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The Bench of Primary Breast Lymphoma Treatment: A Review of the Literature and a Case Report

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ABSTRACT

Background: Primary non-Hodgkin breast lymphoma is a rare pathology, representing 0.5 percent of malignant breast tumors.

Case Presentation: Here, we report a 54-year-old female presenting a mass in the left breast diagnosed by needle biopsy and IHC as a diffuse large B-cell lymphoma (DLBCL). Radiation therapy with conventional fields was applied for whole breast irradiation after the patient received 6 courses of R-CHOP (Rituximab plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone) chemotherapy. At the follow-up period 11 months after radiation therapy, no morbidities occurred and the patient is surviving with no evidence of disease.

Conclusions: The common treatments for breast lymphomas are surgery, radiation therapy, and chemotherapy. Although no agreement has been reached on the best therapy for primary breast lymphomas, these methods are commonly applied alone or in combination. It seems that R-CHOP combined with radiation therapy regimen could be an important treatment modality in avoiding unnecessary surgery.

Introduction

Breast lymphoma is a rare type of extra-nodal lymphoma that could be categorized to primary breast lymphoma (PBL) and secondary breast lymphoma (SBL).¹ The criteria for the diagnosis of PBL were first defined by Wiseman and Liao in 1972, including (a) close anatomic association with mammary and lymphomatous tissue, (b) absence of a previous diagnosis of an extra-mammary lymphoma, (c) lack of any disseminated disease (except involvement of the ipsilateral axillary lymph node), and (d) adequate quality of the histopathological specimen. SBL is considered to be

a presentation of lymphoma in the organs and lymph node regions other than the breast and regional lymph nodes.¹

B-cell lymphomas are considered to be more common than T-cell lymphomas of the breast.² There are 2 stages of PBL, defined as stage IE, which is limited to the breast only, and stage IIE, which involves the breast and ipsilateral axillary lymph nodes.^{1, 3} The treatments for breast lymphomas include surgery, radiation therapy (RT), and chemotherapy. These methods have been used alone and in combination.⁴ The most common symptom of breast lymphoma is a painless mass in the breast, which is similar to breast carcinoma; thus, the initial treatment is considered to be surgery.⁴ However, studies have shown that mastectomy is not the first choice for treatment of PBL, as both disease-specific survival and overall survival (OS) are significantly decreased after this procedure.⁴ Extensive radical surgery could be damaging and surgery should be limited to lumpectomy.⁵ Previous prospective studies have demonstrated that chemotherapy

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improves progression-free survival and OS in PBL and, thus, chemotherapy is the first choice for treatment.^{6,7}

RT for PBL is deemed efficient to prevent ipsilateral relapse.⁴ RT has been applied with conventional fields or three-dimensional conformal RT for whole breast irradiation.⁵ Recently, a prospective study confirmed that combined treatment with RT and chemotherapy was more effective compared to single treatment, as it significantly improves overall and event-free survival.⁶ In this case, we combined chemotherapy and RT as a treatment regimen. The outcome of this case report may help to establish more effective treatment guidelines for PBL.

Case Presentation

Clinical summary—History of patient

A 54-year-old female was referred to our center. She complained of swelling in her left breast. During a physical examination, palpation revealed a mass measuring 4cm in its maximum dimension which was tender, mobile, and firm to hard in consistency located in the upper outer periareolar region of the left breast, and a palpable lymph node of 1.5cm in diameter was found in the ipsilateral axillary tail. The overlying breast skin, areola, and nipple were unremarkable. Clinically, there was a suspicion of the breast lump.

Primary staging procedures comprised the following options: blood chemistry, complete blood

ultrasonography, bone marrow aspiration, MRI and computed tomography of the thorax, abdomen, and pelvis. Needle biopsy of the breast mass and the axillary lymph node were applied by the standard procedure. The results demonstrated that the patient had Stage IIE T-cell lymphomas of the breast.

Clinico-radiologic examination findings

No other abnormalities in any organs and no evidence of lymph node involvement (except for the palpable ipsilateral axillary node) were detected on breast imaging. No abnormality was observed in computerized tomography (CT) of the thorax and abdomen, and only some edematous changes and skin thickening of the left breast were detected. Magnetic resonance (MR) with and without Gd studies revealed that there was a 39×31 mm mass with a heterogeneous increased signal on STIR images at the upper outer periareolar region of the left breast. This mass showed inhomogeneous enhancement on post-Gd images with non-enhancing component and marginal irregularity with type 3 TICs (rapid washout) (suspicious morphology and suspicious kinetic). Enlarged lymph nodes were present at the left axillary region, with the largest one measuring about 21×12 mm. Some of the lymph nodes also showed cortical hypertrophy and eccentric hilum. However, no speculated enhancing mass or architectural distortion was present in the right breast (Figure 1). Furthermore, PET scan was not performed.

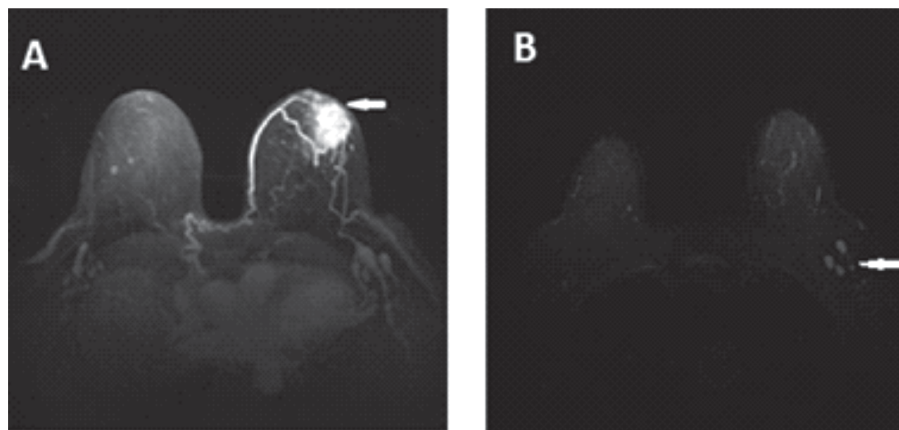


Figure 1. Magnetic resonance imaging (MRI) showing: A, abnormal mass at the upper outer periareolar region of the left breast in axial section (solid white arrow); B, Enlarged lymph nodes present at the left axillary region (solid white arrow) .

Hematologic, Histologic, and Immunohistologic findings

Hematological findings were within normal limits. Left breast mass core needle biopsy was performed. Macroscopically, there were 5 creamy to yellow colored string shape tissue fragments that measured $2 \times 0.4 \times 0.2$ cm. The sections revealed the breast tissue involved by a hypercellular malignant tumor composed of the diffuse proliferation of round and count, breast cuboidal tumor cells with

hyperchromic nuclei and a high N/C ratio. Tumor cells grew among adipose tissue without differentiation. Mixed inflammatory cells, necrosis, and multinucleated histiocytes were also seen. Special staining was negative for fibrosis and mucin production.

Immunohistochemistry (IHC) showed that these fragments of tissues, including parts of neoplasm composed of atypical lymphoid series, have somewhat larger vesicular nuclei. They were mixed



with a smaller form having more hyperchromic nuclei. They were positive for CD20, but negative for CD3 expression. Histopathological findings in the tumor mass and lymph nodes verified the diagnosis of high grade diffuse large B-cell type primary breast lymphoma (DLBCL).

The bone marrow histopathology revealed all hematopoietic lineages with the different stages of maturation. Megakaryocytes exhibited normal morphology and blasts accounted for less than 3% of the population. No increase was seen in lymphocytes. The diagnosis was lymphoma.

Treatment

The patient was treated with 6 cycles of the R-CHOP (Rituximab 375mg/m² i.v. on day 1; Cyclophosphamide 750mg/m² i.v. on day 1; Doxorubicin 50mg/m² i.v. on day 1; Vincristine 2mg i.v. on day 1; Prednisone 100mg p.o. daily, days 1–5) regimen every 3 weeks. No abnormal involvement was observed in the contralateral breast tissue in imaging, so as with the cases of non-lymphoid breast cancer; the breast tangent technique was applied for RT to avoid radiation exposure to the adjacent organs, such as the lung and contralateral breast tissue.

RT was performed, using a linear accelerator high energy device with a dose of 50 Gy/25 F regimen with 2 tangential fields for treatment of the left breast and 2 supraclavicular and posterior axillary fields for the subclavian and axillary lymph node treatment (Figure 2).

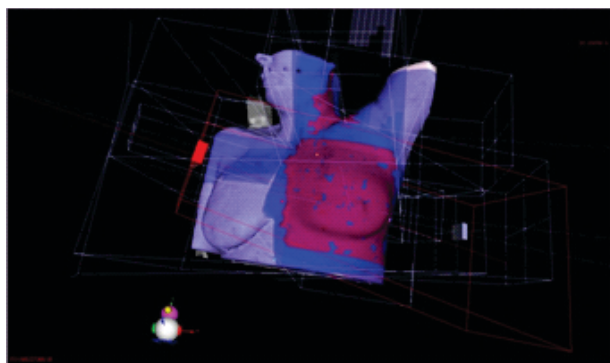


Figure 2. Radiation Therapy fields for treatment of the left breast.

Post-treatment outcomes and patient follow-up

After 6 cycles, no peripheral lymphadenopathy was seen. No pleural fluid was found, but pathological changes were observed in the spleen (splenomegaly).

Follow-up was performed 6 and 11 months later. The results of axillary breast ultrasound and thorax, abdomen, and pelvis CT scan and a whole-body bone scan were normal. Laboratory tests were within normal ranges, too. However, the patient complained of pain in her upper limb during its movements while dressing.

Discussion

The breast is a rare site of malignant lymphomas that can be divided to primary breast lymphoma (PBL) and secondary breast lymphoma (SBL).^{1,8} The median age of incidence of PBL varied between 60 and 65 years, and its mean age of onset has been reported to be approximately 58 years. The most common presentation of PBL is a painless mass (almost 61% of cases). Other symptoms included local inflammation (11%), local pain (12%), and palpable lymph nodes (25%).⁹

In our report, a 54-year-old patient was presented with swelling in her left breast. In physical examination, a mass that was tender, mobile, and firm to hard in consistency was palpated in the upper outer periareolar region of the left breast. Additionally, a palpable lymph node of 1.5cm in diameter was found in the ipsilateral axillary tail. Clinicopathological features indicated primary breast lymphoma. Needle biopsy of the breast mass and the axillary lymph node demonstrated that the patient had stage IIE disease, which was limited to the breast and ipsilateral axillary lymph nodes.¹³ Primary breast lymphoma is a rare non-Hodgkin lymphoma (NHL) of the breast, and diffuse large B-cell lymphoma (DLBCL) is the most common subtype.¹⁰ Breast DLBCL accounts for 2% of all NHL¹⁰, 0.04% to 0.5% of all breast malignancies, and 0.85% and 2.2% of all extra-nodal malignant lymphomas.¹²

The clinicopathology of these cases has been discussed in prior studies.^{4,6,11} Based on World Health Organization (WHO) classification system for breast tumors, the malignant lymphomas of the breast are divided to diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, extra-nodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT), and Burkitt's lymphoma.⁸ In our case, histopathological findings in the tumor mass and lymph nodes confirmed the diagnosis of high grade diffuse large B-cell type primary breast lymphoma (DLBCL).

The immunophenotype of DLBCL can be approved by histochemistry or flow cytometry. Tumor cells in DLBCL express pan B-cell antigens (CD19, CD20, CD22, CD79a) as well as CD45. Expression of CD30 is present in approximately 25% of cases.¹³

The Immunohistochemistry (IHC) showed that the neoplasm was composed of atypical lymphoid series with large vesicular nuclei. They were mixed with smaller forms having more hyperchromic nuclei, which were positive for CD20, but negative regarding CD3 expression.

There are some special scenarios (e.g., gonadal lymphoma, central nervous system involvement), where additional therapy is required (e.g., intrathecal chemotherapy).¹⁴

Treatment options for breast lymphomas include



surgery, radiotherapy (RT), and chemotherapy.⁴ Although no agreement has been reached for the best treatment for PBL, these methods can be applied alone or in combination.⁴ Surgical interventions consist of biopsy, lumpectomy with or without axillary lymph node (ALN) dissection, and mastectomy with or without ALN dissection procedures.⁵ The largest retrospective analysis demonstrated that mastectomy provides no survival benefit compared to lumpectomy or biopsy in PBL;⁴ however, surgery does not have any role in the treatment of DLBCL. The standard care in diffuse large B-cell lymphoma (DLBCL) treatment is Rituximab, Vincristine, Doxorubicin, Cyclophosphamide, and Prednisone (R-CHOP). Rituximab is considered as a chimeric monoclonal antibody against the CD20 B-cell antigen and has more therapeutic role in diffuse large B-cell lymphoma.^{15,16}

In this case, the patient was treated with combination therapy. We chose this regimen to rely on the reports of Lokesh *et al.*, which explained primary breast DLBCL is a rare entity; so, combination therapy involving chemotherapy and radiation could lead to a longer overall survival and avoidance of the morbidity of mastectomy.¹⁷ Moreover, recently such regimens (R-CHOP and RT) are applied in limited stage diffuse large B-cell lymphoma of other sites.¹⁸

RT with three-dimensional conformal was applied for whole breast and axillary lymph nodes irradiation after chemotherapy with R-CHOP. The radiation doses vary greatly, in previous reports, fluctuating between 30 to 60 Gy. Thus, the optimal radiation dose of breast cancer is unknown, and the median dose in most reports is 40 Gy.^{4,19,20} In our case, the mass was irradiated to a total of 50 Gy after a complete response to R-CHOP chemotherapy. After chemotherapy, the mass size was decreased remarkably. Previously doses up to 40 Gy applied for limited cases of breast lymphoma, small masses, and extensive surgery have been reported in various papers, but our choice of treatment for this patient was 50 Gy, 40 Gy for the whole breast and 10 Gy as a boost.^{6,21}

Other studies confirmed that combined treatment with RT and chemotherapy was the best treatment compared to the single modality because it improves overall and event-free survival significantly.⁶ The retrospective research study carried out by the International Extra-nodal Lymphoma Study Group confirmed that after combined radiation therapy and chemotherapy, the 5-year OS was 63%, which was significantly greater than either radiation therapy or chemotherapy alone.⁴

The management of PBL is not currently standardized. However, similar to other lymphomas, a diagnostic biopsy or limited surgery followed by chemotherapy accompanied by radiotherapy is suggested. A recent study emphasized the importance

of combined therapy, which is important for avoiding an unnecessary mastectomy in PBL patients.²² Although there was a clinical suspicion of PBL, an appropriate pre-therapeutic clinical workup with a core needle biopsy and IHC was helpful and avoided an unnecessary mastectomy in our patient. Due to the small number of such patients, the implementation of a single center randomized trial is impossible, so in the event of common multi-trials and using different therapies and prospective studies, it will be possible to evaluate the effects of each treatment separately as well as better staging methods that have not been well established in the case of PBL.

Conflict of Interests

There is no conflict of interest.

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