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ORIGINAL ARTICLE

Breast lymphomas: Clinical and pathological insights from a tertiary cancer care center in India

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ABSTRACT

Background: Breast lymphomas are a rare group of malignancies that are further subdivided into primary and secondary. AIMS: To study the pathological and clinical course of breast lymphomas. **Materials and Methods:** This is a retrospective analysis of patients treated at our institute over a period of 4.5 years from September 2018 to February 2023. The details of all the patients diagnosed with breast lymphoma were reviewed and analysed for the histomorphological, immunohistochemical, clinical, and treatment details. Appropriate statistical analysis including Kaplan-Meier methods was used. **Results:** Out of 11 cases of breast lymphoma, five were primary and six were secondary. It was seen predominantly in females (82%) and the age range was 31 to 73 years. Diffuse large B cell lymphoma (DLBCL) was the predominant morphology (73%), along with single rare cases of ALK-negative anaplastic large cell lymphoma, Burkitt lymphoma, and small lymphocytic lymphoma. The treatment details were analyzed for 7 patients. The median follow-up was 28 months. Rituximab along with CHOP regimen or its variants was commonly used as first-line treatment with initial response rates of 71%. The median progression-free survival was 5 months. The median overall survival was 15 months. **Conclusion:** Lymphomas of the breast are rare but it is crucial to differentiate them from the commoner breast carcinomas as the treatment and prognosis vary vastly.

KEY WORDS: Breast lymphoma, DLBCL, primary, rare, secondary

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INTRODUCTION

Malignancies of the breast are one of the most common causes of cancer-related morbidity and mortality in females. They commonly arise from either the epithelial or stromal component.[1] Breast carcinomas, the most common type, are associated with the second highest mortality rates in females due to cancer.[2,3] Lymphomas of the breast, on the other hand, are a rare group of malignancies comprising less than 0.5% of all breast malignancies and 2% of all extra-nodal lymphomas. They can be further sub-divided into primary and secondary breast lymphomas.[1,4,5]

Primary breast lymphomas (PBLs), first described by Wiseman and Liao in 1972, are postulated to arise either from the lymphoid tissue present in the vicinity of breast ducts and lobes or even from the intra-mammary lymph nodes without any other systemic involvement.[6,7] The criteria to define PBL was initially proposed by Wiseman and Liao[6] and later modified by Hugh *et al.*[8] They include the following: the breast should be the primary site of presentation, the breast tissue should be seen in close proximity with lymphomatous infiltration, and there should not be either a previous diagnosis of lymphoma or any other systemic lymphomatous infiltration beyond the ipsilateral axillary lymph nodes.

Although rare, albeit slightly more common, are secondary breast lymphomas. These are extra-nodal manifestations of systemic disease that may involve the breast secondarily or concurrently. Similar to the primary breast lymphomas on histopathology, the breast tissue should be intermingled with lymphomatous involvement. Conversely, secondary breast

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lymphomas however are one of the most common metastatic diseases involving the breast and comprise 17% of all such metastases to the breast.[9,10]

In this study, we have tried to capture the essence of clinical, pathological, radiological, and treatment details of breast lymphomas diagnosed at our center.

MATERIALS AND METHODS

This is a retrospective study conducted at our institute with data collected for a period of four and a half years from September 2018 to February 2023. All the patients diagnosed as breast lymphomas were included. The file numbers of the patients were retrieved from the archives of the Department of Oncopathology.

Details regarding the age, gender, clinical history, radiological investigations, positron-emitted tomography (PET) scans, treatment details, relapse/recurrence, and survival were collected from the patient's electronic medical records. The corresponding biopsy or excision specimen's slides were retrieved and reviewed for the histomorphological details and immunohistochemical (IHC) analysis, namely, the type of lymphoma and positivity and negativity of various IHC markers. Based on their clinical and radiological findings, they were subsequently labeled as primary or secondary breast lymphoma.

The response was assessed as per the Lugano criteria.[11] The progression-free survival (PFS) was calculated from the date of diagnosis to the time of clinical or radiological progression or death due to any cause. The overall survival (OS) was estimated from the date of diagnosis to death due to any cause. For patients lost to follow-up, we attempted to telephonically contact them. The patients who had progressed on multiple lines of therapy and were planned for supportive care alone were censored on the date of their last follow-up.

Statistical analysis

The data were tabulated and analyzed using Microsoft Excel and the statistical package for social sciences (SPSS) version 20. A Chi-square test with a *P* value of 0.05 was used to test statistical significance. OS and PFS were calculated by the Kaplan–Meier method.

RESULTS

A total of 11 cases of breast lymphoma were found. Nine of these were in females and two in males. The median age at presentation was 52 years (range 31–73 years). Patients presented with single to multiple breast lesions with sizes ranging from 2.7 to 13 cm. All the cases were diagnosed as non-Hodgkins lymphoma (NHL) based on histomorphology. Further IHC work-up on the biopsy specimens classified them as B-cell NHL (10 cases) and T-cell NHL (1 case).

Following the criteria of Wiseman and Liao, out of the 11 cases of breast lymphoma, five were classified as primary, all of which had no evidence of disseminated disease at the time of initial presentation. Four out of the five primary breast lymphomas presented with unilateral breast lesions, while one case had bilateral involvement. Diffuse large B-cell lymphoma (DLBCL) was the most common diagnosis made (three out of five patients), followed by a single case of Burkitt lymphoma and a single case of anaplastic lymphoma kinase (ALK)-negative anaplastic large cell lymphoma (ALCL). Among DLBCL, the activated B-cell type (ABC) was noted in two cases, while a single case of germinal center B-cell-like (GCB) was noted. DLBCL on histomorphology showed large neoplastic cells, with round to irregularly shaped nuclei, prominent nucleoli, and a moderate to scant cytoplasm. On IHC, these cells were negative for AE1/AE3, while they were positive for LCA and B-cell markers (CD20 or PAX5) and generally had a high Ki-67 proliferation index. They were further sub-divided based on Hans algorithm as the GCB and ABC types[1] [Figure 1].

The case of ALK-negative ALCL was observed in a 59-year-old male, presenting with a breast lump for the past 1 year. Histology showed the classical large "hallmark cells" having irregular, horseshoe-shaped nuclei, based on which IHC was applied, which showed positivity of CD3 and CD30 and negativity for ALK-1. The Ki-67 proliferation index was 90–95% [Figure 2].

A case of primary Burkitt lymphoma was also noted, which presented with an initial complaint of a left breast lump for 3 months progressing to a large fungating mass involving the left breast along with right breast lesions. Histology showed sheets of small- to medium-sized atypical lymphoid cells, with coarse chromatin, prominent nucleoli, and a scant cytoplasm. Brisk mitotic activity with plenty of tingible body macrophages was noted, giving the classical "starry-sky" appearance. On IHC, the atypical lymphoid cells were positive for CD20, BCL6, CD10, MUM1, and c-myc with a Ki-67 proliferation index of approximately 95% [Figure 3], while they were negative for CD3, TdT, BCL2, and Mum.

All these patients initially had stage 2 disease, but two of them progressed to stage 4 during treatment.

Secondary lymphomas, classified based on clinical or radiological work-up, pointed to other sites of involvement concurrent with breast involvement. Bilateral breast involvement was more frequently seen at the time of presentation (three out of six), while single cases involving the right and left breast were also noted. The most common diagnosis was that of DLBCL (5 out of 6), of which three were DLBCL-GCB type, one was DLBCL-ABC type, and the other was CD5-positive DLBCL; furthermore, a single case of small lymphocytic lymphoma (SLL) was noted. For the cases of DLBCL, the initial panel included AE1/AE3 and/or GATA-3 to rule out a breast primary.

This case of SLL was noted in a 57-year-old female presenting with a left breast mass along with hepatosplenomegaly and multiple enlarged lymph nodes. The initial suspicion was that of lymphoma along with breast carcinoma, but on breast

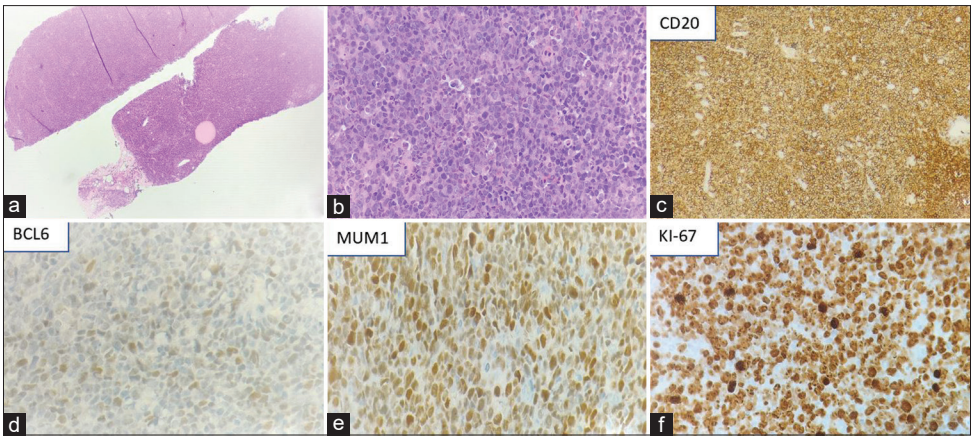


Figure 1: a. Breast cores infiltrated by sheets of large atypical lymphoid cells (10x). b. Cells have round to oval nuclei, with an open chromatin and scanty cytoplasm. Also noted brisk mitotic activity and karyorrhectic debris (40x) c. On IHC, these cells were positive for c. CD20, d. BCL-6, and e. MUM-1. f. Ki-67 proliferation index is high (>95%)

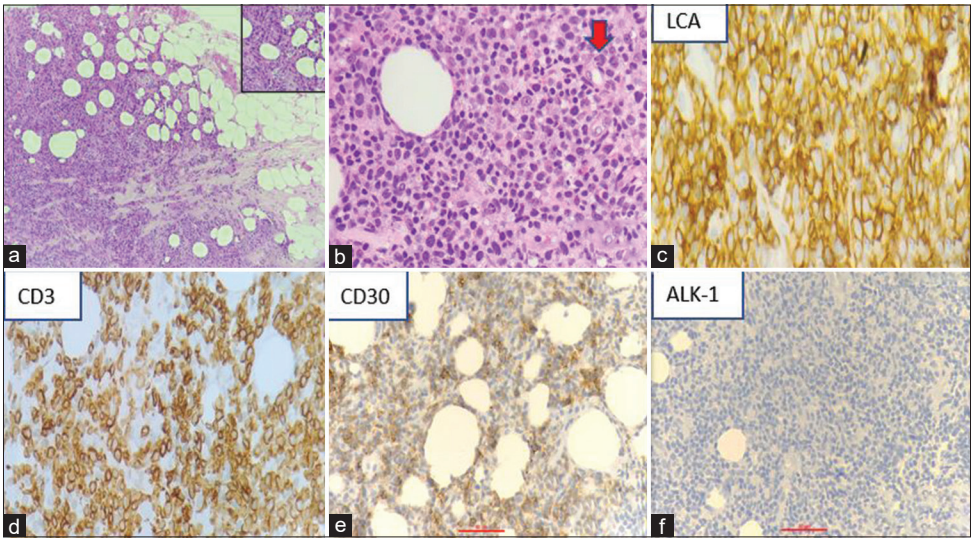


Figure 2: a. Breast core infiltrated by sheets of large atypical lymphoid cells (10x); the inset shows lymphoid cells surrounding the ducts. b. Large cells with oval- to irregular-shaped nuclei, with brisk mitotic activity, admixed with "hallmark cells" (arrow) (40x) c. These cells were positive for c. LCA, d. CD3, and e. CD30. and were negative for ALK-1

biopsy, we noted breast tissue infiltrated by small atypical lymphoid cells with round to oval nuclei, fine chromatin, and a scant cytoplasm. These cells were positive for CD20 and CD23 and focally positive for CD5 on IHC but were negative for CD3, MUM1, BCL6, SOX11, CD10, and cyclin D1 [Figure 4]

Out of the 11 cases, the treatment details with follow-up were available in the records for seven of them. So, these patients were also analyzed for treatment outcomes. For one patient, we did not have any treatment details at our institute and hence, the case was excluded, and the other three patients were recently diagnosed and had only up to 2 months of follow-up and hence were excluded.

The median follow-up of these patients was 28 months (range 6–52 months). The salient clinical, pathological, and treatment details are presented in Table 1. The first line of treatment was CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone), CEOP (cyclophosphamide, etoposide, vincristine, and prednisolone), and EPOCH (etoposide, prednisolone, cyclophosphamide, and hydroxydaunorubicin) regimens, respectively, in two patients each. Rituximab was added in most cases, except when financially not feasible.

One case of secondary lymphoma was initially unfortunately misdiagnosed as the patient on radiology had an ovarian mass with clinical signs and symptoms suggestive of ovarian malignancy. At the time, due to scant resources, a cytological assessment of the mass was done, which revealed scattered atypical epithelial cells, and hence, the patient was started on paclitaxel plus carboplatin regimen. Post chemotherapy, the patient eventually developed breast mass along with multiple visceral involvements, which when biopsied revealed lymphomatous involvement.

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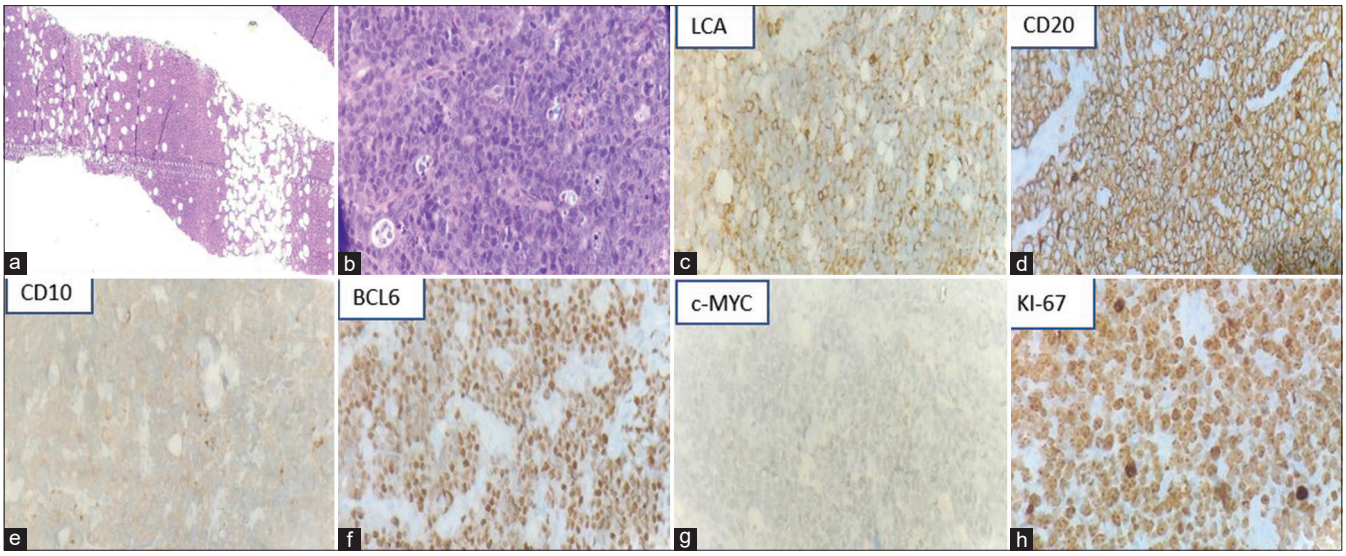


Figure 3: a. Breast cores infiltrated by sheets of atypical lymphoid cells (4x). b. Atypical lymphoid cells with brisk mitotic activity admixed with plenty of tingible body macrophages (40x). c. These cells were positive for c. LCA, d. CD20, e. CD10, f. BCL6, and g. c-MYC. h. Ki-67 proliferation index is high (approximately 95%)

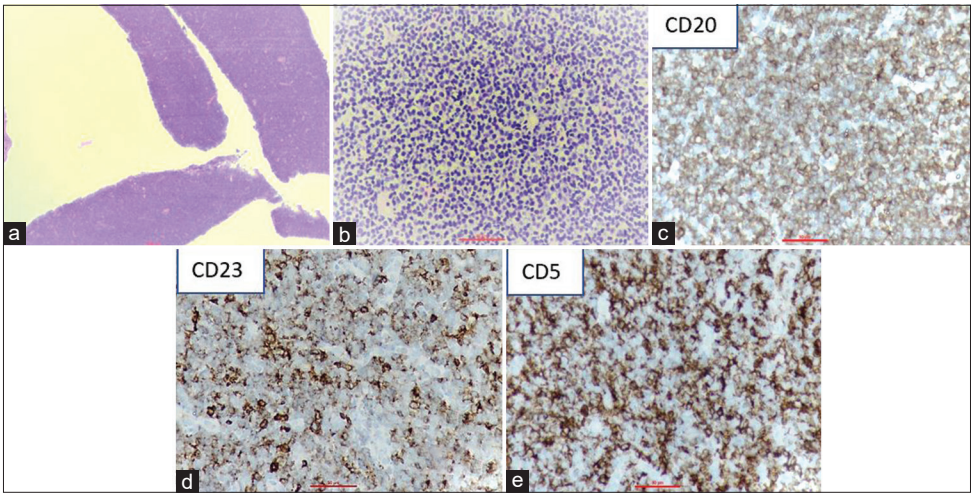


Figure 4: a. Breast core infiltrated by sheets of small atypical lymphoid cells (10x). b. These cells displayed round to oval nuclei with scant cytoplasm (40x). c. On IHC, these cells were positive for c. CD20, d. CD23, and e. CD5

The initial response rate was 5/7 (71%), but this was followed by rapid progression. Hence, the median PFS on first-line treatment was just 5 months (95% CI; 2.5–7.6 months), as depicted in Figure 5. Only 3/7 (43%) went on to receive second-line treatment due to high fatality. The median OS was 15 months (95% CI; 2–28 months), as shown in Figure 6.

DISCUSSION

Hematological involvement of the breast and, more specifically, breast lymphomas are rare occurrences with clinical and radiological findings overlapping with that of the primary breast carcinomas, which in turn makes initial assessment difficult.[12] Hence, there is dependency on histopathological and IHC work-up for proper and timely diagnosis and treatment.

In our study, the demographic, clinical, and pathological features were similar to those of various other published studies in the past. Breast lymphomas are seen more frequently in females, although they can be seen in males [Figure 7] as well with the age of presentation varying from the fifth to seventh decades of life.[4,12] We had 3/11 (27%) patients presenting in the third decade of life, which is in contrast to the data available.[1,4]

Histologically, B-cell NHL is the most commonly diagnosed breast lymphoma; amid this, DLBCL is more frequently noted (more than 50%), followed by marginal zone (9–28%), follicular (10–15%), and Burkitt and Burkitt-like lymphoma (6–10%).[12,13] Similarly, our study showed a predominance of DLBCL, 8/11 (72.7%) with the DLBCL-GCB sub-type as the most common type and single cases of Burkitt lymphoma (9.1%), small lymphocytic lymphoma (9.1%), and ALK-negative ALCL (9.1%).

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Table 1: Clinical, pathological, and treatment details of all patients

Age/ Sex	*Pathology*	*Primary/ Secondary*	*Sites of involvement*	*First-line treatment*	*Second-line Treatment*	*Third-line treatment*	*Status*
33/F	DLBCL GCB	Secondary	Duodenum, peritoneum, bone, breast, liver, kidney, uterus, ovary	P C	CAP	R- DHAP	Death
73/F	CD 5 positive DLBCL	Secondary	Breast, kidney, serosa, chest wall, subcutaneous deposit	CEOP	-	-	LFU
52/F	DLBCL GCB	Primary	Breast, Axillary LN	RCHOP + IT MTX	-	-	On RCHOP
39/F	DLBCL GCB	Secondary	Breast, stomach, LN, peritoneum	RCHOP	-	-	Death
67/F	DLBCL ABC	Primary	Breast, axillary LN, bone	RCEOP	Len	-	Alive
31/F	DLBCL GCB	Secondary	Breast/only cervical LN	REPOCH + HD MTx	-	-	Death
47/F	Burkitt lymphoma	Primary	Breast/axillary LN	REPOCH	Len	-	LFU
61/M	ALK-negative ALCL	Primary	Breast/axillary LN/bone	-	-	-	-
57/F	SLL	Secondary	Breast/Retroperitoneal LN, spleen	Ibrutinib	-	-	On ibrutinib
44/F	DLBCL ABC	Secondary	Breast, kidney, pancreas, peritoneum, ovary, LN	-	-	-	-
57/M	DLBCL ABC	Primary	Breast, axillary LN, intramuscular deposit	RCHOP	-	-	On RCHOP

F - Female, M - Male, DLBCL GCB - Diffuse large B-cell lymphoma germinal center B-cell-like, P C - Paclitaxel + carboplatin, R-DHAP - Rituximab + dexamethasone + high dose cytarabine + cisplatin, CEOP - Cyclophosphamide + etoposide + vincristine + prednisolone, LFU - Lost to follow-up, LN - lymph node, RCHOP – Rituximab + cyclophosphamide + hydroxydaunorubicin + vincristine + prednisolone, IT MTX - Intrathecal methotrexate, DLBCL ABC - Diffuse large B-cell lymphoma Activated B-cell type, RCEOP - Rituximab + Cyclophosphamide + etoposide + vincristine + prednisolone, Len - Lenalidomide, REPOCH - Rituximab + etoposide + prednisolone + cyclophosphamide + hydroxydaunorubicin, HD MTX - High dose methotrexate, SLL - Small lymphocytic lymphoma

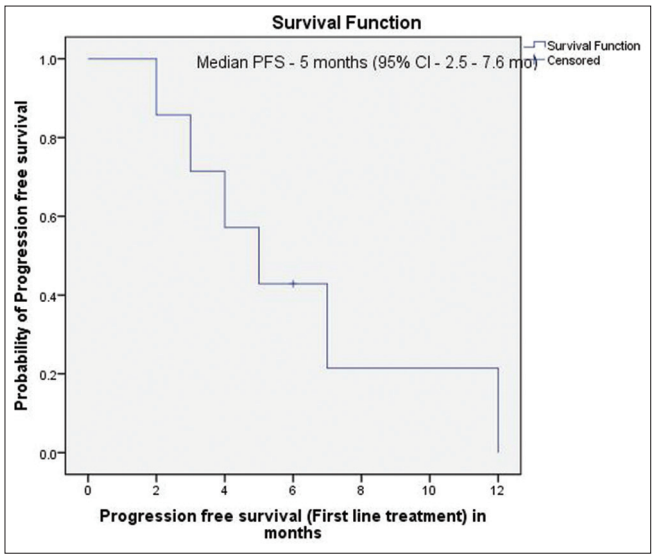


Figure 5: PFS on first-line treatment

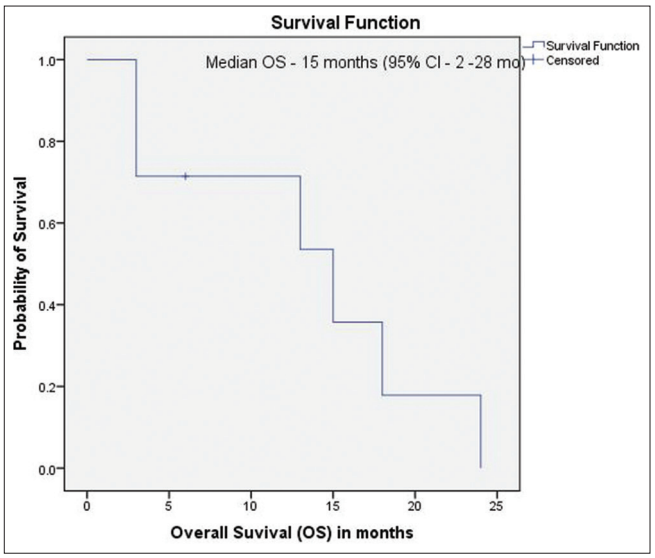


Figure 6: Overall survival

Among the two male patients with PBL, one was a case of DLBCL-ABC type and one of ALK-negative ALCL.[12] ALCL is one of the most common types of PBL of T-cell origin; however, less than 50 cases have been noted in the absence of breast implant.[1] Ours was one of these rare cases of ALK-negative ALCL. Primary Burkitt lymphoma, another rare form of PBL, commonly presents as a bilateral breast mass with a rapid and aggressive course, as similarly noted in our study.[1]

Low-grade lymphomas are very rare in the breast, but we had a patient with SLL involving the breast. Involvement of the breast by chronic lymphocytic lymphoma (CLL)/SLL is highly rare, and to date, less than six cases have been documented.[14] SLL involving the breast typically is seen as a widespread involvement of various organs and lymph nodes, with a similar presentation in our patient. Although CLL/SLL is known to involve the breast diffusely and bilaterally, we noted only a single breast lump in association with lymphadenopathy in this case.[15] On further testing, this patient had an unmutated immunoglobulin heavy chain variable region gene (IgHV) status and did not have either 17p deletion or TP53 mutation.

Our data on breast lymphoma suggest a quite poor prognosis compared to other lymphomas. We will discuss the prognosis of DLBCL of the breast, the most common type. The prognosis of DLBCL varies with the stage, type, GCB versus non-GCB, and other factors like the revised international prognostic index (R-IPI) in the current era of treatment. Patients with the limited-stage disease have a 2-year PFS and OS in the range of 70–90%. For advanced-stage patients, 5-year PFS varied from 30–40% for ABC type to 70–75% for GCB type. Similarly, the 5-year OS varied from 40–50% for the ABC type to 75–80% for the GCB type.[16] Although our treated patient numbers are small, the 2-year PFS and OS are both below 20%, indicating a poorer prognosis than DLBCL in general. The limited-stage breast lymphomas did better than secondary lymphoma in the limited data we have.

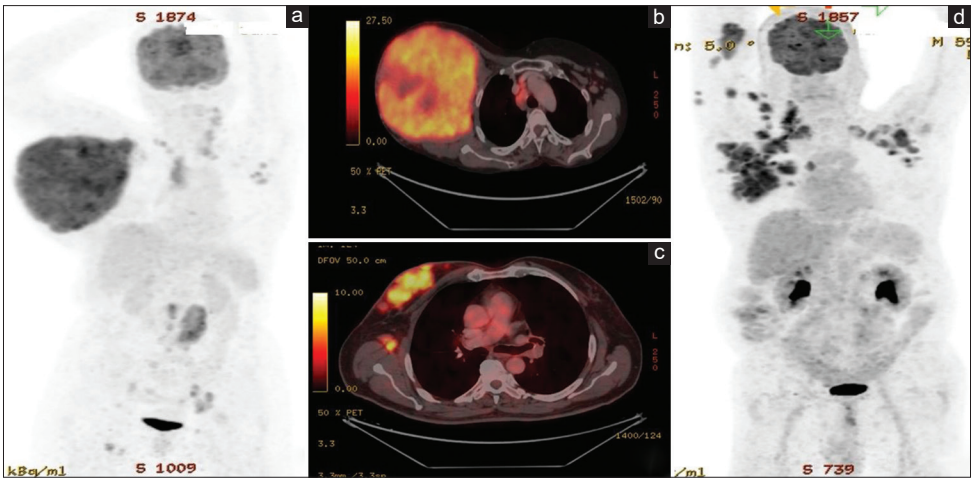


Figure 7: a and b Fluorodeoxyglucose (FDG) avid lymphomatous involvement of breast in a female. c and d FDG avid lymphomatous involvement of breast and axillary lymph nodes in a male

The 4-year PFS and OS for patients with poor risk as classified by an R-IPI score of 3 or more are 53% and 55%, respectively.[17] All but one of our patients came in the poor-risk category. Breast lymphomas have a higher propensity to come under the poor-risk category due to the weightage on extra-nodal involvement. But, even otherwise, their prognosis seems worse than other poor-risk DLBCL. There is a paucity of survival data from other studies of breast lymphoma in the rituximab era.

Misdiagnosis remains a significant issue leading to delays in clinical benefits for patients and disease progression. But, in the analysis by Surov *et al*.,[9] no specific features point toward a diagnosis of breast lymphoma vis another carcinoma apart from histopathology. With the near-universal use of core biopsies for breast lumps to get hormone and HER2 receptor status, in the future, this problem will hopefully be taken care of.

The prognosis of primary breast lymphoma is relatively better than that of secondary breast lymphomas. Our data is small to reach a definitive conclusion, but a trend towards better OS with PBL was seen. Most SBL in our study had numerous other extra-lymphoid organ involvement. As these are also indicators of poor prognosis, this may explain the same.[18]

CONCLUSION

Breast lymphomas are rare malignancies of the breast having a poorer prognosis compared to lymphomas with the same stage without breast involvement. More aggressive treatment and studies are required to improve the prognosis. An accurate pathological diagnosis plays an essential role in the timely and appropriate initiation of treatment.

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Conflicts of interest
There are no conflicts of interest.

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