Breast Lymphoma and Leukemia: Imaging Features and Radiologic-Pathologic Correlation

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Authors: M. J. Magalhães, A. Galagh, C. Fernandes, H. Duarte, J. Abreu e Silva, C. Leal, A. T. Aguiar, A. Guimarães dos Santos, M. V. P. G. Almeida; Porto/PT
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Learning objectives

The purpose of this educational exhibition is to familiarize readers with the clinical features, imaging findings and histopathological characteristics of breast lymphoma and leukemia.

Background

In addition to frequently diagnosed pathologic entities involving breast tissue, a number of less common diseases may be identified at biopsy, such as lymphoma and leukemia. Breast lymphomas constitute about 0.4%-0.7% of breast cancers and approximately 1%-2% of all lymphomas occur in the breast. The rarity of primary breast lymphomas may be related to the relatively small amount of lymphoid tissue that is present in the breast as compared to the gut or lung, in which the occurrence of primary lymphomas are much more frequent. (1) Secondary breast lymphoma, occurring in association with extramammary lymphoma, is slightly more common and represents the largest group of tumours that are metastatic to the breast. (2)

Breast involvement in leukemia is very rare and occurs mainly in patients with acute myeloid leukemia (AML); secondary acute lymphoblastic leukemia involving the breast is uncommon. (4) (3)

Lymphomatous involvement of breast is more frequent in postmenopausal women, but younger patients cases have been reported, as well as in males. Patients usually present with a painless lump, less frequently, it may present as diffuse breast enlargement and, occasionally, may be asymptomatic. Nipple retraction is usually absent and masses may be hard at palpation.

Mammary lymphomas may arise in the breast as a primary tumour, while systemic lymphomas may involve breast secondarily. Primary lymphoma of the breast is often defined as a tumour limited to the breast and regional lymph nodes in a patient with no prior history of lymphoma. However, it has been suggested that they should be defined similarly as other extranodal lymphomas - initial presentation with the dominant mass/symptom in the breast in a patient without prior lymphoma history, even if distant involvement is discovered at staging. (5)

Breast lymphomas are subdivided according to the World Health Organization (WHO) classification system (Table 1) into diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), T-cell lymphoma (anaplastic large cell lymphoma (ALCL), anaplastic lymphoma kinase (ALK)-negative), extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT) and follicular lymphoma. (5)
DLBCL, not otherwise specified, is the most common type of breast lymphoma, accounting for approximately 50-65% of all lymphomas presenting in the breast. Clinical presentation often occurs as discrete tumour masses. Most patients present with unilateral disease, but there is a risk of recurrence in the opposite breast. However, patients are more likely to relapse in other extranodal sites, involving central nervous system in 5-10% of cases.

BL is characterized by three clinical variants - endemic (the most common), sporadic and immunodeficiency-associated. It usually occurs in pregnant and lactating women (BL cells have prolactin receptors), presenting as massive bilateral breast swelling. The presence of Epstein-Barr virus is more common in endemic variant. (5)

T-cell lymphoma can involve the breast as part of disseminated disease, and rarely as a primary site. The most common types of T-cell lymphoma involving breast are systemic or cutaneous ALCL, peripheral T-cell lymphoma, not otherwise specified and T-lymphoblastic leukemia/lymphoma. Small series of cases have described ALK-negative ALCL arising in association with breast implant (both saline and silicone-filled), with a median time from placement to development of ALCL of 8 years. Patients affected with ALCL ALK-negative most often present with a seroma (“seroma-associated ALCL”), which has a good prognosis. (6)

Extranodal marginal zone lymphomas of MALT usually arise primarily in the breast, but secondary involvement can be seen. The etiology is not known, however, an association with underlying autoimmune disorder has been implicated in rare cases. (7) The patients generally present with a solitary breast mass, detected either by palpation or by mammography; involvement of regional lymph nodes may be present in 25% of cases. Clinically, primary MALT lymphomas of the breast are indolent with a 5-year overall survival of >90%, most responding to local therapy (radiotherapy or excision). (5)

Follicular lymphoma is among a variety of low-grade B-cell lymphomas, presenting a wide disparity of percentages between primary versus secondary cases. The differential diagnosis includes other low-grade B-cell lymphoma subtypes and chronic mastitis (cutaneous pseudolymphoma). Biological behavior is comparable to that of conventional nodal disease, but a worse prognosis has also been reported. (5)(8)

The rare involvement of breast in leukemia can be the only complaint at initial presentation in a setting of diffuse systemic disease or seen as relapse. Moreover, radiotherapy performed on breast malignancies can also be associated with acute leukemia in breast tissue. Following a detailed examination, this condition should be added to the series of findings including lung consolidations, pleural effusion, a mass in the mediastinum or a hepatosplenomegaly, which resembles systemic disease. (3)
### Table 1. World Health Organization Classification of Tumours of the Breast 2012

**Epithelial tumours**
- Microinvasive carcinoma
- Invasive breast carcinoma
- Invasive carcinoma of no special type
- Invasive lobular carcinoma
- Tubular, Cribriform and Mucinous carcinoma
- Carcinoma with medullary features
- Carcinoma with apocrine differentiation
- Carcinoma with sinet-ring-cell differentiation
- Invasive micropapillary carcinoma
- Metaplastic carcinoma of no special type
- Rare types
- Carcinoma with neuroendocrine features
- Secretory carcinoma
- Invasive papillary carcinoma
- Acinic cell carcinoma
- Mucoepidermoid carcinoma
- Polymorphous carcinoma
- Oncocytic carcinoma
- Lipid-rich carcinoma
- Glycogen-rich clear cell carcinoma
- Sebaceous carcinoma, Salivary gland/skin adnexal type tumours

**Epithelial-myoepithelial tumours**
- Pleomorphic adenoma
- Adenomyoepitheloma
- Adenoid cystic carcinoma

**Precursor lesions**
- Ductal carcinoma in situ
- Lobular neoplasia

**Intraductal proliferative lesions**
- Usual ductal hyperplasia, Columnar cell lesions, Atypical ductal hyperplasia

**Papillary lesions**
- Intraductal papilloma, Intraductal papillary carcinoma, Encapsulated papillary carcinoma, Solid papillary carcinoma
- Benign epithelial proliferations
- Sclerosing adenosis, Apocrine adenosis
- Microglandular adenosis
- Radial scar/complex sclerosing lesion
- Adenomas

**Mesenchymal tumours**
- Nodular fasciitis
- Myofibroblastoma
- Desmoid-type fibromatosis
- Inflammatory myofibroblastic tumour
- Benign vascular (hemangioma, angiomatosis, atypical vascular lesions)
- Pseudoangiomatous stromal hyperplasia
- Granular cell tumour
- Benign peripheral nerve-sheath tumours (Neurofibroma, Schwannoma)
- Lipoma, Angioliomipoma
- Liposarcoma, Angiosarcoma, Rhabdomyosarcoma, Osteosarcoma
- Leiomyoma, Leiomyosarcoma

**Fibroepithelial tumours**
- Fibroadenoma
- Phyllodes tumour (benign, borderline, malignant, periductal stromal tumour-low grade)
- Hamartoma

**Tumours of the nipple**
- Nipple adenoma
- Syringomatous tumour
- Paget disease of the nipple

**Malignant lymphoma**
- Diffuse large B-cell lymphoma
- Burkitt lymphoma
- T-cell lymphoma
- Anaplastic large cell lymphoma, ALK-negative
- Extramedullary marginal-zone B-cell lymphoma of MALT type
- Follicular lymphoma

**Metastatic tumours**

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*Lyon, France: IARC, 2012*
Breast lymphoma and leukemia may manifest as a solitary mass or multiple masses (unilateral or bilateral), with or without axillary lymphadenopathy. Breast enlargement, particularly during pregnancy, may also occur. (9) (10)

Primary breast lymphomas are morphologically indistinguishable from secondary ones at imaging and histologic analysis, however, the presence of breast tissue in or adjacent to the lymphomatous infiltrate, the absence of concurrent nodal disease (except in ipsilateral axillary nodes) and the absence of a history of lymphoma involving other organs are suggestive of primary disease. (5) Bilateral axillary lymphadenopathy should arise suspicion about the presence of a secondary lymphoma.

The typical mammographic appearance of breast lymphoma is a solitary, noncalcified, circumscribed or indistinctly margined mass with adjacent lymphadenopathy, presenting various densities. The borders of the mammographic masses are usually well circumscribed or incompletely circumscribed but not spiculated, reflecting the absence of marked desmoplasia or scirrhous. (Figures 1 and 2) Less commonly, diffuse increased parenchymal density with skin thickening is observed. (11) (Figures 3-5) This pattern may also be observed in inflammatory carcinomas. (Figures 6 and 7)

At ultrasonography, breast lymphomas usually appear as hypoechoic solid masses, with circumscribed or irregular margins, but mixed echogenicity may also be seen. (Figures 8-10) Indeed, breast malignant lesions that may present as hyperechoic nodules include lymphoma, angiosarcoma and metastases. (12) (Figures 11 and 12) Posterior acoustic enhancement is a common feature and an echogenic rim may be seen around the lesions. (Figures 8)

Currently, computed tomography (CT) is performed for the initial staging of lymphoma and to evaluate any recurrence of the disease in extra-mammary sites. A detailed examination can document findings, including lung consolidations, pleural effusion, a mass in the mediastinum or a hepatosplenomegaly, which resembles systemic disease, as previously described to leukemia.

The value of MRI in breast lymphoma is not yet firmly established, but strong and rapid enhancement of breast lymphomas has been observed on T1-weighted MR images obtained after the administration of contrast material. Breast lymphoma should be considered in the presence of large enhancing lesions of the breast, particularly if they are associated with skin thickening. Compared with other breast imaging modalities, the sensitivity of breast MRI is very high and may be more sensitive and accurate in detecting and representing multicentric lesions. To determine whether or not the apparent coefficient diffusion (ADC) is valuable, further studies are required to measure and
analyze more cases. However, MRI may have an important role in the assessment of multicentric lesions and the staging of mammary malignancies preoperatively. MRI may also be useful in the follow-up of breast lymphoma patients, to monitor response to chemotherapy / radiotherapy and recurrence diagnosis.

The mammographic findings in cases of leukemia in the breast can be a solitary nodule, ill-defined margin with an irregular shaped (Figure 13) or well-defined lesion, sometimes with a benign appearance. Diffusely enlargement with coarse breast parenchyma may also occur. (Figure 14) (14) (13) Most cases of AML involving breasts appears bilaterally, as multiple nodules. (15)

Studies examining the sonographic features of breast metastases range widely, from hypoechoic to hyperechoic findings. The involvement of the breasts in cases of acute myeloid leukemia has been described as areas of mixed echogenicity, with irregular or lobulated margins, conditioning or not acoustic shadowing. (Figures 15 and 16) A pattern with central anechoic lesion and peripheral hyperechoic areas has also been reported. (Figure 15) Some leukemic breast masses have shown increased vascularity at Doppler US. (14)(13) There are studies suggesting that the reduced diagnostic capability of the ultrasonography may be improved by Doppler flow mapping, by depicting the hypervascular stroma as highly resistive index values. (16)

As with mammary lymphoma, the value of MRI in breast leukemia is not yet firmly established, but MRI features include T2 hyperintensity and rapid ring-enhancement of the lesions. The explanation of this ring-enhancement is reported due to the central necrosis and peripheral angiogenesis in the literature. (17) As malignant tumor, leukemic involvement shows attenuated diffusion on diffusion weighted imaging (DWI) and the ADC values are low secondary to high cellular density. Malignant lesions are hyperintense on DWI images and hypointense on ADC maps; necrotic areas are hyperintense in both DWI and ADC maps. (17)

In any case, mammographic and sonographic features of breast and leukemia lymphomas are nonspecific and indistinguishable from other breast malignancies; therefore, a specific diagnosis cannot be made solely on the basis of these modalities.

Histologically, breast lymphoma and leukemia are classified in terms of tumor architecture as well as the predominant cell type observed at histologic examination. Histologic features suggestive of lymphomatous involvement include absence of in situ carcinoma, frequent individual karyorrhectic cells, lymphoepithelial lesions and cellular discohesiveness. Pathologically, breast lymphomas most commonly appear as well-circumscribed tumours of varying size. On cut surface, the neoplastic tissue is similar to that of lymphomas in other sites, fleshy tan-white, with occasional hemorrhagic or necrotic foci in higher-grade tumours. Although grossly circumscribed, the majority have an infiltrating border, with permeation around lobules and ducts. (8) (Figures 16-18)
Figure 1. A 78-years-old female noticed a painless lump in her right breast. Mediolateral oblique (MLO) and craniocaudal (CC) mammograms reveal an indistinctly marginated high-density area in the upper outer right breast quadrant. Axillary region shows no changes, bilaterally. This corresponds to a primary breast diffuse large B-cell lymphoma.
Figure 2. This patient is a 53-year-old woman submitted to a previous lumpectomy, in the outer upper right quadrant, because of a breast carcinoma five years ago. During a follow-up mammography (MLO and CC views are shown above), one nodular opacity in the upper outer left quadrant, with partially distinct margins, was detected. There are also left axillary and intra-mammary lymph nodes (arrows). Biopsy results revealed diffuse large B-cell lymphoma.

Fig. 2
Figure 3. A previously healthy 42-years-old female was referred to our institution with an unilateral (left) breast enlargement. Sonography shows two dominant heterogeneous masses in the outer (a) and inner (b) upper quadrants of the left breast, with mixed echogenicity, predominantly hypoechoic, lobulated, within a hyperechoic surrounding breast. Skin thickening is also present. Homolateral axillary lymphadenopathy (not shown) coexisted. Right breast ultrasound did not document lesions. Biopsy was performed, revealing diffuse large B-cell lymphoma.
Figure 4. Thoracic plain radiography of the same patient of figure 3 (postero-anterior (a) and lateral (b) views) shows asymmetric breast shadow conditioned by left breast enlargement. Contrast-enhanced CT (c-coronal, d- axial) demonstrates a voluminous left breast (partially intercepted) and left axillary lymphadenopathy (arrow). Note that there is no lymphadenopathy on the right side. The remaining thoracic, abdominal and pelvic CT did not show correlated alterations. However, this patient also presented facial paresthesia and brain MRI documented cerebral lymphomatous involvement.

**Fig. 4**
Figure 5. Chest radiography of a different patient (a 69-years-old woman) (a) also reveals assymmetric breast shadow, conditioned by right breast enlargement, as well as contrast-enhanced (b) and non-enhanced (c) axial CT. This woman was also previously asymptomatic, presenting a recent onset of breast swelling. Breast biopsy revealed diffuse large B-cell lymphoma. Bone marrow and brain evaluation were normal and lactate dehydrogenase was increased.
Figure 6. A 34-years-old pregnant women (17weeks of gestation) presented unilateral (right) breast swelling. Mamography (MLO and CC views) reveals skin thickening and diffuse increased parenchymal density in the right breast. Biopsy revealed inflammatory invasive carcinoma. Breast ultrasound and MRI are shown in figure 7.

Fig. 6
Figure 7. Breast sonography (from the patient of figure 6 with an inflammatory invasive carcinoma) documents marked structural heterogeneity involving different quadrants and grossly nodular areas with lower echogenicity (a). T1weighted (w) (b) and T2w (c) MRI before contrast administration demonstrate skin thickening and architectural disorganization. In post-contrast MRI this area avidly enhances in early post-contrast images (d).
Figure 8. Breast sonography shows a heterogeneous mixed hyper and hypoechoic area, irregular in shape, with an indistinct margin. Posterior acoustic enhancement is also present. There was no axillary lymphadenopathy. This corresponds to a primary breast diffuse large B-cell lymphoma in a 78-years-old woman, whose mammography is represented in figure 1.
Figure 9. Breast ultrasound (a) presents a heterogeneous nodule, with central anechoic and peripheral hyperechoic areas in a 53-year-old woman with breast diffuse large B-cell lymphoma, whose mammography is shown in figure 2. This patient also referred gait abnormalities, conditioned by lymphomatous brain involvement, shown in coronal T2w MRI (b).
Figure 10. Ultrasound findings in different breast lymphomas. Screening mammography demonstrated one nodule in a 70-year-old woman, whose ultrasound appearance is represented in (a); biopsy results showed breast follicular lymphoma. In another patient, with a previously known diffuse large B-cell lymphoma, secondary breast lymphomatous involvement expresses as multiple irregular hypoechoic nodules distributed in the right breast (b-d).

Fig. 10
Figure 11. A 47-years-old patient with gastric adenocarcinoma (total gastrectomy 3 years ago) resorted to the emergency department with painful hardening in the right breast. Mammography (CC and MLO views) shows heterogeneous undefined high density area in the upper right quadrants. Right axillary adenopathy is also evident (arrow), as well as skin thickening. Biopsy demonstrated metastatic involvement by gastric adenocarcinoma.

Fig. 11
Figure 12. Complementary breast ultrasound shows a voluminous heterogeneous mass in the upper quadrants (a-c), with mixed hyper and hypoechoic areas, corresponding to metastatic involvement by gastric adenocarcinoma. Skin thickening is also present. Right axillary adenopathy is shown in (d).

Fig. 12
Figure 13. Screening mammography (CC and MLO views) shows one ill-defined lesion in the transition of the outer left quadrants. This patient is a 51-years-old female with previously diagnosed acute myeloid leukemia and breast leukemic involvement.
Figure 14. Sonography appearance of diffuse leukemic breast involvement in a 36-year-old patient with known acute myeloid leukemia. Few months after inaugural diagnosis she presented with hard breast swelling, bilaterally, confirmed by biopsy to correspond to leukemic infiltration.
Figure 15. This sonography shows the lesion of figure 13, presenting as mixed echogenicity, centrally anechoic with peripheral hyperechoic rim. Posterior acoustic enhancement is also present. Histological analysis was consistent with acute myeloid leukemia involving breast tissue.
Figure 16. Breast ultrasound (a) in a 34-years-old woman with left breast lump. A slightly hypoechoic nodule, relatively well-defined, is shown in the transition of upper left quadrants (arrow). Biopsy revealed an extramedullary myeloid tumor. Lumpectomy was performed (b). The patient was asymptomatic with normal analytic study. Bone marrow analysis revealed normocellular marrow, without excess of immature cells but with some atypia.
Figure 17. Photomicrographs (from the patient of figure 16) show breast tissue infiltration with densely cellular proliferation, in an infiltrative growth pattern (a); mammary ducts are obliterated by tumor cells, with thickened basal membrane (b).
Figure 18. (continuation) Cells are small and ill-defined, with intermediate nuclei, round to oval, inconspicuous nucleoli and scanty cytoplasm (a). Some cells demonstrate eosinophilic intracytoplasmatic granules (b). Infiltrative growth pattern "single file"-like is seen (c).

Fig. 18
Conclusion

In a patient with a known malignancy any enlarging breast mass, even with benign sonographic appearance, should be investigated carefully. Although breast lymphoma and leukemia constitute rare breast lesions, it is important to be familiar with these entities in order to contribute to their appropriate management after the initial biopsy.

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Personal Information

mariapinheiromagalhaes@hotmail.com