Primary Breast Lymphomas

A Retrospective Analysis of Twelve Cases

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This study was undertaken to define the natural history and treatment results of patients with primary breast non-Hodgkin's lymphoma (NHL). Twelve female patients who had been followed at Hacettepe University Hospital between 1973 and 1997 were retrospectively evaluated. All patients presented with breast masses (6 in the right breast and 6 in the left) that had recently enlarged. The most common histologic subtype was diffuse, small cleaved-cell lymphoma. Chemotherapy regimens were employed in 9 patients. Radiotherapy was delivered to the breast and its lymphatics in 8 patients. Lumpectomy, simple or modified radical mastectomy was performed in 5 cases. An objective response was attained with surgery, chemotherapy, or radiotherapy alone in 2, 1, and 1 cases, respectively. Combined modality treatment including either two or three modalities was successful in 7 cases. The median progression-free and overall survival times were 49 and 56 months, respectively. Although primary NHL of the breast is a rare disease compared to carcinoma, it should be considered in the differential diagnosis of breast masses.

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Breast involvement is a very rare event in extranodal lymphoma. Primary breast lymphomas (PBLs) represent 0.04–0.5% of all malignant tumors of the breast, 0.38–0.7% of all lymphomas, and 1.7–2.2% of all extranodal lymphomas (1–6). Since extranodal presentation is more common in non-Hodgkin's lymphoma (NHL) than Hodgkin's disease (HD), NHLs comprise the majority of PBLs. In our previous series of 470 patients with NHLs, PBLs were diagnosed in 6 patients (1.3%), and 6 of 192 patients (3.1%) with extranodal presentation had the breast as the primary site (7).

In this study, we present our experience in 12 cases and make a brief review of the literature to define the natural course and treatment results of primary breast involvement of NHL.

MATERIAL AND METHODS

Twelve female patients with primary breast lymphoma who had been followed at Hacettepe University Department of Medical Oncology between January 1973 and December 1997 were retrospectively evaluated. The ages of the patients ranged from 17 to 80 years, with a median of 46 years. The median duration of follow-up was 37 months.

The criteria to be fulfilled for a lymphoma to be classified as primary breast lymphoma were defined as follows: lack of previous diagnosis of extramammary lymphoma, close association between mammary tissue and the lymphomatous infiltrate, and no evidence of concurrent widespread disease except homolateral axillary lymph nodes (8).

Charts were reviewed and information on age, evolution of the breast mass, presence of constitutional symptoms, complete blood count, erythrocyte sedimentation rate, blood chemistry, radiological studies, bone marrow examination, pathologic subtype, clinical stage according to the Ann Arbor staging system, therapeutic modalities, response to the treatment, second malignancies, and the cause of death was subtracted.

After completion of therapy, physical examination and the initial laboratory tests were repeated to verify the response. Complete remission (CR) was defined as the total regression of disease for at least two months. Partial remission (PR) was defined as a more than 50% reduction in measurable disease in the same manner. Progression-free survival (PFS) and overall survival (OAS) were evaluated utilizing the Kaplan–Meier method (9).

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RESULTS

The median age in our series was 46 years. All patients were female and presented with breast masses ranging from 1.5 to 15 cm (most were 2 to 5 cm in size, only one patient had bulky disease involving the whole breast). Six patients presented with mass in the right breast, and 6 in the left breast (Table 1). Bilateral masses were not observed. Axillary involvement was present in 7 cases (58.3%). Only one patient had constitutional symptoms. All patients had good performance status (either 0 or 1) according to the ECOG scale.

Complementary to the physical examination of the breast, mammography was obtained in 7 cases (this was diagnostic in 2 patients, suggestive of lymphoma in 2, and non-diagnostic in 3), and ultrasonography of the breast was available in 6 cases (diagnostic in 2 patients, suggestive of a malignancy in 1, and non-diagnostic in 3). Additional staging studies included: chest x-ray (11 cases), abdominal ultrasonography (7 cases), bone marrow aspiration and biopsy (7 cases), liver and spleen scan (5 cases), computed tomography of the abdomen (1 case), and computed tomography of the thorax (1 case). All patients were clinically staged and had biopsy-established diagnoses.

The most common histologic subtype was diffuse, small cleaved-cell (diffuse, poorly differentiated lymphocytic) lymphoma (5 of 12 cases) and the grade according to Working Formulation was intermediate in 9 of our patients. Immunohistochemistry could be performed only in 5 cases, and all had B-cell phenotype.

Either cyclophosphamide, vincristine, prednisone (CVP), or cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) were administered as chemotherapy regimens in 9 patients. Leukopenia and alopecia were the most common side effects. Radiotherapy at doses of 40–60 Gy was delivered to the breast and its lymphatics (axilla and supraclavicular lymphatics) in 8 patients. Lumpectomy, simple or modified radical mastectomy was performed in 5 cases. Among patients who received combined modality therapy, an objective response (CR + PR) was achieved with chemotherapy + radiotherapy, surgery + chemotherapy + radiotherapy, and surgery + radiotherapy in 4, 2, and 1 patients, respectively. Among patients who were treated with only a single modality of therapy, an objective response was attained with surgery, chemotherapy, and radiotherapy in 2, 1, and 1 cases, respectively (Table 2). The median OAS was 56 months and PFS was 49 months.

One patient (case 10) had Sjögren's syndrome 7 years prior to the diagnosis of lymphoma. In another patient (case 2) carcinoma of the contralateral breast was detected as a second malignancy 38 months after the initial diagnosis of lymphoma.

Six patients (50%) with primary lymphoma died during therapy or follow-up. The causes of death were progressive disease in 3 patients, infection (febrile neutropenia and sepsis) in 2, and myocardial infarction in 1 patient.

DISCUSSION

Although secondary involvement of the breast during the course of lymphomas is not uncommon, the breast is rarely a primary site for lymphomas. The age of occurrence is between 9 and 85 years, with the greatest frequency in the sixth decade (5, 10). The median age in our series was 46 years and the greatest frequency was observed in the fifth decade. Pregnancy also poses a risk for primary breast lymphoma, presumably because there tends to be an increased involvement of organs most stimulated during pregnancy (11, 12). None of our patients was either pregnant or in the postpartum period.

As lymphomas of the breast are uncommon, and the clinical presentation is indistinguishable from that of breast cancer, they are not suspected prior to biopsy. Breast lymphomas tend to be larger at diagnosis than breast cancer, but they cannot be distinguished by the size of tumor. Rapid enlargement of the mass is sometimes

Table 1

Patient characteristics

Case No.	Age	Sex	Side	Axilla	Stage	Pathology	Grade (Working Formulation)
1.	40	F	R	Positive	I I	DSCL	Intermediate
2.	64	F	R	Positive	I I	SLL	Low
3.	47	F	R	Negative	I	DSCL	Intermediate
4.	20	F	L	Positive	I I	Burkitt-like	High
5.	45	F	L	Positive	I I	DSCL	Intermediate
6.	62	F	R	Negative	I	SLL	Low
7.	41	F	L	Negative	I	DLCL	Intermediate
8.	80	F	L	Positive	I I	DML	Intermediate
9.	17	F	R	Positive	I I	DLCL	Intermediate
10.	50	F	L	Positive	I I	DML	Intermediate
11.	26	F	R	Negative	I	DSCL	Intermediate
12.	60	F	L	Negative	I	DSCL	Intermediate

Abbreviations: F = female; R = right; L = left; DSCL = diffuse, small cleaved-cell lymphoma; SLL = small lymphocytic lymphoma; DLCL = diffuse, large-cell lymphoma; DML = diffuse mixed lymphoma.

Table 2

Treatment modalities and outcome

Case No.	Surgery	Radiotherapy	Chemotherapy	Sequence of modalities	Response achieved	PFS/OAS (months)	Outcome	Notes
1.	Biopsy	Breast + Lymphatics	No	RT	PR	2/3	Died of disease, disease progression	
2.	MRM	No	CHOP	S	CR	41/48	Died of disease, disease progression	Breast carcinoma (38 months later)
3.	Lumpectomy	Breast + Lymphatics	No	S + RT	CR	4/5	Died of ischemic heart disease	
4.	Biopsy	No	CVP	No	NR	0/2	Died of neutropenic sepsis	
5.	Biopsy	Breast + Lymphatics	CVP	RT + CT	PR	3/8	Died of disease, disease progression	
6.	Simple Mastectomy	No	No	S	CR	96+/98+	Alive, NED	
7.	Biopsy	Breast + Lymphatics	CHOP	CT + RT + CT*	CR	19+/26+	Alive, NED	
8.	Simple Mastectomy	Breast + Lymphatics	CVP	S + RT + CT	CR	50+/56+	Alive, NED	
9.	Biopsy	Breast + Lymphatics	CHOP	CT + RT + CT*	CR	48+/57+	Alive, NED	
10.	Biopsy	No	CHOP	CT	CR	49/56	Died of neutropenic sepsis	Sjögren's syndrome (72 months earlier)
11.	Biopsy	Breast + Lymphatics	CVP	CT + RT	CR	6+/14+	Alive, NED	
12.	MRM	Breast + Lymphatics	CVP	S + RT + CT	CR	84+/86+	Alive, NED	

Abbreviations: MRM = modified radical mastectomy; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CVP = cyclophosphamide, vincristine, prednisone; RT = radiotherapy; S = surgery; CT = chemotherapy, PR = partial remission, CR = complete remission, NR = No response, PFS = progression-free survival; OAS = overall survival; NED = no evidence of disease.
* Sandwich therapy (radiotherapy was sandwiched between 6 cycles of chemotherapy).

noted in patients with PBL and, when present, would suggest a diagnosis of malignant lymphoma (1, 10). Skin retraction, erythema, peau d'orange appearance, and nipple discharge are uncommon in PBLs. In our series, the most frequent symptom was a breast mass that had recently enlarged. Constitutional symptoms are not common (10, 13). We had only one case with these symptoms (8.3%).

The right breast appears to have a greater chance of involvement than the left (2, 8, 10, 12–15). No predilection for either breast was present in our series. Axillary nodes are involved in 30% to 40% of cases (13), but adenopathy is generally softer than that associated with carcinoma. We had 7 cases (58.3%) with axillary involvement.

According to Paulus, the lymphomatous involvement of the breast has a noticeable predilection to form relatively circumscribed masses on a mammogram (14). However, it is usually difficult to distinguish malignant lymphomas from more common diseases of the breast, such as carcinoma, by mammography and ultrasonography. Gallium scan (Ga-67 scintigraphy), SPECT, and MRI scan are the newer methods that can be employed for the diagnosis and follow-up of these patients (16–18). Recently, it was suggested that MRI identified the multicentric extent of the tumor better than mammography and ultrasonography (18). MRI was not used in our study, while mammography and ultrasonography afforded guidance in only half of the patients. In the literature both fine-needle aspiration and biopsy have been used to establish the diagnosis of primary breast lymphoma. The latter is the preferred method for better histopathological subcategorization (4).

The majority (9/12) of cases in the present series comprised intermediate-grade lymphomas according to Working Formulation, whereas diffuse large-cell lymphomas are

the most common type in the literature (12–15). Some reports suggest that tumor grade may be a useful factor in the assessment of prognosis (19, 20). Our series is too small to evaluate the impact of grade on outcome.

The pathogenesis of breast lymphomas is still unknown. Isaacson & Wright proposed the original concept of 'lymphoma of the mucosa-associated lymphoid tissue (MALT)' 15 years ago (21). It was later shown that, in addition to the gastrointestinal tract, MALT could originate from a wide variety of extranodal sites including the breast (22). Some authors suggest that breast lymphomas are in the group of MALT lymphomas (2, 15, 22), whereas others emphasize that not all of these neoplasms have the clinicopathologic features of this group (5, 12, 23, 24). There are, however, certain characteristics of PBLs that support the hypothesis that these neoplasms are related to MALT lymphomas. An indolent course is common in MALT lymphomas, characterized by the tendency to remain localized for a long period. Hence, bone marrow involvement is uncommon. In our series, none of the patients with PBLs had marrow involvement. In addition to the standard staging procedures, particular attention should be paid to the extranodal sites, as involvement of distant sites is not so rare. Compared to western series, central nervous system relapses are more often in patients from the Far East (25, 26).

Long-standing autoimmune lymphocytic infiltration has been suggested as playing a part as an early process in the development of lymphoma in some extranodal sites such as the thyroid and salivary glands (27–29). In a series of 19 patients with PBL, Aozasa and co-workers found histologic and immunohistochemical evidence of lymphocytic mastopathy, a recently described autoimmune disease of the breast, in 10 out of 11 patients (30). Interestingly, one of our patients (case 10) had Sjögren's syndrome 7 years prior to the diagnosis of lymphoma.

We found only 6 cases of secondary cases during the same 24-year period in which our PBLs were observed; 4 cases with NHL and 2 with HD. Regarding the secondary cases, all patients with NHL had intermediate-grade histology, whereas patients with HD had lymphocyte predominance and mixed cellularity subtypes (data not shown).

Owing to the rarity of this entity, no prospective randomized studies have been conducted to determine the ideal therapeutic approach in PBL. Earlier reports on PBL therapy described surgery as the primary modality of treatment. Subsequently, radiotherapy has increasingly been used in conjunction with mastectomy or excisional biopsy. After 1970s, it was suggested that mutilating surgery should be avoided; instead, excisional biopsy and adjunctive radiotherapy and/or chemotherapy should be preferred. Surgery is usually reserved for debulking or excision if radiotherapy and chemotherapy fail to control the disease (4). De Blasio and colleagues achieved excellent local control with 40 Gy radiation therapy to the breast and regional lymph nodes and local excision in stage I disease. Additional chemotherapy is considered necessary for stage II disease, because of the high (70%) risk of distant relapses (31). CHOP is a standard and widely accepted chemotherapy regimen in the treatment of intermediate- and high-grade lymphomas. In recent years, there have been increasing numbers of reports showing that different aggressive regimens have no superiority over the standard CHOP, either in terms of remission rates or in duration. Our current practice is to use CHOP chemotherapy with radiotherapy in the treatment of PBLs. We refer our patients to surgery whenever these methods fail to achieve a local control. Since our patients were collected over a span of many years, a wide variety of therapeutic approaches ranging from radical mastectomy to local excision with or without radiotherapy and/or chemotherapy were employed.

Although primary NHL of the breast is a rare disease compared to carcinoma, it should be considered in the differential diagnosis of breast masses. The current trend in the treatment of NHL favors the use of combined modality while extensive surgery is being abandoned. Like all other neoplasms, NHL needs to be dealt with by a multidisciplinary approach. The optimum timing, sequence, type and duration of chemotherapy and radiotherapy are issues for further large-scale studies. Reliable statements concerning prognosis in lymphomas of the breast will ultimately depend on these studies. There is no doubt that a better understanding of the biology of NHL and its relationship with MALT lymphomas is crucial, and, it is hoped, could improve the future management of this entity.

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