

Radiological analysis of breast lymphoma

Experiences from cases series studies

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Abstract

This retrospective study aimed to improve the diagnostic accuracy of breast lymphoma (BL) by analyzing the findings of BL on mammography and magnetic resonance imaging (MRI).

Fifteen patients with breast lymphoma (BL, Primary/Secondary: 13/2) were confirmed by pathology. The imaging findings of those patients were analyzed by 2 senior radiologists.

BL commonly showed significant enhancement with penetrating vessels and septation in masses on dynamic contrast-enhanced MRI (DCE-MRI). Diffusion limitation of BL is more pronounced than breast cancer on diffusion weighted imaging.

The study suggests that the penetrating vessels and diffusion restriction of lesions are helpful for the diagnosis and differential diagnosis of BL.

Abbreviations: ADC = apparent diffusion coefficient, BL = breast lymphoma, DCE-MRI = dynamic contrast-enhanced MRI, DLBCL = diffuse large B cell lymphoma, DWI = diffusion weighted imaging, HL = Hodgkin lymphoma, MRI = magnetic resonance imaging, MZL = marginal zone lymphoma, NHL = non-Hodgkin lymphoma, PBL = primary breast lymphoma, ROI = region of interest, SBL = secondary breast lymphoma, T1WI = T1-weighted imaging, T2WI = T2-weighted imaging.

Keywords: breast neoplasms, lymphoma, magnetic resonance imaging, mammography

1. Introduction

Breast lymphoma (BL) is rare, accounting for 0.04–0.5% of malignant tumors of breast.^[1] Although implants associated anaplastic large cell lymphoma was not included in this study, with the popularity of implant transplantation, the incidence of BL will increase indirectly. The imaging findings of BL are similar to those of breast cancer, while the treatment regimens for BL and breast cancer are quite different. Therefore, an accurate diagnosis of BL is necessary, which can avoid unnecessary radical surgery, and is helpful for developing a reasonable treatment plan. Imaging features of BL have few reports to date. In order to determine the

key imaging hallmarks of this disease, we retrospectively analyzed mammography and magnetic resonance imaging (MRI) findings of 15 cases with complete clinical data of BL.

2. Materials and methods

The institutional review board of The First Affiliated Hospital of Zhejiang Chinese Medical University approved this retrospective study and waived informed consent.

2.1. Subjects

A total of 15 patients diagnosed with BL were collected with complete clinical and image data from March 2013 to June 2017 in The First Affiliated Hospital of Zhejiang Chinese Medical University. These patients included 14 females and 1 male. The age ranged from 24 to 85 years old. The average age is 48.4 ± 17.8 years old. About 5 cases out of the 15 patients underwent mammography and all cases underwent MRI examination. The clinical data and images of all patients were de-identified.

2.2. Imaging techniques

Craniocaudal and mediolateral oblique mammographic projections were obtained (Mammomat Inspiration, Siemens healthcare GmbH erlangen, Germany). Bilateral breast images were detected by a 16 channel special surface coil of bilateral mammary gland on 3T MR scanner (Magnetom Verio 3T, Siemens, Siemens healthcare GmbH erlangen, Germany). Scan sequences include fat-suppressed T2-weighted imaging (T2WI): TR: 4000 ms, TE: 70 ms, thickness: 4 mm, FOV: 360 mm × 360 mm, diffusion-weighted imaging (DWI): TR: 7000 ms, TE: 85 ms, thickness: 4 mm, *B* values of 50 s/mm², 400 s/mm², and 800 s/mm² were selected, and the apparent diffusion coefficient (ADC) was reconstructed automatically after the scan, and dynamic

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contrast-enhanced magnetic resonance imaging (DCE-MRI). The DCE-MRI was detected by three-dimensional dynamic imaging sequences with fast and small angle stimulation and used to scan 6 phases: TR: 4.51 ms, TE: 1.61 ms, thickness: 1.0 mm. At the end of the first 15.0 second interval, the high pressure injector was used to administer contrast injection of Gd-DTPA (Beijing Hokuriku Pharmaceutical Company Limited, Beijing, China), administered intravenously via median cubital vein at a dose of 0.2 mmol/kg (15–20 mL), rate of 1.5–2 ml/s injection. The same injection rate was used to inject 20 mL saline to flushing pipe. Scan time of DCE-MRI is about 6 min 10 s.

2.3. Image analysis

The area of highest enhancement was selected as the region of interest (ROI) to measure the ADC value on ADC maps. Syngo random post-processing software was used for measurement. The ROI was selected to describe the time signal intensity curve. All mammography and MRI images were retrospectively reviewed by 2 senior radiologists, and the results were discussed and agreed upon. They reviewed the images by using the criteria of Breast Imaging Reporting and Data System Version 2013. The radiologists were blinded to the clinical data and the final diagnosis.

3. Results

3.1. Clinical characteristics and pathological type

Fourteen cases of BL were confirmed by biopsy or surgical pathology, and 1 case of BL was confirmed by clinical treatment and follow-up observation. Fifteen patients including 13 cases of primary breast lymphoma (PBL) and 2 cases of secondary breast lymphoma (SBL) were enrolled. Thirteen cases of PBL included 10 cases of diffuse large B cell lymphoma (DLBCL), 2 cases of B cell lymphoma, and 1 case of a pregnant woman with Burkitt lymphoma. The two cases of SBL included 1 case of DLBCL and 1 case of peripheral T cell lymphoma. The clinical manifestations of the 3 cases of PBL were: rapid growth of the lesions, accompanied by breast pain with thickening, and edema of the skin. Another 10 cases of PBL were revealed from incidental breast mass findings and showed gradual enlargement to various degrees. The two cases of SBL were breast lumps found after diagnosis of lymphoma.

3.2. Mammography and MRI findings

The mammography and MRI findings of our cases were summarized in Tables 1 and 2. Fifteen patients demonstrated lesions located in the right breast for 7 cases, 5 cases in left breast, and 3 cases in bilateral breast. Mammography was performed in 5 cases that included 4 cases with PBL and 1 case with SBL. Three

cases of PBL showed a single, round, dense mass with well-circumscribed margin. One case of PBL showed focal asymmetry dense within a round, dense, and indistinct margin mass (Fig. 1A) accompanied by axillary lymph nodes. One case of SBL showed multiple, round, and highly dense masses with indistinct margins (Fig. 1B).

Fifteen cases were examined by MRI, including 13 cases of PBL with a diameter ranging from 2.3 cm to 15.1 cm with an average of 5.3 ± 3.8 cm, and 2 cases of SBL with a diameter ranging from 2.1 cm to 5.0 cm with an average of 3.5 ± 2.6 cm. MRI findings of all the lesions showed hyperintensity compared with breast parenchyma on T2WI and isointensity on T1-weighted imaging (T1WI). All the lesions showed hyperintensity on DWI and low ADC values. The average ADC value of PBL was $(0.55 \pm 0.08) \times 10^{-3} \text{ mm}^2/\text{s}$ and the average ADC value of SBL was $(0.54 \pm 0.22) \times 10^{-3} \text{ mm}^2/\text{s}$. After intravenous administration of contrast medium, early rapid enhancement were seen in all lesions, and the kinetic curve was a Plateau or Washout. There were 8 cases of PBL with a unilateral single mass (61.5%, 8/13, Fig. 2A–D), which showed round, circumscribed margins. Four cases of PBL with multiple masses (30.8%, 4/13) were also found. One case of PBL showed diffuse infiltration (7.7%, 1/13, Fig. 3A–D) and the bilateral breast swelling with skin thickening and edema. The mass was characterized as a wide, partial nodular, and lumpy fusion mass. DCE-MRI showed heterogeneous enhancement of the lesion within penetrating vessels (Fig. 2C) and septal enhancement (Fig. 3B) in 5 patients. Seven cases of PBL showed unilateral or bilateral axillary lymph node enlargement. One case of SBL (Fig. 4A and B) showed an unilateral, single, circumscribed margin mass, and DCE-MRI showed early homogeneous enhancement of the lesion with penetrating vessels (Fig. 4B). This was also accompanied by bilateral, multiple enlarged axillary lymph nodes. A single case of SBL showed bilateral, multiple, circumscribed margin masses, with homogeneous enhancement.

4. Discussion

4.1. Diagnostic criteria and pathology of breast lymphoma

BL is divided into PBL and SBL. The clinical diagnosis of PBL refers to the diagnostic criteria proposed by Wiseman in 1972^[2]:

- (1) lymphoma should be confirmed by pathology,
- (2) microscopy should reveal infiltration in the breast duct and lobular tissue, in the breast epithelium with no malignant transformation, and at the junction of the specimen showing both normal breast tissue and invasion of lymphoma,
- (3) no lymph node and lymphoma occurring simultaneously except for involvement of ipsilateral axillary lymph node, and finally
- (4) no history of lymphoma in other organs or tissues.

Table 1
Mammographic findings of primary and secondary breast lymphoma.

Cases	Age	Gender	PBL/SBL	Side	Shape	Margin	Density
1	66	F	PBL	Left	Round	Circumscribed	Hyperdensity
2	81	F	PBL	Right	Round	Indistinct	Isodensity
3	39	F	PBL	Left	Round	Circumscribed	Hyperdensity
4	85	M	PBL	Right	Round	Circumscribed	Hyperdensity
5	36	F	SBL	Both	Round	Indistinct	Isodensity

F = female, M = male, PBL = primary breast lymphoma, SBL = secondary breast lymphoma.

Table 2
MRI findings of primary and secondary breast lymphoma (15 cases).

Cases	Age	PBL/ SBL	Lesions/ Side	Clinical manifestation	Size (cm)	Shape	Margin	ADC (10 ⁻³ mm ² /s)	Internal enhancements	Enhancement curve	Pathology
1	47	PBL	Single/Left	Palpable masses	2.8	Irregular	Indistinct	0.654	Heterogeneous	Washout	Diffuse large B-cell lymphoma
2	66	PBL	Single/Left	Progressive enlargement of mass	3.8	Round	Circumscribed	0.464	Heterogeneous with penetrating vessels and septation	Washout	Diffuse large B-cell lymphoma
3	24	PBL	Diffuse/ Bilateral	Progressive breast enlargement during pregnancy	15.1	Diffuse	Circumscribed	0.446	Heterogeneous with penetrating vessels and septation	Persistent	Burkitt lymphoma
4	81	PBL	Multiple/Right	Palpable masses	3.3	Round	Indistinct	0.588	Heterogeneous	Washout	Diffuse large B-cell lymphoma
5	55	PBL	Single/Left	Palpable masses	3.0	Oval	Circumscribed	0.546	Homogeneous	Washout	Diffuse large B-cell lymphoma
6	39	PBL	Single/Left	Palpable masses	4.6	Irregular	Indistinct	0.649	Heterogeneous with penetrating vessels and septation	Plateau	Diffuse large B-cell lymphoma
7	55	PBL	Multiple/ Bilateral	Multiple breast masses	3.1	Round	Circumscribed	0.622	Homogeneous	Plateau	Diffuse large B-cell lymphoma
8	39	PBL	Single/Right	Palpable masses	8.0	Round	Circumscribed	0.553	Heterogeneous with penetrating vessels and septation	Plateau	Diffuse large B-cell lymphoma
9	32	PBL	Multiple/Left	Swollen, hot, and painful for more than 2 months	10.5	Diffuse	Indistinct	0.567	Heterogeneous	Washout	Diffuse large B-cell lymphoma
10	40	PBL	Single/Right	Palpable masses	5.0	Round	Circumscribed	0.532	Heterogeneous with penetrating vessels and septation	Washout	Diffuse large B-cell lymphoma
11	40	PBL	Single/Left	Progressive enlargement of mass	4.2	Round	Circumscribed	0.623	Homogeneous with penetrating vessels	Washout	Diffuse large B-cell lymphoma
12	55	PBL	Single/Left	Palpable masses	3.0	Oval	Circumscribed	0.543	Homogeneous	Plateau	Diffuse large B-cell lymphoma
13	85	PBL	Multiple/Right	Multiple breast masses	2.3	Round	Circumscribed	0.415	Heterogeneous	Washout	Diffuse large B-cell lymphoma
14	36	SBL	Multiple/ Bilateral	Multiple breast masses (primary mediastinal lymphoma)	2.1	Oval	Circumscribed	0.696	Homogeneous	Plateau	Peripheral T-cell lymphoma
15	32	SBL	Single/Right	Palpable masses (primary lymphoma of left maxillary sinus)	5.0	Oval	Circumscribed	0.389	Homogeneous with penetrating vessels	Washout	Diffuse large B-cell lymphoma

ADC = apparent diffusion coefficient, PBL = primary breast lymphoma, SBL = secondary breast lymphoma.

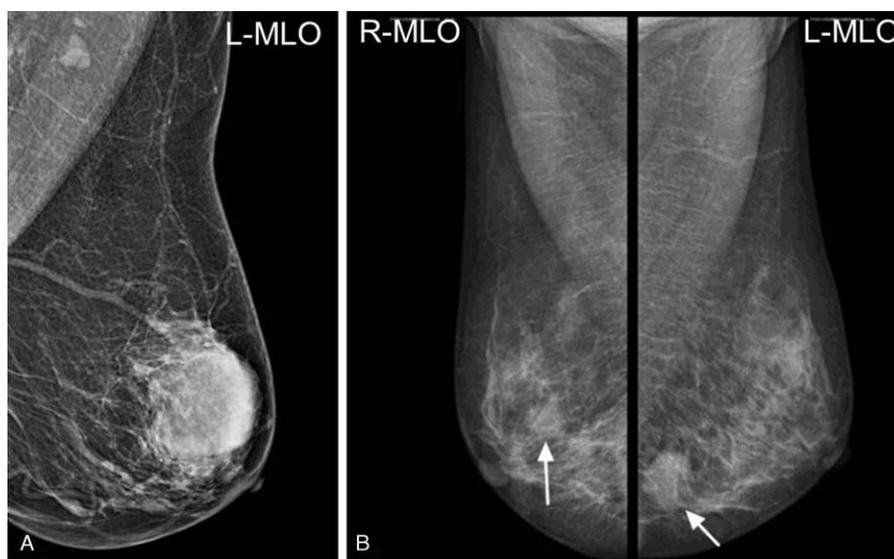


Figure 1. A 66-year-old woman with primary breast lymphoma in left breast showed a round high density mass (A) and a 36-year-old woman with secondary peripheral lymphoma showed bilateral multiple round masses (arrows, B) with indistinct margin on mammography.

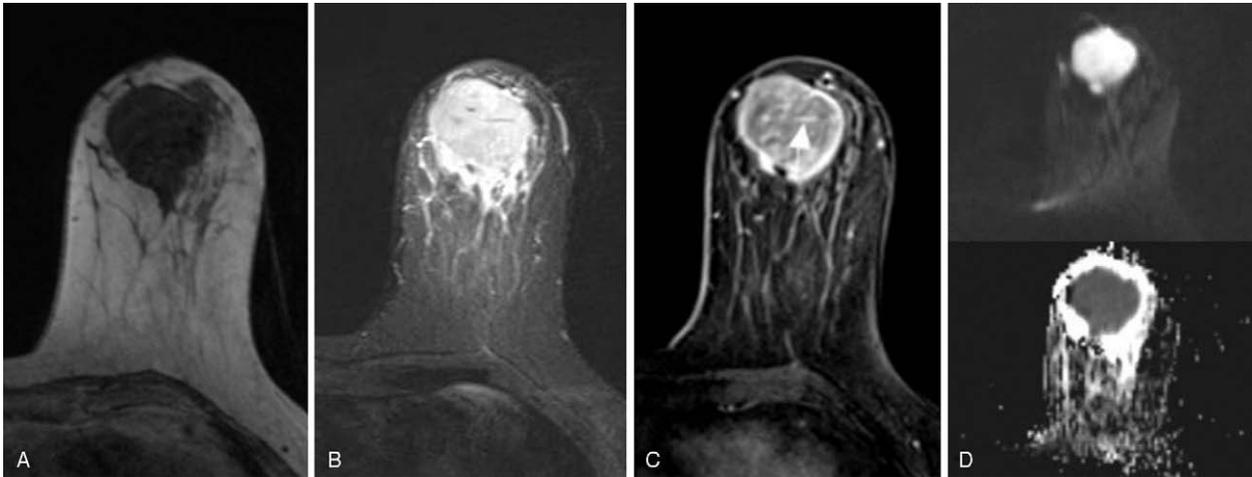


Figure 2. A 66-year-old woman with primary breast lymphoma in left breast. T1WI (A) and fat-suppressed T2WI (B) showed a hypointensity and hyperintensity mass, respectively. (C) Contrast-enhanced MRI showed heterogeneous internal enhancement with penetrating vessels (arrow) and septation. (D) DWI showed hyperintensity and the ADC value is low, the average ADC value is $0.46 \times 10^{-3} \text{mm}^2/\text{s}$ ($b=800 \text{s}/\text{mm}^2$). ADC=apparent diffusion coefficient, DWI=diffusion weighted imaging, MRI=magnetic resonance imaging, T1WI=T1-weighted imaging, T2WI=T2-weighted imaging.

In contrast, SBL refers to systemic lymphoma either along with PBL, or secondary to the breast. According to these rules, 13 patients were diagnosed as PBL, and 2 patients were diagnosed as SBL in this study. It is reported^[3,4] that PBL accounts for 0.85% to 2.2% of extranodal lymphoma, with SBL being more common. However, most reports in literature and in study were cases of PBL. This may be due to the diagnostic criteria of SBL, which is based on clinical examination, leading to fewer imaging studies compared to PBL subjects. Studies^[5,6] have shown that PBL has a higher incidence in pregnant and postpartum women who received estrogen replacement therapy. PBL also comes with an increased risk of lymphoma by 29%. These studies suggested that the growth

of a tumor may be related to hormone stimulation. This group of patients included 14 females and 1 male, of which 1 female case showed progressive enlargement of the bilateral breast during pregnancy. Another female showed bilateral breast lumps during postpartum seventh month of lactation. Most of the clinical manifestations of BL are painless single or multiple masses, with or without axillary lymph node enlargement, involving unilateral and bilateral breast. The masses are tough and movable. A few of the breast diffuse enlargement with skin thickening and edema need to be differentiated from inflammatory breast cancer and acute mastitis.^[7] There are 3 cases of skin thickening and edema in this group, which are consistent with those reported in the literature.

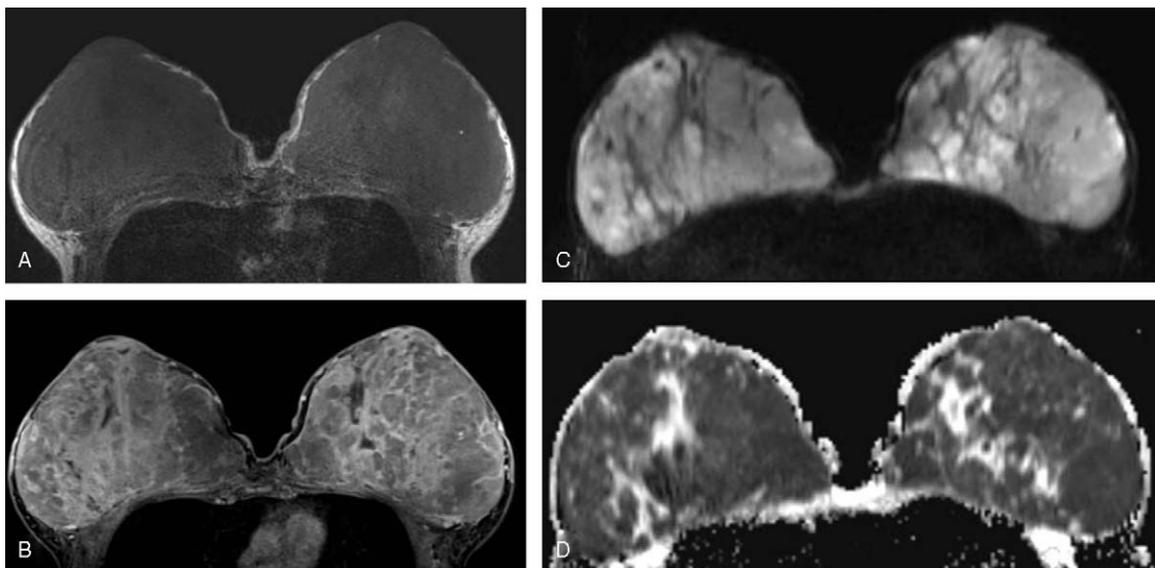


Figure 3. A 24-year-old woman with primary breast lymphoma with the bilateral breast gradually enlarged during pregnancy. T1WI (A) showed asystematic hypointensity in bilateral breast. Contrast-enhanced MRI (B) showed heterogeneous enhancement with penetrating vessels and septation. DWI (C) showed hyperintensity and ADC value (D) was extremely low, the average ADC value was $0.45 \times 10^{-3} \text{mm}^2/\text{s}$ ($b=800 \text{s}/\text{mm}^2$). ADC=apparent diffusion coefficient, DWI=diffusion weighted imaging, MRI=magnetic resonance imaging, T1WI=T1-weighted imaging.

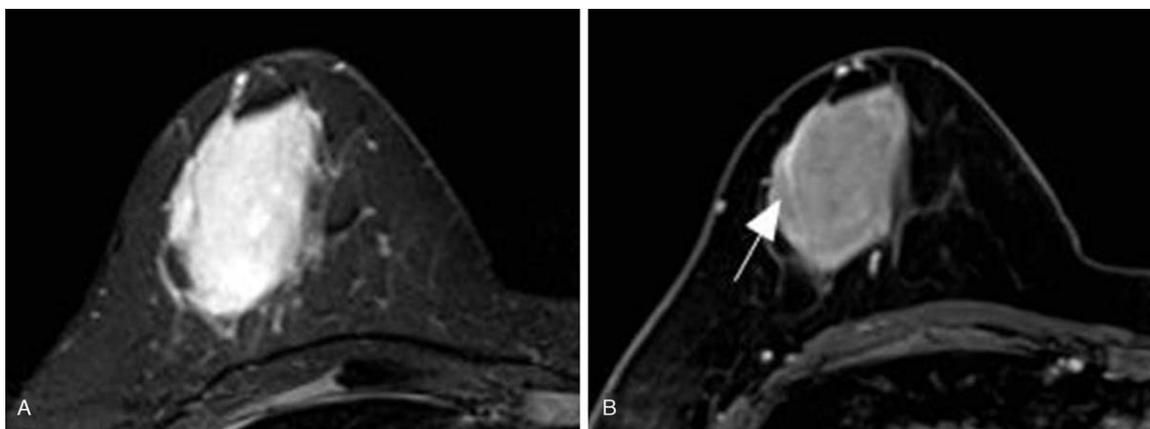


Figure 4. A 32-year-old woman with secondary breast lymphoma. Fat-suppressed T2WI (A) and contrast-enhanced MRI (B) showed a well-defined mass with penetrating vessels (arrow) in right breast. MRI=magnetic resonance imaging, T2WI=T2-weighted imaging.

Histologically, BL can be divided into non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). Most BL are of the NHL subtype, including DLBCL (56–84%), marginal zone lymphoma (MZL, 9–28%), follicular lymphoma (10–19%), and Burkitt lymphoma (<6%).^[8–13] Burkitt lymphoma is relatively rare, occurring primarily in pregnant or lactating women and frequently involving the bilateral breast. The disease progresses rapidly and the prognosis is typically poor.^[14] In this group, 1 case was diagnosed as Burkitt lymphoma during pregnancy and the firstly diagnosis was misdiagnosed as mastitis.

4.2. Mammography and MRI findings of BL

There are few literature reports on BL, especially SBL. Sabaté and Liu et al^[15,16] found that there was no significant difference between PBL and SBL analyzed by the findings of MRI. However, they found that the diameter of SBL lesions is smaller than PBL. Surov et al^[4] found that the number of lesions in SBL is more numerous than PBL, and the lesion of PBL was larger than SBL. Moreover, there were no differences between the PBL and SBL in the morphology and margin features of the lesions^[4]. In this study, the mean diameter of lesions in PBL group was larger than that of the SBL group, and no morphological difference were found between the two groups. However, a meaningful comparison cannot be made due to the limited number of cases. According to the mammography features of BL,^[17,18] BL can be roughly divided into three types: nodular type, mass type, and infiltrative type. The nodular type typically shows non-calcified, clear or obscure margins, round or lobulated nodules, and spicule sign is rare; although lesions may be single or multiple. The mass type typically presents with a single, huge mass, well-defined border, and the skin adjacent to the lesion is not affected. The infiltrative type shows a high density shadow of the breast, invading a single quadrant or the entire breast with diffuse thickening of the skin. The subcutaneous tissue showed a grid-like change, and the affected breast rarely possessed a crater nipple.

Reports document MRI findings of BL are rare. Liu et al^[15] analyzed the MRI findings of 12 patients with PBL and 8 patients with SBL and found no meaningful difference between PBL and SBL on MRI. The main findings of MRI were irregular margins with heterogeneous enhancement. Some lesions showed separa-

tion, or non-entity like inhomogeneous enhancement. The time signal curves were dominated by plateau and washout types. Surov et al^[4] reported 8 cases of mostly smooth edge masses (81%), which showed homogeneous enhancement (82%), and the time signal curves was dominated by the plateau type (90%). The washout type was found in 1 case (5%). Wang et al^[19] analyzed 7 cases of BL. They found most cases of BL demonstrated homogeneous enhancement (87.5%) and time signal curves showed the washout type. However, 1 case revealed a ring-like enhancement and a plateau time signal curve. Histological features of BL are characterized by abundant, closely packed lymphocytes with small extracellular spaces, resulting in a significantly restricted and lower ADC value than that of breast cancer. Moreover, according to published literatures,^[20,21] the ADC value of breast cancer ranged from 0.99 to 1.22, which was obviously higher than that of BL. This feature is helpful for differential diagnosis of BL and breast cancer. Wang et al^[19] analyzed 2 cases of BL and found the ADC value to be $0.876 \times 10^{-3} \text{ mm}^2/\text{s}$ and $0.732 \times 10^{-3} \text{ mm}^2/\text{s}$, respectively. Our results showed that the ADC values of PBL and SBL were lower than the cases reported by Wang et al. Matsubayashi et al^[22] observed the findings of MRI and pathology of 3 patients with PBL. The results showed enhancement with penetrating vessels and septation in their lesions. In this study, five cases of PBL and 1 case of SBL had this characteristics.

Due to a lack of understanding of BL image features in the past, this often lead to misdiagnosis of breast cancer due to a poorly circumscribed lesion, thickening of skin, and enlargement of axillary lymph nodes. Although this study reported some findings, the major limitation of this study was the small sample of BL resulting from the rarity of BL, especially SBL. Meanwhile, the study is predominately a retrospective descriptive study, which was not designed to make specific comparisons between subgroups of BL or between BL and other breast pathology. Therefore, characteristics of BL need to be further investigated in future research.

5. Conclusion

Based on previous studies and data reported in this group, we observed several characteristics of BL:

- (1) BL can be roughly divided into the nodular type, mass type, and infiltrative type on mammography,
- (2) single mass BL does not involve the skin and the infiltrative subtype can present as extensive skin edema, and/or thickening,
- (3) in the early stage of enhancement, BL lesions were significantly enhanced with penetrating vessels and showed septation on DCE-MRI,
- (4) The ADC value of BL was observed to be lower than that of breast cancer.

These findings can be helpful in the diagnosis and differential diagnosis of BL.

Author contributions

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