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# Primary lymphoma of the breast: a report of two cases

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## Abstract

Primary breast lymphoma (PBL) should be distinguished from secondary breast lymphoma arising in the setting of lymphoma elsewhere in the body. Multimodality imaging is key to diagnosing PBL, and imaging manifestations thereof may indicate PBL and alter the treatment course. Treatment options including chemotherapy, radiation therapy, and/or surgery depend on histology. We report two cases of PBL, illustrating the transformative impact that multimodality imaging may have on clinical management.

### Keywords

Primary breast lymphoma; secondary breast lymphoma; non-Hodgkin lymphoma; breast cancer

## 1 Introduction

Breast lymphoma can occur as either primary breast lymphoma (PBL) originating in the breast or secondary breast lymphoma arising in the setting of lymphoma elsewhere in the body [1]. PBL is a rare entity that has not been widely reported, representing less than 1% of all non-Hodgkin lymphoma and 0.05–0.53% of malignant mammary neoplasms [2, 3]. The rarity of PBL may be attributed in part to the relative scarcity of breast lymphoid tissue [4].

The most common subtype of PBL is diffuse large B-cell lymphoma (DLBCL), followed by the more indolent lymphomas, extranodal marginal zone of mucosa associated lymphoid tissue (MALT lymphoma) and follicular lymphoma [4]. DLBCL tends to grow quickly and is therefore treated promptly, most commonly with chemoimmunotherapy or combined

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modality therapy. Meanwhile, secondary breast lymphoma may be DLBCL but is more commonly a low-grade B-cell lymphoma such as MALT lymphoma, follicular lymphoma, or small lymphocytic lymphoma. These tend to grow slowly and may be amenable to active surveillance alone. If treatment is indicated for primary or secondary breast lymphoma, surgical excision, radiation therapy, and/or chemoimmunotherapy may be appropriate [5]. Thus, diagnosis of the correct type of lymphoma is key, as treatment depends on the type and stage of the disease.

The diagnostic criteria for PBL have been previously outlined by Wiseman and Liao, including: (1) breast tissue and lymphoma in close association, (2) absence of history of lymphoma, and (3) absence of non-mammary organ system involvement at diagnosis [6]. These criteria permit ipsilateral lymph node involvement if breast and nodal lesions developed simultaneously. Conversely, the diagnosis of secondary breast lymphoma requires manifestations of lymphoma or leukemia prior to the development of breast lymphoma or concurrent involvement of non-mammary organ systems.

We report two cases of PBL with the aim of illustrating the transformative impact that multimodality imaging may have on clinical management. The first patient was initially diagnosed with findings worrisome for secondary breast lymphoma, but breast imaging facilitated the diagnosis of PBL, thereby altering her treatment course. The second patient was diagnosed with PBL and was under surveillance when a new mammographically-occult mass identified on magnetic resonance imaging (MRI) changed her management and systemic treatment was started.

## 2 Case report

Case 1: A 46-year-old African American woman had a negative screening mammogram which was limited in its sensitivity due to dense breast tissue. However, ultrasound showed a mammographically-occult 0.6 cm solid mass (Figure 1A) of which biopsy yielded a B-cell non-Hodgkin lymphoma with features worrisome for large B-cell lymphoma arising from a low-grade component (Figure 2A, B). Due to concerns for large cell transformation, excisional biopsy was performed for further characterization. Surgical pathology revealed low-grade B-cell lymphoma, marginal zone type, most consistent with MALT lymphoma; no large cell lymphoma was seen. Staging positron emission tomography/computed tomography (PET/CT) and bone marrow biopsy showed no findings of extra-mammary disease. Thus, the patient was diagnosed with a stage 1 indolent primary MALT lymphoma and clinical consensus was to perform surgical excision to excise any residual mass with curative intent.

Approximately 6 months after initial presentation of the mass, pre-surgical imaging (delayed due to non-oncologic healthcare) was performed. Pre-treatment bilateral breast MRI revealed multiple left breast masses and areas of non-mass enhancement (Figure 1B). Targeted left breast ultrasound confirmed the presence of multiple suspicious masses, two of which were biopsied, yielding histologic and immunohistochemical (including high Ki-67 proliferation index) features consistent with DLBCL arising in a background of low-grade marginal zone type B-cell lymphoma (Figure 2C, D). Repeat PET/CT demonstrated several

new left breast fluorodeoxyglucose (FDG)-avid lesions corresponding to pre-treatment MRI and ultrasound findings (Figure 1C). Due to the additional tissue sampling with ultrasound-guided biopsy, the patient's diagnosis changed from an indolent stage 1 primary MALT lymphoma to stage 1E primary DLBCL. Her treatment was changed from surgical excision to chemotherapy with rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (R-CHOP), followed by radiation.

After three cycles of R-CHOP, PET/CT demonstrated fewer foci of involvement with diminished FDG-avidity (Figure 3A). Following completion of combined chemoimmunotherapy and radiation treatment, breast MRI showed resolution of abnormal enhancement (Figure 3B). After six years of follow-up, the patient remains in remission and radiographically without any disease.

Case 2: A 61-year-old Caucasian woman with a family history of breast cancer had a screening mammogram in 2015 (outside hospital, images not available) that showed a new focal asymmetry in the upper outer right breast with no sonographic correlate. The finding of a new focal asymmetry without a sonographic correlate prompted stereotactic biopsy targeting the suspicious mammographic finding, with pathology yielding lymphoid tissue felt to be concordant with the imaging appearance. As such, the patient returned to a routine screening mammography schedule.

Subsequent routine annual screening bilateral mammogram and breast ultrasound were performed in August 2016 and showed increased conspicuity of the previously targeted focal asymmetry, now with a correlative sonographic mass measuring 3.3 cm. The biopsy marker placed at the time of prior biopsy was identified and located 0.8 cm anterior to the mammographic lesion (Figure 4). Given the interval change in the mammographic appearance of the lesion, in addition to the clear sonographic correlate, surgical consultation and repeat biopsy were recommended. Ultrasound-guided core biopsy was performed, yielding atypical lymphoid infiltrate suspicious for follicular lymphoma. PET/CT showed no extra-mammary findings. In 2017, the patient underwent a right breast excisional biopsy with pathology reviewed at our institution showing low-grade B-cell lymphoma, consistent with MALT lymphoma. A retrospective review of the original breast biopsy tissue obtained by stereotactic biopsy in 2015 showed the same histology.

Also in 2017, breast MRI showed a new mammographically-occult non-mass enhancement spanning 4.0 cm in the contralateral left breast (Figure 5A), which was biopsied and showed low grade B cell lymphoma with similar morphology and phenotype to her right breast MALT lymphoma, confirming a bilateral process. A gastrointestinal work-up to evaluate for occult GI involvement was negative. Surveillance was elected.

Surveillance bilateral breast MRI in May 2018 showed a new 0.9 cm enhancing left breast mass which was occult on same-day mammogram. Therefore, MRI-guided biopsy was performed, yielding MALT lymphoma, morphologically similar to prior material. In light of this most recent site of MALT lymphoma, systemic treatment was started including weekly rituximab for four weeks from July–August 2018. Post-treatment breast MRI in November

2018 demonstrated complete resolution of the previously noted enhancement and masses (Figure 5B). One year later, the patient remained disease-free.

## 3 Discussion

PBL primarily occurs in women, with a peak age of incidence in the sixth decade and a typical clinical presentation of a solitary, palpable breast mass [7]. The mass is typically non-tender and mobile, and less commonly it may also be associated with pain or systemic "B" symptoms [3, 8]. Its presentation may also include multiple palpable masses or diffuse breast enlargement and it is rarely diagnosed on screening mammography [3, 5]. Both of our patients were unusual in terms of presentation, as both were asymptomatic and the 46-year-old patient was younger than the reported age demographic.

A review of the literature reveals that imaging manifestations of PBL are variable. Diagnostic imaging work-up of PBL optimally involves more than one modality, as a unilateral approach may be insufficient. When patients present with a palpable mass, diagnostic mammography often demonstrates a parenchymal solitary mass [5]. Margins are non-specific and variable [3, 9, 10]. In a study evaluating 22 PBL and 14 secondary breast lymphoma cases, the most common mammographic finding was one or more breast masses (82%), followed by architectural distortion (9%) and no abnormality (9%) [11]. Rarer mammographic findings include skin thickening or calcifications [3, 5]. Both of our patients had mammographically occult masses and therefore further imaging was essential.

Breast ultrasound findings are also varied. The most common finding is one or more hypoechoic round or oval masses. Variable mass echogenicity has been reported, including hyperechoic or mixed echogenicity [9, 10]. Either posterior acoustic enhancement or shadowing is possible [9], with Liberman et al. identifying posterior acoustic enhancement in 71% of their cases [12]. Importantly, in our first case, several masses on targeted ultrasound confirmed MRI findings, enabling ultrasound-guided biopsy that changed management from therapeutic surgical excision to a combined chemotherapy and limited breast radiation approach.

Breast MRI findings of PBL are less well characterized, with most studies being limited by sample size. In one of the largest series to date, Liu et al. [13] investigated MRI features in 20 patients with breast lymphoma (12 primary and 8 secondary). They found no substantial differences between PBL and secondary breast lymphoma; eleven patients with breast lymphoma presented with a mass on MRI (55%), seven with non-mass enhancement (35%), and two with mixed mass and non-mass enhancement (10%). The most common mass shape was oval (87%), and the most common margin type was irregular (68%). These findings that breast lymphoma typically appears as a mass on MRI are aligned with those of other studies [14–16]. However, contrary to their findings regarding mass shape and margin, a wide spectrum of shapes and margins has been reported in separate case reports. In general, across different studies, masses were iso- to hypointense on T1, and iso- to slightly hyperintense on T2, with variable kinetics. [9, 13–18]. The variety of MRI findings may partially result from the relatively low numbers of cases per study. In both of our patients, breast MRI demonstrated additional sites of lymphoma not visible on mammography.

The treatment of PBL can include radiotherapy, chemotherapy, surgery, or a combination thereof [19]. Generally, the treatment regimen for PBL is similar to that of systemic lymphoma of similar histology. Most PBL are of the histologic subtype DLBCL, which is most often treated with the drug regimen known as R-CHOP [20], as was utilized in our first case. Aviles et al. reported that combined therapy for DLBCL of the breast may be superior to radiotherapy alone or chemotherapy alone, as the 10-year event-free survival was 50%, 57%, and 83%, respectively, in their retrospective study [19]. Separately, a large retrospective study by Ryan et al. demonstrated that patients who underwent combined therapy had a median overall survival of 8.0 years, median progression-free survival of 5.5 years; multimodality treatment was significantly associated with longer overall survival in patients treated for primary DLBCL of the breast [21]. However, modern imaging techniques such as post-treatment FDG-PET are increasingly used to eliminate radiation in early stage favorable DLBCL [22]. In our second case, rituximab alone provided long disease-free survival for MALT lymphoma.

## 4 Conclusion

PBL can present a diagnostic challenge to the oncologist, pathologist, and breast radiologist. As these presentations can be variable both clinically and mammographically, it is important to consider additional imaging modalities including ultrasound and MRI to help elucidate the diagnosis. The finding of additional masses can alter therapy especially if divergent histologies emerge. While PBL remains rare, a multimodality imaging approach is essential prior to treatment considerations in order to achieve optimal clinical outcomes.

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## ABBREVIATIONS

| | |
|---|---|
| **CT** | Computed tomography |
| **DLBCL** | Diffuse large B-cell lymphoma |
| **FDG** | Fluorodeoxyglucose |
| **MALT** | Mucosa associated lymphoid tissue |
| **MRI** | Magnetic resonance imaging |
| **PET** | Positron emission tomography |
| **PBL** | Primary breast lymphoma |
| **R-CHOP** | Rituximab, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunomycin), vincristine sulfate (oncovin), and prednisone |

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## Highlights

- PBL can present a diagnostic challenge to both the oncologist and radiologist.
- Use of multimodality breast imaging can help elucidate the diagnosis.
- Divergent histologies may be seen on breast biopsies.
- Thus, finding additional breast lesions can alter therapy.

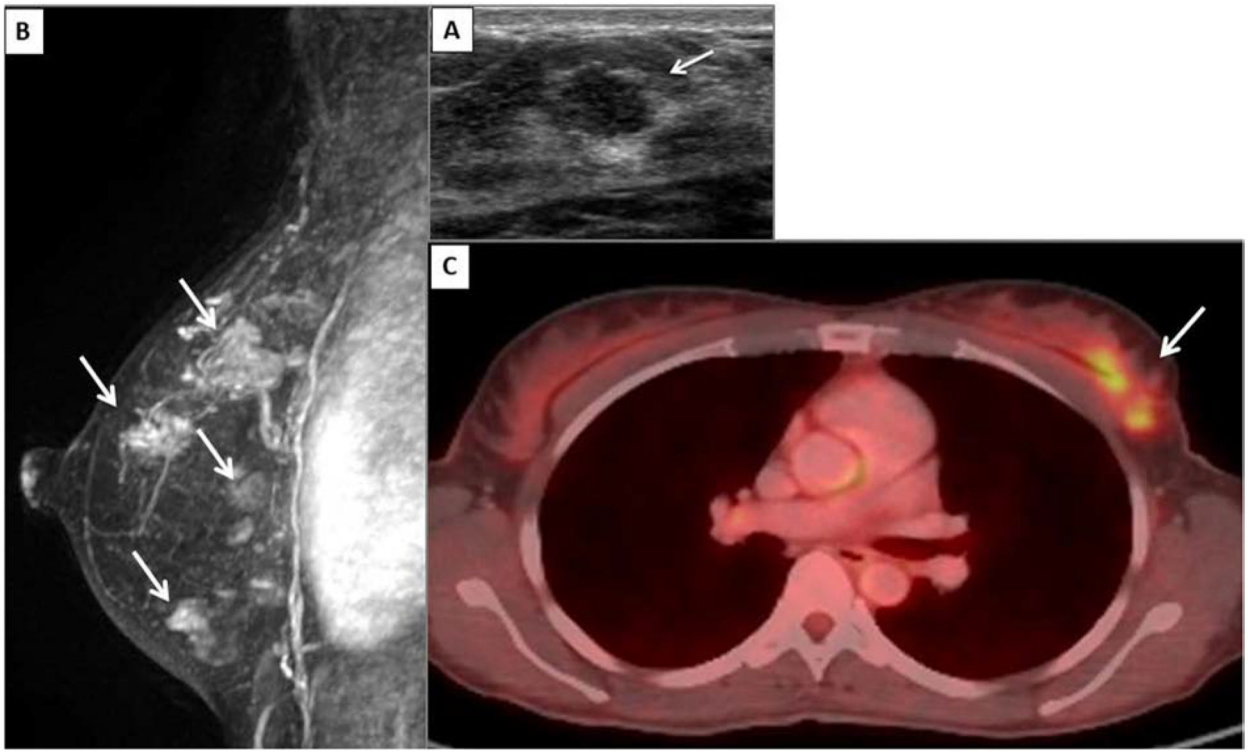


**Figure 1:**

Case 1, pre-treatment. (***A***) Ultrasound shows a hypoechoic mass with irregular margins (arrow). (***B***) Magnetic resonance imaging (MRI) subtraction maximum intensity projection (MIP) image before treatment shows multiple left breast masses in different quadrants (arrows) representing multicentric lymphoma. (***C***) Pre-treatment positron emission tomography/computed tomography (PET/CT) demonstrates multiple foci of fluorodeoxyglucose (FDG) avidity in the left breast (arrow), corresponding to MRI and US findings.

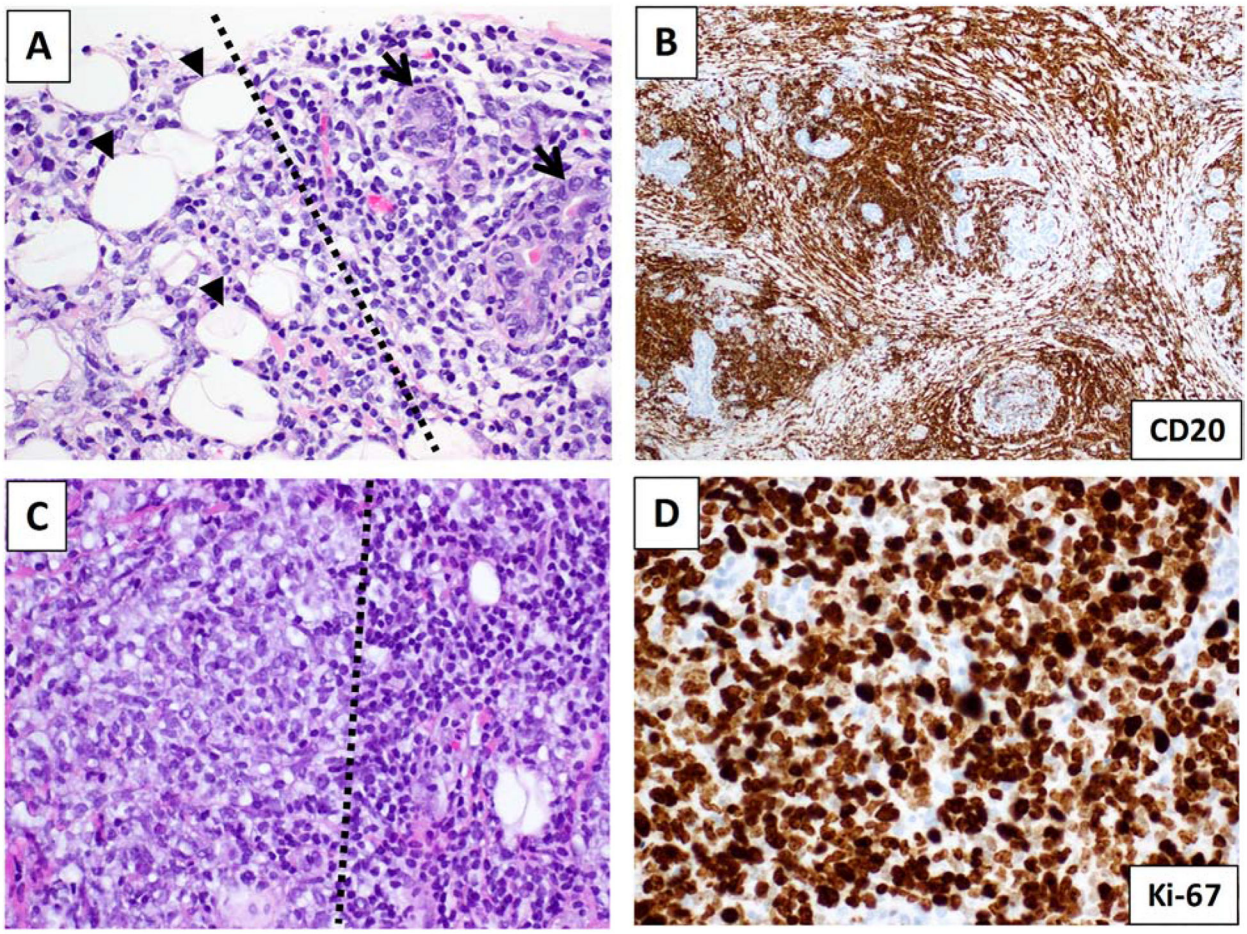


**Figure 2:**

Case 1, initial biopsy **A, B**. (***A***) Hematoxylin and eosin (H&E) sections demonstrate breast parenchyma involved by a lymphomatous infiltrate surrounding the ducts (arrows) and extending into the fat (arrow heads). The lymphoid neoplasm consists of predominantly small lymphocytes (right of dotted line) with condensed chromatin, with focal proliferation of large cell (left of dotted line) with vesicular chromatin and distinct nucleoli. (***B***) On immunohistochemistry, the neoplastic cells (both small and large cell components) are shown to be positive for the B-cell marker CD20. Case 1, additional biopsies, **C, D**. (***C***) H&E sections demonstrate involvement by a large cell lymphoma with similar cytologic features to the previous biopsy (left of dotted line), arising in a background of low-grade lymphoma (right of dotted line). The neoplastic large cells have a high Ki-67 proliferative index at 80% and (***D***) are positive for CD20 and BCL-6 while negative for CD10 and MUM-1 (not shown). Divergent appearances on the same slide highlight the diagnostic challenge of this disease.

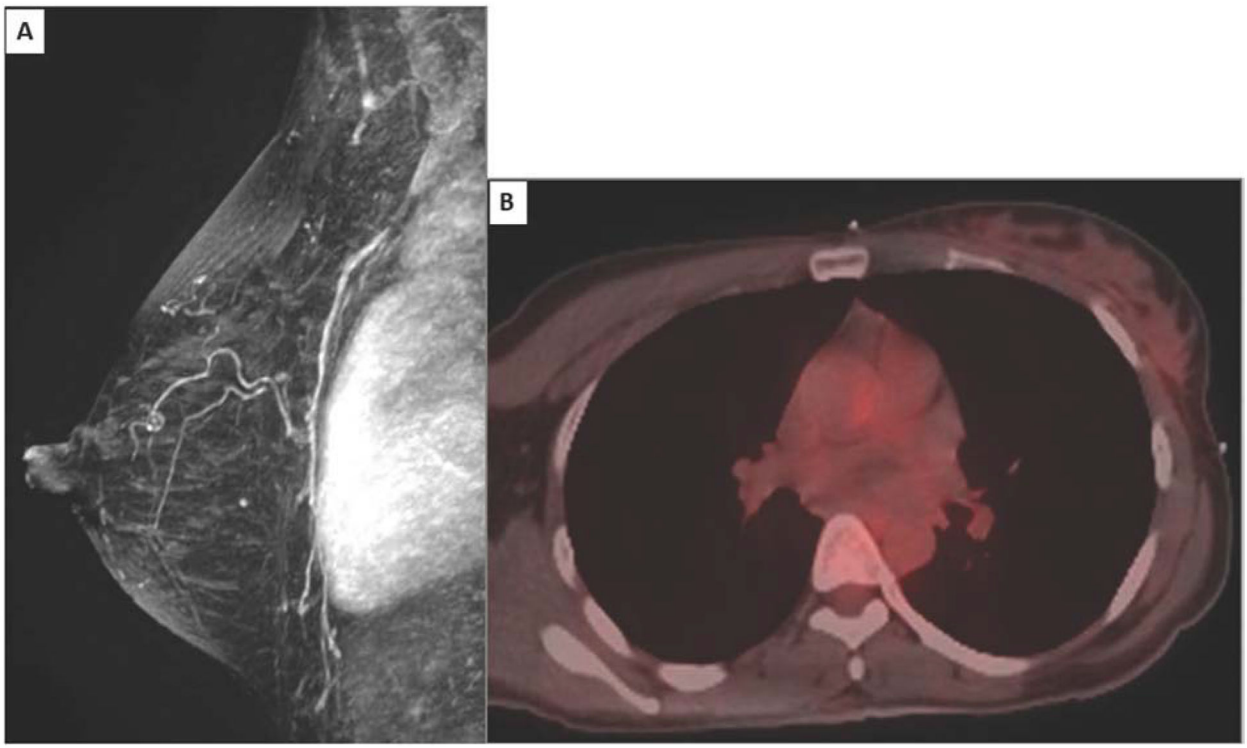


**Figure 3:**
Case 1, post-treatment. (***A***) Subtraction maximum intensity projection (MIP) image from breast magnetic resonance imaging (MRI) after chemoradiation shows resolution of lymphomatous masses. (***B***) Post-treatment positron emission tomography/computed tomography (PET/CT) following three cycles of chemotherapy demonstrates that the previous foci of fluorodeoxyglucose (FDG) avidity are substantially diminished in activity.

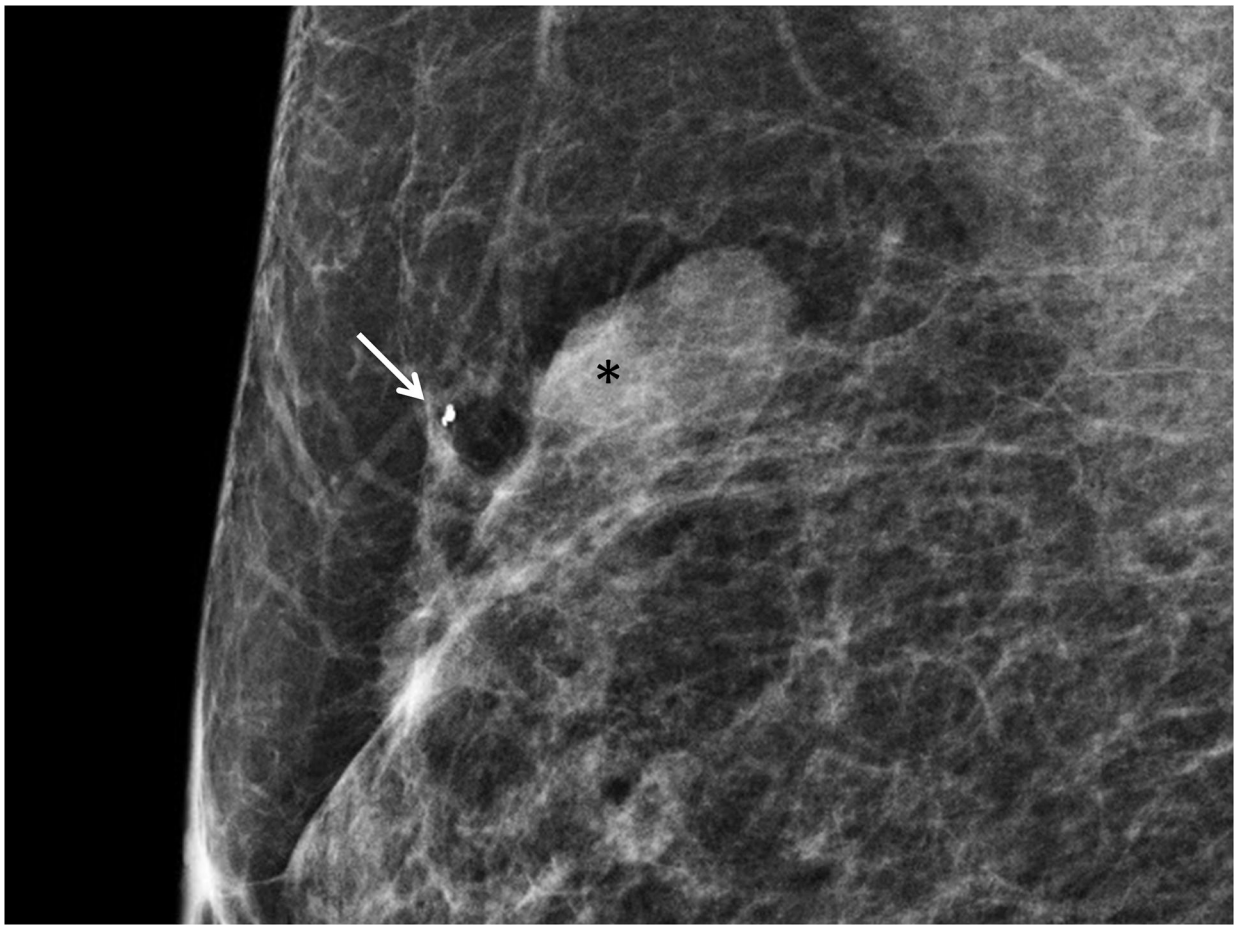


**Figure 4:**
Case 2. Right mediolateral-oblique (MLO) mammogram shows the butterfly biopsy marker in the upper breast (solid arrow), anterior to the biopsied mass (*).

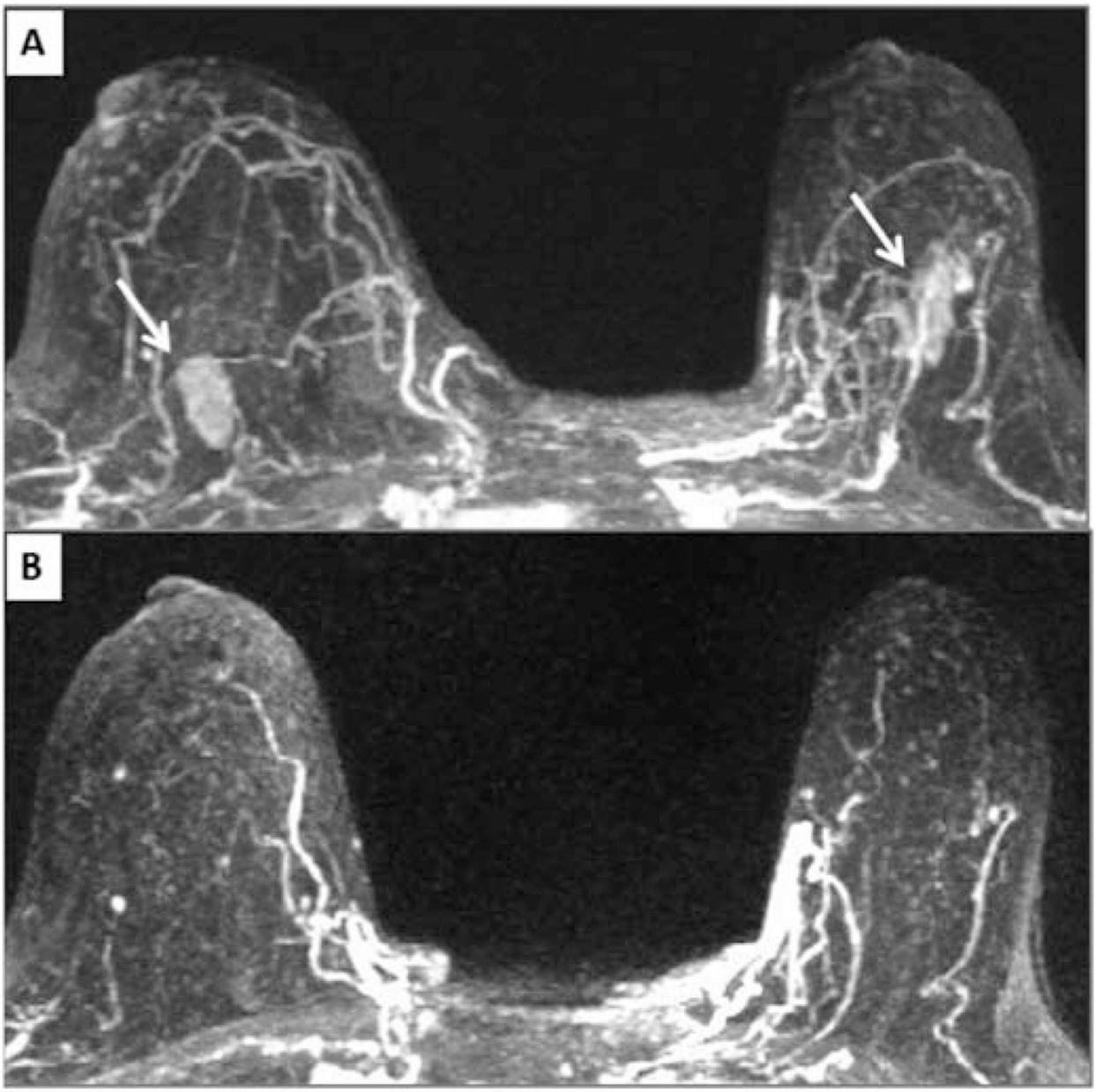


**Figure 5:**
Case 2. (***A***) Pre-treatment breast magnetic resonance imaging (MRI) shows bilateral breast masses on the subtraction maximum intensity projection (MIP) image (arrows). (***B)*** Post-treatment breast MRI shows resolution of breast masses on the subtraction MIP image.