Advanced dual primary male breast cancer and lung cancer: A case report and literature review

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Abstract. The current report presents a unique case of advanced male invasive breast cancer coexisting with synchronous primary lung adenocarcinoma, a rare clinical manifestation. The case contributes to the limited literature on male breast cancer and its association with multiple primary malignancies. The patient, a 59-year-old man, presented with a large ulcerative mass in the left breast (14x10 cm) and ground-glass opacities with calcified nodules in the right lower lung lobe (14x14 mm). Imaging and pathology confirmed stage IIIB invasive ductal carcinoma of the breast [human epidermal growth factor receptor-2-positive, estrogen receptor-positive (80%) and progesterone receptor-positive (5%)] and minimally invasive lung adenocarcinoma. Treatment consisted of neoadjuvant chemotherapy (epirubicin + carboplatin + trastuzumab + pertuzumab), a modified radical mastectomy with latissimus dorsi flap reconstruction and a thoracoscopic lung wedge resection. The therapeutic approach resulted in partial remission of the breast cancer prior to surgery and a stable disease status in the lung, with no recurrence at the 1-year follow-up. This case underscores the importance of comprehensive, integrative strategies and long-term follow-up for managing rare, complex cancer cases.

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Abbreviations: MBC, male breast cancer; CT, computed tomography; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor-2; AR, androgen receptor; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; EpCAM, epithelial cell adhesion molecule; RhoA, ras homolog family member A; RhoC, ras homolog family member C; Rac1, rac family small GTPase 1; PI3K, phosphatidylinositol 3-kinase; MAPK, mitogen-activated protein kinase; TCM, traditional Chinese medicine; WBC, white blood cell

Key words: male breast cancer, lung cancer, case report, invasive ductal carcinoma, genetic mutations

Introduction

Male breast cancer (MBC) is a rare malignancy, representing ~1% of all breast cancer cases worldwide and <1% of all male cancer cases (1). Due to the limited patient population, clinical randomized controlled trials on MBC are scarce, with most studies being retrospective and treatments for MBC are frequently based on protocols designed for female MBC (2). Male breast cancer differs significantly from female breast cancer (FBC) in several aspects, primarily including differences in age at onset and diagnostic stage, as well as differences in survival rate and mortality rate (3). Males are usually diagnosed with breast cancer at an advanced age, and the disease is often at a later stage at the time of diagnosis. Their 5-year relative survival rate is 98.7% for localized disease, while it is only 25.9% for distant metastatic disease. In contrast, FBC has a higher rate of early diagnosis (4). Although there is no significant difference in 10-year breast cancer-specific survival between males and females, the overall survival of males is significantly lower than that of females (68.0 vs. 79.0%) (3). Despite phenotypic similarities, there are molecular-level differences between MBC and FBC (5). MBC is more frequently hormone receptor (HR)-positive and it has a stronger association with genetic susceptibility genes (e.g., BRCA2) (6). The current study presents a case of advanced male invasive breast cancer and lung cancer of dual primary origins, which was successfully treated using an integrated approach combining traditional Chinese and Western medicine.

Case report

Presentation. A 59-year-old male patient with no family history of cancer presented to Guang'anmen Hospital (Beijing, China) in June 2023 with a left breast mass. The mass had been present for 3 years but had not received proper attention, and the patient had not undergone any treatment for it prior to this presentation. Over the past 2 months, the mass had progressively enlarged and ruptured. Initially, the 4-cm soft mass was mobile with indistinct borders, causing no pain, itching or nipple retraction. Over time, the mass hardened and

eventually ulcerated, forming a cauliflower-like lesion with yellowish-brown purulent discharge (Fig. 1).

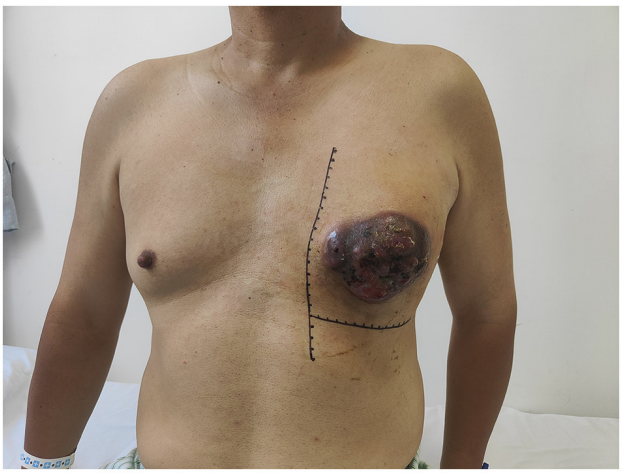

Figure 1. Breast tumor (pre-treatment ulcerative breast mass) image captured in June 2023.

Clinical examination. Asymmetry of the breasts was observed. The left breast displayed a 12x10-cm ulcerated mass with a hard texture, poor mobility and indistinct margins. No normal nipple or areolar structure was visible, and enlarged lymph nodes were palpable in the left axilla. The right breast showed no abnormalities. Auxiliary examinations included computed tomography (CT), which showed a 62x93-mm soft-tissue mass invading the left chest wall, along with axillary lymphadenopathy (Fig. 2A and B). Ground-glass opacity and calcified nodules were detected in the right lower lobe of the lung, the largest measuring 14x4 mm (Fig. 2C). Ultrasound revealed a 10.0x5.8x12.0-cm hypoechoic mass (Breast Imaging-Reporting and Data System category 5) (7) in the left breast and enlarged axillary lymph nodes (Fig. 3). Biopsy confirmed invasive ductal carcinoma with Paget's-like spread of the left breast, grade III (3+3+2=8). The scoring system used was the Nottingham histological grading system (8). Immunohistochemistry (IHC) was performed on paraffin-embedded tissues. The tissue was fixed with 4% formaldehyde at 20˚C for 12 h, embedded in paraffin and sectioned at a thickness of 4 μm. For the staining procedure, hydrogen peroxide was used as the blocking reagent and blocking was conducted at 37˚C for 4 min. Primary and secondary antibodies were used as working solutions (no dilution required). All antibodies were supplied by Leica Biosystems Newcastle Ltd. The catalogue numbers of the primary antibodies were SN 136374, SN 129975 and SN 384122; the catalogue number of the secondary antibody was DS9800. The results were as follows: Estrogen receptor (ER) (80%, strong +), progesterone receptor (PR) (5%, moderate +), human epidermal growth factor receptor-2 (HER-2) (3+), Ki-67 (60%) and androgen receptor (AR) (80%, 2+) (Fig. 4A-E). Images were captured using a Nikon ECLIPSE Ni-U light microscope at x400 magnification. Genetic testing indicated a PIK3CA gene mutation. Among them, Fig. 4A and B show hematoxylin-eosin (H&E) staining. The relevant methodological details are as follows: The tissue was fixed with 4% formaldehyde at 20˚C for 12 h, processed through standard procedures including paraffinization and deparaffinization, sectioned at a thickness of 4 μm and stained with hematoxylin for 5 min and eosin for 1 min at room temperature. Genetic testing, performed by an external institution (Beijing GeneX Health Medical Laboratory Co., Ltd.) using targeted region capture combined with next-generation sequencing technology, indicated a PIK3CA gene mutation. The protocol followed targeted capture of exonic regions and partial intronic regions of 794 genes, with sequencing conducted on an Illumina platform. The assay was designed to detect single nucleotide variations, small insertions/deletions (indels), copy number variations and partial gene fusions. Quality control parameters included DNA extraction yield (tissue ≥30 ng), average sequencing depth (tissue ≥1,000X), sequence alignment rate (≥95%) and base quality Q30 ratio (≥80%), as specified in the 'Sample Quality Control' section of the test report. The reference genome used was GRCh37/hg19. This protocol aligns with standard clinical practices for targeted panel sequencing in oncology, as described in guidelines such as the Chinese Expert Consensus on Tumor Mutation Burden Detection and Clinical Application (2020 Edition) (9) and technical specifications for clinical next-generation sequencing issued by regulatory authorities.

Treatment plan. Due to the ulceration and significant impact on the patient's quality of life, neoadjuvant chemotherapy for breast cancer was initiated, consisting of four cycles of a paclitaxel, carboplatin, trastuzumab and pertuzumab (TCbHP) regimen. The specific dosage of each drug in the regimen is as follows: Albumin-bound paclitaxel 0.5 g, carboplatin 70 ml, trastuzumab 440 mg and pertuzumab 420 mg. All drugs are administered via intravenous infusion, with one chemotherapy cycle lasting 21 days. After the first cycle, the left ventricular ejection fraction dropped by over 30%, necessitating a switch to TCbH (no pertuzumab) for the subsequent 4 cycles. During chemotherapy, the patient received both oral and topical traditional Chinese medicine (TCM). The oral formulation included *Panax ginseng* (15 g), *Panax notoginseng* (6 g), *Curcuma zedoaria* (10 g), *Pinellia ternata* (9 g), *Rhodiola rosea* (15 g) and honey-fried *Glycyrrhiza uralensis* (10 g) x21 doses (1 dose administered twice daily). After the first cycle of chemotherapy, the patient's WBC count was $3.21x10^9$/l (reference range, $3.5\text{-}9.5x10^9$/l). After 20 days of adjunctive herbal treatment, prior to the second cycle, the WBC count increased to $4.62x10^9$/l, indicating hematological improvement. In terms of tumor markers, the α-fetoprotein level decreased from 11.6 to 2.99 IU/ml (normal range, 0-5.8 IU/ml), the carbohydrate antigen (CA)125 level declined from 44.2 to 8.31 U/ml (normal range, 0-35 U/ml) and the CA724 level decreased from 68 to 13.9 U/ml (normal range, 0-6.9 U/ml). According to the Response Evaluation Criteria in Solid Tumors version 1.1 criteria (10), partial remission was achieved after four cycles, with CT showing a ≥30% reduction in tumor size and resolution of the axillary lymphadenopathy (Fig. 5A and B). After completion of 4 cycles of chemotherapy, the patient was admitted to the hospital, and on the 2nd day post-admission in October 2023, the patient underwent a modified radical mastectomy with latissimus dorsi flap reconstruction, followed by postoperative recovery (Fig. 6). Two additional

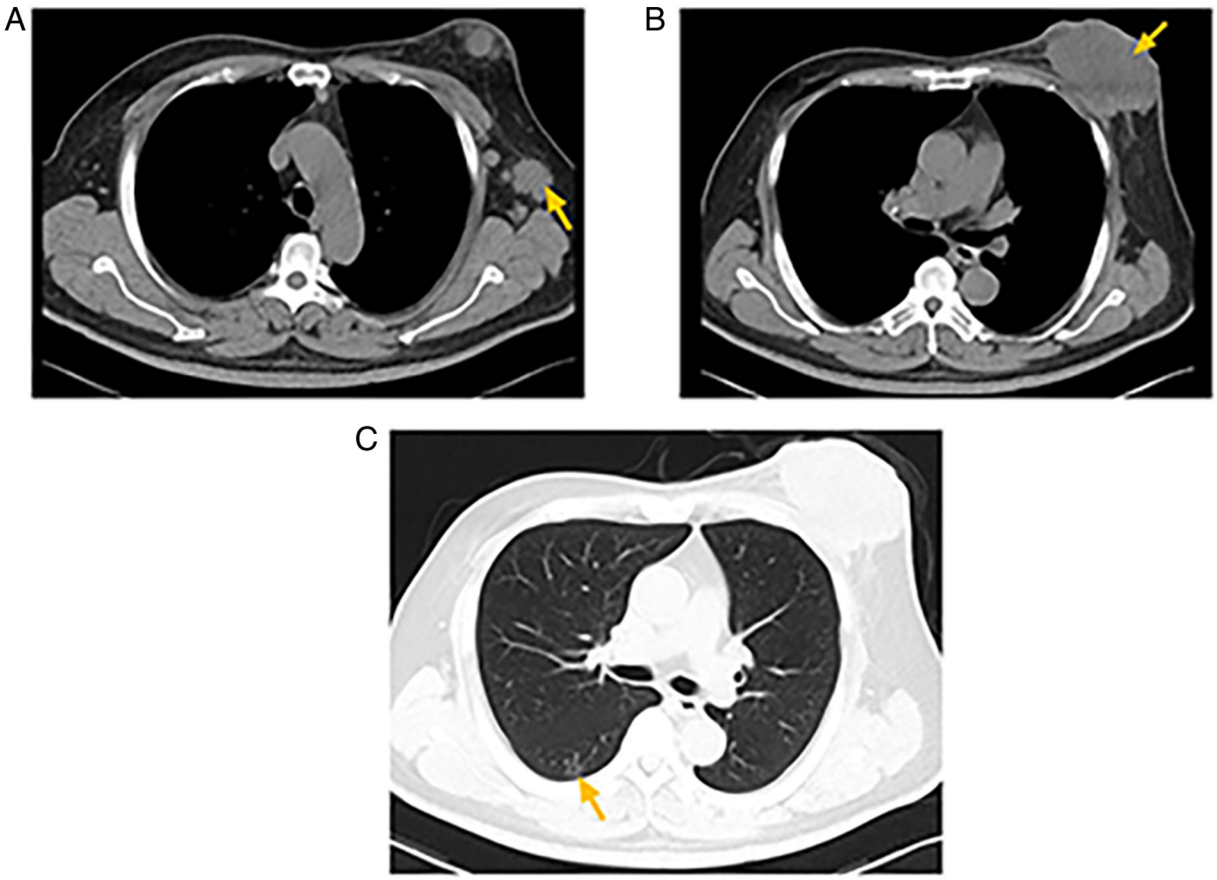

Figure 2. Pre-treatment CT images from June 2023. (A) CT scan showing enlarged axillary lymph nodes (yellow arrow). (B) CT scan showing the breast tumor (yellow arrow). (C) CT scan showing the lung tumor (yellow arrow). CT, computed tomography.

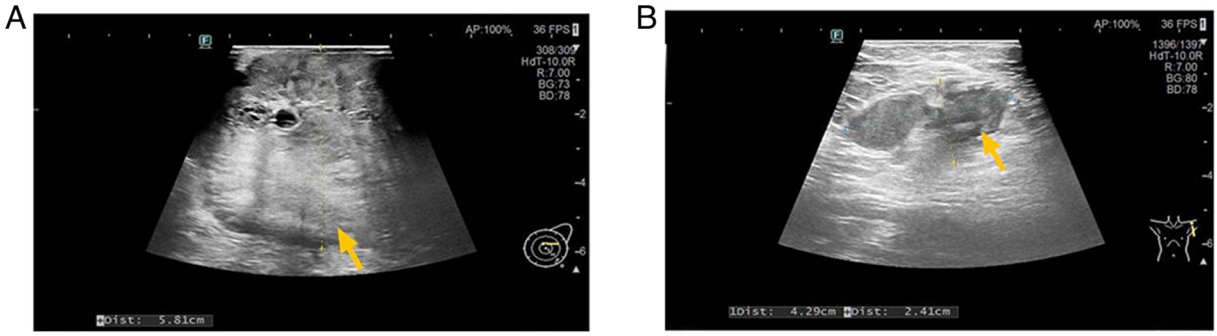

Figure 3. Pre-treatment Ultrasonograms from June 2023. (A) Ultrasonogram of the left breast mass (yellow arrow). (B) Ultrasonogram of the left axillary lymph nodes (yellow arrow).

cycles of chemotherapy were administered postoperatively, totaling six cycles. The lung lesion remained unchanged throughout the chemotherapy (Fig. 7). In December 2023, a thoracoscopic wedge resection of the lung was performed. The diagnosis of minimally invasive adenocarcinoma with no vascular or neural invasion was confirmed by postoperative paraffin pathology. Further IHC staining and H&E staining were performed for verification. The IHC staining procedure involved antigen-antibody binding, followed by hematoxylin counterstaining to visualize cell nuclei.

The patient is currently undergoing tamoxifen and trastuzumab therapy. The dosing schedule is as follows: Tamoxifen is administered at a dose of 10 mg per time, twice a day; the trastuzumab-targeted therapy is maintained for 12 months, with an administration frequency of once every 21 days. Routine follow-up includes physical examinations and tumor marker testing every 3 months, as well as chest and abdominal CT scans every 6 months. As of the last follow-up in May 2025, no signs of recurrence have been observed.

Discussion

With continuous advances in tumor diagnosis and treatment, the incidence of second primary cancers among patients with

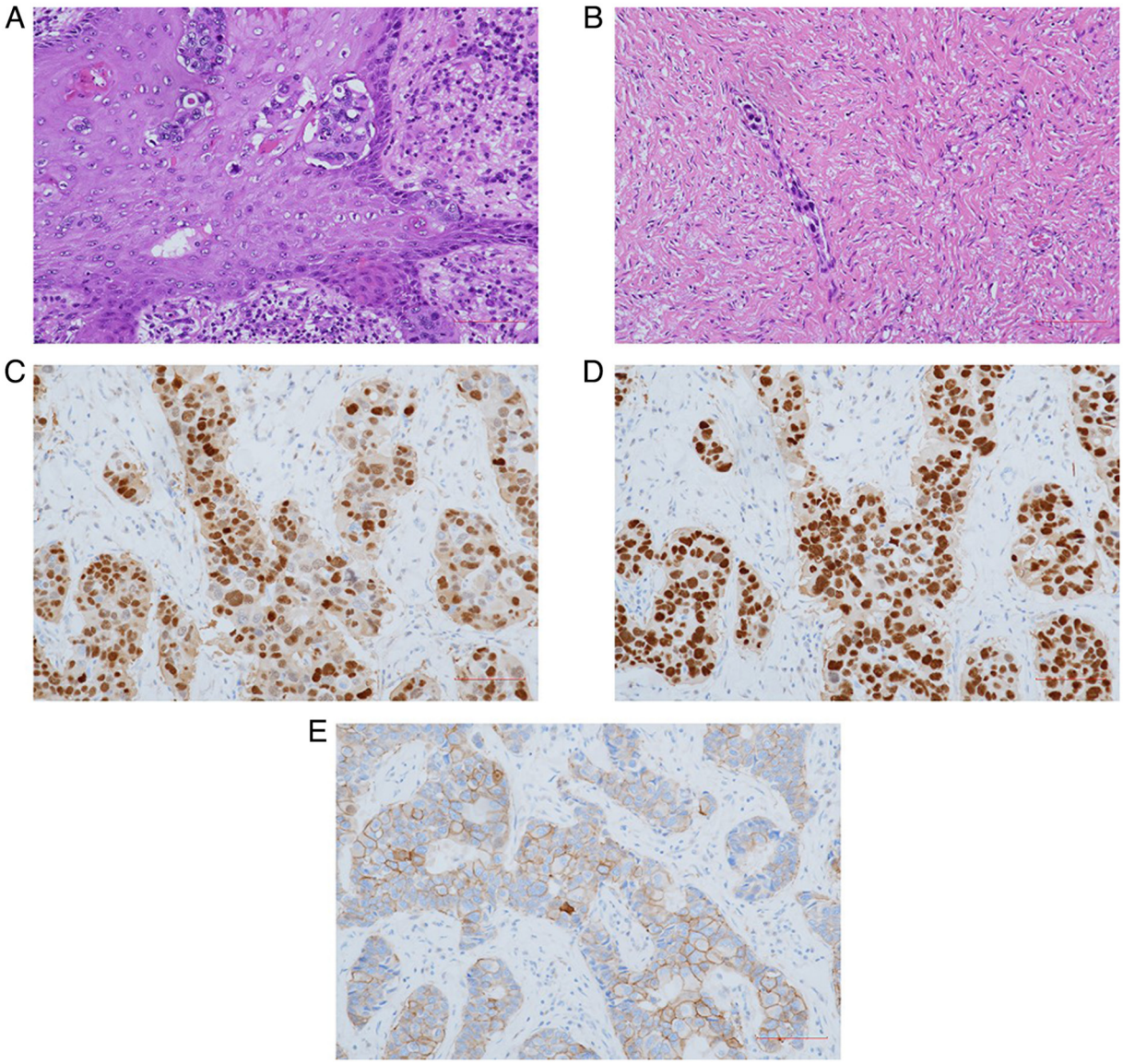

Figure 4. Pathological sections diagnosing invasive ductal carcinoma with labeled expression of specific receptors. (A) Hematoxylin and eosin staining of the left breast tissue showing invasive ductal carcinoma with Paget's-like spread (magnification, x400; scale bar, 100 μm). (B) Hematoxylin and eosin staining of the intravascular tumor thrombus (magnification, x400; scale bar, 100 μm). (C) EnVision staining of progesterone receptor (magnification, x400; scale bar, 100 μm). (D) EnVision staining of estrogen receptor (magnification, x400; scale bar, 100 μm). (E) EnVision staining of HER-2 (magnification, x400; scale bar, 100 μm).

breast cancer has steadily increased. Studies indicate that lung cancer is one of the most common second primary malignancies following breast cancer, with a median onset age of 50-59 years and a median interval of 43.5-60.0 months. Lung cancer accounts for 0.8-1.4% of synchronous second primary cancers in patients with breast cancer. Smoking, radiotherapy and chemotherapy are established risk factors for dual primary breast and lung cancers (11). MBC, accounting for <1% of breast cancer cases, is exceedingly rare, and multiple primary cancers in MBC are even more uncommon. Compared with women, men are diagnosed with breast cancer at an older mean age of 67 years, with a 25% higher mortality rate (12,13). MBC is predominantly hormone-dependent. Research shows a strong correlation between estrogen and lung cancer, with numerous lung cancer cells overexpressing ER (14). While 90% of MBC cases are ER-positive, only 8.7% are HER-2-positive. Most cases present with painless sub-nipple nodules, with 40-50% involving the nipple, and left-sided breast cancer is slightly more common (15,16). Advanced cases may show skin changes, nipple retraction, ulcers or masses fixed to underlying tissues, often with axillary lymphadenopathy. Breast cancer susceptibility (BRCA) gene mutations are the most recognized risk factors for MBC. Additional risk factors include family history, chest radiation exposure, germline mutations (e.g., BRCA2, BRCA1, checkpoint kinase 2, and partner and localizer of BRCA2), and exogenous estrogen use. A large study of 2,175 cases of MBC revealed significantly higher AR/PR positivity rates in MBC vs. female breast cancer, with HER-2 negativity being more common (17). PIK3CA mutations are prevalent in breast cancers and correlate with a poor prognosis (18). The patient in the present case exhibited advanced MBC with synchronous primary lung adenocarcinoma, which is a rare combination. IHC demonstrated HR and AR positivity, HER-2 positivity and PIK3CA mutations.

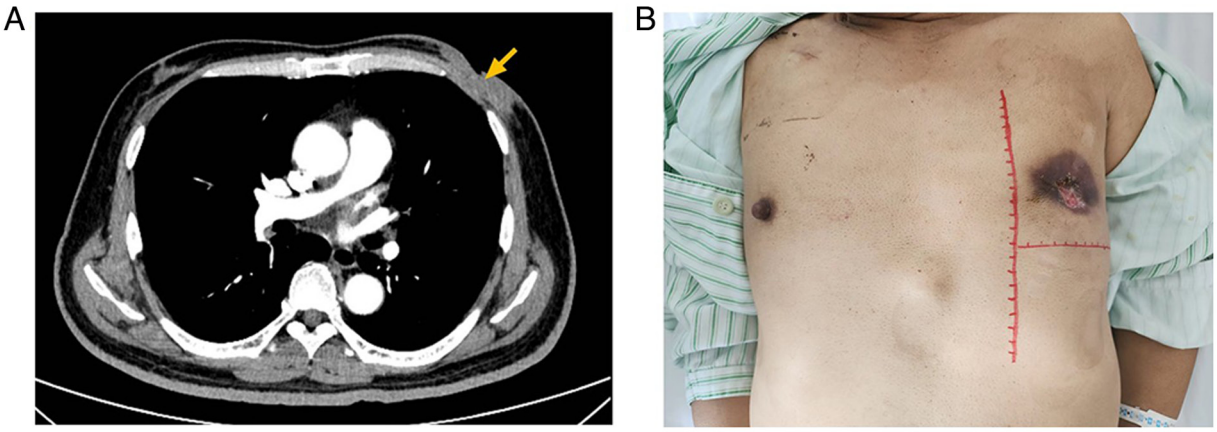

Figure 5. Post-chemotherapy images in October 2023 showing significant reduction of the breast tumor. (A) Computed tomography scan showing the reduced breast tumor size (yellow arrow). (B) Outward appearance of the breast tumor.

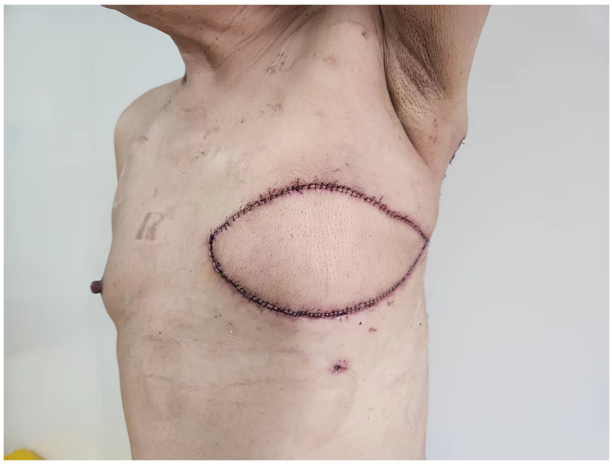

Figure 6. Surgical outcome after mastectomy (October 2023).

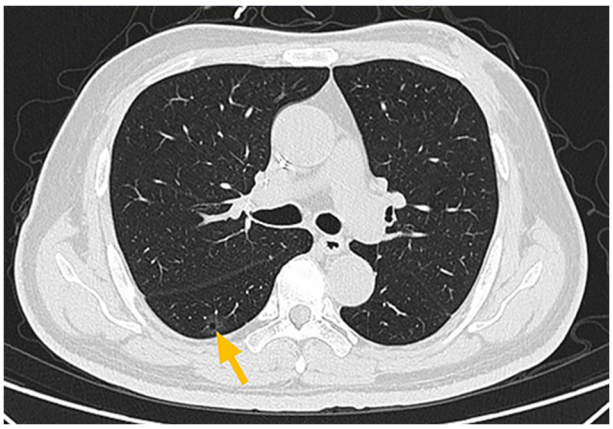

Figure 7. Post-chemotherapy computed tomography image (October 2023) showing stable lung nodule (yellow arrow).

Similarly, an International MBC Program analysis of 1,483 MBC cases showed 99% ER-positivity and only 9% HER2-positivity. However, the present case exhibited HER2-positivity (3+), resembling the molecular profile more common in female breast cancer. This observation aligns with a 2023 New England Journal of Medicine review stating 'the HER2-positivity rate in men is comparable to that in older postmenopausal women' (15). The high ER and AR expression in the present study and its potential link to lung adenocarcinoma also support Fentiman's 'estrogen cross-talk' theory (19). Treatment-wise, a real-world study from China retrospectively collected data from patients with MBC across 36 centers in the country. The study suggested that an anthracycline combined with taxane regimen is a protective factor for disease-free survival in these patients (20). The present case adopted a neoadjuvant TCbHP regimen, using taxane-based drugs. The stable pulmonary lesion in the present study also aligns with the study by Peng *et al* (21), which reported a 74.2% 5-year overall survival rate after surgical resection of synchronous multiple primary lung adenocarcinomas.

Research suggests 22.9-70.0% of patients with breast cancer and lung nodules have primary lung cancer. The epidermal growth factor receptor (EGFR) signaling pathway is vital in tumorigenesis, progression and metastasis. EGFR mutations are the most common driver mutations in lung cancer and are associated with apoptosis inhibition, angiogenesis and tumor vasculature formation (22,23). Evidence shows cross-signaling between ER/PR and EGFR pathways in patients with breast cancer and second primary lung cancer, suggesting shared biological mechanisms and overlapping risk factors such as elevated hormone levels. Clinical data indicate that EGFR mutation rates in patients with dual primary breast and lung cancers are twice those in patients with non-small cell lung cancer (NSCLC). EGFR signaling may thus be critical in lung cancer development as a second primary malignancy in patients with breast cancer (24).

Additionally, epithelial cell adhesion molecule (EpCAM), a single-pass transmembrane glycoprotein, is upregulated in epithelial-derived malignancies such as breast and lung cancers. EpCAM interferes with key tumorigenic signaling pathways, contributing to progression. A study has demonstrated its association with metastasis, drug resistance and prognosis in breast cancer, and its correlation with Tumor-Node-Metastasis staging (25) in squamous cell lung carcinoma (26). Weak EpCAM expression in normal epithelial cells vs. strong

expression in cancer tissues highlights its carcinogenic role. Immunohistochemical analysis of EpCAM expression and exploration of anti-EpCAM immunotherapy may provide new treatment directions (27).

The rhodopsin family is closely associated with tumor biology, including cellular growth, differentiation and migration; its role in the initiation, progression, metastasis and drug resistance of breast and lung cancers is well-studied. Ras homolog family member A (RhoA) and RhoC regulate cytoskeletal reorganization, contributing to tumor cell invasion and metastasis. High RhoC expression promotes breast cancer cell invasion and metastasis by enhancing actin remodeling and extracellular matrix degradation through increased matrix metalloproteinase secretion. Similarly, RhoC is significantly upregulated in NSCLC, facilitating distant metastasis (28). Rac family small GTPase 1 (Rac1) modulates the tumor microenvironment, promoting invasive migration of breast cancer cells. Rac1 also activates the shared phosphatidylinositol 3-kinase (PI3K)/Akt pathway in breast and lung cancers, which is implicated in chemotherapy resistance in breast cancer and targeted therapy resistance in lung cancer (29). Both RhoA and Rac1 activate the mitogen-activated protein kinase (MAPK) signaling pathway in these cancer types, driving cell proliferation and anti-apoptotic processes (30). Additionally, RhoA and RhoC collaboratively reshape the tumor microenvironment, bolstering tumor cell immune evasion (31,32). Targeted inhibition of oncogenes such as Rac1, RhoA and RhoC presents a promising strategy to reduce the invasive potential of breast and lung cancer cells. This approach underscores the therapeutic potential of targeting shared molecular mechanisms to manage dual malignancies effectively.

Furthermore, in the present report of synchronous primary MBC and lung adenocarcinoma, potential biological associations are explored. Previous studies suggest that these cancers may share common risk factors and oncogenic pathways, such as chronic smoking, radiation exposure and elevated hormone levels (33,34). Based on large-scale genome-wide association study data, researchers have analyzed shared pathogenic mechanisms between breast and lung cancers genome-wide. Findings indicate that both malignancies converge on the erb-b2 receptor tyrosine kinase 2 signaling pathway, toll-like receptor 2 signaling cascade, and nuclear factor-κB and MAPK pathways, suggesting possible common genetic origins (35). As breast cancer is an estrogen-dependent tumor, its development and progression are closely linked to ER status. In normal breast tissue, ER mediates downstream cascades, including Ras/Raf/MAPK and PI3K/AKT/mTOR pathways, regulating proliferation, metabolism, survival and apoptosis. Dysregulated estrogen metabolism may impair ER function and contribute to tumorigenesis (36,37). Emerging evidence also indicates that ER status may influence lung cancer pathogenesis. In a study of 110 female patients with both cancer types, 80% of breast tumors were ER-negative, suggesting a potential association (38). This supports a significant association between ER-negative breast cancer and primary lung adenocarcinoma occurrence. In the present study, the patient exhibited HER2 positivity, hormone receptor positivity and a PIK3CA mutation, indicating possible molecular involvement of multiple co-activated oncogenic pathways. Based on this profile, we hypothesize the synchronous tumors may be biologically linked, although larger studies are needed for validation.

Standard MBC treatment follows female breast cancer protocols, including mastectomy and endocrine therapy for hormone receptor-positive cases (39). Currently, in clinical practice, the application of traditional Chinese medicine as an adjunct to radiotherapy and chemotherapy in the treatment of breast cancer is widespread. This addition can enhance therapeutic efficacy, reduce side effects, promote the recovery of physical function after cancer treatment, decrease recurrence and metastasis, and improve quality of life (40). Research has found that Huangqi Sijun Decoction can alleviate fatigue in patients with breast cancer after chemotherapy (41), while Wenshen Zhuanggu Formula can reduce leukopenia, nausea, vomiting, gastrointestinal reactions, hair loss and bone marrow suppression (42). Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events version 5.0 (43).

In the present study, integrating traditional Chinese medicine with Western cancer treatment alleviated the patient's discomfort and chemotherapy-induced bone marrow suppression. Both traditional decoctions and Chinese herbal medicine serve as important approaches in the treatment of breast cancer, and hold important implications for breast cancer therapy. During chemotherapy, no grade 3 or greater nausea/vomiting occurred (43). Multidisciplinary management effectively controlled both malignancies, with the patient remaining recurrence-free for >1 year post-treatment. This underscores the importance of comprehensive, integrative strategies and long-term follow-up for managing rare, complex cancer cases.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

XX was responsible for writing the original draft, provided advice on patient treatment and analyzed patient data. SZ was responsible for conception. JYL, JL and DZ confirm the authenticity of all the raw data, and made contributions to the conception and design of the study. YueW designed the study. YunW obtained the patient's medical pathological smears. DL made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences (Beijing, China). Written informed consent was obtained from the patient for participation in this study.

Patient consent for publication

Written informed consent was obtained from the patient for publication of the present study, including medical case information and images.

Competing interests

The authors declare that they have no competing interests.

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