RESEARCH ARTICLE

Breast Lymphoma Treatment Outcomes in a Pakistani Population: 20 Years of Experience at a Single Center

Razia Bano[1]*, Waleed Zafar[2], Amina Iqbal Khan[1], Sohaib Adil Fiaz[1], Mahwish Abid[1], Mohammad Zulqarnain Chaudhary[1], Neelam Siddique[3], Huma Majeed Khan[1]

Abstract

Background: Breast lymphomas constitute a rare disease entity. To date, limited relevant data have been reported. We therefore here present a review of breast lymphoma patients treated at a single center over a 20 year period, focusing on histological types, treatment modalities and outcomes. Materials and Methods: We identified patients who were diagnosed and treated for breast lymphoma at a single center from January 1995 to January 2014 and extracted data regarding patients' demographics and clinical data. Results: Twenty-seven patients with breast lymphoma were identified, of which 3 were males. The median age at diagnosis was 37 years (range: 22-76 years). Chemotherapy was the main stay of treatment and 55.6% patients also received radiation to the affected breast. At our institute, only 3 patients, all with progressive disease, had surgery performed to achieve local palliation. Complete response after chemotherapy was seen in 63% patients and partial response in 7.4%, while 26% patients demonstrated disease progression. The mean follow up was 46.8 months. Seven patients (33.3%) who were alive at last follow up, as well as 1 patient who died, survived more than 5 years after diagnosis. Conclusions: Patients with breast lymphoma should receive aggressive treatment, with combination of chemotherapy and radiation therapy. Surgery should be limited for diagnosis and palliation of local symptoms in cases of progressive disease.

Keywords: Breast lymphoma - symptoms - chemotherapy - radiotherapy - outcomes - Pakistan

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Introduction

Breast lymphoma is a rare disease entity (Wiseman and Liao., 1972). According to Wiseman and Liao, breast lymphomas are classified as primary when the following criteria are met: (1) patients have adequate tissue sample for histology, (2) close anatomical proximity of breast tissue and lymphomas, (3) the disease is confined to breast and the same side of axilla with no evidence of distant spread, and (4) there is no prior extra mammary lymphoma. Primary breast lymphoma (PBL) is a form of Non-Hodgkin's lymphoma (NHL), representing less than 1% of NHL cases and accounts for 1.7% to 2% of extra nodal forms of NHLs (Schouten et al.,1981; Validire et al., 2009). Right sided predominance has been described by some studies (Vardar et al., 2005; Ryan et al., 2008). Diffuse large B cell lymphoma (DLBCL) is the most common histological subtype while mucosa-associated lymphoid tissue (MALT) lymphomas are a rare form of PBL (Jennings et al., 2007). Breast lymphomas are extremely rare among males (Murata et al., 1996). Clinical presentation is usually a painless lump increasing in size over time (Yang et al., 2011).

To date, very limited data regarding incidence, prevalence or treatment outcomes of breast lymphoma have been reported from Pakistan, a lower middle income country in South Asia with a large and increasing burden of breast cancer (Yaqoob et al., 2006; Aziz et al.,1999). Our aim was to review all patients with breast lymphoma Treated at a single tertiary-care cancer-specialist center over several years and to describe their demographic and baseline clinical characteristics as well as their treatment and outcomes. We believe that this information can provide useful context about the histopathological subtypes and outcome of this rare disease in Pakistan and in other countries.

Materials and Methods

Study setting, population and data extraction

Our institute is a dedicated cancer specialist centre that provides free care to more than half of the patients,

*[1]Department of Surgical Oncology, [2]Department of Cancer Registry and Clinical Data Management, [3]Department of Medical Oncology Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan *For correspondence: raazia240@gmail.com, raziabano@skm.org.pk*

our centre has a referral base from all over the country and adjoining regions. In 2011, the hospital saw over 142,000 outpatient visits, 7800 surgical operations, 54,600 chemotherapy visits, and 44,500 radiation treatments (Sultan et al., 2014). Patient medical records at the hospital are completely electronic and databases can be searched using key words or International Classification of Diseases versions 9 and 10 (ICD-9 / ICD-10) codes.

From the hospital's cancer registry we extracted data for all patients with breast lymphoma who were registered for treatment between January, 1995 and January, 2014. Using a standard data extraction form, we obtained patients' demographic data and clinical information including the clinical presentation, location of disease, presence of B-symptoms (systemic symptoms including fever, night sweat and weight loss), histopathological diagnosis, immunochemistry markers, staging workup, treatment details and outcome. A total of 31 patients with the diagnosis of breast lymphoma were registered , after excluding patients with incomplete information final sample size was 27 patients .

Diagnosis & staging

We reviewed the details of history and physical findings using the hospital online system, all patients underwent imaging of the breast including ultrasound, bilateral mammography and, in patients younger than 40 years with dense breast also underwent , magnetic resonance imaging (MRI) of breasts. Final diagnosis of breast lymphoma was made either on the core biopsy or excision biopsy. Staging investigations included whole body computed tomography (CT), bone scan, and bone marrow trephine biopsy. Patients were staged according to the Ann Arbor staging system (Carbone et al., 1971). Cases were further divided into primary breast lymphoma (PBL) and secondary breast lymphoma (SBL) based on Wiseman and Liao criteria (Wiseman et al., 1972) according to which only stage IE and IIE are classified as PBL while stage IIIE, IVE and lymphomas involving both breasts are classified as SBL. Response to chemotherapy was assessed by photon emission tomography (PET) scan as complete response (CR), partial response (PR) or progressive disease during and after the course of chemotherapy. Patients who had progressive disease received radiation therapy to the affected breast and were later referred to surgery for palliation of local symptoms. Follow up period was calculated in days from the date of start of treatment to the date of last follow up or death.

Data analysis

Standard descriptive summary statistics were used to characterize the sample. Time to death analyses were done by fitting a Cox proportional hazards model. Patients were assumed to be censored at the time of last follow up. The hazard ratios of death were adjusted for the gender of patient, whether younger than 40 years at diagnosis, presence or absence of B-symptoms, whether bone marrow was involved, stage of the disease, and radiation therapy to affected breast. All tests were 2-sided, with a type 1 error level of 0.05. Data were analyzed using Stata version 12.0. The study was approved by the institutional review board (IRB) of our institute.

Results

A total of 12,881 breast cancer patients were registered for treatment at our center during the study period out of which 27 (0.21%) were diagnosed with breast lymphoma, a rare type of breast tumor. The demographic and baseline clinical characteristics of our sample are provided in Table 1. Twenty-four (89%) patients were female and just over half (51.8%) were younger than 40 years at diagnosis. The median age of patients at diagnosis was 37 years (range: 22-76 years). A majority (55.6%) of patients presented with B symptoms. Most lymphomas were Non-Hodgkin's. Only three patients had Hodgkin's lymphoma. In about half of the patients (48%) only the left breast was involved, while 4 patients (14.8%) had bilateral breast involvement. DLBCL was the most common sub-type (59.3%) and MALT lymphoma was diagnosed in only one patient. Common immunochemistry markers were CD-20, CD-30, and Ki-67. Bone marrow involvement was present

Table 1. Demographic characteristics of lymphoma patients (n=27)

Characteristic	N	%
Sex		
Female	24	88.9
Male	3	11.1
Age		
20-29	5	18.5
30-39	9	33.3
40-49	2	7.4
50-59	8	29.6
60 or older	3	11.1
Primary site of lymphoma		
Right breast only	10	37
Left breast only	13	48.1
Both breasts	4	14.8
B symptoms		
Present	15	55.6
Absent	12	44.4
Primary diagnosis		
DLBCL	16	59.3
Hodgkin's lymphoma	3	11.1
Small lymphocytic lymphoma	2	7.4
Anaplastic large cell lymphoma	1	3.7
Follicular lymphoma	1	3.7
Low grade B cell + IDC	1	3.7
Low grade B cell lymphoma	1	3.7
Lymphoblastic lymphoma	1	3.7
MALT lymphoma	1	3.7
Stage at diagnosis		
I	9	33.3
II	4	14.8
III	2	7.4
IV	12	44.4
Bone marrow involvement at presentation		
Present	8	29.6
Absent	19	70.4
Metastatic spread		
To viscera	2	7.4
To bones	0	0
None	25	92.6

Table 2. Details of Treatment of Patients with Breast Lymphoma

Characteristic	N	%
Year of commencement of first-line therapy		
1995-1999	2	7.4
2000-2004	2	7.4
2005-2009	14	51.8
2010-2014	9	33.3
Received breast radiation therapy		
Yes	15	55.6
No	12	44.4
Surgery		
None	7	25.9
Excision biopsy	16	59.2
Response to treatment		
Complete	17	63
Partial	2	7.4
Progression during chemo-therapy	7	25.9
Missing	1	3.7
Outcome at last follow up		
Alive	21	77.8
Dead	6	22.2
Follow up after diagnosis (in days)		
Alive, Mean (Range)	1557.6 (47 – 5394)	
Dead, Mean (Range)	963.3 (172 – 2720)	

Table 3. Time-to-death Analyses Using Cox Proportional Hazards Model

Factor	Hazard ratio	95% Confidence interval	p
Male	1.5	0.4 – 5.2	0.5
Age 40 years or older	0.2	0.01 – 4.5	0.3
B symptoms present	0.3	0.01 – 7.3	0.4
Bone marrow involvement at presentation	3.8	0.2 – 55.8	0.3
Stage of disease	0.7	0.3 – 1.3	0.2
Received radiotherapy	0.4	0.01 – 8.3	0.5

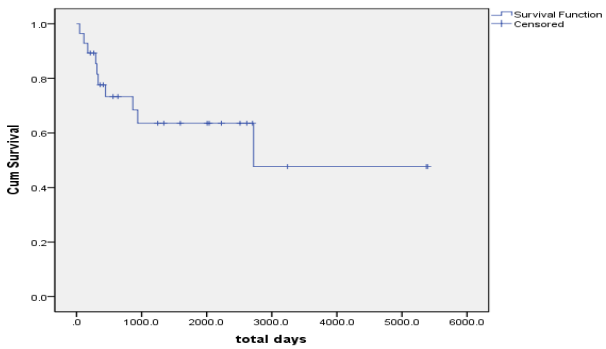

Figure 1. Kaplan Meier Survival Curve

in 8 patients (29.6%) while 25 patients (92.6%) had no distant spread of the disease at the time of presentation. Most patients were diagnosed in stage I (33.3%) or IV (44.4%) of the disease.

Details regarding the treatment are presented in table 2. The main stay of treatment was systemic chemotherapy with CHOP (cyclophosphamide, adriamycin, vincristine, and prednisolone) regimen with rituximab added (R-CHOP) for 8 patients. Patients with Hodgkin's lymphoma received ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) chemotherapy regimen. Fifteen (55.6%) patients also received radiation to the affected breast while a proportion of patients (25.9%) did not have any surgery done or had a diagnostic excision biopsy performed at secondary care centers (59.2%). Only 3 patients, all with progressive disease, had surgery performed at our center to achieve local palliation. Surveillance and regular follow up, without further treatment, was offered to one patient with low grade B-cell lymphoma.

Complete response after chemotherapy was seen in 17 patients (63.0%), partial response in 2 patients (7.4%) while 7 patients (26%) had progressive disease. Six patients (22%) were documented to have died during the study period while the remaining were alive at the last follow up. Mean follow up was 46.8 months (survival of 31.6 months among those who died and a follow up of 51.2 months among those who were alive during the study period; p=0.4). Seven patients (33.3%) who were alive at last follow up, as well as 1 patient who died, survived more than 5 years after diagnosis. Figure 1 shows the overall survival for the 27 patients and time to death analyses using a Cox proportional hazards model are presented in table 3. We found no significant association of sex, age, presence of B symptoms, bone marrow involvement at diagnosis, the stage of disease or whether the patient received radiation to the breast with the hazard of death.

Discussion

Breast lymphoma is a very rare entity , it accounts for about 1 % of Non Hodgkin's lymphomas(Fruchart et al., 2005). PBL is defined as disease confined to breast and ipsilateral axilla, while SBL involves breast as well as other sites of involvement like contra lateral axilla, or disseminated disease (Sabate et al., 2002), Distinction between PBL and SBL is often becomes difficult, PBL strictly follows Wiseman and Liao criteria (Wiseman et al., 1972). In our study we had 13 cases of PBL and 14 cases were of SBL , we included bilateral breast lymphomas in SBL .

In this study we have presented the demographic and baseline clinical characteristics of 27 patients who were treated for breast lymphoma at a single cancer-specialist center in Pakistan over a 20-year period.

Breast lymphomas constituted 0.21% of all malignant neoplasms of breast treated at this center. The risk of mortality in this sample was not found to be associated with age, sex, stage of disease, presence of B symptoms or receipt of radiation therapy.

In our study the mean age of patients at diagnosis was 41.5 years (median 37 years) which is in line with previous reports from Pakistan. A study of 175 Pakistani patients with non-Hodgkin's lymphoma found the patients' median age to be 45 years (Aziz et al., 1999) while studies among breast cancer patients have reported the mean age between 41 years (Carbone et al., 1971) and 48 years (Bhurgri et al., 2007; Badar et al., 2011). Ou et al. have similarly pointed out that most studies of primary breast lymphoma to date have reported a median age less than

50 years among Asian populations (Ou et al., 2014; Guo et al., 2008). On the other hand, the reported median age of patients with PBL in the Western populations have ranged from 62 to 68 years (Validire et al., 2009 ;Ryan et al., 2008; Hosein et al., 2014; Radkani et al., 2014). More work is needed to understand this age variation in presentation across populations.

Like the previous studies (Vardar et al., 2005; Yang et al., 2011; Ou et al., 2014; Radkani et al., 2014), DLBCL was the most common histological subtype of breast lymphoma in our patient population as well. However, none of our patients had Burkitt's lymphoma and three were diagnosed with Hodgkin's lymphoma (nodular sclerosing type with presence of Reed Sternberg cells). Hodgkin's lymphoma of the breast is very rare and only a few cases have been reported recently (Osujiet al., 2013; Modi et al., 2014). We also had a single patient with low grade lymphoma and invasive ductal carcinoma. Coexistence of breast lymphoma and breast carcinoma is also very rare and only few cases have been described in the literature (Zhong et al., 2014). Recent studies have suggested that primary breast DLBCL has a high rate of central nervous system (CNS) relapse and have recommended CNS prophylaxis in high risk patients (Aviv et al., 2013; Hosein et al., 2014). In our study only a single patient developed CNS relapse. Aviv et al. (2013) carried out a review of Primary DLBCL , they looked at pathogenesis, clinical features and therapeutic options ,while it has been suggested that rituximab, a monoclonal antibody, may reduce the rate of CNS relapse (Aviv et al., 2013), many studies have failed to detect any benefit of rituximab on rate of CNS relapse or overall survival (Yhim et., 2012; Hosein et al., 2014; Ou et al., 2014).

Gualio et al describe clinicopathological features of 11 cases of T-cell breast lymphomas, 4 cases were PBL and 7 cases were of SBL. Diagnosis is made either on core biopsy or excision biopsy, an excision biopsy was performed for diagnostic purposes in 16 patients in our study. Most of these patients were referred to our center from peripheral hospitals with the diagnosis of lymphoma after they underwent an excision biopsy for a breast lump. An operation was performed at our facility for palliation in 3 patients, but none underwent an axillary dissection. Earlier literature described the role of surgical intervention in the treatment of breast lymphoma, but more recent studies have found no evidence of improved survival in patients who underwent mastectomy with or without axillary lymph nodes dissection (Jennings et al., 2007; Uesato et al 2005). Other recent studies have also emphasized that chemotherapy and radiation therapy should be considered the gold standard for treatment, and surgical intervention should be limited for diagnostic purposes only , Aviles et al studied the effects of chemotherapy and radiation therapy in 96 patients , and observed that combined chemotherapy and radiation therapy have better disease free and overall survival, they also emphasize the need of central nervous system prophylaxis(Aviles et al., 2005). Avenia et al studied 23 patients of breast lymphoma they describe the role of surgery to be kept limited for diagnostic purpose, aggressive surgery such as mastectomy should be avoided unless required for palliation (Avenia et al., 2010).

Regarding the factors associated with mortality, previous studies have described the Ann Arbor stage as the only predictive factor for five year survival (Zhao et al., 2011), Wong et al studied 26 cases of breast lymphoma and found Ann Arbor staging as the only prognostic factor for survival (P=0.0021). (Wong et al., 2002).

However, unlike these studies, we were unable to detect an association of Ann Arbor stage with risk of mortality in our patient population. Time to event analyses in our patient population also suggest no significant association of age, sex, presence of B symptoms and bone marrow involvement at diagnosis with the hazard of death. It is probable that our findings are a result of our small sample size and reflect the fact that close to half of our patients were diagnosed with stage IV disease. Nevertheless, compared to one study of 175 Pakistani patients with non-Hodgkin's lymphoma that reported a mortality of 96 patients (54.8%), breast lymphoma patients in this study had a markedly lower mortality (6 out of 27 patients; 22.2%) over the study period (Aziz et al., 1999).

This study has several limitations. First, it is possible that we may have missed in the early part of our review period some patients who met the inclusion criteria for this study because the medical records were not completely electronic at that point. Second, this was a retrospective review at a single institution. However, breast lymphoma remains a very rare presentation making prospective studies logistically difficult to conduct. In this context, we have been able to report the baseline characteristics, treatment and outcomes in a relatively large number of patients.

In conclusions, We observed that breast lymphoma is a very rare form of malignant breast neoplasm in a sample of Pakistani population. However, Pakistani patients likely develop this disease at a much younger age than the Western populations. Breast lymphomas should be treated aggressively with chemotherapy and radiation and surgery should be reserved for diagnostic and palliative purposes.

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Ethics:Permission was taken from the Institutional Review Board (IRB) for retrieval and publication of data.

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