

Metachronous Bilateral Primary Breast Diffuse Large B-Cell Lymphoma: A Case Report and Literature Review

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Case Report

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Abstract

Background: Primary breast lymphoma (PBL) is a rare extranodal non-Hodgkin lymphoma originating from the breast parenchyma, with diffuse large B-cell lymphoma (DLBCL) being the most common histological subtype. Metachronous bilateral involvement is exceedingly uncommon, and standardized treatment guidelines remain lacking. Herein, we report a case of metachronous bilateral primary breast DLBCL with a 15-year disease-free interval and present a comprehensive literature review.

Case presentation: A 47-year-old female presented with a palpable left breast mass in February 2026. She had a history of right breast PBL diagnosed in 2011, achieving complete remission after eight cycles of CHOP. Breast ultrasound, mammography, and magnetic resonance imaging (MRI) revealed a BI-RADS category 4B lesion in the left breast. Core needle biopsy confirmed DLBCL with immunohistochemistry demonstrating CD20 positivity (70%–80%), Ki-67 proliferation index of approximately 90%, and negative epithelial markers. Whole-body ^{18}F -FDG PET/CT excluded systemic involvement, confirming the diagnosis of stage IE left breast PBL. The patient received a zuberitamab-containing CMOP (Hi-CMOP). After five cycles, repeat PET/CT demonstrated complete metabolic response with the Deauville score decreasing from 5 to 1, and breast ultrasound confirmed resolution of the breast lesion.

Conclusions: PBL lacks pathognomonic clinical and imaging features, and definitive diagnosis hinges on histopathological examination with immunohistochemistry. For stage IE DLBCL-type PBL, rituximab-based immunochemotherapy followed by consolidative radiotherapy represents a rational therapeutic strategy with favorable short-term outcomes. Long-term surveillance remains essential given the risk of late contralateral recurrence. Multicenter studies with larger cohorts are warranted to establish evidence-based management guidelines.

Background

Breast lymphoma is classified into primary breast lymphoma (PBL), which originates in the breast parenchyma, and secondary breast lymphoma (SBL), which represents mammary involvement by systemic lymphoma [1]. PBL is a rare extranodal non-Hodgkin lymphoma (NHL), with DLBCL constituting the predominant histological subtype. The overall incidence ranges from 0.04% to 0.7% [2], and its rarity is partly attributable to the scarcity of lymphoid tissue within the normal mammary gland. PBL accounts for less than 2% of all NHLs and under 0.1% of all breast malignancies. In clinical practice, distinguishing between PBL and SBL by physical examination and conventional imaging alone is challenging; definitive diagnosis relies on core needle biopsy or excisional biopsy with comprehensive immunohistochemical profiling.

The management of breast lymphoma should adhere to the general principles of lymphoma therapy rather than breast cancer-oriented surgical paradigms. For PBL, systemic immunochemotherapy constitutes the cornerstone of treatment: CD20-positive cases warrant the addition of an anti-CD20 monoclonal antibody, with R-CHOP being the first-line standard [3]. Depending on disease extent, stage, and prognostic factors, consolidative radiotherapy may be administered following systemic therapy to

enhance locoregional control. Radical mastectomy is not routinely advocated and should be reserved for diagnostic purposes or the management of local complications. For SBL, systemic treatment directed at the underlying lymphoma—tailored according to histological subtype, stage, and performance status—remains the mainstay, with the breast lesion managed as part of the overall disease burden. Here, we report the diagnosis and management of a patient with metachronous bilateral primary breast DLBCL and conducted a review of the relevant literature.

Case presentation

A 47-year-old female presented to our hospital in February 2026 with a self-palpated left breast mass of over 20 days' duration. Physical examination revealed a firm, well-circumscribed, non-tender mass measuring approximately 3 cm × 3 cm at the 2 o'clock position, 5 cm from the left nipple, without overlying skin erythema, edema, or peau d'orange changes. There was no palpable axillary or supraclavicular lymphadenopathy.

Her oncological history was notable: in 2011, she was diagnosed with right breast PBL at an outside institution and received eight cycles of CHOP (cyclophosphamide, epirubicin, vindesine, prednisone), achieving complete remission as assessed by clinical and imaging evaluation. She underwent regular surveillance without evidence of recurrence over the subsequent 15 years and received no further anti-lymphoma therapy.

Imaging findings

Breast ultrasound at our institution (Fig. 1) demonstrated a hypoechoic lesion measuring 24 mm × 13 mm at the 2 o'clock position of the left breast, with irregular margins and posterior acoustic enhancement, classified as BI-RADS category 4B.

Mammography (Fig. 2) revealed an ovoid, isodense mass measuring approximately 2.5 cm × 2.0 cm in the upper-outer quadrant of the left breast with indistinct margins (craniocaudal and mediolateral oblique views), along with a partially circumscribed nodule measuring 1.2 cm × 0.8 cm in the central region, both categorized as BI-RADS 4B.

Breast MRI (Fig. 3) showed an irregular, slightly lobulated mass in the upper-outer quadrant of the left breast, measuring 2.50 cm × 2.13 cm × 2.74 cm (anteroposterior × transverse × craniocaudal). The lesion exhibited isointensity on T1-weighted imaging, hyperintensity on T2-weighted fat-suppressed sequences, heterogeneous hyperintensity on diffusion-weighted imaging (DWI), and low signal on apparent diffusion coefficient (ADC) maps. Dynamic contrast-enhanced imaging demonstrated a type III (washout) kinetic curve with rapid initial enhancement and delayed washout, accompanied by heterogeneous internal enhancement and increased perilesional vascularity. Multiple enlarged left axillary lymph nodes (short-axis diameter 0.5–0.7 cm) were noted.

Pathological findings

Core needle biopsy of the left breast mass was performed. Histopathological examination revealed diffuse proliferation of lymphoid cells with a mixed T- and B-cell infiltrate, predominantly composed of medium-to-large B cells with vesicular chromatin and prominent nucleoli, consistent with aggressive DLBCL. Immunohistochemistry (IHC) demonstrated the following profile: CD20 (+, 70%–80%), CD19 (+, 70%–80%), CD3 (–), CD5 (–), Ki-67 (+, ~ 90%), CD10 (focal +), MUM-1 (+, 80%–90%), BCL-6 (+, 80%–90%), BCL-2 (–), C-MYC (Y69) (+, ~ 80%), CD30 (–), CD38 (+, 50%–60%), ALK-1 (–), CD79b (+, 80%–90%), CD22 (+, 80%–90%), CD138 (–), and pan-cytokeratin (AE1/AE3) (–). According to the Hans algorithm, the immunophenotype (CD10 focal+, MUM-1+) was consistent with a non-germinal center B-cell (non-GCB) subtype. Epstein–Barr virus-encoded small RNA (EBER) in situ hybridization was negative.

Staging and systemic workup

Whole-body ^{18}F -FDG PET/CT was performed following the histological diagnosis. The scan demonstrated: (1) a hypermetabolic mass in the upper-outer quadrant of the left breast, with no abnormal uptake elsewhere, corresponding to a Deauville score of 5; (2) a right renal cyst without metabolic activity; and (3) focal increased uptake in the anal canal, interpreted as inflammatory or physiological. No evidence of systemic lymphomatous involvement was identified.

Based on the comprehensive workup, the final diagnosis was left breast primary DLBCL, stage IE (Ann Arbor classification, Lugano modification), non-GCB subtype.

Treatment and response

The patient was treated with the Hi-CMOP consisting of zuberitamab, cyclophosphamide, mitoxantrone liposome, vincristine and prednisone. Following five cycles of Hi-CMOP, restaging was performed.

Whole-body PET/CT demonstrated complete metabolic resolution of the previously hypermetabolic left breast lesion, with the Deauville score decreasing from 5 to 1. No new sites of abnormal ^{18}F -FDG uptake were identified. Breast ultrasound confirmed complete resolution of the breast mass with no residual lesion, and no enlarged axillary lymph nodes were detected. The treatment was well tolerated; the patient experienced grade 1 nausea and grade 1 alopecia, which were managed with supportive care. No grade ≥ 3 adverse events or treatment-related hospitalizations occurred. The patient is currently undergoing further treatment and no signs of disease progression have been observed.

Discussion

This report presents a case of metachronous bilateral primary diffuse large B-cell lymphoma of the breast in a 47-year-old woman. The right breast lesion achieved complete remission following CHOP and remained disease-free for over 12 years before recurrence occurred in the left breast. After systemic

involvement was ruled out by whole-body PET/CT, a diagnosis of left-sided primary breast lymphoma was confirmed. Following five cycles of Hi-CMOP chemotherapy, radiological complete remission was achieved. In this article, we discuss the clinical characteristics, differential diagnosis, treatment strategies, and prognosis-related issues of this case in the context of the existing literature and current clinical guidelines, with the aim of providing a reference for the diagnosis and management of similar cases in clinical practice.

Clinical characteristics and diagnostic challenges

PBL is a rare but clinically distinct subtype of extranodal lymphoma. In 1972, Wiseman and Liao [4] first proposed the diagnostic criteria for PBL, which remain in use: (1) adequate pathological specimen demonstrating lymphomatous infiltration of mammary tissue; (2) no evidence of systemic dissemination (ipsilateral axillary lymph node involvement is permissible); and (3) no prior history of extramammary lymphoma. PBL predominantly affects middle-aged and elderly women (40–60 years), with male cases being exceedingly rare [5]. Clinically, differentiating PBL from breast carcinoma is difficult, as both typically present as painless breast masses. In adults, right-sided involvement is reported to be slightly more common than left-sided [6]. The patient in this report conformed to the typical demographic and clinical profile of PBL. However, both breast ultrasound and MRI demonstrated an irregular, ill-defined mass with type III enhancement kinetics—features more characteristic of breast carcinoma—which is why the initial clinical suspicion was malignancy of epithelial origin.

DLBCL is the most common histological subtype of PBL, accounting for 56%–84% of cases [7]. In the present case, immunohistochemistry revealed CD20 positivity, a hallmark of B-cell lineage, which serves as the pivotal discriminator from epithelial malignancies (e.g., invasive breast carcinoma of no special type). Importantly, the differential diagnostic panel must include pan-cytokeratin, which was negative in our case, excluding carcinoma. The non-GCB immunophenotype (CD10 focal+, MUM-1+) and the high Ki-67 index (~90%) are consistent with an aggressive clinical course and underscore the importance of prompt treatment initiation.

In the present case, the patient was initially diagnosed with "breast cancer" based on clinical presentation and imaging findings. The definitive diagnosis was ultimately established through pathological biopsy and immunohistochemistry, underscoring that histopathological and immunohistochemical examination represents the gold standard for the diagnosis of primary breast lymphoma (PBL) and that the diagnostic criteria for PBL must be rigorously adhered to.

Differential diagnosis

The nonspecific clinical and radiological presentation of PBL—including ovoid iso-to-hyperdense masses on mammography, hypoechoic or mixed-echogenicity hypervascular masses on ultrasound, enhancing masses with type II/III kinetic curves on MRI, and ¹⁸F-FDG-avid lesions on PET—creates a broad differential diagnosis [2]. The following distinctions are clinically relevant:

Breast carcinoma: Typical signs include nipple retraction, pathological nipple discharge, and peau d'orange skin changes. Histologically, carcinoma cells form nests and cords with desmoplastic stroma and express epithelial markers (pan-cytokeratin, EMA)[8]. PBL is consistently negative for epithelial markers and expresses B-cell markers (CD20, CD19, CD79a).

Acute mastitis / inflammatory breast conditions: PBL may occasionally present with erythema, edema, and peau d'orange changes mimicking inflammation. A high index of suspicion for PBL should be maintained in cases of "non-responsive mastitis," particularly during pregnancy and lactation [9].

Benign cystic lesions: PBL may appear cyst-like on grayscale ultrasound, but color Doppler interrogation revealing internal high-resistance arterial flow can distinguish it from benign cysts [10].

Secondary breast lymphoma (SBL): It is even more critical to exclude secondary breast involvement by systemic lymphoma. Whole-body PET/CT is indispensable to exclude systemic disease before a diagnosis of PBL can be established. Therefore, the diagnostic criteria for PBL must be rigorously applied when establishing the diagnosis. Ultimately, confirmation still rests upon pathological biopsy.

Molecular pathology

Advances in next-generation sequencing (NGS) have progressively elucidated the mutational landscape of PBL. Recurrent mutations in PIM1, MYD88, and CD79B have been identified, with implications for lymphomagenesis, disease progression, and prognosis [11]. Franco et al. [11] demonstrated that the mutational profile of primary breast DLBCL partially overlaps with that of nodal DLBCL while harboring site-specific features potentially driven by the unique mammary microenvironment. In the present case, NGS was not performed due to the patient declined additional testing, which precluded correlation between the mutational profile and therapeutic response. This represents one of the limitations of this report, and future prospective studies incorporating comprehensive molecular profiling are warranted to further characterize the genomic landscape of PBL.

Treatment strategies and rationale

No standardized, evidence-based treatment guidelines exist specifically for PBL; management is largely extrapolated from nodal DLBCL protocols and tailored to the histopathological subtype, clinical stage, and individual patient characteristics. For DLBCL-type PBL, chemotherapy forms the therapeutic backbone, with surgery playing an increasingly restricted role limited to diagnostic biopsy [12].

Santiago-Sanabria et al. [13] systematically reviewed the treatment literature for PBL and reported that patients treated with R-CHOP combined with consolidative radiotherapy achieved a complete remission rate of 84.6%, with favorable locoregional control and a low recurrence rate. A growing body of evidence supports the concept that PBL is a systemic disease; surgical resection alone does not improve outcomes and may instead increase treatment-related morbidity and delay systemic therapy. Chemotherapy effectively addresses micrometastatic disease, and the addition of radiotherapy improves

locoregional control and reduces the risk of in-breast recurrence, particularly for stage IE and IIE limited-stage disease, for which combined-modality therapy (chemotherapy + radiotherapy) is currently the preferred approach [3, 13].

Rituximab, a chimeric anti-CD20 monoclonal antibody, specifically binds the CD20 antigen on B lymphocytes and mediates cell killing through complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and direct induction of apoptosis. Its addition to CHOP-based chemotherapy has been shown to significantly improve outcomes in DLBCL across all IPI risk groups [14]. The Hi-CMOP administered in this case—substituting mitoxantrone liposome for doxorubicin to mitigate cumulative anthracycline cardiotoxicity given the patient's prior epirubicin exposure—is consistent with current optimized treatment strategies for relapsed or second-primary DLBCL-type PBL.

Prognosis

Prognosis in PBL is determined by multiple factors, including histological subtype, clinical stage, and treatment modality. DLBCL-type PBL carries a more favorable prognosis than other histological subtypes; patients with stage IE–IIE disease achieve 5-year overall survival rates exceeding 70%, whereas outcomes for advanced-stage disease remain poor [3]. The patient in this report had stage IE DLBCL-type PBL and achieved complete metabolic remission after five cycles of immunochemotherapy, portending a favorable prognosis. However, the follow-up duration is insufficient to evaluate long-term efficacy, late recurrence risk, or treatment-related late effects, and continued surveillance is essential.

Pathogenesis

The pathogenesis of PBL remains incompletely understood, but accumulating evidence implicates a multistep process involving post-germinal center B-cell differentiation, aberrant activation of key signaling pathways, remodeling of the local mammary immune microenvironment, and histological subtype-specific molecular genetic alterations. Immunoglobulin heavy-chain variable region (IgVH) gene analysis has demonstrated that PBL tumor B cells carry a high burden of somatic hypermutation (mutation frequency, 4.0%–25.9%), indicating an origin from B lymphocytes that have traversed the germinal center reaction. This finding provides the cellular-origin basis for the B-cell immunophenotype of PBL [15].

At the signaling-pathway level, constitutive activation of three core pathways—NF- κ B, JAK-STAT, and PI3K-AKT-mTOR—constitutes the central driving events in PBL lymphomagenesis. The NF- κ B pathway can be aberrantly activated through upstream mutations or chromosomal translocations, endowing tumor cells with sustained proliferative capacity and resistance to apoptosis. Gene alterations in the JAK-STAT pathway are detected at high frequency in breast lymphomas, reinforcing proliferative signaling and suppressing apoptosis [16]. Mutations in the PI3K-AKT-mTOR pathway, although present in only approximately 6% of cases, interact extensively with the NF- κ B and JAK-STAT pathways, forming a complex oncogenic signaling network that collectively drives lymphomagenesis [17].

The unique characteristics of the local mammary immune microenvironment should not be overlooked. Under physiological conditions, lymphoid tissue is sparse in the normal breast. However, when persistent antigenic stimulation—mediated by chronic inflammation, autoimmune disorders, or breast implants—is present, acquired mucosa-associated lymphoid tissue (MALT) can form within the breast, providing a microenvironment conducive to clonal B-cell proliferation and malignant transformation, with sex hormones potentially contributing indirectly through immunomodulatory effects [18].

The molecular pathogenesis exhibits site-specific variation across histological subtypes. A subset of breast DLBCL cases is thought to arise from transformation of pre-existing MALT lymphoma, and their molecular features resemble those of nodal DLBCL while bearing the imprint of the mammary microenvironment [15]. Genomic studies of breast MALT lymphoma have characterized it as a mutation-driven disease, with a mutational spectrum enriched in NF- κ B pathway-associated genes, sharing molecular similarities with ocular adnexal MALT lymphoma [19]. In contrast, MALT1 gene rearrangements—common in MALT lymphomas at other anatomical sites—occur at significantly lower or near-absent frequencies in breast MALT lymphoma [20]. This anatomical site-specific molecular heterogeneity suggests that different microenvironmental pressures may select for distinct pathogenic trajectories.

Furthermore, high-frequency mutations in genes such as PIM1 and MYD88 have been implicated in regulating cell proliferation, differentiation, and apoptosis during PBL pathogenesis [11]; however, the precise mechanisms warrant further investigation through both basic and clinical studies. Collectively, the pathogenesis of PBL represents a multistage process driven by the interplay among intrinsic B-cell genetic abnormalities, the local mammary immune microenvironment, and pathogenic gene mutations. An in-depth understanding of these molecular mechanisms may provide a theoretical foundation for the future development of precision-targeted therapeutic strategies.

Limitations

This case report has several limitations: (1) as a single case, the findings have limited generalizability and cannot reflect the full spectrum of diagnostic and therapeutic features across different histological subtypes and stages of PBL; (2) the treatment and follow-up period (approximately five months) is insufficient for long-term assessment of therapeutic efficacy, late recurrence, or late treatment-related toxicity; and (3) NGS was not performed, precluding correlation between the mutational landscape and clinical phenotype, and limiting the discussion of molecularly targeted therapeutic avenues.

Conclusions

The present case offers the following clinical insights: (1) PBL lacks specific clinical and imaging features and may closely mimic breast carcinoma. A high index of suspicion should be maintained when evaluating middle-aged female patients presenting with painless unilateral breast masses, particularly when imaging findings are atypical and nipple discharge or skin involvement is absent. Timely histopathological examination with immunohistochemistry is critical to avoid misdiagnosis. (2)

Histopathology with immunohistochemistry is the gold standard for PBL diagnosis; the detection of lineage-defining markers (CD20 vs. pan-cytokeratin) effectively discriminates PBL from epithelial breast tumors. (3) For stage IE DLBCL-type PBL, rituximab-based chemotherapy combined with consolidative radiotherapy yields favorable therapeutic outcomes with effective locoregional control and improved prognosis. Individualized treatment planning is essential, including consideration of cumulative anthracycline exposure and cardiotoxicity risk. (4) Long-term post-treatment surveillance is mandatory for PBL patients, with attention to the risks of local relapse and central nervous system recurrence. Early detection and intervention for late events may improve long-term quality of life and overall survival.

In summary, PBL is a rare extranodal lymphoma whose diagnosis depends on histopathological and immunohistochemical examination, and whose treatment is anchored in immunochemotherapy with radiotherapy. Individualized, multidisciplinary management can effectively improve patient outcomes. Heightened clinical awareness of PBL among practitioners is essential to reduce misdiagnosis and mismanagement. Multicenter, collaborative studies with larger sample sizes are urgently needed to further elucidate the pathogenesis of PBL, optimize treatment strategies, and improve long-term prognosis.

Abbreviations

DLBCL

Diffuse large B-cell lymphoma

NHL

Non-Hodgkin lymphoma

PBL

Primary breast lymphoma

GCB

Germinal center B-cell

MALT

Mucosa-associated lymphoid tissue

IHC

Immunohistochemistry

NGS

Next-generation sequencing

SBL

Secondary breast lymphoma

R-CHOP

Rituximab, cyclophosphamide, doxorubicin/epirubicin, vincristine, prednisone

R-CMOP

Rituximab, Cyclophosphamide, mitoxantrone liposome, vincristine, prednisone

Hi-CMOP

Zuberitamab, cyclophosphamide, mitoxantrone liposome, vincristine, prednisone

IPI

International Prognostic Index

Declarations

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Contributions

Writing—original draft: WN L, Writing & editing: X Y and J L. All the authors have read & approved the final manuscript.

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Data availability statement

The data generated and analyzed during this study are included in this published article.

Clinical trial number

Not applicable.

Ethics approval and consent to participate

This case report was approved by the Ethics Committee of Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital (approval number: 20260678) and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from the patient for participation in this study.

Consent for publication

Informed consent to publish this case report and any accompanying images was obtained from the patient and the patient's family.

Competing interests

The authors declare no competing interests.

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Figures

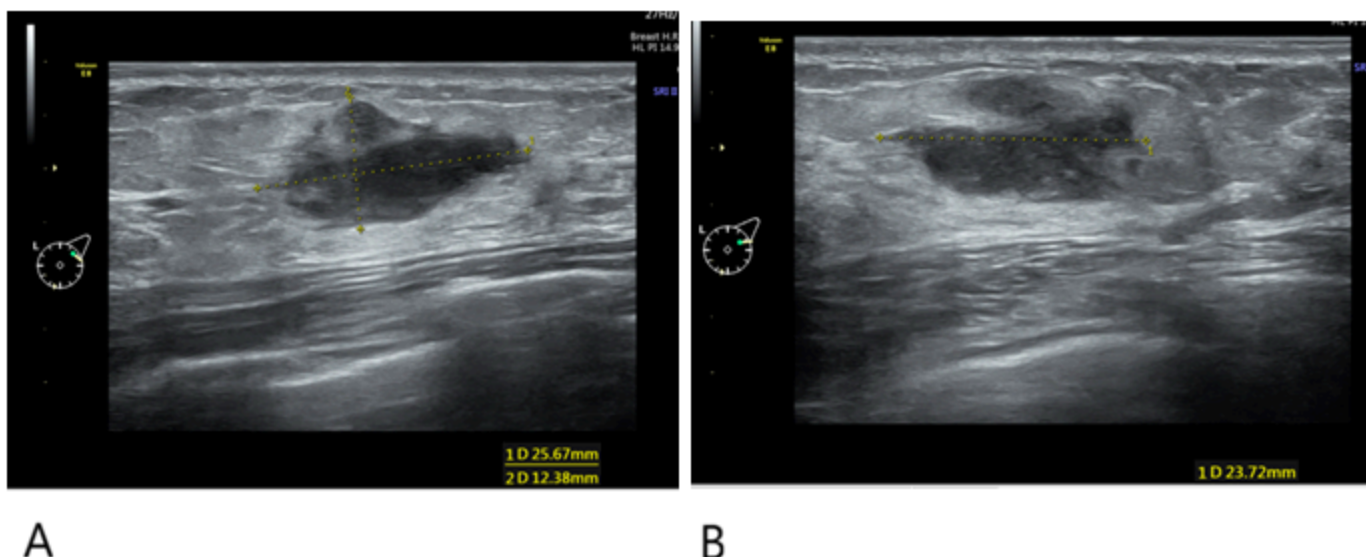


Figure 1

The arrow indicates a hypoechoic nodule at the 2 o'clock position of the left breast

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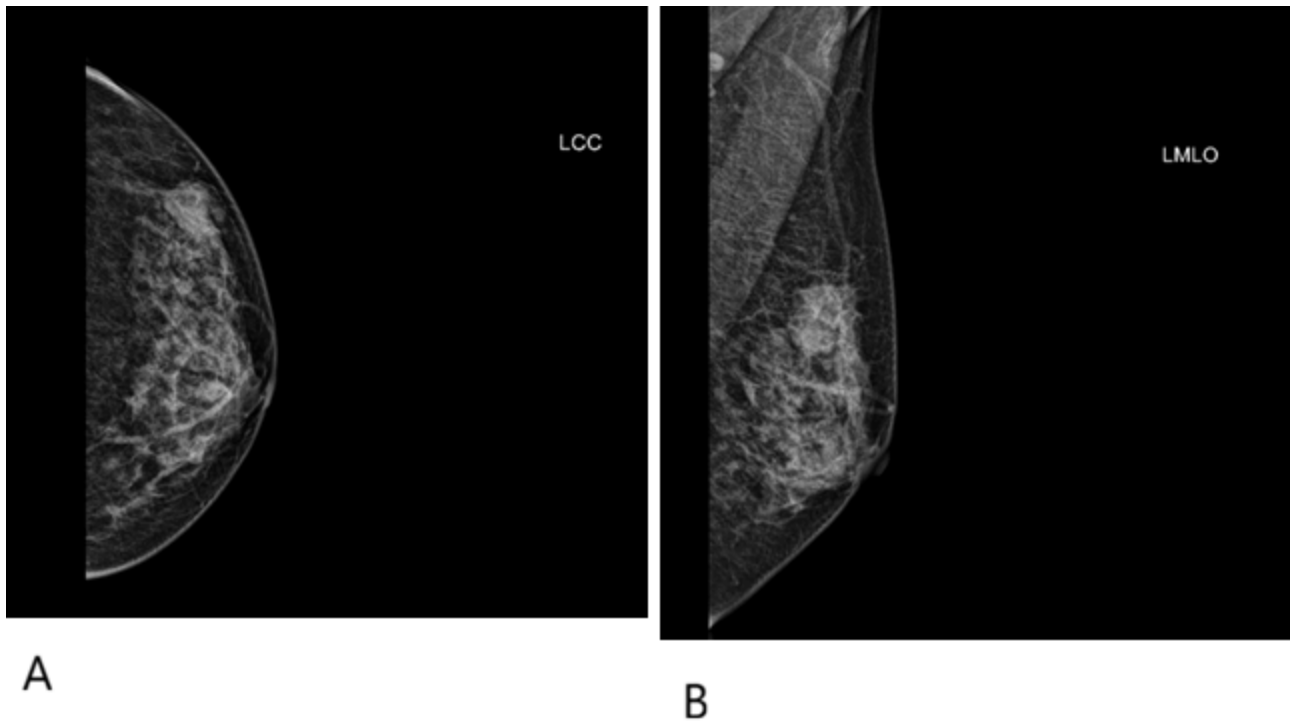
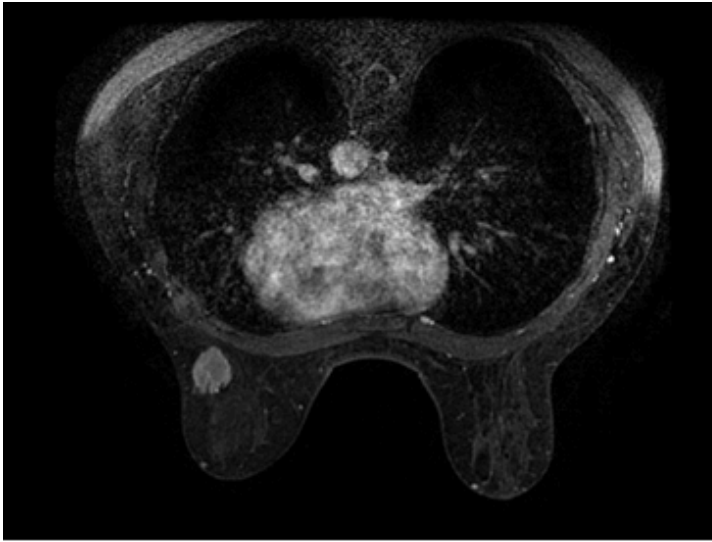


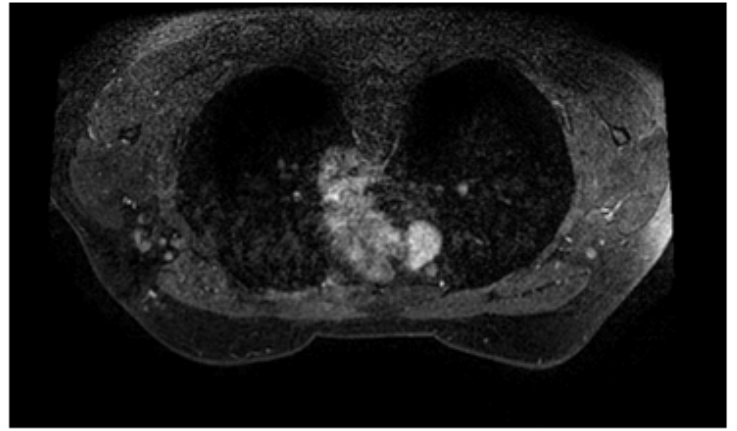
Figure 2

The arrow indicates an ovoid, isodense mass shadow in the upper outer quadrant of the left breast, with ill-defined margins (frontal view)

The arrow indicates an ovoid, isodense mass shadow in the upper outer quadrant of the left breast, with ill-defined margins(lateral oblique view)



A



B

Figure 3

The arrow indicates an abnormal signal mass shadow in the left breast, with an irregular shape and slightly lobulated contour

The arrow indicates enlarged lymph nodes.

Supplementary Files

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