Primary Diffuse Large B-Cell Lymphoma of the Breast: A Rare Case Report and Review of the Literature

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ABSTRACT

BACKGROUND: Breast lymphomas are rare extranodal lymphomas. They constitute a tiny percentage of malignant tumors of the breast and a small subset of extranodal lymphomas. The rarity of breast lymphomas is attributed to the very scanty lymphoid tissue content of the chest wall.

AIMS OF STUDY: This case report aims to provide an up-to-date review of the literature on breast lymphomas and clinicians to consider the possibility of this disease entity while treating a breast mass.

CASE PRESENTATION: A case is reported of primary mammary non-Hodgkin lymphoma in a 52-year-old man. Fine needle aspiration cytology (FNAC) was inconclusive. Incisional biopsy-confirmed primary breast lymphoma was diagnosed as the diffuse large B-cell type: non-Hodgkin lymphoma. He had complete disease remission in response to chemotherapy – Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone (CHOP). After that, the patient did not require further surgical intervention. He was followed up at two-monthly intervals for eighteen months in the surgical outpatient clinic with no disease recurrence and satisfactory clinical outcome, following which he discontinued follow-up visits.

CONCLUSION: While assessing breast masses, clinicians must recognize primary non-Hodgkin lymphoma as a potential differential diagnosis. A core biopsy of breast masses is needed to exclude it, and appropriate treatment must be given if diagnosed.

Keywords: non-hodgkin lymphoma; primary breast lymphoma; diffuse large B-cell lymphoma; breast cancer; combination chemotherapy

ABBREVIATIONS

PBL: Primary breast lymphoma; NHL: Non-Hodgkin lymphoma; DLBCL: Diffuse large B-cell lymphoma; PNHL: Primary non-Hodgkin lymphoma; SBL: Secondary breast lymphoma; MALT: Mucosa-associated lymphoid tissue; IELSG: International Extranodal Lymphoma Study Group; CXCL12 and CXCL13: Cellular receptors and tissue chemo-attractants; GCB: Germinal center B cell subtypes; Non-GCB: Non-Germinatal center B cell subtypes; ABC: Activated B cell subtypes; PFS: Progression-free survival; OS: Overall survival; PB-DLBCL: Primary breast-Diffuse large B-cell lymphomas; IPI: International prognostic index; CISL: Consortium for improving the survival of lymphoma; OED: one extranodal disease; MED: multiple extranodal diseases

INTRODUCTION

Primary breast lymphoma (PBL) is a rare clinical entity but a well-defined subtype of non-Hodgkin lymphoma (NHL). Several reports suggest that PBL is uncommon, representing only 0.5% of malignant breast tumors; 1% of all NHL, and 2% of extranodal lymphomas [1–5]. Most breast lymphomas are non-Hodgkin’s type, which represents approximately 70-90% [6]. Diffuse large B-cell lymphomas (DLBCL) constitute 46-71% of all PBL [7].

However, primary NHL (PNHL) is the most frequent hematopoietic tumor of the breast [8, 9].

Definition of Terms

Breast lymphoma has been classified into primary and secondary types. PBL is described as the co-existence of lymphoid infiltrate and mammary tissues at the same site, and in the absence of evident widespread lymphoma or other extra-mammary lymphomas [10–12]. On the contrary, secondary breast lymphoma (SBL), therefore, is a clinical scenario in which the breast has lymphoid infiltrate, in addition to the presence of other extra-mammary sites of lymphoma. The clear difference between PBL and SBL is sometimes tricky and, in some cases, not readily distinguished [13, 14]. Interestingly, there are also other less frequent NHL subtypes, including mucosal-associated lymphoid tissue (MALT) lymphoma, follicular lymphoma, Burkitt’s lymphoma, and T-cell lymphoma [1, 2, 15–17]. In 1972, Wiseman and Liao [18] redefined PBL according to four criteria that are summarized in Table 1 below. They include (i) mammary tissue and lymphoma must be in close anatomic proximity, (ii) no preceding diagnosis of extra-mammary lymphoma, (iii) no evidence of disseminated disease,
Pathogenesis of Breast Lymphomas

The pathogenesis of breast lymphomas is still not wholly known. However, the documented evidence of what is known might suggest different pathogenesis for PBL. One study on PB-DLBCL conducted by the International Extranodal Lymphoma Study Group (IELSG), revealed that about 40% of relapses were initially in the breast [3]. A related study by the same group regarding testicular lymphoma revealed an ipsilateral and contralateral relapse rate of only 20% [21].

The phenomenon of ‘organ-specific relapse’ might reflect poor local disease control but also brings to mind the possibility likelihood of homing of tissue. This phenomenon may be mediated by cellular receptors and tissue chemo-attractants such as CXCL12 and CXCL13, as reported in other extranodal lymphomas [22].

Sub-classifications of DLBCL

There has been progressing in the area of gene expression profiling and immunohistochemistry. On this basis, DLBCL in now being characterized as germinal center B cell (GCB) and activated B cell (ABC/non-GCB) subtypes, with the latter having a more unsatisfactory outcome [23–25]. Only a few studies have examined this sub-classification in PBL, but results are fascinating. Nitsu et al. [26] mentioned that a non-GCB pattern in 57% of PB-DLBCL found in their study confirmed a poor progression-free survival (PFS); but, not representative of the overall survival (OS). Furthermore, Yhim et al. [27] performed a comparison of PBL and nodal DLBCL and reported significantly higher rates of non-GCB in PBL (95% versus 62%, \(P=0.001\)), with similar 3-year OS and PFS rates as the GCB cohort [27].

Lymphoma and Sex Hormones

While the overwhelming majority of patients with PBL are females, there are a few rare reports in males [3, 28–33]. These distinct gender differences suggest that sex hormones may be necessary for the pathogenesis of PBL. Further evidence in support of the likely involvement of sex hormones is the relatively high rate (5%–20%) of bilateral disease at diagnosis [3, 14, 34].

The latest effort has been geared towards establishing a possible link between lymphoma, estrogen, and prolatin, which has also come from in vitro and epidemiological studies. Still, the results remain inconclusive [35–40]. Only two reports are referring to sex hormone expression in human PBL tissue. Ariad et al. [41] examined eleven PBL specimens, none of which stained positively for estrogen receptor (ER). At the same time, Hugh et al. [42] reported ER positivity in two PBL tissue specimens. Therefore, there may be a link between sex hormones and the development of NHL in general and PBL in particular. However, further research is required to establish the role of sex hormones in PBL.

Systemic B Symptoms and DLBCL

Reviews of the data from large clinical trials of DLBCL reveal that about 25% ~ 37% of these patients have systemic symptoms [43–45]. However, in 26 publications on PBL, the range was usually between 0% and 22%, suggesting a low prevalence of systemic B symptoms [1–5, 13, 21, 28, 46–59]. Moreover, using the Wiseman–Liao criteria [18], patients with systemic involvement are not part of the original definition resulting in the pre-selection of patients with the loco-regional disease and reduced chances of developing B symptoms. Taken together with the lymphoma international prognostic index (IPI), the prevalence of systemic B symptoms in the vast majority of PBL patients is low to the intermediate-range [18].

Clinical Considerations

The clinical presentation and radiological features of PBL are similar to those of breast carcinoma. PBL is mostly observed in females with scarce documentation of cases in males. In most patients, the most common presentation is a painless enlarging breast mass. Patients with PBL often present with signs of skin edema, retraction, erythema, and nipple involvement. On a mammogram, breast lymphomas may lack the irregular borders of infiltrating carcinomas, and more than half the tumors exhibit no calcification [59, 60].

Notwithstanding the clinical and radiographic similarities between the two tumor types, their treatments differ radically. Routine fine needle aspiration cytology (FNAC) reveals diagnosis in most cases performed for breast lumps, but sometimes it is inconclusive as with the current evidence that was originally misdiagnosed as poorly differentiated duct carcinoma [61, 62]. Hence, it is essential to accurately distinguish lymphomas from other breast malignancies to assign patients to treatment appropriately. However, no clear consensus about the treatment of PBL has emerged. Therefore, the accumulation of data in the form of case reports and other clinical studies is essential [63, 64].

Staging and Prognostication

Prognostic indicators include the clinical stage, histologic type, and patient's age [12]. In clinical practice, the Wiseman–Liao definition confirms the clinical phase of PBL to Ann Arbor IE or IIE, and patients are by definition ‘early-stage’ [18]. The significant difference between stages IE and IIE (involvement of regional lymph nodes) is vital because of variation with stage IIE (20%–57%) [20, 46, 54, 65]. In this respect, the use of positron emission tomography (PET) scan becomes relevant to better mark the stages due to its high sensitivity in DLBCL. There is a lack of data on PB-DLBCL, yet from the few cases described, it seems that PET yields similar advantages as in nodal DLBCL [66, 67]. Bilateral PBL is rare, and both staging and prognostication are controversial. The most extensive series of PB-DLBCL reported until now, classified cases with bilateral breast involvement as stage IV [3], whereas others have defined them as stage IE [47] or II [46, 49, 53, 54, 68, 69]. For the sake of uniformity, and given a possible worse prognosis of bilateral PBL [2, 4, 42, 47, 70], these rare cases may well be classified as stage IV disease. The stratification of PBL into risk groups is usually based upon the international prognostic index (IPI) [71]. Several reports have suggested alternative models for PBL prognostication, identifying increased microvascular density or increased levels of soluble interleukin-2 receptors (>1000 U/ml) [26] as predictors of worse outcome [46]. “The report by the Consortium for improving the survival of lymphoma (CISL) summarized 68 cases of PB-DLBCL; from the existing definition of one extranodal disease (OED) category when one breast was involved and multiple extranodal diseases (MED) when additional extranodal sites are present” [2]. In both types, the presence of nodal disease was not seen as relevant. The OED group had better 5-year PFS than the MED group (64.9% versus 27.5%, respectively) and better 5-year OS (74.3% versus 24.5%, respectively) [2]. Further, tumor dimension has been noted by several investigators as vital, with a size of 4–5 cm possibly predicting worse outcome [12, 16, 26, 47, 65]. This cutoff is probably derived from the breast TNM classification, which defines tumor size >5 cm as T3.
being the largest diameter of interest [72]. “Analysis of available data on the outcome of PBDBLCL (Table 2), and comparison with nodal DLBCL, has led us to the conclusion that both categories have a similar prognosis as long as all patients are treated primarily with anthracycline-containing regimens followed by radiotherapy” [11].

In addition to the above, there is growing interest in an in-depth database of breast lymphomas in general. Many reports suggest that “the breast is an unfavorable site” [86], but no prior diagnosis of breast carcinoma [6, 10].

AIMS OF STUDY:
This case report aims to provide an up-to-date review of the literature on breast lymphomas and encourage clinicians to consider the possibility of this disease entity whenever they manage a patient with a breast mass.

CASE PRESENTATION
A 52-year-old male industrial chemist presented to the surgical outpatients’ department at a tertiary hospital, with a left breast lump, which increased in size progressively. There was darkish skin discoloration but no nipple discharge. The patient also had significant weight loss and intermittent fever over the 8 months period. The patient had no family history of cancer. He initially received herbal medications for some months and was only presented to the tertiary hospital due to herbal medications’ failure. Physical examination revealed a middle-aged man who was chronically-ill looking and cachectic. The left breast was diffusely enlarged with a 4cm x 3cm size mass in the central portion with a darkening of overlying skin. Also, he had discrete tiny ulcers in the nipple-areolar complex oozing very scanty serosanguinous fluid. Axillary lymph nodes and other lymph node fields were unremarkable, as was the remainder of his physical examination.

FNAC was suspicious of malignancy but inconclusive. He subsequently had an incisional biopsy with histopathological analysis, which confirmed PBL diagnosed with a large B-cell type (non–Hodgkin lymphoma). The clinical photograph of this patient is as displayed in Figure 1. Figure 2 shows the characteristic diffuse lesion, as seen in the mammographic study, and Figure 3 shows DLBCL with activated B cell type. The tumor cells were negative for CD3, CD5, CD15, CD30, CD45, and cytokeratin (CK) pan but were positive for CD20, CD10, and BCL6, as seen in Figures 4 to 7. The breast scan showed multiple heteroechoic tiny masses of variable sizes in the central portion of the right breast. Cranial and abdominal computed tomography (CT) scans were mainly typical. However, a chest CT scan showed left pulmonary infiltrates with hilar lymphadenopathy but no pleural effusion. The biochemical profile and complete blood count were also standard. Subsequently, the patient had six courses of chemotherapy courses – Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone (CHOP). Interestingly, the patient did not require further surgical intervention. He had complete disease remission and was followed up at two-monthly intervals for eighteen months in the surgical outpatient clinic with no disease recurrence and satisfactory clinical outcome, following which he discontinued follow-up visits.

DISCUSSION
We are here reporting the case of a male patient with a lesion involving the left breast. While “both nodal and extranodal lymphomas are slightly predominant in males, breast involvement is seen mostly in females” [73]. Thus, our report is rare. “Some have previously reported that cases of PNHL of the breast involve the right breast and that almost all affected patients are females” [7, 8].

Primary breast lymphomas are generally regarded as rare, but they remain the most frequent hematopoietic tumor of the breast [6-9, 59]. Clinicians presenting breast carcinomas should be aware of this entity to distinguish its clinical presentation, management, and prognosis from breast carcinoma [6, 10-12]. Single-breast involvement is more common, particularly in the upper quadrant of the right side [74-77].

Interestingly, 1% to 14% of reported PBL cases have bilateral disease [20]. Many criteria have been formulated for the diagnosis of primary lymphoma of the breast [77]. In 1972, Wiseman and Liao defined diagnostic criteria for PNHL of the breast to include 1) the presence of technically adequate pathologic specimens, 2) the close association of mammary tissue, 3) lymphomatous infiltrate, 4) no prior diagnosis of extramammary lymphomas and 5) positive immunophenotyping of axillary lymph nodes involvement [8, 77-80]. The patient we are reporting on fulfilled these criteria, which further supports our conclusion that this was a case of primary breast lymphoma. PBL and breast cancers, in general, are not the disease of the younger age group. There is a slight preference for the right breast, but the explanation remains unclear [81]. It presents most commonly as a palpable mass, as seen in this patient [82, 83].

Open biopsy supported with immunophenotyping proved to be a very reliable confirmatory diagnostic tool in this case. Tru-cut biopsies have equally established the diagnosis of breast malignancies with a very high accuracy rate [84, 85]. Radiographic examinations, including mammography, sonography, and CT, are generally nonspecific for PBL [86-89]. Immunophenotyping in the diagnosis of PNHL of the breast is very important. Several reports in the literature confirm that immunophenotyping continues to be the key in evaluating these patients [42, 90-96]. In this case, we are reporting; the histopathological diagnosis was PBL of the large B-cell type (non – Hodgkin type). Tumor cells were negative for CD3, CD5, CD15, CD30, CD45, and CK but were positive for CD20, CD10, and BCL6. There was clinical evidence of distant metastasis to the lung parenchyma (T2 N0 M1).

Several treatment options are available for PBL: surgery, radiation, and chemotherapy have been used alone or in combination. The most common therapeutic approach is chemotherapy with or without adjuvant radiotherapy [64, 95-97]. The impact of surgery in PBL treatment is restricted to obtaining adequate tissue for accurate diagnosis and classification, PBL treatment is similar to that for lymphomas at other sites [94, 95], mastectomy offers no survival benefit or protection from recurrence [14]. In patients with PBL, the survival rates are comparable to those with other lymphomas in general. They are highly favorable when compared to the survival rates of those with breast carcinoma. Prognosis depends on the histological tumor grade [18, 70, 94]. Predictors of survival according to the International Prognostic Index include 1) age, 2) LDH levels, 3) performance status, 4) Ann Arbor staging, and 5) the presence of extranodal tumors in predicting the 5-year survival [95, 96]. For stage I disease, the 5-year survival is 89% [97].
CONCLUSION
In conclusion, clinicians are encouraged to assess breast masses carefully and perform core biopsy to determine if the breast mass is PBL and then give appropriate treatment.

DECLARATIONS
ACKNOWLEDGMENTS:
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AVAILABILITY OF DATA AND MATERIALS:
Not Applicable

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AUTHORS' CONTRIBUTIONS: The authors did the conception, design, coordination, drafting, reading, and approval of the final manuscript.

ETHICAL APPROVAL: Ethical approval is not required for case reports at St Elizabeth Catholic General Hospital & Cardiac Center, Cameroon.

CONSENT FOR PUBLICATION: A written informed consent was obtained from the patient for publication of this case report and any accompanying images.

COMPETING INTERESTS: None declared

REFERENCES


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TABLE 1: WISEMAN AND LIAO CRITERIA FOR PBL [18]

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<td>2</td>
<td>No preceding diagnosis of extra-mammary lymphoma</td>
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<tr>
<td>3</td>
<td>No evidence of disseminated disease, other than ipsilateral axillary lymphadenopathy, and</td>
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<td>4</td>
<td>Adequate quality of the histopathological specimen</td>
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<tr>
<td>5</td>
<td>These criteria are widely accepted in general [3, 12, 15, 16, 19, 20]</td>
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TABLE 2: TREATMENT MODALITIES AND OUTCOME IN SELECTED SERIES OF PBL BASED ON WHO CLASSIFICATIONS

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<th>RADIATION N (%)</th>
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Abbreviation in Table
NR= Not Reported
Int. IPI= Intermediate risk international prognostic index
X* = Percentage of patients in whom IPI was available
FIGURE 3: H&E STAIN, X400

FIGURE 4: DLBCL WITH Activated B CELL TYPE

FIGURE 5: CD 45

FIGURE 6: CD 20

FIGURE 7: CD 10

FIGURE 8: BCL6+ (UNCOMMON)