Primary breast lymphoma: A case series and review

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ABSTRACT

The primary breast lymphoma (PBL) is a rare manifestation of extranodal non-Hodgkin's lymphoma. The clinical features are indistinguishable to that of breast carcinoma. They usually do not have characteristic clinical and imaging findings. The pre-operative diagnosis of PBL is difficult and the diagnosis is based on biopsy and immunohistochemical staining. Diffuse large B-cell lymphoma is the most common histological diagnosis. We retrospectively analyzed four cases of PBL who attended at our center, between 1997 and 2019 and discussed to determine the common clinical features and therapy. These cases were originally treated by chemotherapy, that is, rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP/CHOP) or combined chemotherapy and radiotherapy and had recurrence in the central nervous system (CNS). Due to the high incidence of CNS involvement in these patients, many authors strongly believe that patients with aggressive forms of PBL should receive CNS prophylaxis, even in the early stages, as this may improve the outcome and significantly reduce the risk of a CNS relapse.

Key words: Diffuse large B-cell lymphoma, Extranodal non-Hodgkin’s lymphoma, Primary breast lymphoma

Breast involvement by lymphoma is very rare and presents as a primary breast tumor or as a secondary disease. Primary breast lymphoma (PBL) represents 1% of all non-Hodgkin’s lymphoma, 2.2% of extranodal lymphomas, and approximately 0.04–0.5% of malignant breast tumors [1-7]. A limited number of cases have been reported in the literature so far. The most common histology is diffuse large B-cell lymphoma (DLBCL), although other less frequent diverse lymphoma subtypes have been reported [1-10].

PBL is mainly found in female patients, accounting for 95%-100% and having bimodal age distribution [2,11-13]. It usually presents as a clinically palpable mass which is similar to that of breast cancer and is rarely detected on screening. Although the imaging characteristics are not specific and are less helpful in the diagnosis of this entity compared with breast carcinoma, they may sometimes mimic benign masses. Its diagnosis relies on surgical biopsy or fine-needle aspiration cytology (FNAC).

Unlike primary breast carcinoma surgery is not the key treatment for PBL. The treatment is mainly a combination of chemotherapy and radiation therapy [5,14,15]. However, confidential data regarding appropriate treatment strategy, including radiotherapy (RT) techniques such as RT field, RT dose, and RT fraction size in PBL, are still lacking. Due to the rarity of PBL, limited information about this disease in Indian women is available. We present four cases of PBL from our institution to summarize the clinical characteristics and treatment outcomes.

CASE SERIES

Case 1

A 22-year-old married woman without any comorbidities presented with a lump in the right breast with prominent veins and milky discharge for the past 1 month. The patient had normal vaginal delivery 3 months before the presentation when she noticed the enlargement of her right breast with a lump. She was given a course of oral antibiotics (amoxicillin plus clavulanic acid) to treat suspected mastitis, but her condition was not improved. On physical examination, the patient was found to have right breast enlargements, with 12 cm×10 cm mass occupying all the quadrants without nipple retraction. Palpable, single, and mobile lymph node of size 3 cm×3 cm was noted in the right axilla.

Core biopsy was taken and the histological analysis showed Burkitt’s lymphoma. Her computerized tomography (CT) scan of the thorax and abdomen was normal. The bone marrow examination did not reveal any infiltration. The patient was given chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisolone [CHOP] protocol) for a total of six cycles. After six cycles, the primary lesion disappeared and she developed brain metastasis after 1 month. Whole-brain palliative RT was given with a total dose of 30 Gy/10 fractions, followed by palliative chemotherapy. However, she died after 6 months.
Case 2

A 35-year-old married female presented with a history of two subcutaneous right breast lumps and a single subcutaneous nodule on the upper outer quadrant of the left breast for 2 weeks. On examination, two right breast lumps and one left breast lump were found which measured 3 cm × 2 cm, 1.5 cm × 1 cm, and 1.5 cm × 1 cm, respectively and there was no axillary lymph node enlargement. Ultrasound confirmed two small solid hypoechoic superficial masses in the lower outer right breast and small, rounded hypoechoic nodule on the left breast upper and outer quadrant.

Excision of bilateral subcutaneous swelling was done and the histological analysis showed a DLBCL. A CT scan of the thorax and abdomen and a bone marrow examination showed no evidence of the disease’s dissemination. She was given chemotherapy with six cycles of CHOP. She presented with headache and seizure after 1 month of completion of chemotherapy. A CT scan of the brain reveals a central nervous system (CNS) metastasis. A course of palliative RT 30 Gy in 10 fractions was given to the whole brain. She expired after 2 months.

Case 3

A 60-year-old woman presented with a right breast mass for 1 month. On physical examination, the breast mass measured 5 cm × 4 cm at the upper and outer quadrant without any evidence of skin changes or nipple retraction. Palpable and mobile lymph node of size 2 cm × 2 cm was noted in the right axilla. Ultrasonography showed well-defined, lobulated, and heterogeneous echotexture with areas of hyperechogenicity and small, rounded hypoechoic nodule with a single axillary lymph node enlargement.

The patient underwent a partial resection and the histological analysis showed a DLBCL (Figs. 1 and 2). A CT scan of the thorax and the abdomen, as well as her bone marrow examination, showed no evidence of the disease dissemination. She was given six cycles of R-CHOP chemotherapy. Relapse was observed after 7 months with multiple subcutaneous nodules on the abdominal wall and liver lesions. Palliative chemotherapy was started, but she died after 1 year.

Case 4

A 60-year-old woman presented with a complaint of the left breast mass. On physical examination, the breast mass measured 4 cm × 4 cm at the lower outer quadrant without any evidence of skin changes or nipple retraction. A palpable, single, and mobile lymph node of size 2 cm × 1.5 cm was noted in the left axilla. Ultrasonography showed well-defined, lobulated, and heterogeneous echotexture with areas of hyperechogenicity and small, rounded hypoechoic nodule in the left axilla. She was also found HIV positive.

The patient underwent a partial resection of the breast mass and the histological diagnosis showed a DLBCL. A CT scan of the thorax and the abdomen, as well as a bone marrow examination, showed no evidence of the disease dissemination. She was given six cycles of R-CHOP chemotherapy followed by RT. On follow-up after 1 year, she relapses with multiple abdominal lymph nodes and hepatic lesions. Palliative chemotherapy was started, but she lost to follow-up.

DISCUSSION

The PBL is an unusual condition with poor clinical outcome. The definition of PBL is to include systemic DLBCL with breast involvement because, in most cases, it is difficult to prove that the breast was the primary extranodal site. Therefore, we maintained the traditional definition of PBL in our study which was set out by Wiseman and Liao [16], focused on cases with involvement limited to the breast and the regional nodes. Although the peak age for PBL is usually the sixth decade, it is different between ethnicities. The median age in Western countries is over 60 years (62–64 years), whereas, in East Asian countries, it is 45–53 years [1,17,18]. Two of our patients were diagnosed in the third and fourth decades.

PBL almost always occurs in females. Many studies have reported that the right breast is more frequently involved and has a relatively high rate (5%–20%) of bilateral involvement at the time of diagnosis especially observed during pregnancy.

Figure 1: Microscopic image of primary breast lymphoma. ×100 (Case 3)

Figure 2: Primary breast lymphoma immunohistochemistry ×400 showing (a) leukocyte common antigen-negative and (b) CD 20 positive (Case 3)
or postpartum [5,11,19-22]. In our study, the right breast was involved in three patients with two patients having ipsilateral axillary lymph nodes involvement and one patient had bilateral breast disease, whereas one patient had a left-sided disease.

More than 80% of PBL are B-cell lymphomas, mostly CD20+. The most frequent histopathological type is DLBCL which accounts for more than 50% of all PBL, while follicular lymphoma (FL) accounts for 15%, mucosa-associated lymphoid tissue lymphoma accounts for 12.2%, and Burkitt’s lymphoma (BL) and Burkitt-like lymphoma account for 10.3%. Our three cases showed a DLBCL histology, whereas the fourth one showed BL.

Clinically, breast lymphoma presents as a single or multiple painless rapidly growing, palpable lumps, with or without axillary lymph node involvement, which may involve unilateral or bilateral breast and is difficult to distinguish the entity from breast carcinoma. PBL tends to be larger in size at the time of diagnosis compared with breast carcinoma, but it cannot be regarded as a distinguishable feature. Nipple retraction, skin erythema, peau’d’orange appearance, and nipple discharge are rare in PBL as compared with breast carcinoma. It may sometimes present as diffuse breast enlargement with edema and may mimic an inflammatory process [4,13,23]. The usual B symptoms seen with lymphomas such as fever, weight loss, and night sweats are rare with PBL. Enlarged ipsilateral axillary lymph nodes are reported in 13–50% of cases [13,24,25]. It has also been identified that the disease has a tendency for CNS progression [5,9,11,26].

On imaging, these lesions usually appear as a well-circumscribed homogenous hypoechoic mass with the absence of microcalcification, spiculation, and distortion of surrounding tissue [18]. The diagnosis of PBL includes radiologic investigations (X-mammography, ultrasound, magnetic resonance imaging, and positron emission tomography), FNAC, biopsy, and immunohistochemical biomarkers.

Treatment of PBLs follows treatment guidelines for lymphomas of the same stage in other locations. The choice of chemotherapy should be based on the histologic subtype, disease extent, and the individual patient. Jennings et al. [1] reviewed all published PBL reports over the three decades (1972–2005) and concluded that mastectomy offers no benefit, nodal status predicts outcome, and guides the optimal use of chemo-RT. Ryan et al. [5] concluded that the combination of limited surgery for diagnostic purposes, anthracycline-based chemotherapy, and involved field radiation therapy produced the best outcome in the pre-rituximab era. Adding rituximab (monoclonal antibody against CD20 cells) for the treatment in patients with primary breast DLBCL is recommended in studies [27,28].

Prospective randomized trials with rituximab for primary breast DLBCL are needed. A similar opinion was expressed by Aviles et al. on the basis of their prospective study in which 96 patients were treated using combined modality treatment with chemotherapy and radiation [14]. Liu et al. conducted a large population-based analysis and found that adding RT was associated with the improvement of overall survival in the rituximab era [15]. They recommended RT for PB-DLBCL patients treated with rituximab regardless of age, stage, tumor laterality, and race.

However, the surveillance, epidemiology, and end results database has some limitations that are lacking information on a specific treatment regimen and its time course. Another limitation is that the volume and dosing of RT. In our case, RT was given by conventional technique using Co60 by tangential portals with a dose of a 50.4 Gy in 28 fractions (36 Gy to locoregional followed by boost). In the previous literature, it was concluded that combined modality approaches such as chemotherapy in combination with RT produce superior outcomes for PBL. It is not clear whether R-CODOX-M/RIV AC protocol “the standard protocol for BL” is superior to R-CHOP in the treatment of primary BL of the breast and needs further studies. Our single BL case treated with CHOP chemotherapy as the case was of the pre-rituximab era.

However, there is currently no consensus on CNS prophylaxis for primary breast DLBCL, and the addition of rituximab to chemotherapy may decrease the relapse rate of CNS as well as a systemic disease. Studies have shown high CNS relapse rates in up to 20% of patients resulting in poor overall survival rates and recommend adding central nervous system prophylaxis to systemic treatment in PBL [14,15,27-29]. In our study, none of the patients received CNS prophylaxis. Two patients received rituximab did not have CNS relapse and CNS relapses occurred in two patients who did not receive rituximab.

**CONCLUSION**

Breast lymphoma must be considered in the differential diagnosis of a breast lump, even in the presence of cutaneous inflammatory changes. PBL is considered a non-surgical disease and can be treated successfully with combined chemotherapy and RT. Further prospective studies are needed to evaluate the role of R-CHOP and RT, their treatment course, dose, and volume of RT with a proper sequence in PBL.

**COMPLIANCE WITH ETHICAL REQUIREMENT**

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institution and nation) and with the Helsinki declaration of 1975, as revised in 2008.

**REFERENCES**


