthesia on the third day after admission for abdominal septal compartment syndrome. A large amount of dark brown, turbid fluid was released, and continuous peritoneal dialysis was performed to reduce intra-abdominal pressure and effectively remove inflammatory factors from the body. 5. The patient's condition stabilized after one week, and a jejunal nutrition tube was placed intranasally under intervention with Chinese herbal medicine "Qingyi Decoction" (clear pancreas) injected. After intestinal function was restored, enteral nutrition was started, and a probiotic injection was given to prevent severe secondary infections induced by the displacement of intestinal flora.

The patient continued to experience upper abdominal distension and pain with fever in the fourth week after admission. A repeat CT examination suggested peripancreatic fluid infection

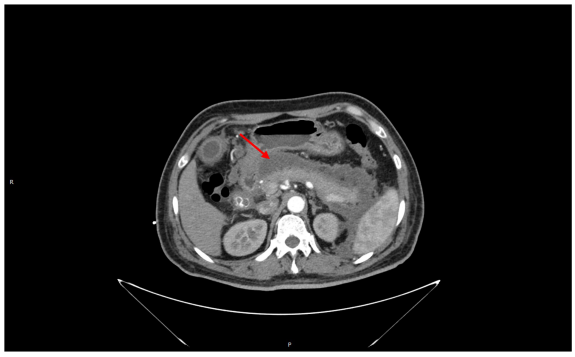

FIGURE 1
Massive peripancreatic exudate with pancreatic necrosis.

with multiple small bubbles and calcitoninogen 13.5 ng/ml. Percutaneous puncture and drainage were performed under CT guidance (see Figure 2). Selected antibiotic treatment was taken based on the result of the drug sensitivity test for the patient. The patient recovered well and was discharged after two weeks with the drainage tube removed. After three months, the patient's CT was rechecked, and no significant abnormality was found, and the peripancreatic exudate was basically absorbed. Triglycerides and total cholesterol were normal. Since the patient had a normal body shape with no obvious obesity, special diet, or apparent cause of hyperlipidemia, we considered that hyperlipidemia might be related to long-term endocrine therapy with tamoxifen after breast cancer surgery. Hence, we stopped prescribing tamoxifen for the patient. The endocrine therapy regimen was changed to goserelin combined with exemestane and was discontinued after a total of two years of treatment. By following up so far, the patient has had no recurrence of breast cancer metastasis or pancreatitis, and lipid monitoring is within the normal range (Table 1).

Case 2

A 47-year-old female patient was admitted to the emergency department on 9 March 2020, due to "persistent epigastric pain with vomiting and dyspnea for 1 day." Past history: she underwent "modified radical surgery for right breast cancer" in 2017 for "right breast cancer." Medical examination: right invasive breast cancer, no nerve or vascular invasion or intravascular cancer thrombus, 21 axillary lymph nodes without cancer metastasis; immunohistochemistry: ER (3+, 80%), PR (3+, 90%), Her-2 (80%), PR (3+, 90%), Her-2 (−), Ki-67 (10%). According to the TC regimen, the patient was treated with four periods of postoperative chemotherapy and continued to take tamoxifen for endocrine therapy at 20 mg/day without interruption until the end of chemotherapy. She had been taking tamoxifen for 30 months until the onset of the latest symptoms. She had no previous history of diabetes, hyperlipidemia, pancreatitis, or biliary system disease. She had a regular lifestyle and had no triggers such as overeating, alcohol consumption, or seafood consumption before the onset of the disease. Physical examination on admission: T38.5°C, R33 times/min, P120 times/min, BP 90/56 mmHg, BMI 22.59.

Respiratory sounds were thickened in both lungs, and significant wet rales could be heard in both lower lungs; a cardiac examination did not show any significant abnormalities. The abdomen was slightly distended, and the whole abdomen was positive for pressure pain, especially in the subxiphoid and left epigastrium, with suspicious rebound pain. Murphy's disease is negative. There is no mobile dullness, and the bowel sounds are weak. Hematological parameters of the patient are listed here: blood amylase 1,248 U/L, lipase 349 U/L, triglycerides 49.8 mmol/L, total cholesterol 8.7 mmol/L, blood calcium 1.80 mmol/L, blood glucose 8.6 mmol/L, white blood cells 18.5 × 109/L, neutrophils 88%, and red blood cell pressure 45%. Liver function indicated no abnormalities in bilirubin and transaminases. CT of the chest and abdomen (see Figure 3) shows bilateral lower lung inflammation, bilateral pleural effusion, acute pancreatitis with massive peripancreatic exudate and abdominopelvic effusion, and no abnormalities in the biliary system. The patient was considered to have acute severe pancreatitis, which was induced by severe hyperlipidemia, and biliary pancreatitis and other factors were excluded.

Treatment process: 1. The conventional treatment was the same as in case 1; 2. For severe hyperlipidemia, insulin combined with low-molecular heparin was used. Insulin was continuously micropumped to control blood glucose between 5 and 8 mmol/L, and low-molecular heparin (6,150 u) was administered subcutaneously twice/day. Under treatment, the patient's triglycerides and total cholesterol fell to normal on the third day after admission. 3. The patient's abdominal distension became obvious after three days, and a repeat abdominal CT indicated an increase in peritoneal fluid. Therefore, a peritoneal dialysis tube was placed under local anesthesia, releasing a large amount of dark red, turbid fluid. Continuous peritoneal dialysis was performed to reduce intra-abdominal pressure and effectively remove inflammatory factors from the body. 4. The patient's condition stabilized after one week, and a jejunal nutrition tube was placed nasally under intervention. Chinese herbal medicine "Qingyi Decoction" (clear pancreas) was injected to start enteral nutrition

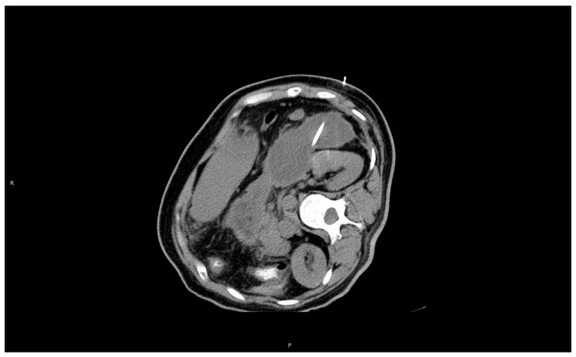

FIGURE 2
Peripancreatic fluid with infection, CT-guided puncture, and drainage was performed.

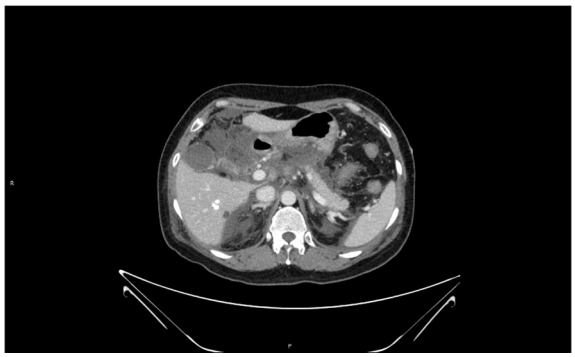

FIGURE 3
Loss of pancreatic contour, massive oozing from the head of the pancreas, and pancreatic necrosis.

TABLE 1 Triglycerides and cholesterol level for 24 months after HAP treatment.

	Triglycerides (mmol/L)							Cholesterol (mmol/L)						
Times points afters HAP treatment	1W	3M	6M	9M	12M	16M	24M	1W	3M	6M	9M	12M	16M	24M
case 1	2.84	2.16	1.28	1.56	1.28	1.31	1.82	3.74	4.6	4.91	4.99	3.85	4.89	3.7
case 2	2.46	1.66	1.67	1.86	1.19	1.64	1.3	3.32	4.1	4.26	3.25	2.81	2.7	3.26

after intestinal function recovered, and a probiotic injection was given to prevent severe secondary infection induced by intestinal flora displacement. 5. The patient was admitted to the hospital in the third week without obvious abdominal distension and abdominal pain, and no positive abdominal signs were seen on physical examination. Routine blood, liver function, and amylase were normal on re-examination. The re-examination CT showed that the peripancreatic fluid was significantly reduced compared with the previous one, and there was no obvious fluid in the abdominopelvic cavity. The patient gradually resumed a transoral diet and was discharged without obvious discomfort. Nearly three months after treatment, the CT was reexamined (see Figure 4), and no significant abnormalities were seen. The peripancreatic effusion was basically absorbed. Triglycerides and total cholesterol were normal on reexamination. The condition of the second patient was like that of case 1, with no obvious obesity, a body mass index in the normal range, no special diet, and no obvious trigger for hyperlipidemia. We considered that hyperlipidemia might be related to long-term tamoxifen endocrine therapy after breast cancer surgery, so we stopped using tamoxifen for her. Because she was approaching menopause and the patient and her family members strongly requested an ovariectomy for castration after consultation, a laparoscopic ovariectomy was performed. Exemestane was continued as endocrine therapy after the operation. So far, no recurrence or metastasis of breast cancer has been seen. Pancreatitis, monitor blood lipids are within the normal range (Table 1).

We summarized the clinical and lab values for the two cases in Table 2 and monitored the triglycerides and cholesterol levels for 24 months after HAP treatment and summarized them in Table 1.

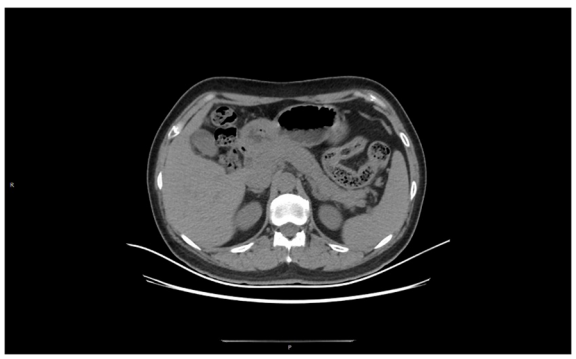

FIGURE 4
At 11 weeks after treatment, the peripancreatic exudate was largely absorbed and the pancreatic contour was largely restored.

Conclusion

The mechanism of tamoxifen-induced hyperlipidemia

Tamoxifen (TAM), as a selective estrogen receptor modulator, occupies an important position in the endocrine treatment of hormone receptor-positive (HR-positive) breast cancer patients. It is a cornerstone drug in the clinic for endocrine therapy in HR-positive breast cancer patients because of its low price and established efficacy. However, long-term use of tamoxifen can lead to menopausal symptoms and endometrial cancer, which are taken seriously. In contrast, tamoxifen-induced hyperlipidemia is overlooked. Saphner et al. (3) showed that the incidence of fatty liver in patients on long-term tamoxifen was 4.5%. In a study by Akhondi-Meybodi et al. (4), mean triglyceride levels were significantly higher in tamoxifen-induced patients with fatty livers than in normal controls.

Reviewing the relevant literatures (5–7), tamoxifen-caused hyperlipidemia was mainly manifested by a significant increase in serum triglyceride levels, whereas serum cholesterol and ultra-low density lipoprotein levels were unaffected or reduced. In our center, we observed two cases in which triglyceride levels exceeded the normal level by 29 and 53 times, respectively, while cholesterol levels exceeded the normal level by only about two times, which is consistent with literatures. Although there are reports suggesting that hypertriglyceridemia after tamoxifen may be related to preexisting conditions such as diabetes, chronic kidney disease, and nonalcoholic fatty liver disease (8), none of these preexisting diseases were found in our cases. The possible mechanisms behind tamoxifen-induced hyperlipidemia include: 1) Tamoxifen is a selective estrogen receptor modulator, which exerts partial estrogenic effects on lipid metabolism, inhibits post-heparin lysyl lipase (PHLA) activity, inhibits triglyceride lipase, and increases serum triglyceride concentration; 2) Tamoxifen can significantly downregulate the expression and activity of fatty acid synthase (FAS), thereby inhibiting fatty acid β-oxidation; and 3) Tamoxifen can affect the expression of nuclear receptors involved in lipid metabolism (androgen receptor, hepatocyte nuclear factor 4α, sterol regulatory element binding protein-1c), promote fatty acid synthesis, and increase TG levels significantly.

Treatment of hyperlipidemia pancreatitis

Hyperlipidemic acute pancreatitis (HAP), also known as hypertriglyceridemic pancreatitis, is closely related to serum triglycerides (TG) but not to serum cholesterol (TC) (9). Based

on excluding biliary obstruction and other factors inducing acute pancreatitis (AP), the diagnosis of HAP can be confirmed when the fasting blood TG value after admission is over 11.3 mmol/L. HAP can also be diagnosed when the blood TG value is 5.65–11.3 mmol/L with celiac serum presented. Tamoxifen-induced hyperlipidemic pancreatitis has both the general characteristics of acute pancreatitis and its specificity. Therefore, based on the standardized treatment of AP, the key to the treatment of HAP is to rapidly remove the factors causing HL and rapidly reduce the blood TG value.

To summarize the data of this group, we believe that (1) the key to the treatment of this disease is timely and accurate diagnosis and an active search for possible predisposing factors. Therefore, for suspected cases of HAP, in addition to routine CT\MRCP examinations to exclude biliary factors, lipid examinations should be performed, and drug intake history should be asked. If such factors are present, the relevant drugs should be discontinued immediately (2). Rapid and effective reduction of serum TG levels plays a decisive role in the treatment of this disease. The relevant literature reports (10, 11) that the main lipid-lowering measures for HAP are oral lipid-lowering drugs (fibrates), blood purification, plasma exchange combined with lipid adsorption, and intravenous heparin combined with insulin. Analyzing the treatment of this group of cases, we used a comprehensive treatment plan of diet abstinence, strict fat-free total parenteral nutrition, and insulin combined with subcutaneous injection of low-molecular heparin, which could rapidly and effectively lower the serum TG level to normal within 3–6 days of admission. Oral lipid-lowering drugs, hemodialysis, and plasma exchange were not used in either case. This method is simple, inexpensive, safe, effective, and easy to promote clinically. However, for patients with early combined multi-organ failure, we believe that hemofiltration combined with lipid adsorption is also a practical and effective treatment (3). For the treatment of peritoneal septal compartment syndrome in the early stages of severe pancreatitis, our center routinely places peritoneal dialysis tubing (12) and continuous peritoneal dialysis to reduce intra-abdominal pressure and effectively remove inflammatory factors from the body to reduce the occurrence and development of MODS (4). For the treatment of peripancreatic infection in the middle and late stages of the disease, we mostly use CT-guided percutaneous puncture placement of negative pressure flushing and drainage (13), combined with sensitive antibiotic treatment. Such a strategy can effectively control infection, avoid traditional open abdominal debridement and drainage, and reduce the incidence of postoperative gastrointestinal injury and fistulas (5). For the comprehensive treatment of severe pancreatitis, we believe that, on the basis of traditional treatment, a jejunal nutrition tube should be placed as early as possible, with external application of mannitol and injection of clear pancreatic soup through the nutrition tube. After the recovery of intestinal function, enteral nutrition should be started as early as possible to protect the intestinal mucosa to prevent severe secondary infections induced by intestinal flora displacement.

Endocrine therapy for breast cancer

Endocrine therapy has become an integral and important part of the comprehensive treatment of hormone receptor-positive breast cancer patients. Commonly used drugs include selective estrogen receptor modulators (tamoxifen, toremifene, and fulvestrant), nonsteroidal aromatase inhibitors (letrozole and anastrozole), steroidal aromatase inhibitors (exemestane), etc. Among them, tamoxifen can exert a unique lipoprotective advantage due to its weak estrogenomimetic effect (14), and it is used as the drug of choice for endocrine therapy in premenopausal HR-positive breast cancer patients in clinical practice because of its established efficacy and affordability. However, its lipoprotective effect is limited to lowering serum cholesterol (TC) levels and ultra-low-density lipoprotein (LDL-C) levels but can significantly increase serum triglyceride (TG) levels (15). Some authors suggest that after tamoxifen-induced hyperlipidemic pancreatitis, letrozole can be replaced to complete subsequent endocrine therapy (16, 17). However, numerous publications suggest that nonsteroidal aromatase inhibitors such as letrozole can induce severe dyslipidemia (hypercholesterolemia) and should be closely monitored during clinical use (14, 15, 18).

Therefore, by summarizing our data and reviewing the relevant literature and guidelines (14, 15, 18, 19), we have the following conclusions: (1) When breast cancer patients undergo endocrine therapy, lipid levels should be routinely monitored, with preoperative levels as the baseline standard, and tested every 6–12 months. If combined with high-risk factors or dyslipidemia, lipid-modifying drugs should be given promptly for intervention. (2) Complications such as tamoxifen-induced hypertriglyceridemia and fatty liver are often overlooked, which often occur after 12 months of tamoxifen treatment, and some patients have life-threatening severe pancreatitis induced by severe hypertriglyceridemia. Only sporadic cases have been reported both domestically and internationally, and the causes of pathogenesis, treatment options, and follow-up endocrine therapy options have not been explored in depth (16, 17). The two patients in our group did not routinely monitor their lipids after surgery, and both had severe hyperlipidemic pancreatitis complicated by tamoxifen treatment for more than two years. Although they recovered after active treatment, it should be given our great attention that when using tamoxifen, we should not assume that it

TABLE 2 The clinical and lab values about the two cases.

	age	FH*	BMI**	Triglycerides (mmol/L)		Cholesterol (mmol/L)	
				Before TAM	After TAM	Before TAM	After TAM
case 1	46	None	23.51	1.68	91.7	4.79	12.14
case 2	47	None	22.59	1.42	49.8	3.71	8.7

*FH, Familial Hypertriglycerid-emia.
**BMI, Body Mass Index.

has lipoprotective effects because it can lower TC and LDL-C levels and neglect monitoring of lipids. (3) Toremifene lowers TC and LDL-C levels comparable to tamoxifen and does not affect TG levels. Exemestane has comparable effects on TC and LDL-C levels to tamoxifen, can effectively lower TG levels, and can be used safely in postmenopausal patients. Therefore, toremifene and steroidal aromatase inhibitors (exemestane) are alternative drugs that can be used in patients with severe hypertriglyceridemia or hyperlipidemic pancreatitis to complete subsequent endocrine therapy. However, non-steroidal aromatase inhibitors (letrozole and anastrozole) should not be use. (4) When endocrine therapy is administered to a special group of male breast cancer patients, more attention should be paid to the occurrence of such complications. In cases of uncontrollable hyperlipidemia, it is recommended to change to toremifene or use goserelin combined with exemestane treatment. Patients should be encouraged to quit smoking and alcohol, exercise, change bad habits, and monitor lipid levels closely.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Committee of Han-Zhong 3201 Hospital Affiliated to Xi'an Jiao-Tong University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

MZ: the conception or design of the work. CZ, XL, DX, LC, and CW: the acquisition, analysis, or interpretation of data for the work. CZ and MZ: drafting the work or revising it critically for important intellectual content. CZ and MZ: final approval of the version to be published. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Is CT or FDG-PET more useful for evaluation of the treatment response in metastatic HER2-positive breast cancer? a case report and literature review

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Response evaluation criteria in solid tumors version 1.1 (RECIST ver1.1) has been widely adopted to evaluate treatment efficacy in solid tumors, including breast cancer (BC), in clinical trials and clinical practice. RECIST is based mainly on computed tomography (CT) images, and the role of fluorodeoxyglucose-positron emission tomography (FDG-PET) is limited. However, because the rate of tumor shrinkage on CT does not necessarily reflect the potential remaining tumor cells, there may be a discrepancy between the treatment response and prognosis in some cases. Here we report a case of metastatic human epidermal growth factor receptor 2 (HER2)-positive BC where FDG-PET was preferable to CT for evaluation of the treatment response. A 40-year-old woman became aware of a lump in her right breast in September 201X. She was pregnant and underwent further examinations, including a biopsy, in November. The diagnosis was HER2-positive BC (cT2N2bM1, stage IV). Trastuzumab plus pertuzumab plus docetaxel (TPD) therapy was initiated in December 201X. CT performed in February 201X+1 showed cystic changes in the metastatic lesions in the liver, and the treatment response was stable disease (SD) according to RECIST. However, FDG-PET in March 201X+1 did not detect abnormal uptake of FDG in the hepatic lesions. The disease remained stable thereafter. Thus, tumor shrinkage may not be apparent in situations where the response to treatment results in rapid changes in blood flow within the tumor, which is associated with cystic changes. When patients with hypervascular liver metastases receive treatment with highly effective regimens, the target lesion may show cystic changes rather than shrinkage, as observed in the present case. Therefore, FDG-PET is sometimes superior to CT in judging a tumor response.

KEYWORDS

breast cancer, HER2, liver metastasis, CT, FDG-PET, RECIST

1 Introduction

Response evaluation criteria in solid tumors version 1.1 (RECIST ver1.1) has been widely adopted to evaluate treatment efficacy in solid tumors, including breast cancer (BC), in clinical trials and clinical practice (1). RECIST ver1.1 is mainly based on computed tomography (CT) images and is useful for the evaluation of cytotoxic anticancer therapy as well as molecular-targeted drug therapy (2). The role of ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) in the determination of the treatment efficacy is limited. However, because tumor shrinkage based on CT images does not always correspond to tumor cell residuals, scattered cases have been reported in which the treatment efficacy determination and prognosis are divergent (3–7). Conversely, FDG-PET can evaluate tumor activity by glucose uptake. Hence, in Europe and the United States, quantitative treatment response determination by FDG-PET has been attempted, with the recommendation of FDG-PET by the European organization for research and treatment of cancer (8) and the PET Response Criteria in Solid Tumors (9). Although several studies have used FDG-PET to determine the efficacy of neoadjuvant chemotherapy against human epidermal growth factor receptor 2 (HER2)-positive BC (10–13), few studies have examined the utility of FDG-PET in determining the efficacy of treatment for metastatic HER2-positive BC (14). Here we report a case of metastatic HER2-positive BC where FDG-PET was preferable to CT for evaluation of the treatment response.

2 Case report

A 40-year-old woman became aware of a lump in her right breast in September 201X. Because she was pregnant, she underwent a cesarean section in mid-November and underwent further examinations, including a core needle biopsy, in late November. Physical examination at the initial visit to our department revealed a body temperature of 36.5°C; a heart rate of 78 beats/min; blood pressure of 122/74 mmHg; a respiratory rate of 12 breaths/minute; no eyelid conjunctiva pallor; no heart murmur; flat, soft, non-tender abdomen; no edema; a palpable, 2-cm, elastic, firm mass in the upper outer quadrant of the right breast; and palpable and swollen right axillary lymph nodes. Breast ultrasound revealed a hypoechoic mass measuring 32.6 × 16.2 mm and showing well-defined borders and a heterogeneous interior in the upper outer quadrant of the right breast. Blood tests showed mildly elevated liver enzymes, high serum alkaline phosphatase and serum lactate dehydrogenase (LDH) levels, and markedly elevated carcinoembryonic antigen (CEA) and carbohydrate antigen 15-3 (CA15-3) levels (Table 1). FDG-PET/CT revealed high FDG accumulation in the upper outer quadrant of the right breast (standardized uptake value (SUV) max, 7.519), enlarged lymph nodes, and high FDG accumulation in the level I–II region of the right axilla and internal mammary lymph node region (SUV max, 3.525), numerous low-density areas with high FDG accumulation in the liver (SUV max, 7.816), and high FDG accumulation in the left iliac bone (SUV max, 7.356) (Figure 1). The histopathological diagnosis based on core needle biopsy from the breast mass was invasive ductal carcinoma of the breast (estrogen receptor (ER)-positive, progesterone receptor-negative, HER2 3+, Ki-67 40%). The clinical stage by imaging was cT2N2bM1[OSS, HEP], stage IV. Trastuzumab plus pertuzumab plus docetaxel (TPD) therapy for metastatic HER2-positive BC was initiated in December 201X. Blood tests on the day after treatment showed the following: aspartate aminotransferase (AST), 341 IU/L; alanine aminotransferase (ALT), 155 IU/L; LDH, 4021 IU/L; and liver dysfunction. However, there were no findings indicating suspected tumor lysis syndrome, with a serum creatinine level of 0.48 mg/dL, uric acid level of 5.2 mg/dL, potassium level of 3.9 mmol/L, and phosphorus level of 3.6 mg/dL. Blood tests performed 2 days after the start of chemotherapy showed the following: AST, 187 IU/L; ALT, 143 IU/L; and LDH, 2151 IU/L, with liver dysfunction and LDH levels also showing an improvement trend. At the start of the second course of treatment, the patient's liver enzymes were within normal limits, and she continued treatment. In February 201X+1, the CEA and CA15-3 levels were 90.2 ng/mL and 33.0 IU/mL, respectively. CT performed in the same period showed cystic changes in the metastatic lesions in the liver, and the treatment response was stable disease according to RECIST (Figure 2). However, FDG-PET performed in March 201X +1 did not detect abnormal uptake of FDG in the hepatic lesions (Figure 2; Supplementary Figure 1). CT performed in June 201X+1 showed shrinkage of the liver metastases, and the disease remained stable for more than three years (Figure 2).

3 Discussion

We presented a case of HER2-positive BC with liver metastasis where FDG-PET was valuable for the assessment of the therapeutic response. The patient, who showed an early response according to FDG-PET, continued to respond to treatment three years after the start of treatment.

In some reports, the pathological complete response rate after neoadjuvant chemotherapy for HER2-positive BC has correlated with the treatment response evaluated by FDG-PET (10–13, 15–21), whereas no correlation has been observed in other studies (22–26). Furthermore, for BC, the utility of FDG-PET may differ between primary sites and metastatic lymph nodes (27). Furthermore, the ability of PET to detect breast cancer is highly dependent on tumor size: the sensitivity for tumors less than 1 cm in diameter was 25%, whereas the sensitivity for tumors between 1 cm and 2 cm in diameter was 84.4% (28). On the other hand, RECIST ver1.1, based on CT imaging, reportedly shows efficacy in determining the therapeutic effect of molecular-targeted drug therapy (2). Therefore, the routine use of FDG-PET for determining the treatment response in BC is not recommended.

However, HER2/ER-positive breast cancer may be the most suitable breast cancer subtype for FDG-PET. The rationale for their suitability is that glucose transporters (GLUT) on cell membranes and cell proliferative capacity influence FDG accumulation (29). The Phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway is also involved in the expression and function of GLUTs, which are involved in glucose uptake (30). HER2/ER-positive breast cancer often has high Ki67 levels, a marker of cell proliferative potential, and the PI3K/Akt/mTOR pathway is also activated (31). If treatment for this breast cancer subtype is successful, a decrease in FDG accumulation may be detected earlier

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TABLE 1 Laboratory data obtained at the initial visit to our department for a patient with human epidermal growth factor receptor 2-positive breast cancer.

Blood components	Patient		Normal range
Complete blood count			
White blood cells	7340	/μL	3300–8600
Red blood cells	$466x10^4$	/μL	$386\text{-}492 \times 10^4$
Hemoglobin	14.1	g/dL	11.6–14.8
Hematocrit	43.9	%	35.1–44.4
Mean corpuscular volume	94	fL	83.6–98.2
Platelets	$30.9x10^4$	/μL	$158\text{-}348 \times 10^4$
Neutrophils	79	%	40.0–70.0
Lymphocytes	10	%	20.0–50.0
Monocytes	6	%	0.0–10.0
Eosinocytes	2	%	1.0–5.0
Basocytes	1	%	0.0–1.0
Biochemistry			
Total protein	6.8	g/dL	6.6–8.1
Albumin	3.7	g/dL	4.1–5.1
C-reactive protein	0.27	mg/dL	0.00–0.14
Aspartate aminotransferase	55	IU/L	13–30
Alanine aminotransferase	48	IU/L	7–23
Alkaline phosphatase	925	IU/L	106–322
Total bilirubin	0.7	mg/dL	0.4–1.5
Lactate dehydrogenase	605	IU/L	124–222
Blood urea nitrogen	13.1	mg/dL	8.0–20.0
Creatinine	0.46	mg/dL	0.46–0.79
Uric acid	4.8	mg/dL	2.6–5.5
Na	142	mEq/L	138–145
K	3.7	mEq/L	3.6–4.8
Cl	104	mEq/L	101–108
Ca	9.4	mg/dL	8.8–10.1
P	2.9	mg/dL	2.7–4.6
Creatine kinase	78	IU/L	41–153
Amylase	75	IU/L	44–132
Glucose	152	mg/dL	73–109
CEA	2365	ng/mL	0.0–5.0
CA15-3	154	IU/mL	0.0–37.0

Na, sodium; K, potassium; Cl, chlorine; Ca, calcium; P, phosphorus; CEA, carcinoembryonic antigen; CA15-3, carbohydrate antigen 15-3.

than morphological shrinkage by CT because of the expected reduced expression of GLUT and Ki67 values. Furthermore, there are reports that FDG-PET affects the prognosis of breast cancer patients (32, 33). That is because FDG-PET has a high diagnostic ability for distant metastasis, especially in breast cancer patients with bone metastasis (34, 35). Therefore, FDG-PET may be useful not only for detecting distant metastases that are difficult to detect with CT in staging but also for follow-up.

In addition, FDG-PET is useful for determining the response to drug treatment in patients with gastrointestinal stromal tumors (GISTs) (3, 4, 36–38). Therefore, FDG-PET is preferred over RECIST for evaluation of the response to treatment (39). The

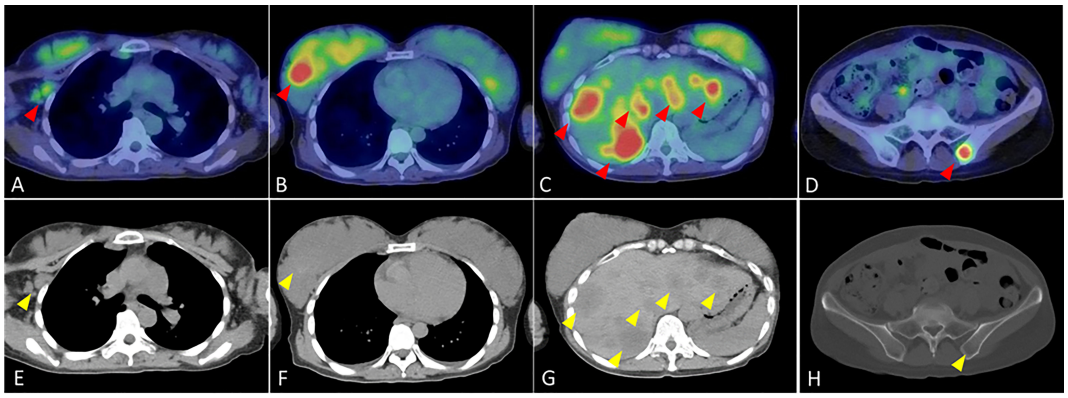

FIGURE 1
Fluorodeoxyglucose-positron emission tomography/computed tomography findings at the initial visit to our department for the patient with human epidermal growth factor receptor 2-positive breast cancer. **(A)** High FDG accumulation in the level I–II region of the right axilla (red arrow) **(B)** High FDG accumulation in the upper outer quadrant of the right breast (red arrow) **(C)** Numerous foci of high FDG accumulation in the liver (red arrows). **(D)** High FDG accumulation in the left iliac bone (red arrow). **(E)** Enlarged lymph node in the level I-II region of the right axilla (yellow arrow). **(F)** Mass in the upper outer right breast (yellow arrow). **(G)** Multiple low density areas in the liver (yellow arrows). **(H)** Low density area in pelvic region (yellow arrow).

characteristics of GISTs and their treatment include the presence of hypervascular liver metastases (40–42) and a high response rate to imatinib therapy (43). Approximately two-thirds of GISTs have *KIT* exon11 mutations (40, 44). The response rate for imatinib in patients with untreated metastatic GISTs with *KIT* exon11 mutations reportedly ranges from 68% to 72% (45–47) (Table 2). High-response chemotherapy for hypervascular tumors leads to rapid blood flow changes. This can result in internal necrosis and cystic transformation without tumor shrinkage, which may occur during the treatment of GISTs (55). In such cases, FDG-PET is more suitable for determining the treatment response than RECIST.

The response rate for the TPD regimen used for untreated HER2-positive BC reportedly ranges from 80.2% to 88.6% (48–50) (Table 2), and some cases of hepatic metastases from BC show hypervascular

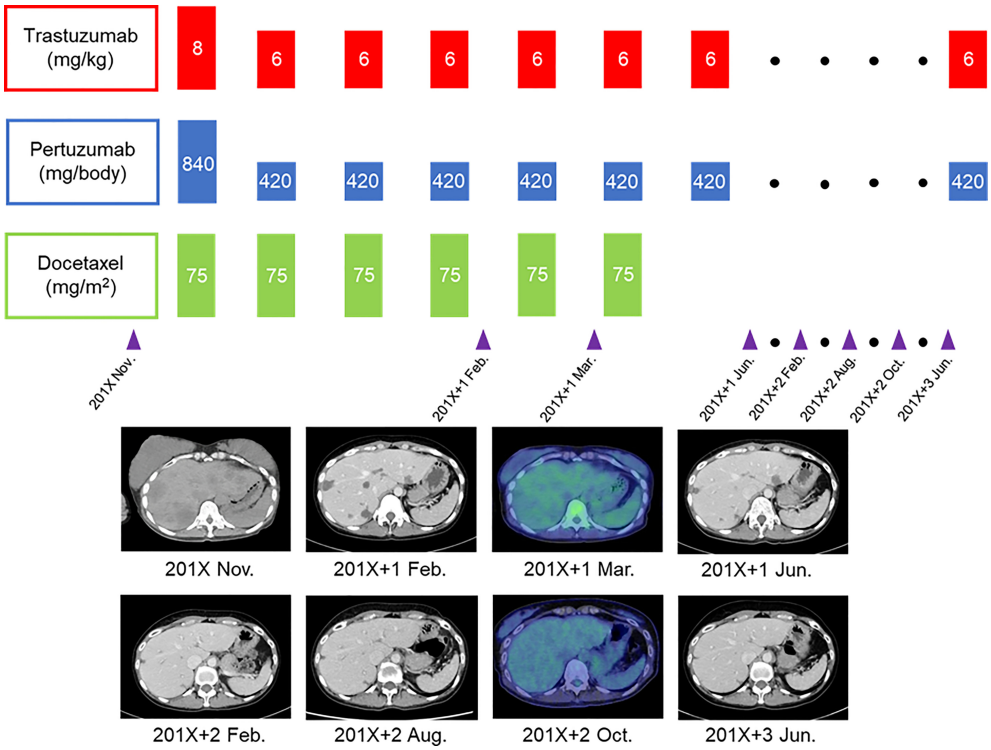

FIGURE 2
Course of treatment and imaging changes in multiple liver metastases for the patient with human epidermal growth factor receptor 2-positive breast cancer.

TABLE 2 Reported response rates for chemotherapy according to the cancer type.

Cancer type	Subtype	Phase	Setting	Regimen	ORR
BC (48)	HER2-positive	II	NAC	TPD	88.00%
BC (49)	HER2-positive	III	NAC	TPD	88.60%
BC (50)	HER2-positive	III	Palliative	TPD	80.20%
GIST (45)	*KIT* exon11 mutant	III	Palliative	Imatinib	67.70%
GIST (46)	*KIT* exon11 mutant	III	Palliative	Imatinib	71.70%
GIST (47)	*KIT* exon11 mutant	III	Palliative	Imatinib	68.80%
CRC (51)	All comer	II	LM only	FOLFOXIRI+Bev	80.50%
CRC (52)	All comer	II	LM only	FOLFOXIRI+Bev or C-mab	75.00%
CRC (53)	*RAS/BRAF* wild	II	LM only	FOLFOXIRI+C-mab	95.50%
CRC (54)	*KRAS* wild	II	LM only	FOLFOXIRI+P-mab	60.00%

ORR, overall response rate; BC, breast cancer; NAC, neoadjuvant chemotherapy; TPD, trastuzumab plus pertuzumab plus docetaxel; GIST, gastrointestinal stromal tumor; CRC, colorectal cancer; LM, liver metastasis; FOLFOXIRI+Bev, 5-fluorouracil/leucovorin/oxaliplatin/irinotecan plus bevacizumab; C-mab, cetuximab; P-mab, panitumumab.

patterns (56, 57). In addition, the response rate for triplet plus bevacizumab or anti-epidermal growth factor receptor antibody treatment in patients with untreated colorectal cancer (CRC) with liver metastases ranges from 60.0% to 95.5% (51–54) (Table 2). However, liver metastases from CRC are generally hypovascular tumors (55). Therefore, they are less frequently cystic, similar to GISTs. Meanwhile, when angiogenesis inhibitors are administered, the tumor blood flow is rapidly altered and the liver metastases from CRC may become cystic; this suggests that RECIST is inappropriate for determining the treatment efficacy (58).

The present case involved untreated HER2-positive BC with liver metastases, and the LDH levels after initiation of the TPD regimen suggested a high response within a few days. Patients with such a significant reaction to hypervascular liver metastases within a few days are prone to cystic transformation of the liver metastases.

In summary, when liver metastases do not shrink and become cystic despite a high response to chemotherapy, FDG-PET may be more suitable than CT-based RECIST for determination of the treatment response.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patient provided written informed consent to participate in this study. Written informed consent was obtained from the patient for the publication of this case report.

Author contributions

Conceptualization, HS and AO. Methodology, HS and AO. Investigation, HS, YI, and AO. Data curation, HS, YI, and AO. Writing—original draft preparation, HS. Writing—review and editing, HS, YI, and AO. Supervision, AO. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Maintained complete response to talazoparib in a *BRCA-2* mutated metastatic luminal breast cancer: case report and review of literature

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PARP inhibitors are progressively becoming a part of our therapeutic arsenal against BRCA-defective tumors, because of their capacity to induce synthetic lethality in cells with a deficiency in the homologous recombination repair system. Olaparib and talazoparib have been approved for metastatic breast cancer in carriers of germline BRCA mutations, which are found in approximately 6% of patients with breast cancer. We report the case of a patient with metastatic breast cancer, carrier of a germline mutation in BRCA2, with a complete response to first-line treatment with talazoparib, maintained after 6 years. To the best of our knowledge, this is the longest response reported with a PARP inhibitor in a BRCA-mutated tumor. We have made a review of literature, regarding the rationale for PARP inhibitors in carriers of BRCA mutations and their clinical relevance in the management of advanced breast cancer, as well as their emerging role in early stage disease, alone and in combination with other systemic therapies.

KEYWORDS

breast cancer, *BRCA*, germline, PARP inhibitors, olaparib, talazoparib

1 Introduction

Breast cancer (BC) accounts for approximately 30% of malignancies in women worldwide (1), with an incidence ranging from 27 in 100000 (Africa and East Asia) to 97 in 100000 (North America and Western Europe), reflecting its association with lifestyle and social factors (2). Metastatic BC remains a virtually incurable disease and is still the leading cause of cancer-related death in women globally (3), though the prognosis of this

condition has been improved by the incorporation of novel therapies beyond conventional chemotherapy (CT).

Around 10% of malignant breast tumors are associated with a genetic predisposition (3). Although several breast cancer susceptibility genes have been identified, the most common germline mutations that lead to a family history of BC affect *BRCA1* and *BRCA2*. Pathogenic variants in these genes are associated with an increased risk of several tumors, being the strongest hereditary risk factors for breast and ovarian cancers. A contemporary prospective cohort study with 9856 carriers of pathogenic *BRCA* variants, reported a cumulative BC risk to 80 years of 72% in *BRCA1* mutation carriers (95% confidence interval [CI] 65-79%) and 69% in *BRCA2* mutation carriers (95% CI 61-77%) (4). Germline *BRCA2* mutation is more present in the ER+/HER2- population compared to *BRCA1* (5).

The biological functions of *BRCA1* and *BRCA2* are related to the repair of DNA double-strand breaks (DSBs) by homologous recombination (HR), whereas PARP is an enzyme involved in base excision repair, which is key to repair of DNA single-strand breaks (SSBs). The blockade of PARP function causes an increase in SSBs, which are converted during cell replication to DSBs -usually repaired by HR-. In *BRCA1/2* defective cells, the inhibition of PARP leads to the accumulation of DSBs that cannot be repaired due to a deficiency in the HR system, causing cell death, a phenomenon known as synthetic lethality. This is the biological rationale for the use of PARP inhibitors (PARPi) in *BRCA*-defective tumors.

BRCA1/2 mutations are classified as ESCAT I/OncoKb I actionable alterations. PARPi have been approved by the FDA for the treatment of four BRCA-associated tumors. In ovarian cancer, several drugs (olaparib, niraparib, rucaparib) have demonstrated clinical benefit both in recurrent tumors and as maintenance treatment after first-line CT in platinum-sensitive disease (6–12). In pancreatic and castrate-resistant prostate cancers, olaparib has been approved for patients with mutations in *BRCA* and other HR-related genes (13, 14).

In breast cancer, both olaparib and talazoparib have received FDA approval for carriers of *BRCA* mutations (pathogenic or likely pathogenic variants) with metastatic Her2-negative disease, based on the results from the OlympiAD (15) and EMBRACA (16) trials, respectively. In the phase III trial BROCADE-3 (17), addition of PARPi (veliparib) to an active platinum doublet (carboplatin/paclitaxel) resulted in significant improvement in progression-free survival (PFS) in patients with metastatic BC and germline *BRCA* mutations.

2 Case report

Our patient was a 38-year-old female, with no relevant previous medical history -except for mild bronchial asthma and chronic treatment with low-dose steroids, due to primary adrenal insufficiency-. Regarding family history, her mother had been diagnosed with breast cancer at 42 years of age, her father had been diagnosed with prostate cancer at 78 years, and her maternal aunt had been diagnosed with breast and ovarian cancer at 46 years.

In September 2014, the patient consulted for a palpable lesion, approximately 3 cm in size, in the inner upper quadrant of her right breast. Physical examination confirmed the lesion and did not reveal skin retraction, ulceration, tangible lymph nodes, or any other pathological findings. Mammogram, breast echography and breast magnetic resonance imaging (MRI) revealed the presence of a highly suspicious mass with irregular margins, with a maximum diameter of 32 mm, together with two satellite nodules approximately 8 mm in size. No pathological lymph nodes were identified.

A core needle biopsy was performed, which confirmed the diagnosis of multifocal infiltrating ductal carcinoma, with histologic grade 3 and a Ki67 proliferation index of 90%. Estrogen and progesterone receptor expression was detected in 70% and 15% of the cells, respectively. Immunohistochemical analysis revealed intense expression of E-cadherin and cytokeratin 19, with no Her2 overexpression (score 0+). Considering her family history and her age at diagnosis, the patient was referred to the hereditary cancer unit. She and her mother underwent a genetic study that revealed a pathogenic germline mutation in *BRCA2*.

In October 2014, she started neoadjuvant treatment with 5-fluorouracil, epirubicin and cyclophosphamide for 4 cycles (FEC scheme), followed by 8 cycles of weekly paclitaxel. In April 2015, she underwent bilateral mastectomy, with no relevant surgical complications. Histological examination of the surgical piece demonstrated pathological complete response [grade 5 of the Miller and Payne system (18)]. She started adjuvant hormone therapy with tamoxifen in May 2015 and began usual post-treatment surveillance. In January 2016, the patient underwent prophylactic bilateral oophorectomy after detailed genetic counseling.

In October 2016, she consulted with a rapidly growing lump on the right side of her head. A core needle biopsy was performed, demonstrating bone relapse of breast carcinoma, with positive expression of estrogen and progesterone receptors. The score for the immunohistochemical determination of Her2 was 2+, but gene amplification was discarded by fluorescence *in situ* hybridization (FISH).

Whole-body positron emission tomography with 18F-fluorodeoxyglucose (FDG-PET) revealed pathological deposits of radiotracer, with high metabolic activity, in the right frontal bone, corresponding with the biopsied lesion, the right acetabulum and the tenth right rib, all of which were suggestive of tumor viability (Figure 1), as well as two non-specific liver nodular lesions. Bone scintigraphy confirmed the bone metastases, and MRI confirmed the metastatic nature of the liver nodules. These findings led to a diagnosis of stage IV hormone-receptor (HR)+ breast cancer with bone and liver infiltration.

Due to the early relapse of the disease while on adjuvant treatment with tamoxifen, the patient declined hormone therapy, alone or in combination with a cyclin-dependent kinase inhibitor (CDKi). After being informed about the non-curative intent and potential adverse effects of conventional CT, the patient discarded this option, and asked about additional therapeutic options. Preliminary data regarding the promising results of PARP inhibitors in untreated BRCA mutation carriers with BC (19–21),

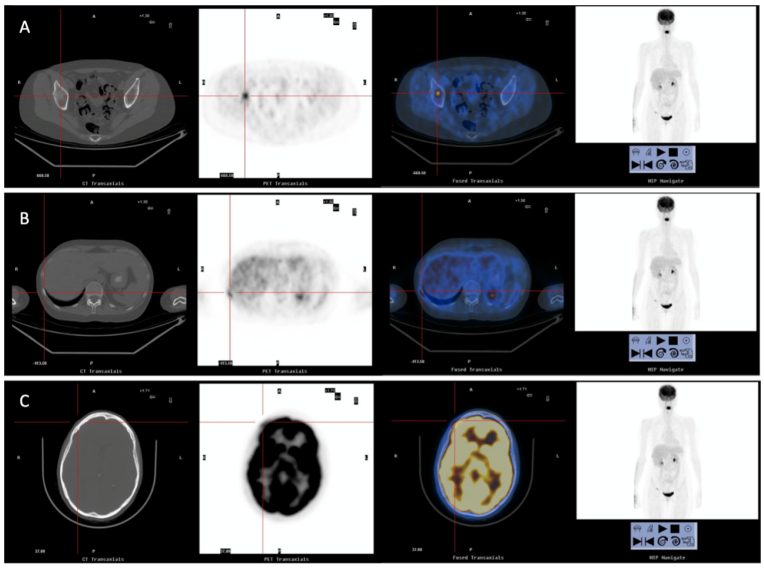

FIGURE 1
Images from computerized tomography (CT), FDG-PET and bone scintigraphy, showing bone relapse in right acetabulum **(A)**, tenth right rib **(B)** and right frontal bone **(C)**.

were discussed with the patient, and talazoparib was solicited as a compassionate drug.

She started treatment with talazoparib 1 mg/24 h in February 2017, achieving a complete clinical and metabolic response after two cycles. In April 2017, bone scintigraphy and liver MRI showed no evidence of disease (Figure 2). She has completed 90 cycles of treatment to date, with good tolerance, except for mild hematologic toxicity (grade 1 anemia). The disease remains in complete response on the last FDG-PET scan, performed in November 2022. A timeline of the case is presented in Figure 3.

3 Discussion

3.1 PARPi in metastatic BC

The OlympiAD (15) was a phase 3 clinical trial that compared olaparib (300 mg twice daily) with standard non-platinum single-agent CT (eribulin, capecitabine or vinorelbine) in 205 patients who were carriers of g*BRCA*m with metastatic Her2-negative BC (randomization 2 to 1). Among the patients in the experimental group, 57.1% had mutations in *BRCA1*, 41.0% had mutations in *BRCA2* and 2.0% had mutations in *BRCA1* and *BRCA2* simultaneously. The patients had received no more than two previous lines of CT (12.7% had new metastatic BC and 71.2% had been previously treated with CT in the olaparib group). In the olaparib group, 77.6% of patients had two or more metastatic sites. Among the patients who received olaparib, 50.2% had HR+ tumors and 41.0% had triple-negative tumors. The median PFS, set as primary endpoint, was significantly longer in the olaparib group (7.0 months vs 4.2 months; HR 0.58, p <0.001). Patients in the olaparib arm achieved a median overall survival (OS) of 19.3 months, versus 17.1 months in the control arm (p = 0.51). The objective response rate (ORR) was 59.9% in the olaparib group (28.8% in the control group). The experimental group also appeared to have a favorable rate of grade 3-4 adverse events and treatment discontinuation. An analysis of OlympiAD patients treated in the first-line setting demonstrated a survival benefit with olaparib, suggesting a higher benefit with the earlier use of PARPi (22).

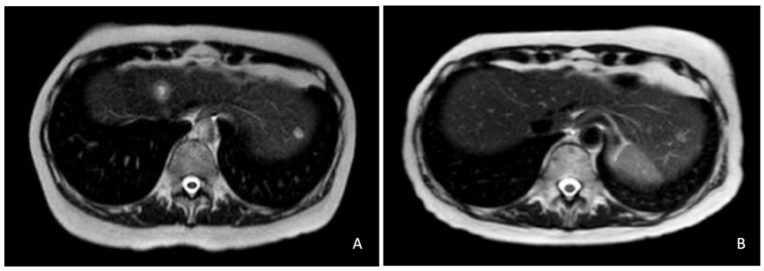

FIGURE 2
MRI study showing two liver metastases in January 2017 **(A)**. Complete response of liver lesions after 2 cycles of talazoparib in April 2017 **(B)**.

FIGURE 3
Timeline of the case.

In the phase 3 trial EMBRACA (16), 431 patients with advanced BC and g*BRCA*m were randomly assigned (2:1) to receive talazoparib (1 mg once daily) or standard single-agent CT (eribulin, capecitabine, vinorelbine, or gemcitabine). Of the patients treated with talazoparib, 42.9% harbored mutations in *BRCA1*, and 51.2% of them had mutations in *BRCA2*. The patients had received no more than three previous lines of CT (38.7% had new metastatic BC, 37.3% had been treated with 1 prior regime of CT, and 24% had received 2 or 3 previous lines of CT). In the talazoparib group, 45.3% were triple-negative and 54.7% HR+ tumors based on the most recent biopsy. The experimental group obtained a higher median PFS (8.6 months vs 5.6 months; HR 0.54; $p < 0.001$), a higher median OS (22.3 months vs 19.5 months; HR 0.76; $p = 0.11$) and a higher ORR (62.6% vs 27.2%) -complete response in 5.5% and partial response in 57.1% of patients-. Hematologic grade 3-4 adverse events were more frequent with talazoparib (55% vs. 38%), although globally tolerance, quality-of-life reports, and time to clinical deterioration favored the experimental group.

The use of a PARP inhibitor in the first-line setting, due to the unwillingness of our patient to receive hormone therapy or conventional CT, was an unusual situation out of the context of a clinical trial. The combination of hormone therapy and CDKi is currently the standard first-line therapy for HR+ BC. Pivotal phase III clinical trials with CDKi reported median PFS rates of 24.8 months for letrozole + palbociclib [PALOMA-2 (23)], 20.5 months for letrozole + ribociclib [MONALEESA-2 (24)] and 28.2 months for letrozole + abemaciclib [MONARCH-3 (25)].

Information regarding the effectiveness of CDKi in g*BRCA*m BC is limited. A real-world study published by Collins et al. (26) shows that the outcomes with CDKi may be worse in patients with g*BRCA*m, with a shorter time-to-first subsequent therapy or death and a shorter median OS, suggesting biological differences between g*BRCA*m and g*BRCA* wild-type BC. Frenel et al. (27) demonstrated that patients with HR+/Her2- metastatic BC from PADA-1 trial, who were carriers of *BRCA* and *PALB2* germline mutations, seemed to have a poorer benefit from palbociclib plus hormone therapy than non-mutated patients (mPFS 14 months vs. 26.7 months), presumably because of frequent emergence of *ESR1* resistance mutation in this subgroup.

On the other hand, there is also scarce evidence about the efficacy of PARP inhibitors in the first-line setting of HR+ BC, since both OlympiAD and EMBRACA studies mainly included pretreated patients. Rugo et al. (28) published a subanalysis of outcomes in the prespecified patient subgroups from the EMBRACA study, reporting a median PFS of 9.8 months with talazoparib (95% CI 8.5-13.3) in patients that had not received any previous CT, compared to 8.7 months with physician choice CT (95% CI 5.5-18.0). However, it is presumable that a significant proportion of these patients had triple-negative BC, and among those with HR+ tumors, many had previously received hormone therapy. Well-designed studies are required to properly compare the outcomes of CDKi and PARPi as first-line therapy in advanced g*BRCA*m BC.

Although the prognosis of metastatic BC is worse in cases of endocrine-refractory tumors and visceral involvement (29), the oligometastatic presentation of the disease might have played a role in the favorable outcomes observed in our patient.

3.2 PARPi in early-stage BC

PARPi have also shown efficacy in early stage disease. In the OlympiA trial (30), 1 year adjuvant olaparib was compared with placebo in g*BRCA*m carriers with Her2-negative BC and a high risk of recurrence. The olaparib arm was superior, with better invasive disease-free survival (iDFS) (HR 0.58, $p < 0.0001$), distant disease-free survival (dDFS) (HR 0.57, $p < 0.0001$), and OS (HR 0.68, $p = 0.009$). According to these results, not only metastatic patients, but also newly diagnosed patients with localized high-risk disease, should undergo germline testing if a PARP inhibitor may be used for treatment.

The OlympiA eligibility criteria included patients with TNBC and high-burden HR+ BC with residual disease after neoadjuvant CT, as well as patients directly undergoing surgery who had an HR+ tumor with at least four involved axillary nodes, TNBC > 2 cm, or with any axillary involvement. Our patient, who suffered an early relapse of HR+ BC during adjuvant hormone therapy, would not have met the inclusion criteria of the OlympiA study, whose patients with HR+ tumors comprised a particularly high-risk cohort -with a 3-year iDFS of 77% in the placebo arm (15)-. It is inevitable to question whether adjuvant PARPi may have prevented or delayed relapse in our case. Further research is necessary to assess whether a larger population of g*BRCA*m carriers with HR+ BC, with lower-volume tumors or fewer involved axillary nodes than the OlympiA RH+ population, could also benefit from adjuvant PARPi.

Another question relates to the possible role of PARPi in the neoadjuvant setting, which may allow de-escalation or even omission of CT in some g*BRCA*m carriers, especially those with lower-risk BC. Comparable pCR rates were observed with paclitaxel/carboplatin and paclitaxel/olaparib in the GeparOLA trial (31). The use of PARPi alone as neoadjuvant treatment has also been explored, with a 48% pCR rate with talazoparib in g*BRCA*m carriers with TNBC in the NeoTALA trial (32).

Several studies have demonstrated that patients with *BRCA1/2* mutations are more sensitive to cytotoxic drugs that induce DSBs,

mainly platinum analogs, because of the deficiency of the HR system. The TNT trial (33) showed that *BRCA*m patients had an increased ORR with carboplatin compared to docetaxel (68% vs. 33%). In both the Geparsixto (34) and CALGB40603 (35) trials, the addition of neoadjuvant carboplatin in TNBC achieved a higher pathologic complete response (pCR). Available data support the efficacy of combining PARPi and platinum in *BRCA*m metastatic BC (36), though phase III trials are warranted to approve its clinical use.

However, there is growing evidence regarding the association between previous platinum exposure and lower response rates to PARPi. In the Olympia trial (30), the improvement in invasive disease-free survival was significantly lower among patients who had previously received platinum-based chemotherapy (HR 0.52) than in platinum-naïve patients (HR 0.77). Desnoyers et al. (37) published a meta-regression analysis of 43 studies, confirming that previous platinum-based treatment was also associated with a lower ORR (p = 0.02) in patients with metastatic BC.

3.3 The future of PARPi in BC

Several questions remain unanswered regarding the optimal use of PARPi, both in metastatic and (neo)adjuvant scenarios. Further research is required to explore the possible role of PARPi in combination with other systemic therapies, such as CDKi in HR+ tumors and immune checkpoint inhibitors (ICIs) in TNBC. In advanced BC, the combination of PARPi with ICIs -in g*BRCA*m carriers- has shown promising results, for both olaparib plus anti-PDL1 durvalumab [MEDIOLA trial (38)] and niraparib plus anti-PD1 pembrolizumab [TOPACIO/Keynote162 trial (39)]. In the adjuvant setting, up to 12.5% of TNBC patients from the OlympiA study still had distant recurrence even after an accurate treatment with olaparib and intense CT, leaving a wide room for improvement in results, which may be achieved by the addition of ICIs to PARPi. This combination may seem reasonable in TNBC with a large tumor size, nodal involvement, or residual disease after neoadjuvant CT (40), although prospective data are required to validate this hypothesis.

Some preclinical studies have even brought up the concept of 'chemopreventive' PARPi, suggesting their potential benefit in healthy g*BRCA*m carriers to reduce the risk of *BRCA*-related cancers, maybe avoiding early prophylactic surgeries (41). Clinical evaluation of the prophylactic effect of PARPi is challenging, because of the limitations in generating prospective evidence, and the difficulty in assessing the risk of contralateral BC in patients treated with PARPi, since most of g*BRCA*m carriers with BC undergo bilateral mastectomy.

The exponential expansion of PARPi from a restricted group of metastatic patients to a much wider population. regarding their use in early stage disease and even their potential prophylactic role in healthy g*BRCA*m carriers, should be accompanied by careful evaluation of their long-term safety. A recent meta-analysis of 31 randomized controlled trials, including 5693 patients treated with PARPi and 3406 in control groups, demonstrated a significant increase in the risk of myelodysplastic syndrome and acute myeloid leukemia (HR 2.63, p = 0.026), although the absolute risk remained low (0.73% vs. 0.47%) (42) and PARPi are generally well-tolerated drugs.

In our patient, with no adverse effects, except for mild hematologic toxicity, interruption of talazoparib has not been considered. However, in long-responding patients with worse treatment tolerance and a negative impact on quality of life, one might consider the use of lower-dose schedules, an intermittent exposure to the drug, or even a temporary interruption of PARPi. Prospective studies are needed to explore whether these are feasible strategies, and their impact on clinical outcomes.

To our knowledge, our patient has the longest response to a PARP inhibitor reported to date, as well as the first reported long-term response to talazoparib. Wang et al. (43) have recently published the case of a patient with advanced TNBC and a germline deletion of exon 2 in *BRCA1*, with a complete response to olaparib since September 2017. Exman et al. (44) have reported a partial response to olaparib in a *gBRCA2m* carrier with metastatic BC and leptomeningeal carcinomatosis. Little is known about the biological features of BC or possible predictive factors related to these long-term responses, and further studies are needed to identify this subgroup of patients.

Although somatic *BRCA* mutations (classified as ESCAT IIA) have not the same value as germline alterations (ESCAT I), the potential benefit of PARPi in this subgroup of patients is also a matter of research. In the RUBY trial, rucaparib monotherapy was evaluated in 41 patients with HRR deficiency, including 4 patients with somatic BRCA mutations, reporting 1 partial response and 1 stable disease (45). The TBCRC048 trial evaluated olaparib in 54 patients with metastatic BC and germline mutations in various non-BRCA DNA damage repair genes (cohort 1) and somatic mutations in several genes, including BRCA (cohort 2), with ORR of 33% and 31% respectively (46).

Kuemmel et al. (47) reported a partial response to olaparib in a patient with metastatic HR+ BC harboring a germline sequence variant affecting *PALB2*, supporting the possible benefit of PARPi not only in patients with alterations in *BRCA*, but also in other genes implicated in the HR repair system. Further research is needed to explore whether the benefits of PARPi can be extended to patients harboring germline alterations in other HR-related genes, such as *BARD1* and *RAD51D* mutations or *BRCA* promoter methylation (48).

4 Conclusion

Germline mutations in *BRCA1* and *BRCA2* are the most relevant causes of a genetic predisposition to breast cancer. Dysfunction of the homologous recombination repair system makes *BRCA*-deficient cells sensitive to PARP inhibitors, because of the phenomenon of synthetic lethality. In carriers of germline *BRCA* mutations with metastatic BC, olaparib and talazoparib achieved better median PFS than conventional CT, according to the results of the phase III trials OlympiAD and EMBRACA.

Olaparib has also shown efficacy as an adjuvant therapy for triple-negative and high-risk HR+ tumors. Neoadjuvant olaparib may be useful to increase the rate of pCR and allow de-escalation or omission of conventional CT in some g*BRCA*m carriers.

Further research is required to answer open questions regarding the use of PARPi, such as their benefit as adjuvant treatment for lower-risk HR+ BC, their possible combination with other systemic therapies, their potential role as prophylactic agents for healthy g*BRCA*m carriers, biological predictive markers of long-term responses, feasibility of de-escalation strategies in long responders, and efficacy in patients with other alterations involving the HR repair system beyond germline *BRCA* mutations.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

VA - conception of the work, writing and review of literature JC, JP, MS, DR – contribution to writing and review of literature CS, MG, AC, EE, EG, EL, MF – treating oncologists and provision of study material NM – treating oncologist, provision of study material and supervision of the work. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Pseudo-Meigs' syndrome secondary to breast cancer with ovarian metastasis: a case report and literature review

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Ovarian metastasis of breast cancer with pseudo-Meigs' syndrome (PMS) is extremely rare. Only four cases of PMS secondary to breast cancer with ovarian metastasis have been reported to date. In this report, we present the fifth case of PMS caused by ovarian metastasis of breast cancer. On the 2nd of July 2019, a 53-year-old woman presented to our hospital with complaints of abdominal distension, irregular vaginal bleeding, and chest distress. Color Doppler ultrasound examination revealed a mass approximately 109×89 mm in size in the right adnexal area, accompanied by multiple uterine fibroids and a large amount of pelvic and peritoneal effusions. The patient had no common symptoms and showed no signs of breast cancer. The main manifestations were a right ovarian mass, massive hydrothorax, and ascites. Lab workup and imaging revealed raised CA125 (cancer antigen 125) levels and multiple bone metastases. At first the patient was misdiagnosed with ovarian carcinoma. After the rapid disappearance of oophorectomy hydrothorax and ascites, and decreased CA125 levels, from 1,831.8u/ml to normal range. According to the pathology report, breast cancer was finally diagnosed. The patient underwent endocrine therapy (Fulvestrant) and azole treatment after oophorectomy. At the 40-month follow-up, the patient was still alive and doing well.

KEYWORDS

breast cancer, Pseudo-Meigs' syndrome, ovarian metastasis, endocrine therapy, oophorectomy

1 Introduction

Ovarian metastasis from breast cancer is extremely rare. Pseudo-Meigs' syndrome (PMS) secondary to ovarian metastasis is also a rare phenomenon. The uncommon metastatic site and rarity of PMS make ovarian metastasis of breast cancer with PMS extremely rare. To the best of our knowledge, only four cases have been reported

worldwide; all of these case reports were reported in Japan (1–4). We reviewed our hospital records, from January 1990 to December 2021, to find all the recorded cases which occurred at our hospital; our search only generated one case.

As early as 1934, Salmon reported two cases of pelvic benign tumor with pleural and peritoneal effusion (5). In 1937, Meigs and Cass reported seven cases of patients who presented with ovarian fibroma with ascites, and pleural effusion, which disappeared after the ovarian fibroma was removed; these cases were clinically established as Meigs' syndrome (6). According to the literature there are four types of Meigs' syndrome: thecoma, fibroma, granulosa cell tumor, and Brenner's tumor. Later, researchers defined PMS according to its tumor histology: other benign or malignant pelvic tumors that cause pleural and peritoneal effusions similar to Meigs' syndrome (7), including primary malignant tumors, metastases, or other benign tumors of the ovary. The mechanism of hydrothorax and ascites in patients with Meigs' and PMS remains unclear. Hydrothorax and ascites disappear spontaneously after oophorectomy, and the reason is currently unknown.

The incidence of PMS is very low and it is easily misdiagnosed. PMS is often secondary to digestive tract tumors, while ovarian metastasis of breast cancer is extremely rare. Here, we not only report the first case from China, but also summarize the previous four cases.

2 Case representation

On the 2nd of July 2019, a 53-year-old woman presented at our hospital with complaints of abdominal distension (for 3 months), irregular vaginal bleeding (for 2 months), and chest distress (for 1 month). Color Doppler ultrasound examination revealed a mass of approximately 109×89 mm in size in the right adnexal area, accompanied by multiple uterine fibroids and a large number of pelvic and peritoneal effusions. The computed tomography (CT) of the pelvic cavity considered that the space occupying lesion in the middle and lower abdomen originated from the right ovary. The chest CT showed moderate effusion in the bilateral pleural cavity and partial dilatation of the lower lobe of both lungs (Figure 1). SPECT showed abnormal bone metabolism in the left 8^{th} posterior costal vertebra, the 4^{th} and 5^{th} lumbar vertebra, and the 1^{st} sacral vertebra (Figure 2A). Lab work revealed that the tumor marker CA125 (cancer antigen 125) was 1,831.8U/mL.

The patient underwent a comprehensive ovarian cancer staging on July 16, 2019. The surgeons removed the patient's uterus, bilateral adnexa, bilateral pelvic lymph nodes, abdominal para-aortic lymph nodes, greater omentum, and appendix. During the operation, an irregularly shaped solid multiple nodular mass of approximately 12×10 cm in size was found on the right ovary with soft texture and a ruptured tissue surface. The abdominal cavity was characterized by yellowish-green ascites of 3,500 ml and multiple uterine fibroids. Intraoperative rapid freezing pathology revealed adenocarcinoma of the right adnexa. The pathological report showed right adnexal adenocarcinoma, accompanied by intravascular carcinoma thrombectomy and right fallopian tube invasion. The surgeon re-requested the patient's medical history and found she had a history of a left breast mass for 2-3 years. She had no discomfort and never went to the hospital for an examination. Combining the immunohistochemical results and clinical history, it was necessary to exclude breast tumor

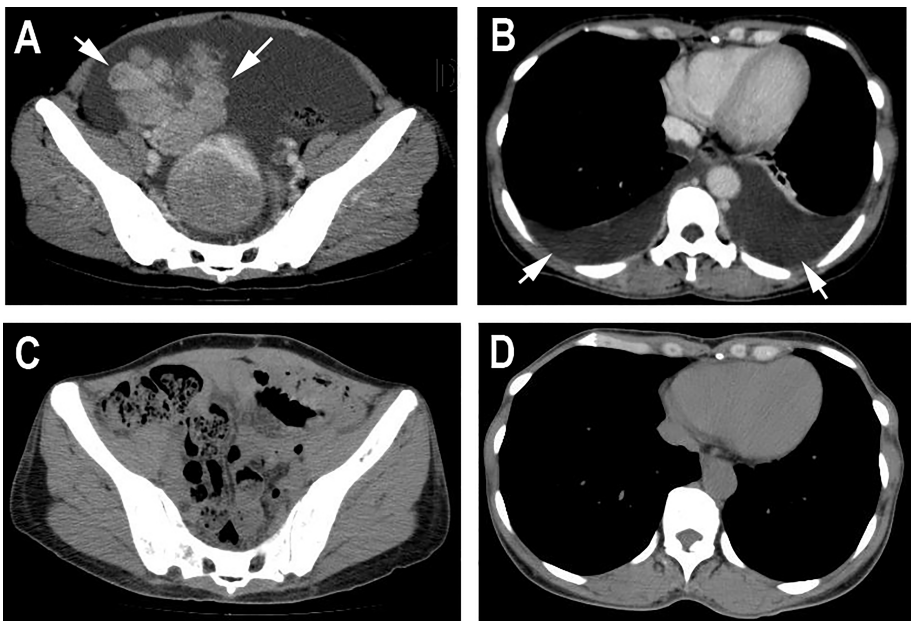

FIGURE 1
Computed tomography. **(A)** Pelvic CT before the surgery showed a huge mass in the middle and lower abdomen accompanied by ascites. **(B)** Chest CT before the surgery showed bilateral pleural effusion and partial dilatation of the lower lobe of both lungs. **(C, D)** CT after the surgery showed that the huge masses in the pelvis and the bilateral pleural effusion had disappeared.

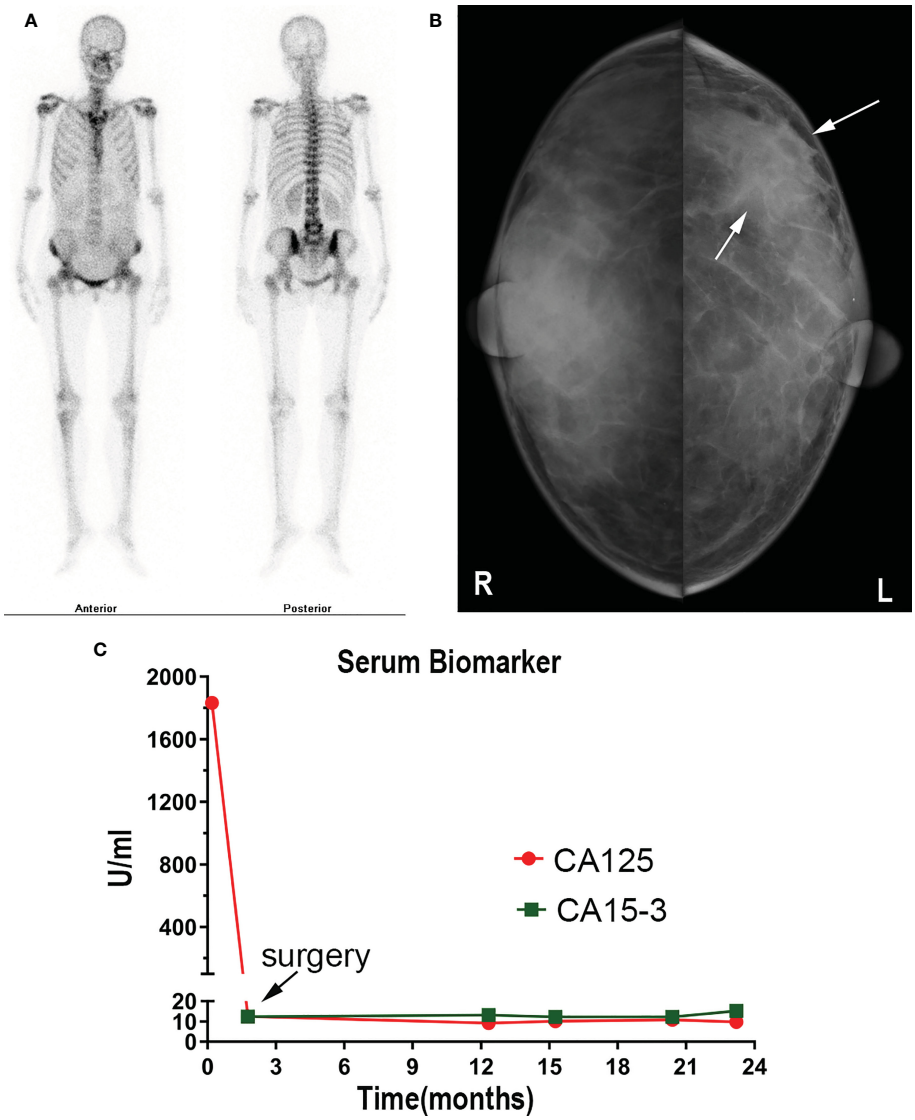

FIGURE 2
(A) SPECT showed abnormal bone metabolism in the left 8th posterior costal vertebra, 4th and 5th lumbar vertebra, and 1st sacral vertebra. **(B)** Mammography showed a dense mass in the left breast. **(C)** CA15-3 and CA 125 level changes are shown.

metastasis before considering primary ovarian tumor. Metastatic lymph node cancer was found 12/15: 5/6 left pelvic lymph nodes, 3/5 right pelvic lymph nodes, 2/2 left para-aortic lymph nodes, and 2/2 right para-aortic lymph nodes. Immunohistochemistry tests revealed Ki-67 30%, P53 (+), vim (-), CA125 (-), estrogen receptor (ER) (+), progesterone receptor (PR) (+), a-inhibin (-), Placental alkaline phosphatase (PLAP) (-), S-100 (-), mammaglobin (+), GATA-3(+), and gross cystic disease fluid protein 15 (GCDFP15) (+) (Figures 3A–D). Nuclear heterogenous cells were found in ascites. The result of pleural fluid puncture suggested inflammatory exudative lesions. One week after the removal of the ovarian mass, the patient's pleural and abdominal effusion completely disappeared, the symptoms of abdominal distension and chest distress were relieved, and CA125 levels decreased from 1,831.8 U/ml back to the normal range (Figure 2C). Post-surgery, the patient underwent various breast examinations according to pathological indications to trace the primary lesion. Mammography suggested that there was a dense mass near the chest wall in the deep upper outer quadrant of the left breast with the surrounding structural disorder (Figure 2B). Breast ultrasound revealed a hypoecho group with a size of 87×10×20 mm in the outer upper quadrant of the left breast, categorized according to the Breast Imaging Reporting and Data System (BI-RADS) as a category 4B. Accompanied by left axillary lymph node enlargement (18×8 mm). The patient underwent a biopsy of the left breast, and the pathology report revealed invasive breast carcinoma. Immunohistochemistry tests revealed ER (+), PR (+), CA125 (-), cytokeratin (CK) (+), CK7 (+), p53 (-), GCDFP15 (+), Ki-67 (5%), and Human epidermal growth factor receptor 2 (HER2) (2+) (Figures 3E–H). FISH showed HER2 without amplification. The patient was diagnosed

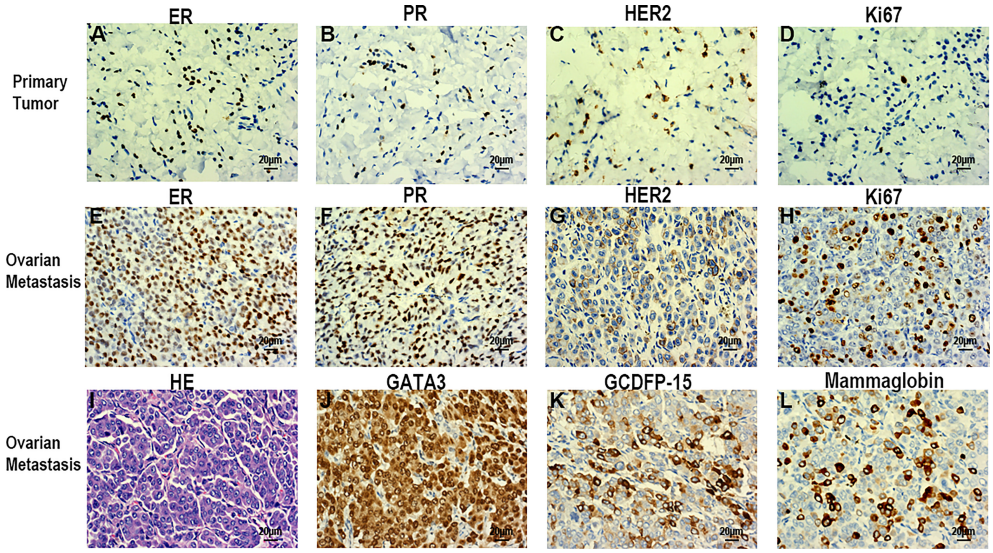

FIGURE 3
Immunohistochemical examination of breast cancer **(A-D)**. **(A)** ER (+). **(B)** PR (+). **(C)** HER2(+). **(D)** Ki-67(30%). Histopathological and immunohistochemical examination of the ovarian tumor **(E-L)**. **(E)** ER (+). **(F)** PR (+). **(G)** HER2 (+). **(H)** Ki-67 (5%). **(I)** HE staining. **(L)** GATA-3(+). **(K)** GCDFP15(+). **(L)** Mammaglobin (+). Scale bars: 20 μm; magnification, x40.

with the following: left breast cancer with ovarian and multiple bone metastases, staging T3N1M1 (ovarian, bone), and Luminal type A. Hormone receptor positive (HR+) patients without visceral crisis, according to NCCN guidelines therapeutic principles, the patient was treated with Fulvestrant and azolephosphonic after the breast cancer diagnosis. At the 40-month follow the patient was doing good and stable.

3 Discussion

Ovarian metastases account for 15% of ovarian tumors, mainly from organs such as the gastrointestinal tract (8–10) and the endometrium (11). The ovarian metastasis rate from the breast differs significantly, accounting for approximately 1.8-38% (12–14). Fujii believes that the difference in the incidence of different cancer types could be due to ethnic differences, but the reported difference in ovarian metastasis rate may be more related to the small statistical sample size (1). Nevertheless, less than 10% of patients with breast cancer have evidence of distant metastasis at the time of initial diagnosis (3). Pseudo-Meigs' syndrome caused by ovarian metastasis of breast cancer is extremely rare, whether it is found at the same time with PMS or heterochronous breast cancer, it is clinically confusing.

Although several theories have been proposed, the etiology of ascites in this clinical syndrome remains unclear. As a first theory, Meigs suggested that the irritation of the peritoneal surface by a hard solid ovarian tumor could stimulate the production of peritoneal fluid (15). A second theory suggests the lymphatics of the tumor (16). A third theory suggests that stromal edema and transudation may occur as a result of a discrepancy between the arterial supply to the large tumor and the venous and lymphatic drainage of the same mass (17). A fourth theory suggests that the excessive production of fluid by the peritoneum leads to ascites (18). The final theory, but probably the most plausible, is that increased capillary permeability and the resultant third-space fluid shift occur due to increased levels of inflammatory cytokines and vascular endothelial growth factor (VEGF) (19).

The main clinical challenge of PMS is that it can easily be misdiagnosed as carcinomatous peritonitis or pleurisy, but the cytological results of pleural and ascites effusion in Meigs' syndrome/PMS should be negative. The conditions of patients with PMS are often confused with terminal stage malignant diseases, for which curative surgical treatment is not an option and surgery is merely introduced as a palliative approach.

Table 1 summarizes the previous four cases as well as the case presented in this report. The four patients were aged 34, 50, 54, and 49 years old. Our patient was 53 years old at the time of the diagnosis and treatment. Two of the previous four cases were metachronous, accompanied with ascites and pleural effusion, with elevated CA15-3 (cancer antigen 15-3) levels. Two of the previous four cases presented with both pleural effusion and elevated CA125 levels. Our case presented with both ascites and pleural effusion, as well as elevated CA125 levels. Oophorectomy was performed in all of the five cases. CA125 levels was significantly elevated in this case, while CA15-3 was only elevated in some patients and normal in others. Thus, the tumor origin may be difficult to determine by merely relying on these serum tumor markers. Primary tumor differentiation ultimately depends on the diagnosis of the pathological specimens. GATA-3, GCDFP-15, and

TABLE 1 The clinical characteristic and survival of all the cases.

Author (year)	Age (years)	Onset (interval/ months)	CA125 (U/ml)	CA15-3 (U/ ml)	ER (breast/ ovary)	PR (breast/ ovary)	HER-2 (breast/ ovary)	Metastasis of other organs	Primary tumor resection	oophorectomy	CT/RT	ET/anti-Her2	Follow-up
Fujii (2006) (1)	34	M (52)	ND	High	-/+	-/+	ND/+	Uterus, abdominal cavity, sigmoid colon and omentum	Yes	Yes	Capecitabine, mitomycin-C +methotrexate +mitoxantrone hydrochloride	Aromatase inhibitor, toremifene citrate and trastuzumab	Dead after 2.2 years of oophorectomy
Kawakubo (2010) (2)	50	S	4488	10.5	+/+	-/-	-/-	Bone and liver	No	Yes	Docetaxel	ND	Dead after 4 months of oophorectomy
Naito (2012) (4)	54	M (69)	ND	High	+/+	+/+	-/-	ND	Yes	Yes	Paclitaxel and carboplatin	Aromatase inhibitor	40 months (stable)
Akizawa (2021) (3)	49	S	692	93.9	+(left) &-(right)/ +	+(left) &-(right)/ +	-(left) &-(right)/-	Bone	Yes	Yes	Capecitabine	Palbociclib, letrozole	17 months (stable)
present case	53	S	1831.8	12.36	+/+	+/+	-/-	Bone	No	Yes	No	Fulvestrant	40 months (stable)

M, metachronous; S, synchronousm; ER, estrogen receptor; PR, progesterone receptor; ND, no document; CT, chemotherapy; RT, radiotherapy.

Mammaglobin are important immunohistochemical indexes that indicate the origin of breast cancer (20). Compared with the ER, PR, HER2, Ki67 and other immunohistochemical indexes of primary breast and ovarian metastases, there may be inconsistencies between metastatic lesions and primary lesions (Figure 3).

Ovarian metastases are usually large, and surgery to reduce the tumor load may be helpful (1–4, 21). In all the reported cases, the hydrothorax and ascites rapidly disappeared after resection of the ovarian metastases. In contrast, the resection of the primary breast tumor is currently a big debate. PMS caused by breast cancer is often accompanied by distant metastasis. Three of the previous four cases had multiple metastases of abdominal organs, liver and bone, respectively. But one of the previous four cases had remained stable for 40 months (Table 1).

In our reported case, there was only bone metastases but no signs of visceral metastases. The effective disease management and treatment approach was determined using the NCCN guidelines. This patient was Luminal type A and had no visceral crisis, so she was given endocrine therapy with Fulvestrant. Under these circumstances, the primary question to answer is whether primary breast tumor resection should be carried out? To answer this primary question, surgeons always work in coordination with a multidisciplinary team. Which was the case in our report, the case was discussed by the multidisciplinary team. The breast surgeon was of the opinion that the primary breast lesion should not be removed. After surgery, there was no recurrence of hydrothorax and ascites, no new metastases, and at the 40-month follow up in November 2022, the patient's KPS score was 90.

4 Conclusion

Cases of ovarian metastasis of breast cancer with PMS is extremely rare. To the best of our knowledge, this is only the fifth case. Our case report demonstrates that curative surgery for PMS secondary to breast cancer with ovarian metastasis resulted in a good KPS score and could be possible. At the 40-month follow-up, dated November 2022, the patient was still alive and doing well, with no indication of decline.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

Data acquisition: Z-JL, X-JZ and J-XZ. Data analysis and interpretation: Z-JL, S-PY. Radiological analysis of ultrasound and CT images: Z-JL, X-YL. Manuscript preparation: X-YL and Z-JL. S-PY contributed the idea of this article writing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found onlineat: https://www.frontiersin.org/articles/10.3389/fonc.2023.1091956/full#supplementary-material

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Case Report: Intraoperative radiotherapy as the new standard of care for breast cancer patients with disabling health conditions or impairments

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In selected patients, intraoperative radiotherapy (IORT) offers an alternative to standard external beam radiotherapy (EBRT) while providing equivalent breast cancer control outcomes. After IORT, most patients do not require external beam radiotherapy and thus avoid the need to travel to and from a radiotherapy centre in the weeks after surgery. EBRT is associated with an increased risk of non-breast cancer mortality and poorer cosmetic outcomes while increasing patient travel time, emissions associated with travel and time spent in the hospital. Consequently, EBRT is associated with an overall reduction in quality of life compared to IORT. Patients with other on-going health conditions or clinical impairments are likely to be affected by the daily radiotherapy requirement. Should these patients be consulted during their pre-operative assessment as to options to undergo IORT? This paper describes a case of IORT and follow up in a functionally blind patient. Quality of life effects are elucidated and further support the use of IORT in selected breast cancer patients with health conditions or impairments.

KEYWORDS

intraoperative radiotherapy, breast cancer, radiotherapy, TARGIT, IORT, quality of life, breast

Introduction

Breast cancer is the most common cancer, accounting for 15% of all cancers in the United Kingdom. Approximately 56,000 new cases of breast cancer are diagnosed annually (1). Breast cancer incidence increases with age, with 80% of new diagnoses occurring in women aged 50 years or older (2). Treatment is largely determined by the patient's health,

menopause status, tumour size, nodal status and evidence of any metastatic disease. With high screening rates in the UK, most breast cancers are discovered at an early stage and 80% will be treated with breast conserving surgery, by wide local excision or mastectomy. Adjuvant whole breast external beam radiotherapy (EBRT) is delivered to 80% of patients post lumpectomy to improve tumour control and reduce mortality (1, 3).

Adjuvant radiotherapy is a valuable component of breast cancer therapy in those receiving breast conserving treatments. At present in the UK, EBRT is delivered with a five-fraction regime as the standard of care. However, this may come with considerable physical, psychological and financial consequences (3–5). After breast conserving surgery, 80% of patients need to travel daily to radiotherapy centres, to receive at least five treatments. Other longer regimes extending over several weeks might be necessary (6, 7). Following the trauma of surgery, travelling to and from radiotherapy centres can be physically challenging for some, especially given that many breast cancer patients are elderly and have comorbidities (8, 9). Alongside this, daily travel can incur a significant monetary charge if travelling long distances. A large financial and time burden is placed upon many, as two thirds of breast cancer patients live over 13 miles away from their nearest radiotherapy centre. Accompanying this significant travel is the environmental impact of travel for cancer treatments (7, 10).

As an alternative, the targeted intraoperative radiotherapy (TARGIT-A) trial has demonstrated that intraoperative radiotherapy (IORT) can deliver non inferior treatment outcomes compared to EBRT for eligible patients (7, 10). Furthermore, IORT significantly reduces the rate of non-breast cancer mortality and eliminates the need for external beam radiation therapy in 80% of patients. Patients who receive IORT have a better quality of life (QOL) and have a reduced financial and time burden post lumpectomy. Reducing the pressure on existing radiotherapy departments through the use of IORT would further reduce strain placed on the NHS and may reduce spending (7, 11). This paper highlights the benefits of using IORT to treat elderly breast cancer patients and those with comorbidities.

Case

A 64-year-old female presented with a small mass in her left breast during her mammography screening appointment. The mass within the upper inner quadrant of the left breast was irregular, spiculated and with calcifications (Figure 1). Subsequently, breast ultrasound confirmed the presence of a mass, but with no obvious enlargement of the axillary nodes. Ultrasound guided core biopsy demonstrated a grade 2, hormone positive [ER+ve 280/300, PR+ve 300/300], HER2-ve invasive ductal carcinoma with no ductal carcinoma *in situ* (DCIS). The patient had a previous diagnosis of a right breast cancer treated in another breast centre, with a mastectomy as well as reconstruction and axillary clearance for DCIS (with no invasion) 13 years earlier. The patient had long-standing significant lymphedema of her right arm as well as a past medical history of cervical spondylosis, osteoarthritis of the carpo-metacarpal joints, distal interphalangeal and proximal interphalangeal joints of the hands, and fibromyalgia. She also had a history of Meige syndrome, characterised by involuntary and often forceful contractions of the muscles around the eyes, jaw and tongue and tearing which caused a functional blindness. There was no family history of breast disease.

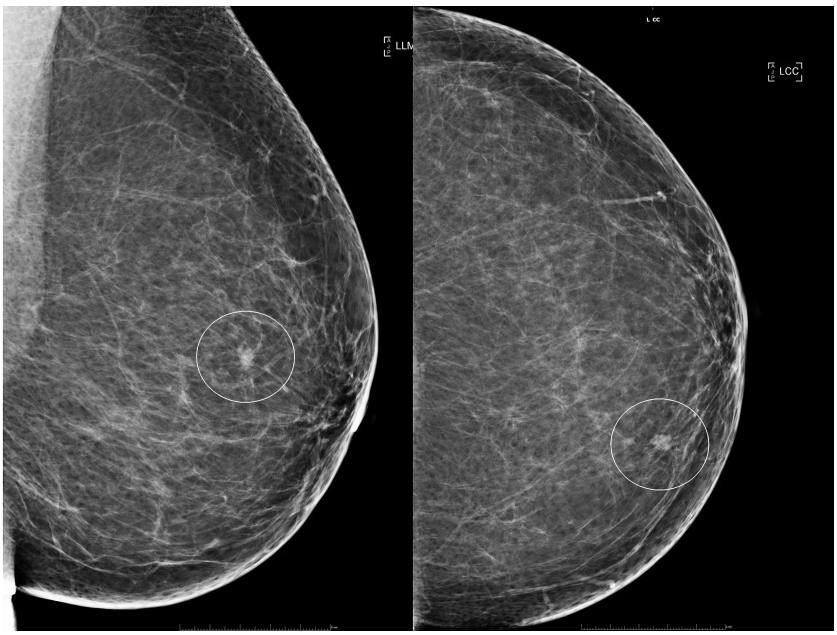

FIGURE 1
Plain x-ray mammograms demonstrating a small spiculated mass (circled) within the upper inner segment of the breast. Left image: Mediolateral oblique view. Right image: Craniocaudal view.

The risks and benefits of four treatment options were discussed with the patient:

1. A wide local excision and sentinel node biopsy followed by adjuvant external beam whole breast radiotherapy for 5 days a week over three weeks. (This was the EBRT standard of care at the time of diagnosis)
2. A wide local excision and sentinel node biopsy with the omission of radiotherapy. (Though strictly speaking, the evidence for omission of adjuvant radiotherapy is in patients 65 years and older and required patients to be compliant with 5 years of adjuvant endocrine therapy. Given the various comorbidities there was a high likelihood that this lady would not be able to tolerate the side effects of endocrine therapy, particularly the musculoskeletal side effects associated with Aromatase Inhibitors. A treatment plan including radiotherapy should be prioritised in case the patient cannot tolerate the side effects.)
3. Consideration of neoadjuvant endocrine treatment for a short period of time whilst NHS funding for IORT was being sought, after which a wide local excision and delivery of IORT would take place. (Again, there were concerns about tolerability of endocrine therapy side effects.)
4. A wide local excision with self-funded IORT. The patient was made aware that a fifth of patients who receive IORT may be treated with adjuvant EBRT depending on the histology findings.

After discussion with the patient and the multidisciplinary team, it was decided that she would be a good candidate for a wide local excision with IORT. Sight difficulties were the major factor that influenced her decision. EBRT would have required her to travel 40 minutes each way by car, and 3 hours each way by public transport. The guilt of putting pressure on her disabled husband to assist with daily travel for three weeks was immense, and the thought of having nothing further to face after the surgery brought relief. The patient's daughter chose to fund her treatment to allow surgery and IORT in a timely manner.

Intra-operative radiotherapy was delivered immediately after wide local excision using a miniature electron beam driven X-ray source (Intrabeam™ (Carl Zeiss Meditec, Oberkochen, Germany)) (12). Twenty gray of radiation was delivered from the surface of a 4cm spherical applicator directly to the excision cavity for 27 minutes (Figure 2). The patient chose to stay overnight for observation. Recovery was uneventful with no complications. Final histology reported a 7mm, grade 1, hormone receptor positive tumour resected with microscopically clear margins. Sentinel node biopsy was free from tumour. The patient was commenced on a 5-year course of an aromatase inhibitor, anastrozole, along with Vitamin D and B12 supplements, which immediately caused distressing muscular and joint pain in upper and lower limbs, polydipsia, polyurea, hot flushes and tiredness. After discussion, the patient agreed to take 2-4 week anastrozole breaks to relieve side effects and extend the duration to 10 years. Since then, the patient has remained stable having only taken three, two-week breaks over the seven-year period. Annual blood tests and bone density scan results have remained within normal ranges and annual surveillance mammography has shown no signs of recurrence for seven years.

Discussion

Post-surgical EBRT has been described as fatigue inducing, possibly owing to its daily radiotherapy requirements. Symptoms are exacerbated in comorbid and physically impaired groups (3, 13–15). Moreover, Muszalik et al. (16) reports that the 61-70 age group suffer the worst fatigue symptoms. Given that many breast cancer patients undertaking radiotherapy are older and have co-morbidities, efforts should be made to relieve stressors and prioritise QOL. The TARGIT-A trial, undertaken by Vaidya et al. (7) showed that targeted intraoperative radiotherapy can prevent the need for adjuvant EBRT in 80% ofpatients. This is done without compromising patient safety or increasing the rate of disease occurrence (7).

Other methods of delivering IORT have been demonstrated, including that described in the ELIOT trial. On the contrary, the

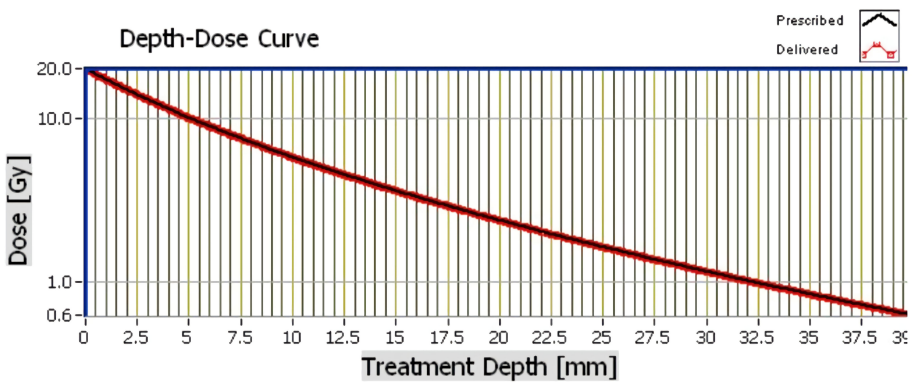

FIGURE 2
Radiotherapy depth dose curve for intra-operative radiotherapy delivery.

ELIOT trial demonstrated that IORT was inferior to EBRT (17). The difference in efficacy may be explained by the difference in radiation type, applicator or methodology. The ELIOT method employs a linear electron accelerator to deploy radiation in an anterior to posterior manner. IORT delivered in the TARGIT trial uses a probe that contacts the excised tumour bed (18, 19).

Over the last 30 years there has been little improvement in breast cancer survival in patients with severe comorbidities. Furthermore, breast cancer mortality is increased by the severity and number of comorbidities even after adjusting for age and stage and these may be as important as cancer stage in predicting survival (20). Given that 65% of breast cancer patients have co-morbidities, clinicians should consider that the use of IORT negates the need for EBRT and may reduce the exacerbation of these comorbidities. Thirty-two percent of patients suffer with arthritis and a quarter suffer with cardiovascular disease. These conditions are commonly aggravated by the stress and the travel needed for EBRT (21–23). The x-rays delivered by the Intrabeam™ system have a steep dose gradient, thus only the tissues to a depth of 3cm, directly surrounding the excision site are irradiated. The therapeutic depth however is 6mm. Unnecessary collateral irradiation to the nearby chest wall, heart and lungs is therefore reduced significantly (24). This may explain the published data that demonstrates a significant reduction in non-breast cancer mortality (7).

Moreover, patients are more likely to report poor emotional health and QOL during the course of EBRT (21). A prospective cohort study of women over 65 with a diagnosis of early-stage breast cancer demonstrated that poor health related QOL is directly detrimental to survival, independent of breast cancer prognostic variables (25). Physical function, mental health and social support are three domains that constitute health related QOL, and all are negatively affected by the radiotherapy (21, 25–27). In addition, 90% of patients have reported fatigue as a side effect of radiotherapy, with 30% describing it as severe to intolerable. Schnur et al. (3) captured the thoughts of these patients, with some describing their fatigue as, "totally exhausted to the point I could hardly move", and "total shutdown". Mental health in breast cancer radiotherapy patients is also largely affected, with 31% of patients experiencing moderate to severe levels of negative affect and two-fifths experiencing anxiety. Statements such as, "I'm giving in to imagined or real side effects of radiation" and, "I should be finished with crying" were expressed by patients (3, 28). Lack of perceived social support from families, co-workers, bosses and friends is reported by 40% of patients undergoing breast radiotherapy (3). Statements such as, "My co-worker doesn't seem to understand my need to rush out of work for my treatment", and "I should have stayed in my abusive marriage because I would not be alone", highlight the severity of the social issues that some patients experience (3, 28). IORT as a sole treatment in 80% of patients can prevent the exacerbation of these poor quality of life outcomes and should therefore be considered in eligible patients with comorbidities, mental health and those with poor perceived social support (7).

One in five people aged 70 or over are visually impaired. Vision loss is a factor that impairs radiotherapy access (29). In 2013 approximately 1.99 million people in the UK suffered with sight loss or blindness. The prevalence of sight loss has increased by 7.5% in the last decade. This proportion is set to increase further with demographic ageing. The cost of blindness affects patients significantly and restricts their ability to travel independently (30, 31). The travel requirements for EBRT place a burden on visually impaired patients, their families, and their support networks. Patient's sight and their ability to access safe travel, and support should be seriously considered when determining appropriate radiotherapy (31).

There are numerous advantages with the use of the IORT Intrabeam™ system. Being portable, it can easily be used in most operating rooms within a hospital. IORT is intended as a single-dose treatment and adds about 30 minutes to operative time. This is less than the total time undertaking EBRT radiotherapy. Although EBRT may take only 5-10 minutes to deliver each fraction, the preparation and appointment times often allow 20 minutes (32). Therefore, each patient spends over 100 minutes receiving EBRT. This ignores the time taken for travel to and from a radiotherapy centre. If the TARGIT-A inclusion criteria were to be used as selection criteria, 54% of patients receiving breast conserving surgery could be offered single dose IORT treatment. Implementing this could save UK patients 2 million miles of journeys and reduce UK CO_2 emissions by up to 588 tonnes annually (11). Over the past 20 years, TARGIT-IORT has been used in 260 centres worldwide, where around 45,000 patients have been treated. Through this, an estimated 20 million travel miles have been avoided (33).

Currently available cost analyses compare TARGIT-IORT to previous 15+ fraction standard of care (34). The shift to ultra-hypofractionation has undoubtably reduced patient costs, radiotherapy waiting times and allowed more patients timely treatment (35, 36). Radiotherapy department costs are largely fixed and dependent on departmental throughput, therefore the new 5 fraction regimen reduces costs per patient but may not significantly reduce costs if units stay busy. An updated cost benefit analysis comparing TARGIT-IORT to the current standard of care must be elucidated (37, 38).

Vaidya et al. (7) compared the TARGIT-IORT arm against a 15 fraction EBRT regime, contrary to the FAST-forward method introduced as the UK's standard of care in 2022. Compared to the previous 15 fraction regime, the FAST-forward method reduces the labour, time and financial burden on patients and health systems. The FAST-forward trial reported no statistically significant differences between tumour relapse, survival, normal tissue effects and photographic change in breast appearance, compared to the 15-fraction method (4, 39). Although this may weakly imply that TARGIT-IORT may replicate its efficacy and side effect profile compared to FAST-forward, further studies must be undertaken to compare the two directly. Furthermore, recurrence rate after lumpectomy with the omission of radiotherapy is associated with an increased incidence of local recurrence but no

detrimental effect on distal recurrence, therefore TARGIT outcomes should also be compared to a no radiotherapy group (40, 41). Alongside this, authors have scrutinized the TARGIT-A trials, with most criticism describing inadequate data collection, an inappropriately lenient use of the non-inferiority criterion, and focusing data collection from a favourable subgroup of patients (42–46). Current follow up data at 5 years show an increase in local recurrence with TARGIT-IORT, but no overall increase in mortality (7). Further follow up must also be undertaken to properly establish long term efficacy as risk of tumour reoccurrence continues to increase after 7 years (47).

Conclusion

As healthcare professionals, we have a responsibility to uphold patient care, well-being and quality of life as well as delivering optimal treatments individualised to patients' needs. More can be done to optimise breast cancer treatments in thousands of patients in the UK. Consideration should be put towards the development and use of IORT in order to improve patients' quality of life by considering their physical health, mental health and social support before prescribing radiotherapy.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics Statement

Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

MO contributed to the conceptualisation and original draft. SDSM contributed to manuscript review and editing. NC contributed to supervision, conceptualisation, manuscript review and editing. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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