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Primary Breast Lymphoma in a Woman: A Case Report and Review of the Literature

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Patient: Female, 43
Final Diagnosis: Primary breast lymphoma
Symptoms: —
Medication: —
Clinical Procedure: CT scan • PET • chemotherapy • radiotherapy
Specialty: Oncology

Objective: Rare disease

Background: Primary breast lymphoma (PBL) is an unusual clinical entity accounting for 0.4–0.5% of all breast neoplasms. The usual presentation includes a painless palpable mass similar to that of breast carcinoma. Diffuse large B-cell lymphoma (DLBCL) is the most common identifiable type of PBL based on the histopathological examination.

Case Report: We report an unusual case of a 43-year-old Indonesian woman who presented with a 7-month history of a painless mass in the left breast. A core needle biopsy revealed diffuse infiltration of large atypical lymphoid cells. The immuno-histochemical biomarkers confirmed the diagnosis of a DLBCL. A bone scan showed no evidence of bone metastasis. It was treated non-surgically, based on the decision of the breast multidisciplinary team (MDT). The patient was treated with 4 cycles of combination chemotherapy with R-CODOX/IVAC. A follow-up PET scan revealed non-significant mild F-18 fluorodeoxyglucose (FDG) uptake at the periphery of the residual left breast mass, indicating a radiologically favorable response.

Conclusions: Early and accurate diagnosis of PBL is crucial for selecting the appropriate MDT treatment strategies to avert potentially harmful surgical interventions.

MeSH Keywords: Breast Neoplasms • Fluorodeoxyglucose F18 • Lymphoma, B-Cell

Full-text PDF: <http://www.amjcaserep.com/abstract/index/idArt/896264>



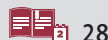
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Background

Primary breast lymphoma (PBL) is an unusual tumor accounting for 0.4–0.5% of all breast carcinomas [1]. It is a rare neoplasm because lymphoid tissue is absent in the breast region. The neoplasm can develop in both sexes, but it is more frequent among females. Breast lymphoma has been classified into primary and secondary types. PBL is defined as the presence of both mammary tissue and lymphoid infiltrate in close association with no evidence of widespread lymphoma or preceding extra-mammary lymphoma [2,3]. It has been reported that high-grade lymphomas commonly manifest as diffuse breast enlargement, whereas low and intermediate-grade tumors often have nodular patterns [4,5]. PBL is usually non-Hodgkin's B-cell type, which accounts for around half of breast lymphomas, and the diffuse large B-cell lymphoma (DLBCL) is the most frequent subtype [6,7].

The usual presentation of PBL is painless palpable mass similar to that of breast carcinoma. Patients with PBL infrequently present with signs of skin edema, retraction, erythema, and nipple involvement [8]. The confirmed diagnosis of PBL is mainly based on findings of the initial biopsy or postoperative pathology results [8].

The treatment options for PBL vary from surgical intervention to chemotherapy and/or radiotherapy [9]. Herein, we report a rare case of primary non-Hodgkin lymphoma of the breast, with B-cell phenotype, diagnosed by mammography and computed tomography and confirmed by histopathological examination. It was successfully treated non-surgically according to the breast multidisciplinary team (MDT).

Case Report

A 43-year-old Indonesian woman, previously healthy, presented with a left breast lump that became noticeable 7 months before. The mass had rapidly increased in size. She had no pain or retraction, no skin changes, and no nipple discharge. Her family history was negative for breast cancer. She was married, menstruating, and had 2 children. Physical examination revealed a hard, non-tender mass involving the whole left breast with a 2×1.5 cm palpable left axillary node. Radiological imaging (mammogram and ultrasound) and histopathological investigation (fine-needle aspiration (FNA) and core biopsy) were performed. The mass was staged with computerized tomography (CT) scan chest/abdomen, and bone scanning. The ultrasonography findings revealed a large, ill-defined, dense mass with internal increased vascularity in color Doppler imaging and multiple enlarged, hypoechoic, axillary lymph nodes (Figure 1). These findings were highly suggestive of breast carcinoma with metastatic axillary lymph nodes. Mammography findings were also suggestive of breast cancer with metastatic axillary lymph nodes; BI-RADS 5 (Figure 2). A bone scan showed no evidence of bone metastasis. The positron emission tomography (PET) scan demonstrated intense hypermetabolism in the left breast, indicating diffuse large B-cell lymphoma (DLBCL). Fine-needle aspiration of the left axillary lymph node showed atypical lymphoid cells suggestive of malignancy. The histopathology findings confirmed the diagnosis with stage IV BEx DLBCL; active B-cell type. Hematoxylin and eosin staining showed large atypical lymphoid cells in sheets (Figure 3). Figures 4 and 5 demonstrate the immunohistochemistry profile. The lymphoid cells showed diffuse cytoplasmic staining for CD20, CD79, and BCL2. There was nuclear staining for BCL6

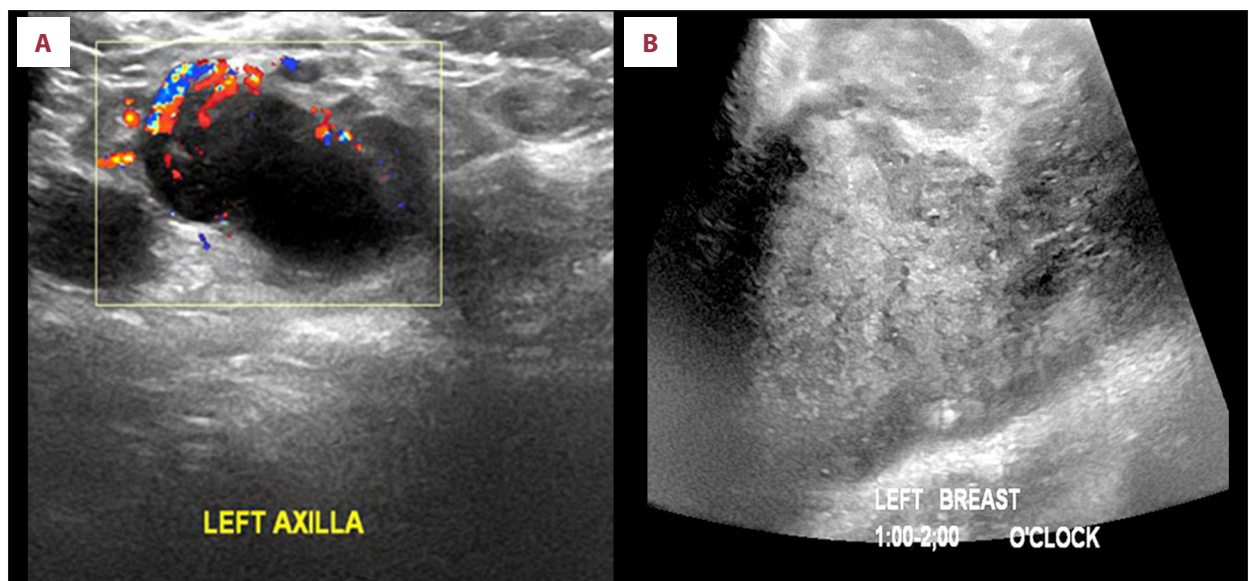


Figure 1. (A, B) Ultrasonography revealed a large ill-defined dense mass lesion with internal increased vascularity in color Doppler imaging.

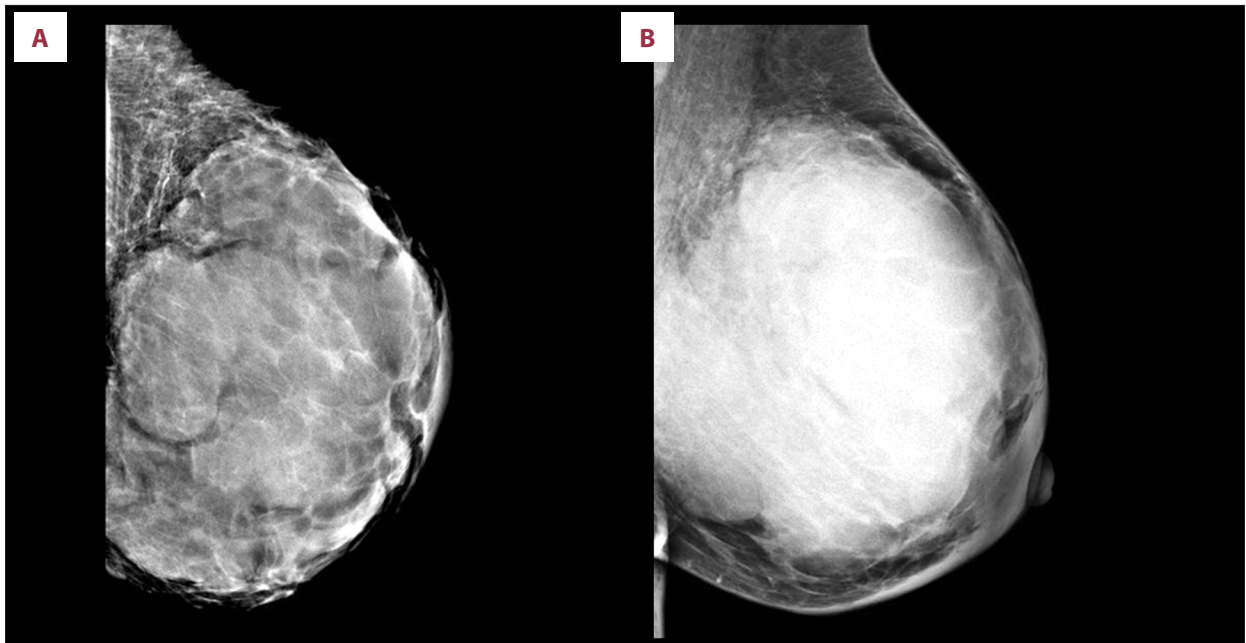


Figure 2. Mammography findings are suggestive of breast cancer with metastatic axillary lymph nodes.

and MUM-1. Staining for CD10 was weak and uncertain. The neoplastic cells were negative for CD3 and CD5, which highlight scattered small T-cells in the background. The proliferation index was approximately 70%.

In summary, the patient had diffuse large B-cell lymphoma, stage IV B, with bulky disease (multiple enlarged lymph nodes at left axillary, left subclavicular, splenic hilum, retroperitoneal, and mesenteric regions) and multiple extranodal localization (breast, muscle, and lung).

The case was discussed in the breast MDT meeting which recommended the treatment with 4 cycles of combination chemotherapy with R-CODOX/IVAC.

R-CODOX-M regimen included rituximab, cyclophosphamide, vincristine, and doxorubicin. The R-IVAC regimen consisted of rituximab, etoposide, ifosfamide, and cytarabine. After chemotherapy, there was a persistent left breast mass, but a PET/CT scan showed no significant uptake. Breast biopsy showed myxomatous and fibrous tissue. The patient was then scheduled for radiotherapy (20 fractions). Two months post-treatment, PET/CT showed a favorable response, resolution of PDG avid lymphadenopathy, and around 90% decrease in PDG avidity of the breast. Intrathecal cytarabine was given as a CNS prophylaxis. By completing the recommended chemo- and radio-therapy, the patient remained in a remission status. The patient had 3 PET scans: at presentation, after the 2nd therapy course, and 3 weeks after the 4th course. Figure 6 shows a follow-up PET scan that revealed a radiologically favorable response in terms of non-significant mild

F-18 fluorodeoxyglucose (FDG) uptake at the periphery of the residual left breast mass.

Discussion

Primary breast lymphoma (PBL) remains an infrequent neoplasm, so clinicians treating breast carcinomas should be aware of this entity in order to distinguish its clinical presentation, management, and prognosis from breast carcinoma cases [10]. With the development of newer diagnostic modalities, the incidence of PBL is increasing, which substantiates the importance of clinical information and awareness of this rare disease. It is predominantly (95%–100%) reported among female patients and is very rare in males [8]. Single-breast involvement is more common, particularly in the upper quadrant of the right side [9,11]. Approximately 1% to 14% of all PBL cases have bilateral breast lymphomas [12]. In our patient, the breast lump was detected on the left side. PBL can be classified based on the presenting symptoms as type A (atypical symptoms) and type B (fever, night sweats, 10% weight loss within half a year) [8]. The investigational findings of our case showed large B-cell lymphoma (non-germinal center type). However, the lower incidence and atypical clinical manifestations makes it difficult to discriminate from breast carcinoma without confirmation by pathological biopsy and immunohistochemical staining [8,13]. Of note, the rapid increase in the breast mass size should be first considered as PBL.

Based on the histopathological findings, breast tumors can be categorized as large cell B-cell lymphomas, monocytoid B-cell

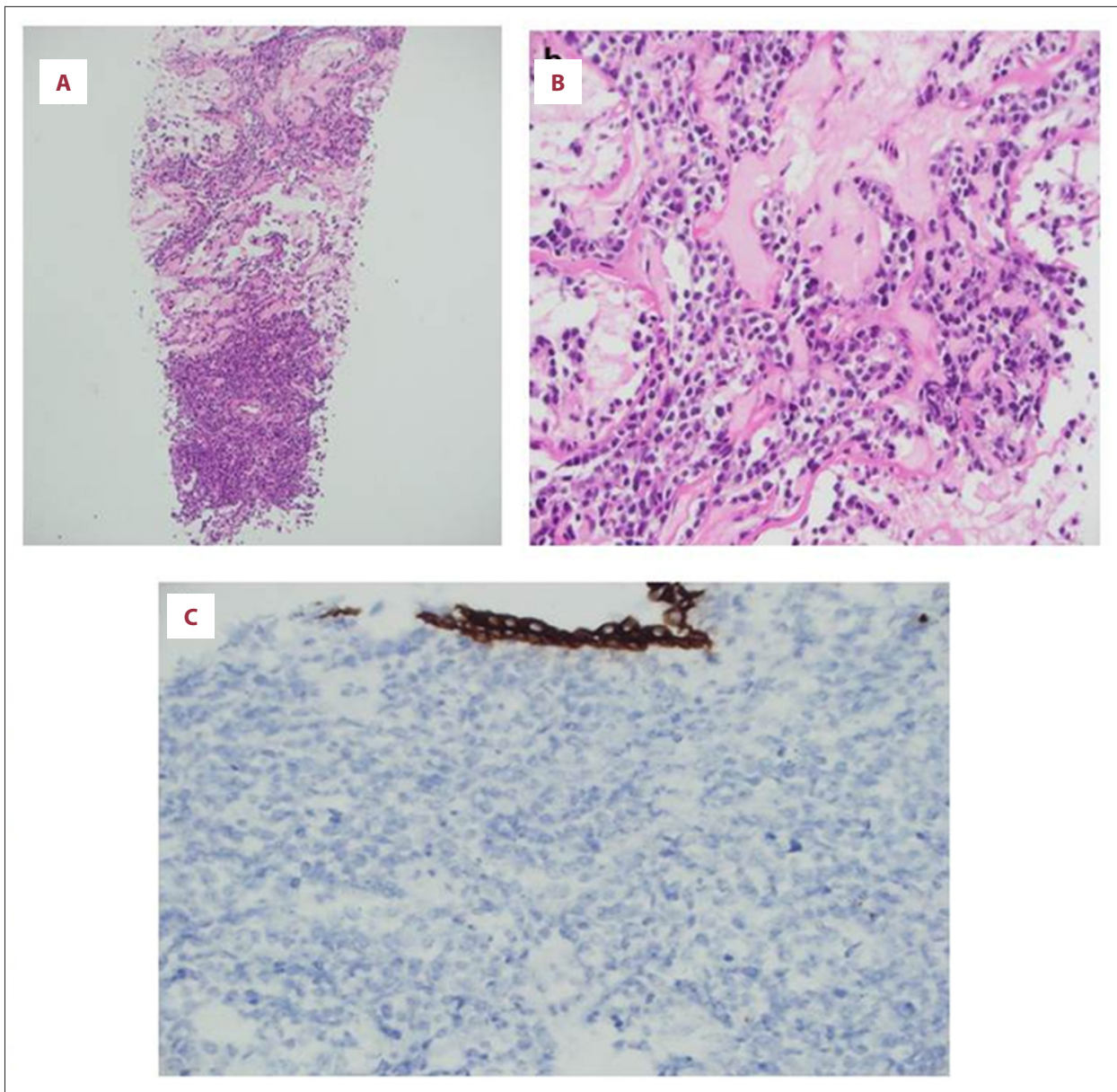


Figure 3. Core biopsy (A) low power magnification (100 H&E stain) showed diffuse cellular infiltrate. (B) High power magnification (400 H&E stain) showed large lymphocyte cells with prominent nuclei. (C) Pankeratin AE1/AE3 (epithelial marker) showed normal duct in the section (central plastic) diffuse large cell.

lymphomas (MBCL), and undifferentiated [14]. It has been reported that the majority of PBL cases have a B-cell lineage and diffuse large B-cell lymphoma (DLBCL), which accounts for 40–70% of all breast lymphomas with features of non-germinal center cells [8]. The assessment of our case revealed DLBCL of the breast with multiple extranodal presentations, which is consistent with the current literature. The diagnostic approach of PBL cases includes radiological investigation (mammography, ultrasonography, magnetic resonance imaging, and positron emission tomography), fine-needle aspiration cytology (FNAC), and immunohistochemical biomarkers [15]. In the present

case, FNA of the left axillary lymph node showed atypical lymphoid cells suggestive of malignancy. The immunohistochemistry profile was consistent with diffuse large B-cell lymphoma, non-germinal center-type. The malignant lymphoid cells were positive for the B-cell markers CD20 and CD79 and negative for T-cell markers CD3 and CD5. FNAC is ideal for the primary diagnosis of PBL as it helps in early detection and treatment. However, the differential diagnosis of PBL should be made according to the pathological findings [16], which is crucial for understanding the typing and staging of these tumors. To distinguish PBL based on its origin from the immune tissues,

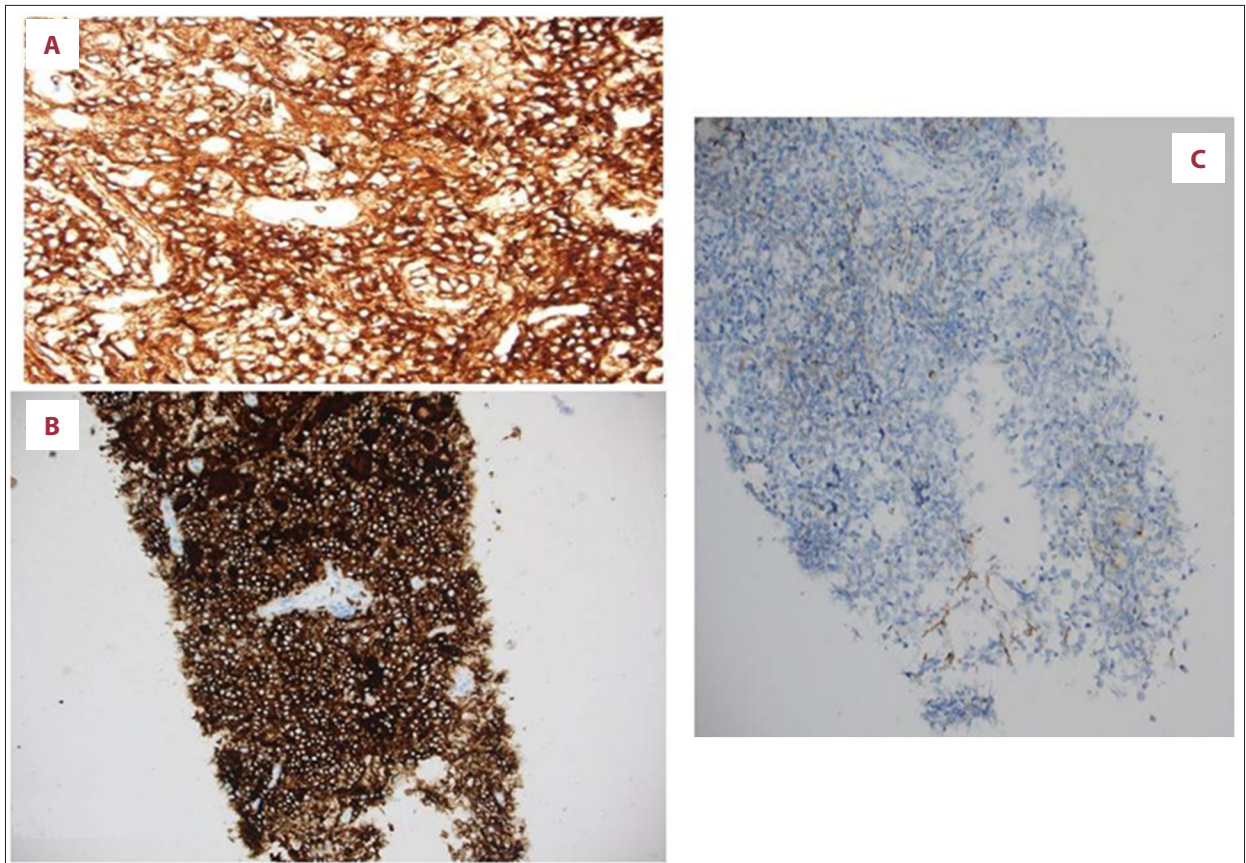


Figure 4. Immunohistochemistry. (A) CD20 (positive); (B) CD79a (positive); (C) CD10 (weak/negative).

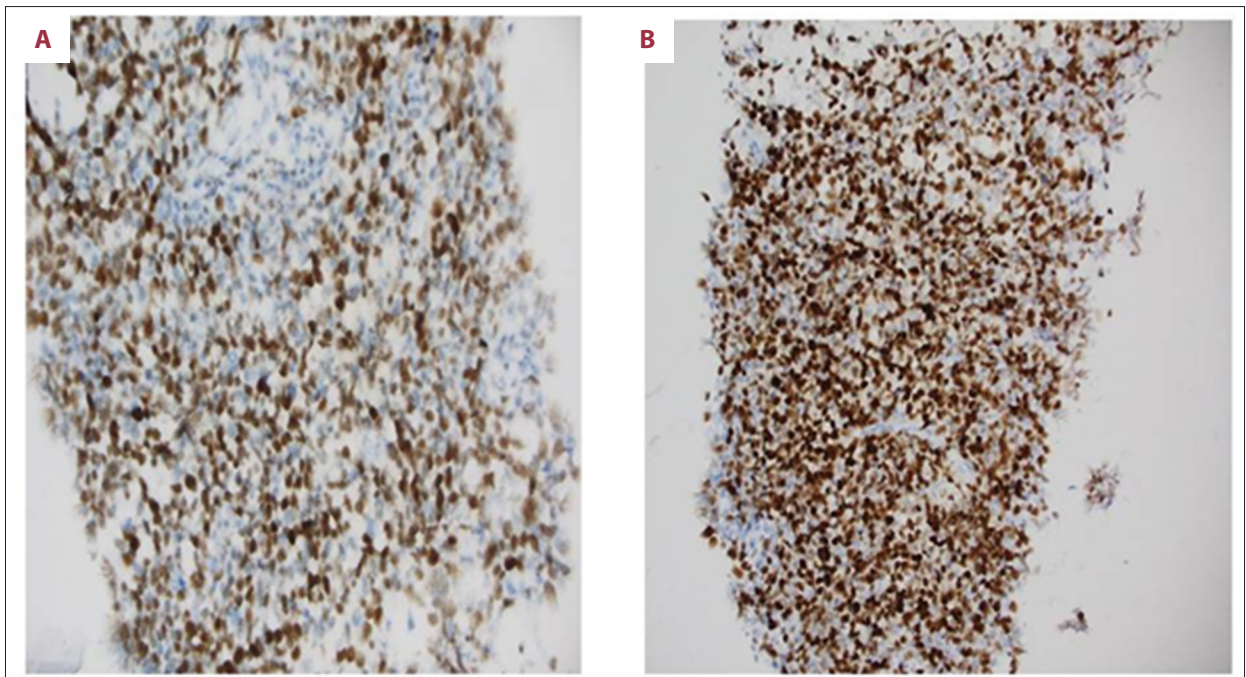


Figure 5. Immunohistochemistry. (A) BCL6 (positive); (B) MUM-1 (positive).

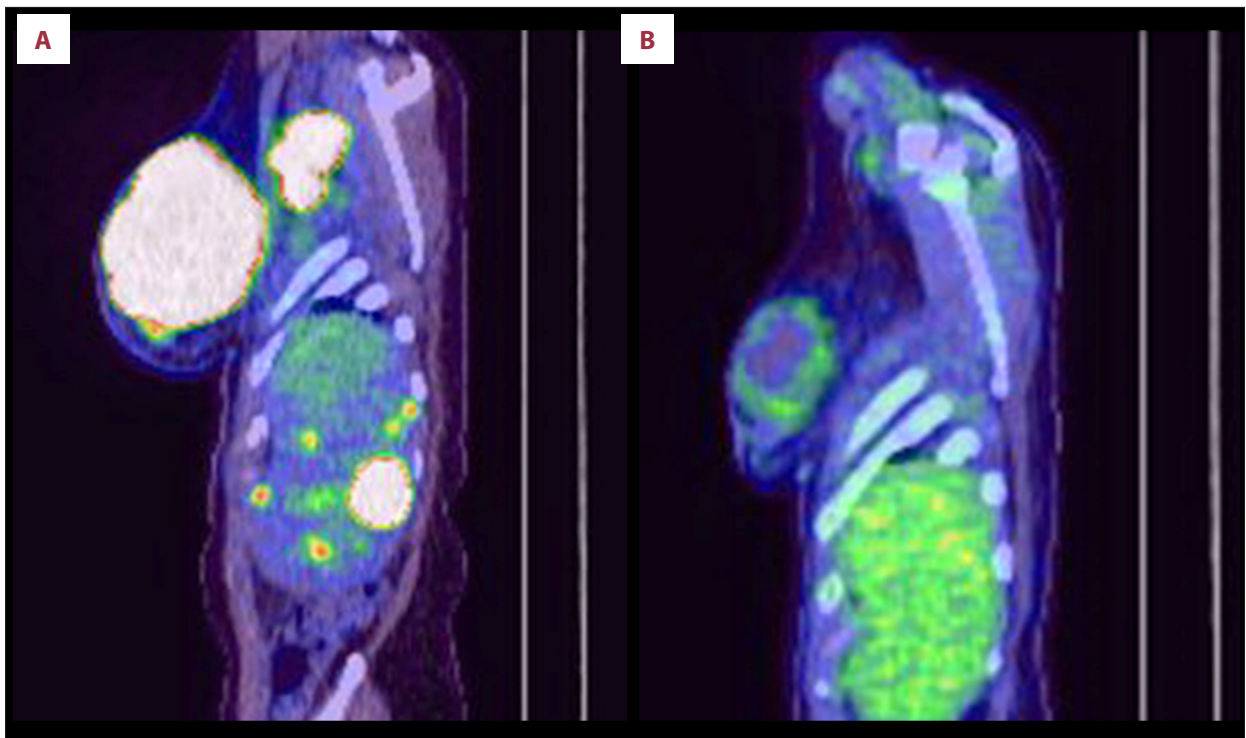


Figure 6. PET scan (A) initial scan showed intense hypermetabolism in the left breast DLBCL (B) follow-up PET scan revealed non-significant mild FDG uptake at the periphery of the residual left breast mass after treatment.

these tumors can be accurately classified as originating from the hematopoietic lymphatic or epithelial systems. Moreover, lymphoma evaluation and management are dramatically improving due to the rapidly growing database on gene expression patterns and protein expression [17]. Recently, Ondrejka and Hsi summarized the essential data on pathogenesis, clonal or tumoral evolution, and identification of the biomarkers that may be useful for prognostic or therapeutic strategy in lymphomas patients [18].

The management strategies for PBL vary broadly, from surgical intervention to combination chemotherapy and radiotherapy [19]. However, there is no up to date standard guideline for PBL treatment. Mastectomy for PBL is not well-supported because it shows neither improved survival nor reduced risk of re-currence [20–22]. Several studies have recommended that surgery should be offered for diagnosis only and that minimally invasive surgery is the preferable option because extensive surgery may carry a high risk of morbidity. Also, axillary dissection adds no therapeutic advantage [20–22].

At present, early stages of PBL can be successfully treated with combination therapy, in which CHOP regimen is the most common chemotherapeutic agent [23]. Several investigators have recommended a treatment regimen involving combination chemotherapy with or without radiation therapy [6,19]. Consistent with these studies, our patient was treated with 4 cycles of

combination chemotherapy with R-CODOX/IVAC along with radiotherapy [24–26]. The patient presentation was aggressive with a stage IV BE (PET scan at presentation showed lesions in the lung, spleen, and multiple lesions in the bone). The size of the mass was 7 cm and lactate dehydrogenase level was high. The age-adjusted international prognostic index (aalPI) was high (score=3). Therefore, our patient was at high risk because 3 prognostic factors were present (LDH, performance, and staging). It is well known that CNS relapse is common in this type of lymphoma. Therefore, our MDT decided to start with an aggressive chemotherapy regimen (R-CODOX-M/R-IVAC) containing high-dose methotrexate, which can penetrate the blood-brain barrier, followed by involved-field radiotherapy (IFRx). There is currently no consensus on the treatment of this subtype of lymphoma; however, combining radiotherapy with chemotherapy is considered the most successful therapy. The risk of CNS involvement and relapse are high; most authors believe that addition of CNS-directed treatment is essential [27,28]. Many authors believe that this subtype of disease is associated with poor prognosis and is considered an unfavorable primary site.

This is a novel case report from our region in the Middle East, as no studies have been published yet regarding breast lymphoma and its frequency in this part of the world. With the recent implementation of the breast MDT and discussion of breast cancer cases in a weekly MDT involving all the relevant

specialties, we have started to investigate many aspects of breast cancer in Qatar. Therefore, this case report paves the way to explore breast lymphoma management, outcomes, and prognosis.

Conclusions

This is an unusual case of non-germinal (activated B-cell type) breast lymphoma in a woman with a painless mass in the left breast. Screening and diagnosis of PBL based on advanced radiological investigations are useful for identification of this unusual neoplasm. Moreover, early and accurate diagnosis of PBL is crucial for selecting the appropriate treatment strategies to avert potentially harmful surgical interventions. This case

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report opens the way for early diagnosis, appropriate treatment and favorable outcomes of breast lymphoma.

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Statement

The authors have no conflict of interests and no financial issues to disclose. This case report has been approved by the Medical Research Center (IRB #15270/15), Hamad Medical corporation, Doha, Qatar.