

## Primary Diffuse Large B-cell Lymphoma of the Breast: Treatment and Long-Term Outcome of Two Cases

### Abstract

Primary breast lymphoma (PBL) is a rare form of extranodal non-Hodgkin's lymphoma (NHL). It accounts for <0.5% of all breast malignancies and 2% extranodal NHL. Diffuse large B-cell lymphoma (DLBCL) is the most common histological subtype. We report three cases of PBL diagnosed and treated at our center. The clinical records of three female patients diagnosed with PBL from 2004 to 2015 were reviewed. Two patients had DLBCL, and the third patient had anaplastic large cell (ALCL) NHL. The mean age at presentation was 56 years. One patient with DLBCL was treated with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) chemotherapy and the second patient with rituximab plus CHOP chemotherapy. Both the patients showed complete response and have had a disease-free survival of 84 and 96 months, respectively. The third patient with ALCL refused further treatment after confirmation of diagnosis. PBL-DLBCL can be successfully treated with chemotherapy, and long-term survival is similar to nodal NHL.

**Keywords:** Breast lymphoma, chemotherapy, diffuse large b-cell lymphoma, rituximab

### Introduction

Primary breast lymphoma (PBL) is a rare form of extranodal non-Hodgkin's lymphoma (NHL) and accounts for <0.5% of all breast malignancies. It represents <1% of all NHL and 2.2% of extranodal NHL.<sup>[1,2]</sup> It is postulated that PBL originates in the lymphatic tissue present within the breast adjacent to ducts and lobules or from intramammary nodes.<sup>[3,4]</sup> Wiseman and Liao,<sup>[5]</sup> first proposed the diagnostic criteria for PBL as follows

1. The clinical site of presentation is the breast
2. A history of previous lymphoma or evidence of widespread disease is absent at diagnosis
3. Lymphoma is demonstrated with close association to breast tissue in the pathologic specimen
4. Ipsilateral lymph node may be involved if they develop simultaneously with the primary breast tumor.

This definition of PBL comprises only tumor that are Stage I (lymphoma limited to the breast) and Stage II (lymphoma

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limited to the breast and axillary lymph nodes), excluding those tumor that may have originated at nonbreast sites. Surgery, radiotherapy, and chemotherapy have been used alone or in combination in its management.<sup>[6]</sup> However, the optimal therapy of PBL still remains undefined.

We report three cases of PBL which we have diagnosed and managed. The issues involved in its diagnosis and management are discussed in this communication.

### Materials and Methods

In a retrospective analysis, the medical records of all diagnosed with NHL between the period January 2004 and December 2014 at the Department of Hematology were searched for cases of PBL.

Three cases were diagnosed to have PBL as per the criteria defined by Wiseman and Liao.<sup>[5]</sup> The diagnosis was established on histopathological evidence of tumor specimen based on the WHO nomenclature.<sup>[7]</sup> All the patients underwent computed tomography (CT) of the chest, abdomen, and pelvis and bone marrow biopsy for staging of the disease as per the Ann Arbor staging system.<sup>[8]</sup>

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**Rajesh Kashyap<sup>1</sup>,  
Pradeep Kumar<sup>1</sup>,  
Hira Lal<sup>2</sup>,  
Ram Naval Rao<sup>3</sup>**

<sup>1</sup>Department of Hematology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India, <sup>2</sup>Department of Radio Diagnosis, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India, <sup>3</sup>Department of Pathology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

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**Address for correspondence:**  
Dr. Rajesh Kashyap,  
Department of Hematology,  
Sanjay Gandhi Postgraduate  
Institute of Medical  
Sciences, Rae Bariely  
Road, Lucknow - 226 014,  
Uttar Pradesh, India.  
E-mail: rajkashyapmd@yahoo.  
co.in

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## Results

The clinical and laboratory findings and treatment outcome are summarized in Tables 1 and 2.

### Clinical and laboratory features

Three multiparous postmenopausal females were diagnosed with PBL. The mean age at presentation was 56 (range 50–66) years. All three patients presented with unilateral breast mass. Two patients (Cases 2 and 3) swelling in the right breast and the third case (case1) had a left breast mass. The average time from onset of symptoms to presentation at the hospital was 6 (range 1–12) months. None of the patients had any symptoms or signs of local inflammation or tumor infiltration (local erythema, puckering of the skin, or nipple retraction) at presentation. “B” symptoms were reported in only two patients. None of the three patients had any clinical features to suggest central nervous system involvement (CNS) at the time of initial presentation. The clinical stage of the disease was IIE in all the three cases [Table 1].

Radiological evaluation showed the disease localized to the breast tissue only; there was no evidence of systemic disease [Figure 1a and b]. On histopathological examination (HPE), two patients had CD 20 positive diffuse large B cell lymphoma (DLBCL) [Figures 2 and 3]. The third patient (Case 3) had anaplastic large cell lymphoma (ALCL).

### Treatment and outcome

Case 1 underwent modified radical mastectomy along with axillary lymph node resection. Postoperatively, the patient received a total of 6 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) chemotherapy. No radiotherapy was given, and the patient achieved complete remission (CR) after the end of the

treatment. Case 2 underwent a core tissue biopsy for the evaluation of the right breast mass. The biopsy was suggestive of CD 20 positive DLBCL and the patient received rituximab plus CHOP (Rituximab 375 mg/m<sup>2</sup> IV on day 1 plus CHOP) chemotherapy administered every 3 weeks. Before the third cycle of chemotherapy, she developed hoarseness of voice, difficulty in swallowing, and weakness of the left side of the face. Clinical examination revealed lower motor neuron type of unilateral left 7<sup>th</sup> cranial nerve and bilateral 9<sup>th</sup> and 10<sup>th</sup> cranial nerve palsies. Magnetic resonance imaging showed no focal deposits of lymphoma. Cytological examination of cerebrospinal fluid showed the presence of atypical lymphoid cells suggestive of CNS involvement. The patient was administered triple intrathecal (methotrexate, cytosine arabinoside, and hydrocortisone) chemotherapy as per recommendations for her CNS disease. No cranial irradiation was given. The patient showed complete resolution of her CNS disease following further therapy. The subsequent clinical course was uneventful, and

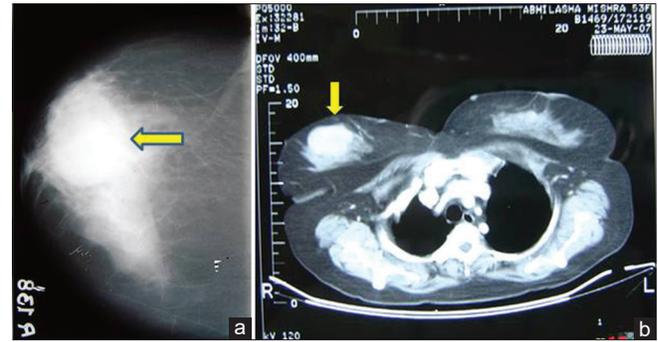


Figure 1: (a) Mammography of the right breast inpatient Case 2, shows smooth radiodense mass without spiculations or calcification. (b) Contrast-enhanced computed tomography of the thorax in the axial plane at the level of the breast in Case 2 shows enhance round mass lesion in the right breast

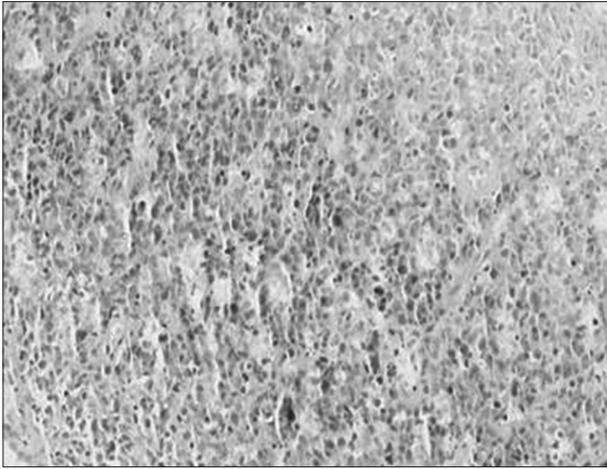
**Table 1: Clinical and pathological profile of the primary breast lymphoma patients**

Case number	Age (years)	Year of diagnosis	Duration of symptoms	Site of tumor	Size of tumor (cm)	Lymph nodes	Performance status ECOG	Ann arbor staging	Histological subtype
1	66	2004	5 months	Left breast	7×6	Single ipsilateral axillary	3	IIE	DLBCL
2	52	2007	1 month	Right breast	4×2	Right axillary	1	IIE	DLBCL
3	50	2011	12 months	Right breast	7×5	Right axillary	3	IIE	ALCL

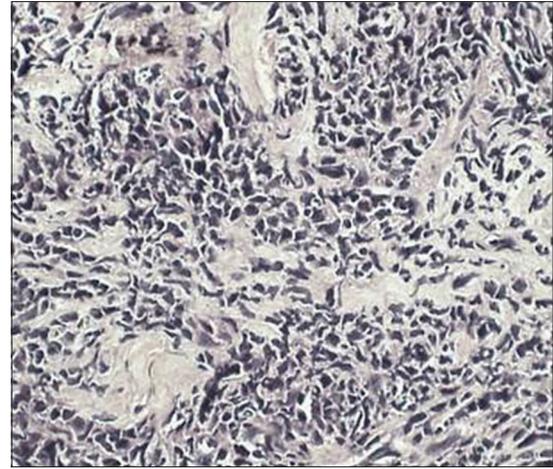
DLBCL – Diffuse large B-cell lymphoma; ALCL – Anaplastic large cell lymphoma; ECOG – Eastern Cooperative Oncology Group

**Table 2: Treatment and follow-up of primary breast lymphoma patients**

Case number	Treatment	Type of response	Follow-up	Remarks
1	Radical mastectomy plus CHOP X 6 cycles	Complete remission	84 months	Relapsed after 7 years. developed 2×3 lump right breast. DLBCL
2	R-CHOP X 8 cycles Triple intrathecal chemotherapy	Complete remission	96 months	In remission
3	No treatment	-	-	



**Figure 2: (Case 1) Diffuse large B-cell lymphoma.** The sections show breast parenchyma with infiltration by sheets and cords of atypical lymphoid cells in a dense fibrocollagenous stroma. The cells display high n/c ratio, round-to-oval nuclei, dispersed chromatin, and scant cytoplasm



**Figure 3: (Case 3) Diffuse large B-cell lymphoma.** The section from the right breast lump shows diffuse sheet and cords of atypical lymphoid cells infiltrating the fibrocollagenous stroma. The tumor cells are round to irregular have moderately pleomorphic hyperchromatic nuclei and variable amount of cytoplasm, Mitotic figures are discernible

the patient received a total of eight cycles of R-CHOP chemotherapy.

The third patient who was diagnosed to have ALCL of breast refused treatment for socioeconomic reasons.

#### Follow-up and survival

Both case 1 and 2 achieved CR following chemotherapy. Case 1 remained in disease-free state for the next 84 months of follow-up. In April 2011, the patient developed a new lump in the right breast measuring 2 cm × 3 cm in size. A lumpectomy was performed, and the HPE was diagnostic of DLBCL. The patient was counseled for disease relapse; however, she refused further treatment. Case 2 remains in clinical remission for the last 96 months (8 years) of follow-up.

#### Discussion

PBL is a rare but potentially curable disease. The term PBL is used to define NHL occurring exclusively in the breast tissue with or without regional draining lymph node involvement and absence of any evidence of disease at another site. The disease usually occurs in the 5<sup>th</sup> and 6<sup>th</sup> decade of life and presents as a unilateral rapidly expanding painless mass.<sup>[9,10]</sup> The right breast is more frequently involved 3:2 ratio. Bilateral breast involvement is seen in 6% to 11% of cases.<sup>[11]</sup> The mass may be associated with local pain and signs of inflammation in up to 12% of patients.<sup>[9]</sup>

The pathogenesis of PBL is still not clear. It is postulated that the tumor arises from mucosa-associated lymphoid tissue (MALT). It may also develop from the lymphatic tissue present within the breast adjacent to ducts and lobules or from surrounding lymph nodes.<sup>[3,4]</sup> Majority of the PBL are B-cell lymphomas and express CD 20 antigen. DLBCL is the most common histological type and accounts

for 50% of all cases. Follicular lymphoma 15% and MALT 12.2% are the next frequent subtypes.<sup>[12]</sup>

On mammography, the tumor appears as oval shaped margins high-density mass without speculated margins or calcifications.<sup>[13]</sup> Fine-needle aspiration cytology, tissue core, or excisional biopsy of the breast mass and draining lymph nodes are essential to establish the histopathological diagnosis. Bone marrow biopsy, CT of the thorax, and abdomen and positron emission tomography scan are required to rule out systemic NHL and for staging of disease.

Patients with PBL have been treated with radical mastectomy, chemotherapy, and radiotherapy either alone or in combination with varying results. Disease stage, tumor size, performance status, and IPI score influence the disease prognosis.<sup>[14]</sup> Early-stage disease is associated with good prognosis and tumor size >4 cm has an adverse prognosis.<sup>[9]</sup>

Ganjoo *et al.*<sup>[11]</sup> in a retrospective analysis of 37 patients with PBL found that DBL was the most common histologic subtype (49%). Seventy percentage of the DLBCL patients were treated with doxorubicin-based chemotherapy and involved field radiotherapy (IFRT). The 5-year progression-free survival (PFS) was 61% with median follow-up of 3.8 years and a 5-year overall survival (OS) was estimated at 82%.

Ryan *et al.*<sup>[14]</sup> in a retrospective study of 204 patients with PBL (DLBCL subtype) attending the International ExtraNodal Lymphoma Study Group found that there was no benefit from mastectomy. Chemotherapy was associated with a median OS of 8.0 years and median PFS of 5.5 years. They concluded that limited surgery combined with chemotherapy and IFRT is associated with better outcome.

Avilés *et al.*<sup>[15]</sup> in a prospective study of 96 patients with PBL compared treatment outcome with radiotherapy ( $n = 30$ ), chemotherapy (CHOP-21  $\times$  6 cycles;  $n = 32$ ), and combined therapy (radiotherapy 30 Gy plus CHOP  $\times$  6 cycles;  $n = 34$ ). CR was observed in 66.71% (20/30) treated with radiotherapy, 59.4% (19/30) with chemotherapy, and 88.2% (30/34) with combined modality. At 10 years median follow-up, the event-free survival was 50%, 57%, and 83%, respectively ( $P < 0.01$ ) and the OS was 50%, 50% and 76% ( $P < 0.01$ ), respectively.

In a meta-analysis of 464 PBL cases diagnoses between 1972 and 2005, by Jennings *et al.*,<sup>[13]</sup> it was observed that 53% of all cases were of DLBCL subtype and the median age of presentation was 54 (range 17–95) years. Mastectomy showed no benefit regarding OS and recurrence rate. Radiotherapy showed benefit in survival and recurrence rates in Stage I patients. Chemotherapy showed benefit in Stage II patients. Rituximab is anti-CD 20 monoclonal antibody addition, of this agent with CHOP chemotherapy (R-CHOP), has shown high efficacy for DLBCL. Avilés *et al.*<sup>[16]</sup> observed no CNS relapse in PBL patients treated with R-CHOP regimen compared to that CHOP regimen alone. THE CNS relapse rate was 11% in patients treated with CHOP regimen only. Sun *et al.*<sup>[17]</sup> have observed that patients treated with rituximab plus chemotherapy have a superior 5-year PFS and local control. A study comparing the OS in patients with PBL and nodal DLBCL treated with R-CHOP and IFRT found no difference between the two groups.<sup>[18]</sup>

The role of CNS prophylaxis in PBL-DLBCL has been much debated A CNS relapse rate of 11.0%–17.6% has been reported in some studies.<sup>[15,19]</sup> In contrast, other studies have reported a lower relapse rate of 4% to 5%, which is similar to that observed in nodal DLBCL.<sup>[14,20]</sup> Nearly 5%–14% has been observed in various retrospective studies.<sup>[9,14]</sup> The present consensus is that PBL patients should be treated similar to nodal lymphoma of the same stage and histology. Anthracycline-based chemotherapy in combination with IFRT is the recommended modality of treatment.<sup>[6]</sup>

## Conclusion

At our institute, both our PBL-DLBCL patients (Case 1 and 2) were treated with chemotherapy alone and had a DFS of 84 and 96 months, respectively. No CNS disease relapse or recurrence was observed in both our patients during the follow up period.

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## Conflicts of interest

There are no conflicts of interest.

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