Hematologic Malignancies of the Breast: A Contemporary Series Investigating Incidence, Presentation, Accuracy of Diagnosis on Core Needle Biopsy, and Hormone Receptor Expression

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ABSTRACT

BACKGROUND: Distinguishing breast hematologic malignancies in core needle biopsies from other entities can be challenging. Misclassification as a breast carcinoma could result in inappropriate treatment. The aim of this study was to characterize the types, incidence, and helpful diagnostic features of hematologic malignancies of the breast.

DESIGN: All hematologic malignancies of the breast diagnosed at our institution from 2004 to 2017 were identified. Clinical notes, imaging, and slides were reviewed. Immunohistochemical analysis of estrogen receptor α (ERα), estrogen receptor β (ERβ), and androgen receptor (AR) was performed when tissue was available.

RESULTS: In all, 43 hematologic malignancies from biopsies of 37 women and 6 men were identified. Core needle biopsies (35 or 81%) were more common than excisions (8 or 19%). For 14 patients (40%), the core biopsy was the first diagnosis of a hematologic malignancy. Diagnoses included 37 lymphomas (7 primary), 4 leukemias, and 2 myelomas. There was 1 misdiagnosis of carcinoma. Low positivity for hormone receptors was observed in a minority of lymphomas. A definitive diagnosis of hematologic malignancy was made in 31 (89%) of the core needle biopsies. Only 3 patients undergoing core biopsy required excision for diagnosis.

CONCLUSIONS: Most of the hematologic malignancies of the breast are currently diagnosed on core needle biopsy and 40% of patients do not have a prior history. To avoid errors, pathologists need to be aware of diagnostic features and morphologic mimics. A hematologic malignancy should be considered if tumor cells are discohesive, carcinoma in situ is absent, and hormone expression is low or absent.

KEYWORDS: breast hematologic malignancies, breast lymphoma

Introduction

Hematologic malignancies involving the breast are very rare, comprising less than 1% of all breast tumors.[1] Image-guided core needle biopsy is the standard initial method of tissue sampling for breast lesions. However, this type of biopsy could potentially create challenges for accurate diagnosis given the limited size of the sample and the broad differential diagnosis for hematologic malignancies including normal structures (lymph nodes), inflammatory lesions, reactions to trauma, autoimmune disease, normal physiologic infiltrates, carcinomas, and lymphocytic responses to carcinomas.

It is important for diagnosis to be accurate as most of the patients with hematologic malignancies do not require surgery for treatment.[2] Misdiagnosis as carcinoma could lead to breast and nodal surgery as well as inappropriate systemic therapy. Some breast carcinomas closely resemble lymphomas. For example, lobular carcinomas infiltrate as single cells and tumor cells can closely resemble lymphocytes.[3] The reported

expression of hormone receptors by some breast lymphomas could also make diagnosis difficult.[4,5] In 1 study, 7 of 41 breast hematologic malignancies (17%) were misdiagnosed as carcinomas.[6] Some of the lymphomas in this study showed frequent signet ring cells and resembled lobular carcinomas.

In older series, most of the breast hematologic malignancies were diagnosed on excisional specimens or mastectomies.[4] This study of a contemporary series of hematologic malignancies of the breast diagnosed at a single institution was undertaken to determine the current type of biopsy used for diagnosis, to describe diagnostic features and possible pitfalls, evaluate accuracy of diagnosis, and to determine expression of hormone receptors.

Materials and Methods

After institutional review board approval, pathology reports of breast specimens accessioned at our institution between December 1, 2004 and June 30, 2017 were searched for the

terms "lymphoma," "leukemia," "Hodgkin," and "myeloma." For comparison, cases of lymphocytic (diabetic) mastitis, T-cell lymphocytic lobulitis, amyloidosis, intramammary lymph nodes, and known or suspected IgG4 sclerosing mastitis were also identified. Consult cases received for a second diagnostic opinion were not included. Pathology reports, breast imaging reports, and clinical records were reviewed. Glass slides were reviewed when available.

For cases of lymphoma with paraffin blocks and sufficient tissue available, immunoperoxidase studies for estrogen receptor α (ERα), estrogen receptor β (ERβ), and androgen receptor (AR) were performed. Immunohistochemistry was performed on 4-μm-thick paraffin-embedded tissue sections following pressure cooker antigen retrieval in citrate buffer (pH 6.1; Dako Target Retrieval Solution, Dako, Carpinteria, CA, USA) using a rabbit anti-estrogen receptor alpha monoclonal antibody (clone SP1; 1:50 dilution; Thermo Fisher Scientific, Waltham, MA, USA), a mouse anti-estrogen receptor beta monoclonal antibody (clone 14C8; 1:50 dilution; Abcam, Cambridge, MA, USA), and a mouse anti-AR monoclonal antibody (clone AR441; 1:200 dilution; Dako). Dako Envision + secondary antibody was used. The sections were developed using 3,3′-diaminobenzidine as substrate and counterstained with Mayer hematoxylin. A semi-quantitative score was used to evaluate the results for each antibody. Normal breast epithelial cells in the core needle biopsies were used as a positive internal control for ERα, ERβ, and AR.

Cases were classified as primary breast lymphoma if they met the following criteria: (1) adequate pathology specimen, (2) close association of the lymphomatous infiltrate and breast parenchyma, (3) no widespread lymphomatous infiltrate at the time of diagnosis, with the exception of the ipsilateral axillary lymph node(s), and (4) no prior history of extra-mammary lymphoma.[7] Cases were included if there was no breast parenchyma, but the imaging study reported the lesion was in the breast and no microscopic evidence of a lymph node was seen.

Results

In the 12 and a half years of this study, 43 hematologic malignancies of the breast were diagnosed. Of the procedures, 35 (81%) were core needle biopsies and 8 (19%) were excisions. Excisions were only performed when a core needle biopsy could not be performed (2 cases), a prior core needle biopsy was nondiagnostic (1 case), or to confirm the diagnosis of a residual or recurrent hematologic malignancy of the breast after treatment (5 cases). The incidence of hematologic malignancy on core needle biopsy was 0.2% (35 of 16 590 breast core needle biopsies) and comprised 0.8% of malignancies (35 of 4166 breast malignancies on core needle biopsy).

Of the hematologic malignancies, 42 were present in breast parenchyma. In only 1 case was an intramammary lymph node involved by a lymphoma.

Diagnoses included B-cell lymphoma (31 cases), T-cell lymphoma (6 cases), leukemia (4 cases), and myeloma (2 cases; Table 1). Most of the patients (37 of 43 or 86%) were women. There were only 6 men and all had diffuse large B-cell lymphoma (DLBCL). Ages ranged from 35 to 89 (mean 62 years) and most of the patients were in the 6th to 7th decades of life.

Of the 43 patients, 25 (58%) had a prior history of a hematologic malignancy. For 14 of 35 patients (40%) undergoing core needle biopsy, this was their first diagnosis of a hematologic malignancy. A first diagnosis of lymphoma was also made for 2 of the 8 patients (25%) undergoing excision. These patients did not have clinical features that would have raised suspicion for a hematologic malignancy such as B symptoms (fever, night sweats, and weight loss) or diffuse lymphadenopathy.

Most of the hematologic malignancies were detected as palpable masses, followed by masses detected on mammographic screening (Table 1). For 5 patients who had a history of a hematologic malignancy, the breast mass was discovered on imaging performed as part of their work-up or surveillance. The lesions were not associated with calcifications. Margins were described as irregular, ill-defined, or circumscribed. There were no radiologic features that specifically identified the lesions as hematologic malignancies.

Of the 35 core needle biopsies, 32 were performed under ultrasound guidance; 2 were stereotactic guided for an asymmetry and for an irregular mass without a sonographic correlate. One was a manual tru-cut core needle biopsy for a palpable mass. Most of the core needle biopsies (31 of 35 or 89%) were performed with a 14-gauge needle.

Of the 31 B-cell lymphomas, 7 (23%) were primary in the breast. These included 5 DLBCL, 1 marginal zone lymphoma (MZL), and 1 unclassified low-grade B-cell lymphoma; 6 presented as palpable masses and 1 was detected by mammographic screening; 5 occurred in women and 2 in men.

Immunoperoxidase studies for hematologic markers were performed in all cases, with an average of 9.5 immunostain per case. In some cases, cytogenetic studies (17 of 43 cases) and/or flow cytometry (15 of 43 cases) were also performed. A definitive diagnosis was determined for all 8 excisional biopsies. For patients undergoing core needle biopsy, a definitive diagnosis was provided in 89% of cases (31 of 35). In 4 cases (4 of 35 or 11%), the lymphoid infiltrate was considered atypical, but a definitive diagnosis of lymphoma could not be rendered. Two of the patients did not have a prior history of lymphoma. Both underwent a subsequent excisional biopsy, 1 showing a MZL and 1 showing a low-grade B-cell lymphoma that was not further classified. Both of the other patients had a history of follicular lymphoma (FL). Excisions were not performed because a more certain diagnosis would not have changed clinical management. In 1 of the 35 cases, a large B-cell lymphoma was misdiagnosed as carcinoma, and this case will be discussed later. Therefore, of the diagnoses on core needle biopsy, 86%

Table 1. Hematologic malignancies of the breast undergoing core needle biopsy or excision at our institution.

DIAGNOSIS	NO.	SEX (F/M)	AGES (RANGE)	PRESENTATION[a]	DIAGNOSTIC BIOPSY		PRIMARY OR SECONDARY B-CELL LYMPHOMA[b]		MEAN SIZE (CM; RANGE)	FIRST DX CORE BIOPSY[c]
					CORE	EXCISION	PRIMARY	SECONDARY		
Non-Hodgkin lymphomas										
Diffuse large B cell	14	8/6	Mean 69 (35-88)	12 palpable, 2 imaging	10	4	5	9	3.4 (1-9)	7
Marginal zone	7	7/0	Mean 61 (47-89)	4 palpable, 3 screening	7	0	1	6	3.5 (1.6-5.3)	5
Follicular[d]	4	4/0	53, 59, 64, 65	3 screening, 1 imaging	4	0	0	3	1.1 (0.4-2)	0
Mantle cell	2	2/0	61, 67	1 palpable, 1 imaging	2	0	0	2	1.3, 2.0	0
Lymphoma, not specified	3	3/0	63, 66, 77	3 screening	2	1	1	2	1.2, 1.3, 1.5	0
Small lymphocytic	1	1/0	74	1 screening	1	0	0	1	2.2	0
T cell	4	4/0	38, 48, 72, 83	4 palpable	3	1	NA	NA	2.7 (2.2-3.5)	1
Breast implant-associated T cell	2	2/0	46, 57	2 palpable	0	2	NA	NA	4.3, 8	NA
Leukemias										
Acute	3	3/0	46, 51, 69	3 palpable	3	0	NA	NA	1.5, 1.5, 2.7	0
Hairy cell	1	1/0	49	1 palpable	1	0	NA	NA	2	1
Other										
Myeloma	2	2/0	46, 60	1 palpable, 1 imaging	2	0	NA	NA	2.0, 2.0	0
Total	43	37/6	Mean 62 (35-89)	28 palpable, 10 screening, 5 imaging	35	8	7	24	1.9 (0.4-9)	14 (40%)

NA: not applicable; F/M: female/male.

[a]Presentation was as a palpable mass detected on mammographic screening or detected on other types of imaging.

[b]Primary breast lymphomas were limited to the breast. Involvement of ipsilateral axillary nodes was allowed. Patients were excluded if they had a history of a hematologic malignancy or were found to have widespread involvement on further work-up.

[c]First diagnosis on core needle biopsy. These patients did not have a prior history of a hematologic malignancy. For some of these patients, subsequent studies showed other sites of disease. Two of the 8 excisions were the first diagnosis of lymphoma. In 1 case, a prior core needle biopsy performed at another institution was suspicious for lymphoma. The second patient could not undergo core needle biopsy due to the posterior location of the lesion.

[d]Three of the patients with follicular lymphoma had involvement of breast parenchyma. In 1 case, the lymphoma involved an intramammary lymph node.
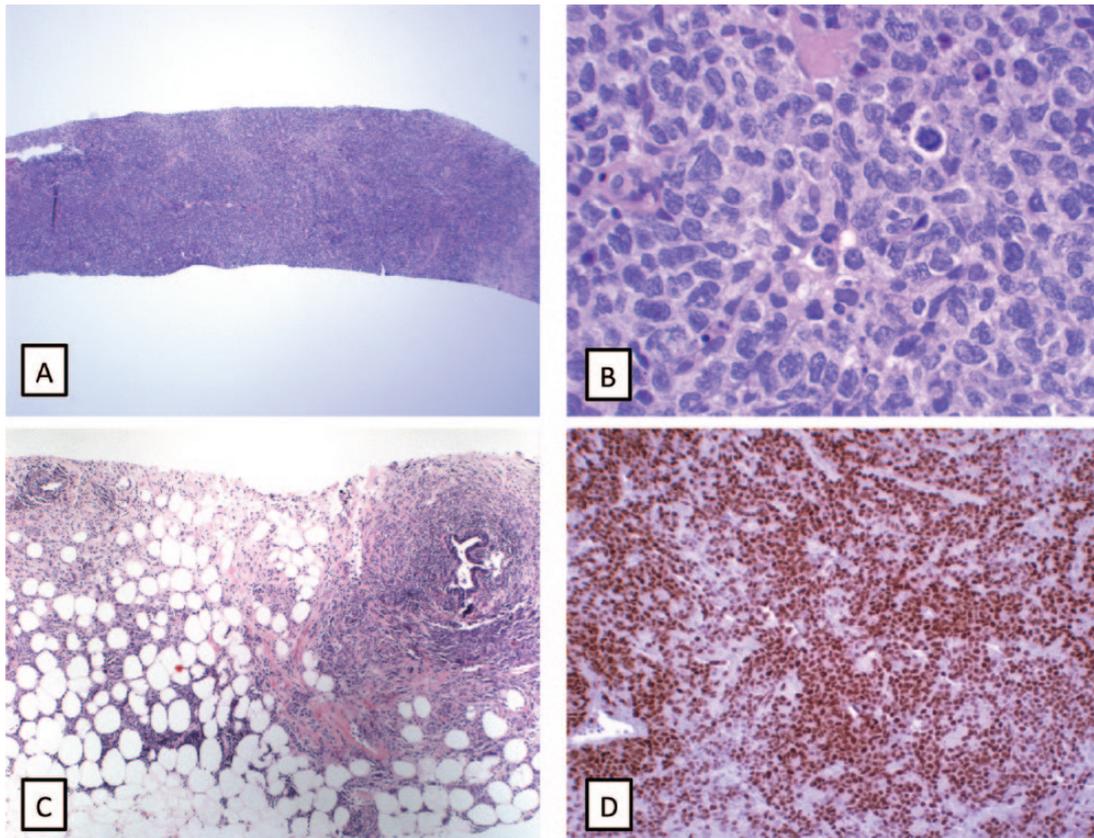
Figure 1. Diffuse large B-cell lymphoma (DLBCL). (A) DLBCL typically involved most of the core needle biopsy (20×, H&E). Breast epithelium was often absent or only present focally at the periphery of the biopsy. (B) The tumor cells had pleomorphic nuclei and numerous mitotic figures were present (400×, H&E). (C) This DLBCL was initially mistaken for an invasive carcinoma (40×, H&E). Unlike other cases, this lymphoma invaded around breast epithelium and into adipose tissue, rather than forming solid areas of tumor cells. (D) This DLBCL shows strong diffuse nuclear immunoreactivity for p63 and does not express keratin (100×, immunohistochemical study for p63 and keratin AE1/AE3). H&E indicates hematoxylin and eosin stain.

were accurate and definitive, 11% were atypical and not definitive, and 1 case (3%) was a misdiagnosis.
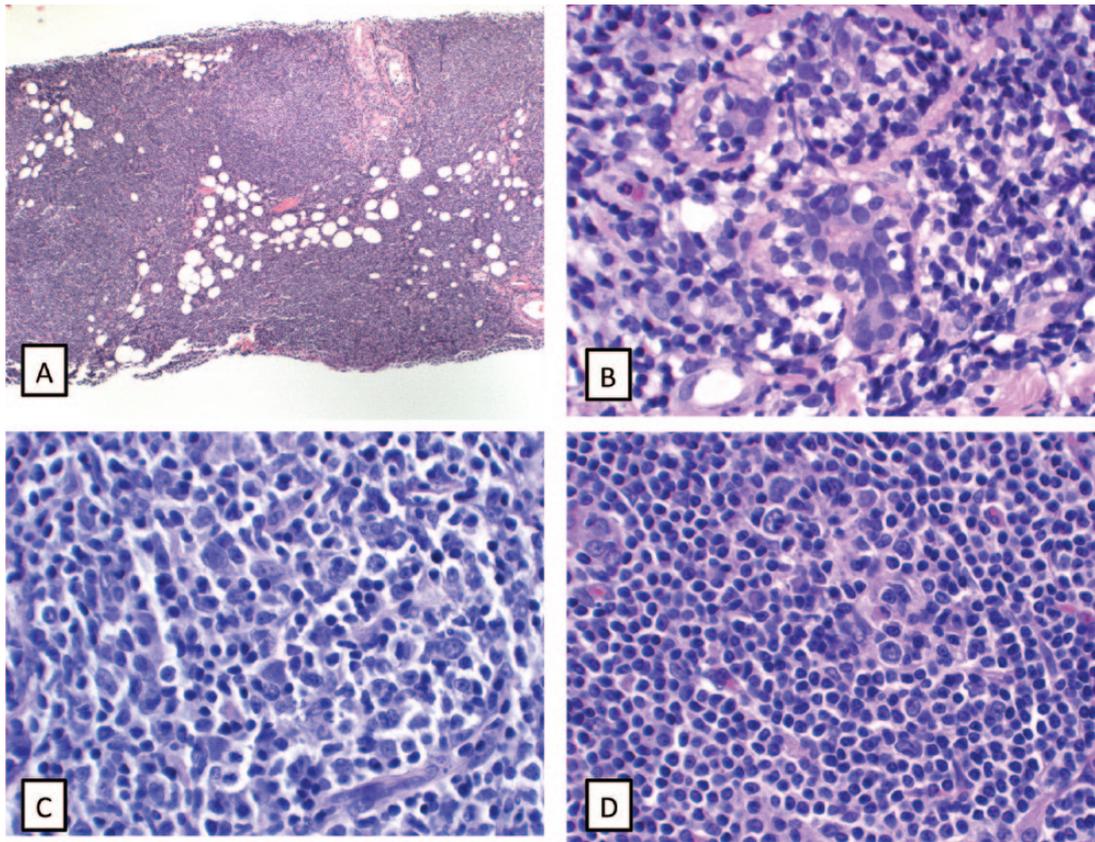
Diffuse large B-cell lymphoma

The most common type of hematologic malignancy was DLBCL, which occurred in 14 patients (Table 1). This was the only lymphoma that involved the breast of males in this study. Seven patients had a prior history of DLBCL and 2 cases were detected on imaging work-up for recurrence or surveillance in patients with a prior history of lymphoma. None of the cases were detected by mammographic screening.

Of the lymphomas, 10 were diagnosed by core needle biopsy, which showed large contiguous areas of involvement by tumor cells ranging from 0.4 to 1.8 cm (mean 1.0 cm; Figure 1A); 4 did not show any breast epithelium, 5 showed only focal areas of breast epithelium (typically at the periphery of the lymphoma), and 1 case had a more extensive area of breast epithelium.

The tumor cells were clearly malignant by H&E, and the differential diagnosis for DLBCL was with other types of malignancies, particularly poorly differentiated lobular carcinoma or metastatic melanoma (Figure 1B). Immunoperoxidase

studies for keratin were performed in 6 of the 10 cases and S100 in 5 cases to exclude carcinoma and melanoma. In the 4 cases without keratin performed, 2 were patients with a prior history of lymphoma and 1 patient had a prior core needle biopsy at an outside institution that was suspicious for lymphoma. The fourth patient did not have a history of lymphoma and was initially misdiagnosed as having an invasive carcinoma that was negative for ER, progesterone receptor, and HER2. The lymphoma differed in appearance from the other cases of DLBCL as the tumor cells infiltrated around breast parenchyma and into fat instead of forming a solid area of involvement (Figure 1C). A diagnosis of DLBCL was made on the excisional specimen. This case has been previously reported as part of a quality assurance study.[8] This was a primary breast lymphoma with no sites of disease detected elsewhere.

In 1 case, a double labeling immunohistochemical study for keratin AE1/AE3 and p63 was performed. The lymphoma showed strong diffuse immunoreactivity for p63 but was negative for keratin (Figure 1D). Prior studies have reported expression of p63 in a subset of B-cell lymphomas.[9,10] Expression of p63 in DLBCL has been reported in 32%-53% of cases and has been associated in some studies with a less favorable prognosis.[11,12]

Figure 2. Marginal zone lymphoma. (A) Most of the core is involved by a diffuse proliferation of small lymphocytes. Occasional residual follicles are present. Scattered plasma cells and a minor population of larger cells were typically present. (B) Breast epithelium was either absent or only focally present. In 2 cases, lymphoepithelial lesions were present but were focal and inconspicuous. (C) In 1 case, scattered larger lymphocytes were present. The findings were not considered sufficient for a diagnosis of high-grade lymphoma. (D) Plasmacytoid features in lymphomas can mimic invasive lobular carcinoma. In 1 case, keratin was performed to exclude carcinoma.

Marginal zone lymphoma

Marginal zone lymphoma (MZL) was the second most common malignancy, occurring in 7 women with 1 woman having bilateral breast involvement (Table 1). Four of the women had a history of autoimmune disease including rheumatoid arthritis, ulcerative colitis, myasthenia gravis, and idiopathic thrombocytopenic purpura.

Microscopically, a lymphocytic infiltrate measuring from 0.3 to 0.8 cm was present (Figure 2A). Residual normal follicles were present in 2 cases. Six of the 7 cases showed scant areas of normal breast tissue. Lesions typically associated with an inflammatory reaction, such as cysts or fat necrosis, were not present. The extent of the infiltrates consisting predominantly of monomorphic lymphocytes favored a neoplastic process in all of the cases.

Lymphoepithelial lesions are predominantly associated with extranodal MZL of mucosa-associated lymphoid tissue (MALT) and can be diagnostically useful in some settings. The lesions consist of a cluster of at least 3 neoplastic lymphoid cells that infiltrate and distort epithelial structures.[13] These lesions are reported to be less common in breast MALT lymphomas as compared with MALT lymphomas at other sites.[14] Focal lymphoepithelial lesions were seen in 3 of

the 7 cases but were small and inconspicuous (Figure 2B). Scattered normal lymphocytes can be seen in ducts in benign conditions with inflammatory cells and, thus, are not a specific feature only seen in lymphoma (Figure 4C). Therefore, these lesions were not helpful for diagnosis in most of the cases.

In 1 case, there was a population of large lymphoid cells and possible transformation of MZL to a higher grade lymphoma was considered (Figure 2C). However, the cells did not form sheet-like aggregates and sufficient features to diagnose transformation were not seen.

The possibility of carcinoma was only considered in 1 case. This lymphoma had a plasmacytoid appearance with occasional cells infiltrating in a single-cell pattern with frequent mitoses (Figure 2D). This was the only primary breast lymphoma in this group. A keratin immunoperoxidase study was performed to exclude the possibility of invasive lobular carcinoma.

Follicular lymphoma

Four cases of FL were diagnosed in women, 3 occurring in the breast and 1 in an intramammary node (Table 1). All of the patients had a history of FL.
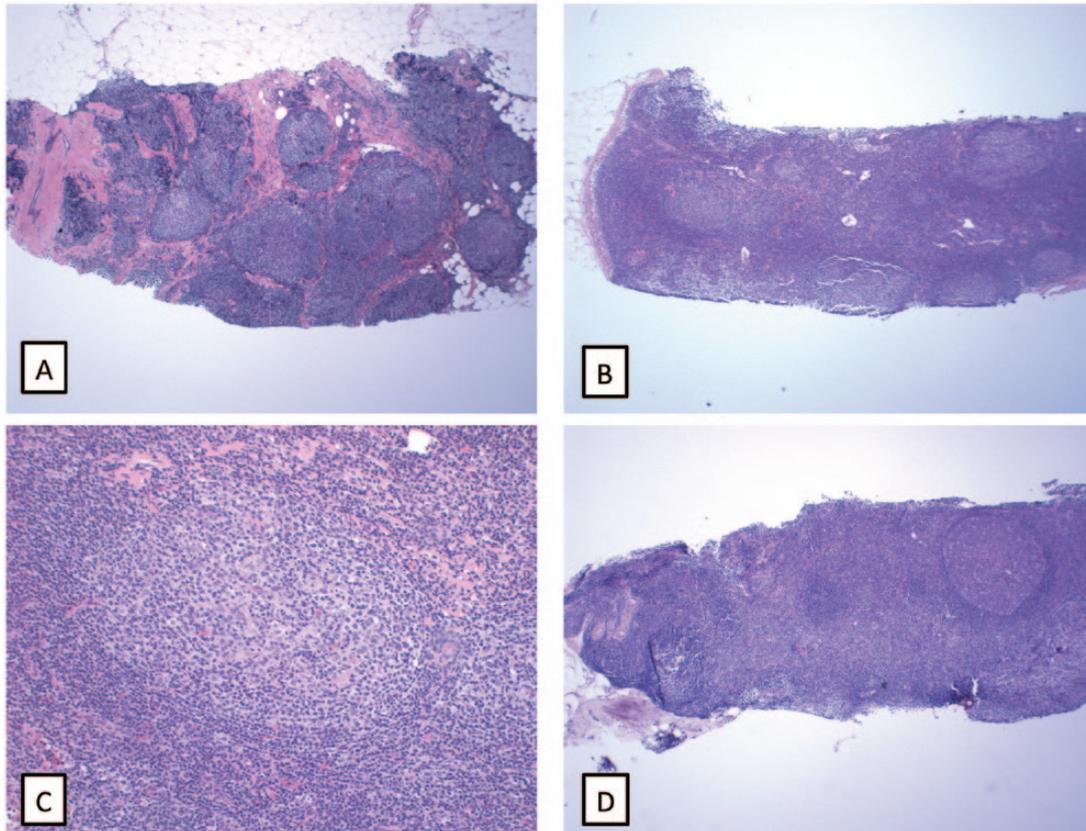
Figure 3. Follicular lymphoma. (A) This follicular lymphoma surrounds breast epithelium but also extensively involves interlobular stroma (40×, H&E). Neoplastic follicles are present. (B) This intramammary lymph node involved by follicular lymphoma shows numerous closely spaced follicles (20×, H&E). (C) A neoplastic follicle of follicular lymphoma lacks tingible body macrophages and mitoses are absent (100×, H&E). (D) This reactive lymph node shows enlarged normal germinal centers (20×, H&E). H&E indicates hematoxylin and eosin stain.

The tumor cells infiltrated around breast epithelium but also formed sheets of cells in the intervening stroma (Figure 3A). The intramammary node was a 0.5 cm breast mass detected by mammographic screening. The mass could be documented as a lymph node due to the presence of the capsule. The neoplastic follicles in the node were more closely spaced than typical for reactive lymph nodes (Figure 3B). The follicles generally lacked tingible body macrophages and mitoses were absent or rare (Figure 3C). The appearance could be distinguished from a reactive intramammary lymph node with prominent normal germinal centers (Figure 3D). There was focal adjacent normal breast tissue.

Because the FLs were low grade and comprised small monomorphic lymphocytes associated with neoplastic follicles, carcinoma and melanoma were not considered as possible diagnoses and immunoperoxidase studies for keratin or S100 were not performed.
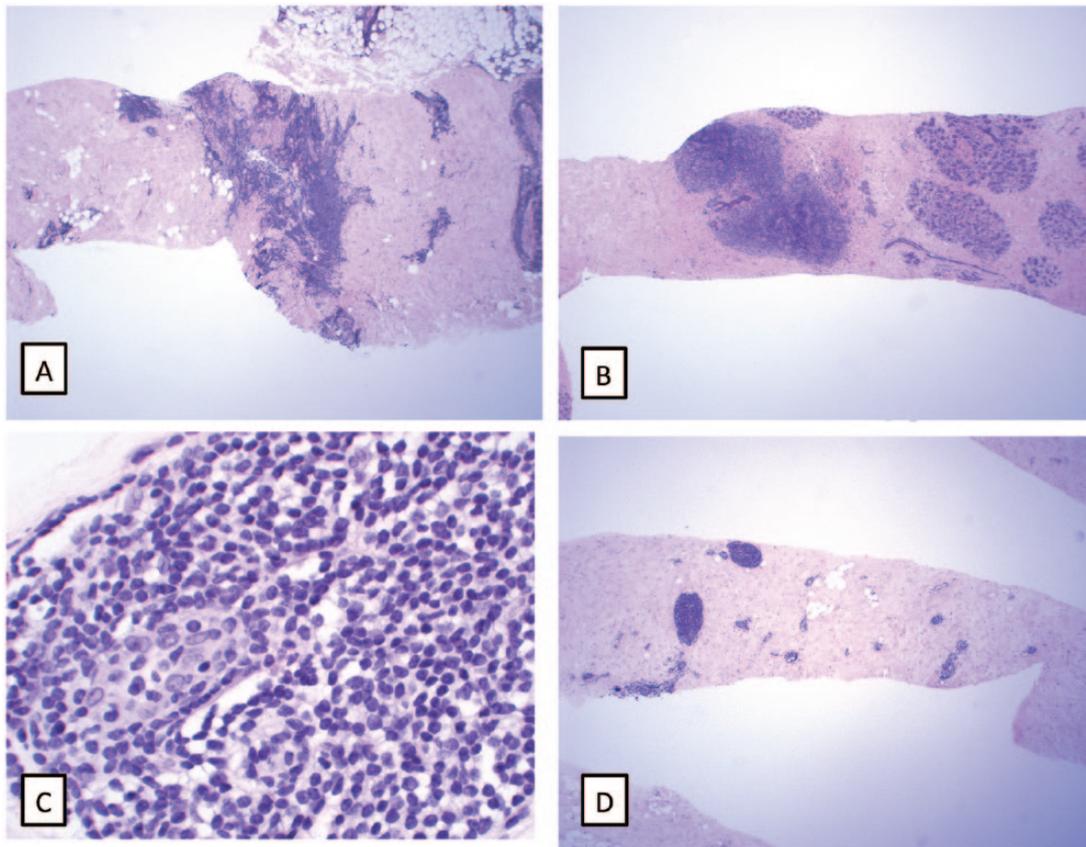
Mantle cell lymphoma

There were 2 cases of mantle cell lymphoma occurring in the breasts of 2 women with a prior history of mantle cell lymphoma (Table 1). Both cases showed dense lymphoid infiltrates composed of small cells with slightly irregular nuclei, involving contiguous areas of the cores measuring 1 and 1.2 cm. There was only scant normal breast epithelium, which was only focally involved by tumor cells. Keratin and S100 were not performed as the histologic appearance was consistent with the known lymphoma and confirmed by immunohistochemical studies for lymphocytic markers.

Small lymphocytic lymphoma

One case of small lymphocytic lymphoma (SLL) was diagnosed in the breast of a 74-year-old woman with a history of chronic lymphocytic leukemia (Table 1). The tumor cells surrounded ducts, lobules, and blood vessels and also involved intervening breast stroma (Figure 4A). The stroma was dense, but did not have a paucicellular collagenous appearance. The breast epithelial elements did not appear atrophic.

The pattern of lymphocytic infiltrates centered on epithelium and vascular spaces raises the differential diagnosis of other similar lesions including lymphocytic mastopathy (also known as sclerosing lymphocytic lobulitis and diabetic mastopathy), T-cell lymphocytic lobulitis, and reactive infiltrates after pregnancy and lactation.

Figure 4. (A) Small-cell lymphocytic lymphoma involving the breast surrounds epithelium but also extends into the interlobular stroma (20×, H&E). The epithelium is not atrophic and the stroma appears normal. (B) In lymphocytic mastopathy, clouds of lymphocytes surround atrophic lobules and blood vessels (20×, H&E). The stroma is densely hyalinized. (C) Lymphocytes can involve epithelium in benign lesions, such as in this case of lymphocytic mastopathy. Therefore, this finding is not specific for lymphomas. (D) T-cell lymphocytic lobulitis is seen as lymphocytes surrounding lobules (20×, H&E). Blood vessels are not involved. The stroma and non-involved lobules appear normal. H&E indicates hematoxylin and eosin stain.

For comparison, over the time period of this study, 25 women were diagnosed with lymphocytic mastopathy on core needle biopsy. In contrast to the case of SLL, in lymphocytic mastopathy, the lymphocytic infiltrates were always centered around epithelium and blood vessels, the intervening stroma had a dense glassy collagenous appearance, and the epithelium appeared atrophic (Figure 4B). Extensive involvement of breast stroma by the lymphocytic infiltrate was not seen. Occasional lymphocytes were present within epithelium, resembling lymphoepithelial lesions (Figure 4C). The lymphocytes associated with lymphocytic mastopathy are predominantly B cells.[15,16] Although lymphocytic mastopathy is often associated with diabetes or autoimmune thyroid disease, 9 of the 25 women (36%) did not have such a history. In addition, autoimmune disease can also be associated with lymphoma.[17]

In the same time period, 1 case of T-cell lymphocytic lobulitis was seen on core needle biopsy. A dense infiltrate of T cells surrounded normal appearing lobules in normal stroma (Figure 4C). The lymphocytes did not involve the intervening stroma and did not surround blood vessels. This lesion may be seen in women with BRCA1 mutations and/or who have triple-negative carcinomas.[18,19] The lesion lacks the vascular involvement and hyalinized stroma of lymphocytic mastopathy and does not typically involve interlobular stroma like SLL.

Reactive lymphocytic infiltrates can be seen associated with lobules during regression after pregnancy. However, these infiltrates do not form masses and are generally seen as an incidental finding in a biopsy for another lesion. Therefore, these lesions are unlikely to be confused with a lymphoma.

Unclassified low-grade B-cell lymphoma

Three women were found to have non-palpable breast masses on mammographic screening measuring from 1.2 to 1.5 cm (Table 1). One woman had a prior history of a low grade B-cell lymphoma and the core needle biopsy was consistent with breast involvement. The other 2 women did not have a history of lymphoma. A definitive diagnosis could not be made on the core needle biopsy for 1 of these women because the infiltrate consisted of both B and T cells and immunoperoxidase studies were inconclusive. As previously discussed, a subsequent breast excision showed diagnostic features of a low grade B-cell lymphoma.

The mass detected in the third woman was too posterior to be sampled by core needle biopsy. She underwent a wire-localized excision showing a low grade lymphoma. This was a primary breast lymphoma.

T-cell lymphoma

Four T-cell lymphomas not associated with breast implants were diagnosed; 2 patients had a history of cutaneous T-cell lymphoma and 1 had a history of human T-lymphotrophic virus I (HTLV-I) lymphoma/leukemia.

The core biopsies showed dense infiltrates of small- to intermediate-sized lymphocytes with irregular to folded nuclear contours forming solid masses in the core biopsies measuring 0.5 and 1.5 cm. Breast epithelium was only present at the periphery. The tumor cells were uniform in appearance with scant cytoplasm and carcinoma was not considered.

The fourth patient's first diagnosis of a T-cell lymphoma was on the core needle biopsy performed when she presented with a 3.5 cm palpable mass. Intermediate to large tumor cells with irregular nuclei and moderate amounts of cytoplasm infiltrated in fibroadipose tissue over a 1.6 cm area. Carcinoma was considered in the differential diagnosis and a keratin immunoperoxidase study was performed. Subsequent testing showed positivity for HTLV-I and the diagnosis was revised HTLV-I leukemia/lymphoma.

Although a pattern of T-cell lymphomas surrounding breast lobules that could mimic SLL, lymphocytic mastopathy, or T-cell lymphocytic lobulitis has been reported, this pattern was not seen in this study.[20]

Breast implant–associated anaplastic large-cell lymphoma

Two women had a history of anaplastic large-cell lymphoma arising in the context of breast implants (Table 1). The original diagnoses were at outside hospitals. Both women had undergone chemotherapy with subsequent relapse. Excisions were performed to confirm the diagnosis and for palliation of large breast masses refractory to treatment.

Leukemias

Four women were diagnosed with leukemia involving the breast, all presenting as palpable masses (Table 1). Three of the women had a history of acute myelogenous leukemia treated with bone marrow transplant, and the breast involvement was a relapse. The tumor cells infiltrated around breast epithelium and closely resembled invasive lobular carcinoma (Figure 5A). However, unlike lobular carcinoma, the tumor cells were closely apposed to the epithelium. Lobular carcinomas more typically infiltrate in collagen in a concentric or targetoid pattern around ducts with stroma separating files of tumor cells. Keratin studies were performed in 2 of the 3 cases to exclude carcinoma.

The fourth patient presented with a palpable breast mass and was diagnosed with hairy cell leukemia (HCL). This case has been reported previously and is the first case of HCL localized to the breast without other sites of involvement.[21] The tumor cells occupied a 1 cm area with breast epithelial elements only at the periphery. The cells had a nested pattern, abundant cytoplasm, and low-grade nuclei suggestive of alveolar or solid invasive lobular carcinoma (Figure 5B). The epithelioid variant of myofibroblastoma was also considered. Keratin was performed and excluded carcinoma.

Myeloma

Two women with a history of plasma cell myeloma were found to have 2 cm breast masses (Table 1). Both of the lesions showed diffuse infiltration of stroma by plasma cells over areas measuring 0.6 and 0.8 cm in the core biopsies (Figure 5C). Breast epithelial cells were present at the periphery. No amyloid was seen.

For comparison, during the period of this study, 5 women were diagnosed with amyloid of the breast on core needle biopsy. Of the biopsies, 3 were performed for mammographic calcifications and 2 for an ill-defined mass. In only 2 of the cases was the amyloid associated with a lymphocytic infiltrate (Figure 5D). Neither of these women was found to have systemic disease on further work-up. Only 1 of the 5 patients with amyloid was found to have a monoclonal gammopathy.

Hormone receptor expression of lymphomas

Paraffin blocks with sufficient tissue were available for 18 cases of breast lymphomas from 14 women and 4 men. Cases included 16 B-cell lymphomas: 8 DLBCL, 2 MZLs, 2 FLs, 2 mantle cell lymphomas, 1 SLL, and 1 unclassified low-grade B-cell lymphoma. Two T-cell lymphomas were also studied: 1 cutaneous T-cell lymphoma and 1 HTLV-1 lymphoma/leukemia. Four cases qualified as primary breast lymphomas: 3 DLBCL and 1 MZL. The primary breast lymphomas occurred in 2 women and 2 men.

Low positivity for ERα was observed in a minority of cases: 4 cases showed weak-to-moderate staining in 1%-10% of lymphoma cells. Most cases were negative (0% in 7 cases and <1% in 7 cases). Seven cases showed faint nuclear staining for ERβ, but scoring was rendered difficult by the weakness of the signal. Four cases showed weak positivity for AR in 1%-5% of cells, the remaining of cases showing no staining (0%).

Discussion

This is the largest contemporary series of hematologic malignancies of the breast with most of the cases diagnosed by core needle biopsy. Similar to previous studies, DLBCL was the most common type, followed by other types of B-cell lymphoma, T-cell lymphoma, leukemia, and myeloma.[1,6,20]

Since the introduction of image-guided core needle biopsy in the 1990s, this has become the preferred method for the initial evaluation of breast lesions. In older series of breast lymphoma, many patients underwent complete excision or mastectomy and some patients underwent lymph node evaluation.[2] Rather than improving outcome, more extensive surgery has
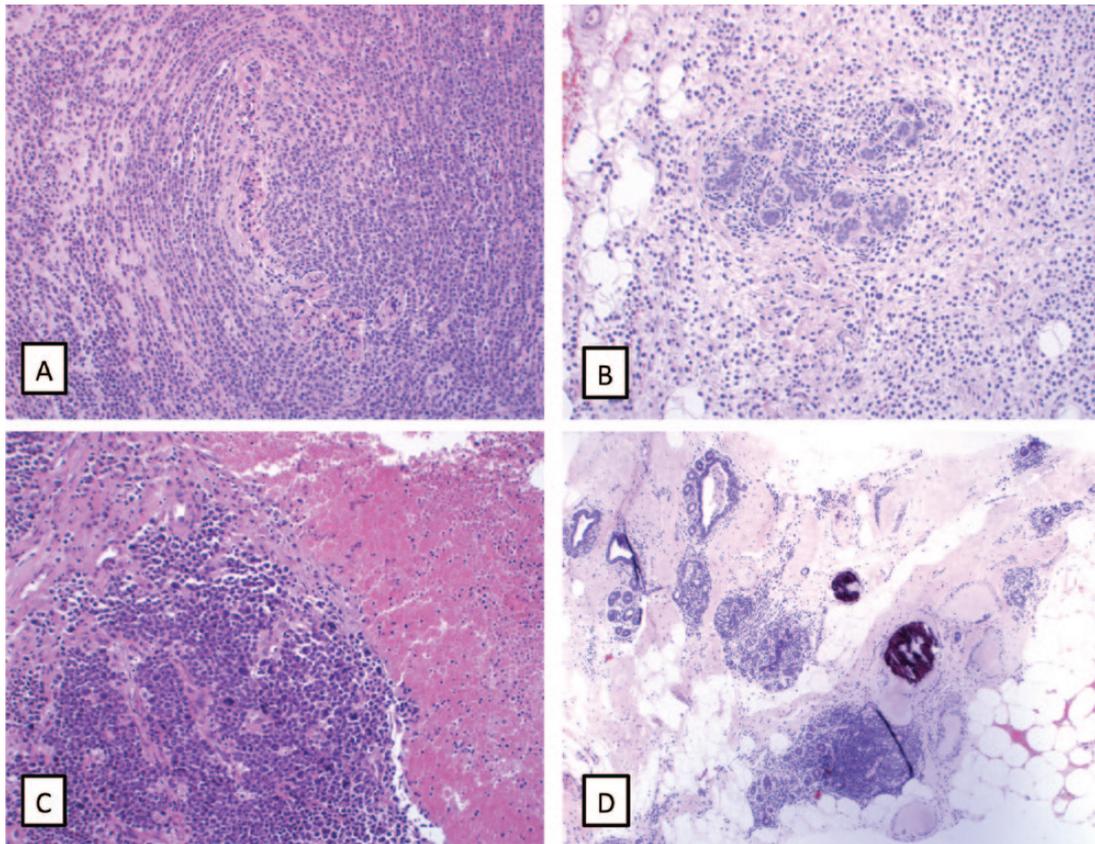
Figure 5. (A) This case of acute myelogenous leukemia resembles invasive lobular carcinoma due to the rounded discohesive cells infiltrating as linear arrays and solid nests (100×, H&E). The tumor cells encircle a duct. Although this pattern is also seen in lobular carcinoma, the tumor cells usually form wider circles in stroma and do not abut the basement membrane. (B) This case of Hairy cell leukemia is present as nests and single cells (100×, H&E). The monomorphic round nuclei are surrounded by a moderate amount of pale cytoplasm. (C) Myeloma involving the breast consisted of markedly atypical plasma cells with nuclear pleomorphism and numerous mitotic figures (100×, H&E). Extensive necrosis was present. (D) Amyloid can be detected on mammographic screening due to the formation of masses or calcifications (40×, H&E). A minority of patients with amyloid in the breast have myeloma. Although focal areas of lymphocytes are present, this patient did not have a monoclonal gammopathy. H&E indicates hematoxylin and eosin stain.

been associated with increased morbidity and an increased risk of death.[22] In this study, core needle biopsy was the initial diagnostic procedure for 36 of the 43 patients (84%, including 1 patient whose core needle biopsy was performed at an outside institution). Excision was used only when core needle biopsy did not yield a definitive result, was not technically feasible or to remove refractory disease after treatment.

Accurate diagnosis of hematologic malignancies is challenging on core needle biopsy due to the limited amount of material and the broad differential diagnosis for inflammatory infiltrates in the breast. In this series, an accurate diagnosis was provided in 86% of cases, an "atypical" diagnosis in 11% of cases, and there was only 1 misdiagnosis (3%).

For patients with a prior history of hematologic malignancy, this diagnosis will be considered by the pathologist and a misdiagnosis is unlikely. For the 29 patients with a prior history, a definitive diagnosis was provided for 27 patients and confirmed breast involvement by the previously diagnosed malignancy. For 2 patients with a history of FL, the findings were considered atypical and suspicious for involvement by the known

lymphoma. Excision for a more definitive diagnosis would not have changed their clinical management and was not performed.

Diagnosis is more problematic for patients without a history of hematologic malignancy due to the frequent lack of clinical or imaging features that would point to this diagnosis. Both breast carcinoma and lymphoma most commonly present in women in the 7th decade. In addition, the 14 patients in this study without a history of hematologic malignancy did not have clinical findings such as B symptoms (fever, night sweats, and weight loss) or diffuse lymphadenopathy that would have been suggestive of lymphoma. Hematologic malignancies have not been reported to have specific imaging features that distinguish them from other breast lesions.[23] Most present as mass forming lesions, as was also seen in this study. It is essential for pathologists to recognize the histologic appearance of hematologic malignancies both to make the correct diagnosis and to avoid unnecessary studies on benign inflammatory infiltrates. Four major histologic patterns were identified that characterized the majority of the cases in this study (Table 2). The

Table 2. Four major histologic patterns of hematologic malignancies involving the breast were identified.

HISTOLOGIC PATTERN	FEATURES FAVORING HEMATOLOGIC MALIGNANCY	HEMATOLOGIC MALIGNANCY TYPES	DIFFERENTIAL DIAGNOSIS
Diffuse involvement of cores by large malignant cells	Discohesive appearance	DLBCL[a]	Lobular carcinoma (grade 2 or 3)
	Solid pattern	Leukemia	Melanoma
	Lack of carcinoma in situ	Myeloma	
	Lack of prominent infiltration by single cells or nests	Breast implant-associated T-cell lymphoma	
Diffuse involvement of cores by small monomorphic cells ± follicles	Extent of involvement large (>0.3 cm)	Follicular lymphoma	Reactive infiltrates
	Absence of lesions associated with inflammatory reactions	Small lymphocytic lymphoma	Lobular carcinoma (grade 1 or 2)
	Monomorphic population of cells	Marginal zone lymphoma	
		Mantle cell lymphoma	
Periductal and perivascular infiltrates	Involvement of intervening stroma	Small-cell lymphocytic lymphoma	Lymphocytic mastopathy
	Monomorphic population	T-cell (some cases) lymphoma	T-cell lymphocytic lobulitis
	Normal appearing stroma	Leukemia	Reactive infiltrates
	Lobules not atrophic		
Diffuse involvement of cores by mixed infiltrate of large and small cells ± follicles ± plasma cells	Extent of involvement large (>0.3 cm)	Marginal zone lymphoma	Reactive infiltrates
	Absence of lesions associated with inflammatory reactions		
	Lymphoepithelial lesions (if prominent)		IgG4-sclerosing mastitis
	No obliterative phlebitis		

Abbreviation: DLBCL, diffuse large B-cell lymphoma.

presence of tumor cells forming the mass detected by palpation or imaging resulted in most of the core biopsies showing diffuse involvement by tumor cells. This was an important feature that helped distinguish hematologic malignances from reactive infiltrates due to other causes. Once an infiltrate is recognized as a malignancy, immunohistochemical studies, and additional studies when necessary, identified the specific type of lesion. For the lesions that were clearly malignant by histologic evaluation, there was only 1 misdiagnosis of a primary DLBCL as an invasive carcinoma. This case had a somewhat unusual pattern of infiltration around breast epithelium that closely mimicked carcinoma, and an immunohistochemical study for keratin was not performed. Lymphoma should be considered in the differential diagnosis for malignancies with a discohesive pattern of infiltration when carcinoma in situ is absent, particularly in the absence of receptor expression.

It is important to note that there are very few benign lesions of the breast in which the lymphocytes form the mass. Other lesions in the differential diagnosis such as physiologic changes (e.g. regression after pregnancy or breastfeeding), reactions to benign epithelial lesions (e.g. cysts) or trauma, lymphocytic

mastopathy, T-cell lymphocytic lobulitis, or lupus mastitis usually show a focal mixed inflammatory infiltrate that is associated with epithelium or stroma and/or fat necrosis. The lymphocytes are typically not the major component of the mass. Most of the hematologic malignancies occupied relatively large areas (several millimeters) of the core needle biopsy as solid areas of tumor cells. When present, the breast epithelium and stroma appeared normal and was often only present focally at the periphery of the lesion.

Most of the breast lymphomas occur in women, contrasting with the generally higher incidence of non-Hodgkin lymphoma in males.[24] In our series, only 6 of the 43 patients were males (14%) and all were diagnosed with DLBCL. Primary breast lymphomas in male are anecdotal; most reported cases are DLBCL, but cases of FL,[25,26] SLL,[27] and MZL[28] have also been reported. This sex-based difference in incidence suggests that hormones may play a role in breast lymphoma pathogenesis.[2,29] The possibility that endocrine therapy could be useful for treatment has also been suggested. Estrogen receptor β has 2 forms designated as α and β. Both forms are expressed in circulating lymphocytes.[30] Estrogen receptor β

expression has been reported in lymphoma cell lines, including Burkitt lymphoma and Hodgkin lymphoma, and in lymphocytes associated with breast cancer.[31] However, the expression of hormone receptors in breast lymphoma has not been extensively studied. In 3 older studies, 4 of 17 (24%) breast lymphomas expressed ERα.[4,5,32] The positive findings were obtained using the dextran-coated charcoal cytosolic assay, whereas a study using immunohistochemistry did not detect expression.

This is the largest series reporting the expression of ERα by immunohistochemistry in breast lymphomas and the first to investigate expression of ERβ and AR. These hormone receptors were not significantly expressed in the 18 breast lymphomas tested, and no differences in expression were found between men and women. Thus, prominent ERα expression has not been seen in any of the 29 breast lymphomas studied using immunohistochemistry.[32]

This contemporary series of breast hematologic malignancies demonstrates that most of the diagnoses are currently made by core needle biopsy and that for 40% of patients this is their first diagnosis. The challenge for low-grade lymphomas is to obtain a definitive diagnosis using a limited specimen and to avoid unnecessary studies on benign reactive inflammatory infiltrates. The challenge for high-grade lesions is to avoid misdiagnosis as an invasive carcinoma, particularly carcinomas of lobular morphology. Thus, pathologists need to be aware of the typical appearance of these lesions and the common mimics and pitfalls as described in this study.

Author Contributions

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