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Non-Hodgkin's Lymphoma of the Breast: Report of Five Cases and Review of the Literature

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SUMMARY

Non-Hodgkin's lymphoma (NHL) of the breast can be either primary or secondary. Both are rare diseases accounting less than 0.6% of all breast malignancies. In this study we report our experience with five cases of breast lymphoma, 3 of them being primary and 2 of them being secondary breast lymphoma, retrospectively. All patients were female with a median age of 47 years and presented with breast masses (3 in the right breast and 2 in the left). The histologic subtype showed broad spectrum, one patient had peripheral T-cell lymphoma and 4 patients had B-cell lymphomas; 2 were diffuse large B-cell lymphomas, 1 was a diffuse small B-cell lymphoma, and the last patient was a marginal zone lymphoma. Partial mastectomy was performed in 2 patients to carry out diagnosis. Anthracycline-based chemotherapy regimens were employed in 4 patients. Radiotherapy was added to other treatment modalities in 3 cases. At a median follow-up of 5 years, all patients were alive other than one who had been diagnosed with peripheral T-cell lymphoma just after pregnancy and showed resistance to the applied treatment. The treatment and the prognosis of breast lymphomas were not different from the currently indicated for nodal NHL with the same stage and histological subtype.

Keywords: Breast mass, Lymphoma

ÖZET

Meme Non-Hodgkin Lenffomaları: Beş Olgu Sunumu ve Literatürün Gözden Geçirilmesi

Memede saptanan Non-Hodgkin lenfomalar primer ya da sekonder olabilir. Her ikisi de oldukça nadir olup, meme kanserlerinin yaklaşık %0.6'sını oluştururlar. Bu çalışmada, kliniğimizde izlenen 3'ü primer, 2'si sekonder meme lenfoması olan olguları geriye dönük olarak inceleyerek kendi tecrübelerimizi bildirmek istedik. Bütün hastalar kadındı ve ortalama yaş 47 idi. Bütün hastalarda memede kitle şikayeti vardı (3 hastada sağ, 2 hastada sol). Histolojik alt tipleri geniş bir spektruma sahipti; 1 hastada periferal T hücreli lenfoma, 4 hasta B hücreli lenfoma (2 hasta diffüz büyük B-hücreli, 1 hasta diffüz küçük B-hücreli, 1 hasta marjinal zon lenfoma) olarak tanı aldı. İki hastada tanısal amaçlı parsiyel mastektomi yapıldı. 4 Hastada antrasiklin esaslı kemoterapi rejimi uygulandı. Üç hastada tedaviye radyoterapi eklendi. Ortalama 5 yıllık takip sonrası, gebelikten hemen sonra periferal T hücreli lenfoma tanısı alan ve kemoterapiye dirençli olan olgu dışındaki diğer 4 olgu hayattaydı. Meme lenfomalarının tedavi ve prognozları, aynı evre ve histolojik tipteki nodal lenfomalardan farklı değildir.

Anahtar Kelimeler: Memede kitle, Lenfoma

INTRODUCTON

Breast involvement by malignant lymphoma, whether primary or secondary, is a rare event.[1] It accounts for 2.2% of all extranodal lymphomas and less than 0.5% of all malignant breast tumors.[1-6] Primary and secondary lymphomas of the breast are defined according to the criteria used for other extranodal lymphomas. Primary breast lymphoma (PBL) was diagnosed when the breast was the site of first or major manifestation of the lymphoma and there was no documentation of lymphoma elsewhere, excluding the presence of ipsilateral axillary node involvement by Wiseman and Liao's definition.[7] However, these criteria are overly restrictive, since they limit the definition of PBLs to those exclusively localized to the breast. Patients with lymphoma of the breast that have disseminated elsewhere before diagnosis are not accepted. All lymphomas involving the breast but not including these criteria are considered as secondary breast lymphomas (SBLs). Pathologically there are no differences between primary or secondary lymphomas of the breast.[2]

Here we present the clinical and pathological features, treatment outcomes of 5 cases with extranodal lymphomas involving the breast that were followed-up at our hematology unit, retrospectively.

CASE 1

A 50-year-old woman was admitted to hospital with the complaint of mass in her right breast and axillary region. She denied fever, night sweats and weight loss. On physical examination, the right breast was edematous and a painless mass of 5x5 cm was present in the upper lateral quadrant of the ipsilateral breast. Bulky lymphadenopaty (LAP) package was also palpated in the right axilla. Left breast and axilla were normal. Mammography of both breasts showed a mass measuring 5x5 cm in upper outer quadrant of the right breast. Histopathological and immunohistochemical examination of the excisional biopsy material revealed diffuse large B-cell non-Hodgkin's lymphoma (DLBCL). Computed tomographic (CT) examination of neck, thorax and abdomen and bone marrow biopsy showed that there were no further lymphoma infiltrations. She was classified as stage IIE according to Ann Arbor classification system and treated with 8 cycles of cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) chemotherapy. The patient has been followed-up at out-patient clinics in complete remission (CR) for ten years without any recurrence.

CASE 2

A 46 year-old woman was referred to our hematology unit with a mass in the upper outer quadrant of the left breast measuring 2x2 cm detected during routine mammography examination. She underwent partial mastectomy operation. Histological and immunohistochemical examination of the mass revealed CD20 positive diffuse small B-cell NHL. She had no weight loss, night sweats or fever. On physical examination, there was no pathological finding such as peripheral LAP or organomegaly other than the surgical scar in the left breast. Total body CT and bone marrow biopsy examination were all normal. She was treated with radiotherapy locally with a total dose of 4000 cGy. She has been followed in CR for three years.

CASE 3

A 65-year-old woman admitted with two months history of non-productive cough and dispnea. She had 10 years history of a mass in the right breast which was enlarged in the last two months. Two years before, a fine needle aspiration biopsy performed from the breast mass had been reported as benign. At presentation, cutaneous edema, erythema and local heat were present in the right breast. A huge mass greater than 10cm in diameter in the upper outer quadrant of right breast and right axilla were detected on physical examination. Chest auscultation revealed that respiration sounds were decreased in the bottom of right hemithorax. CT of the neck, thorax and abdomen showed the presence of a 12x10 cm well circumscribed and uncalcified mass in the upper outer quadrant of the right breast, multiple LAPs the largest one measuring 2x2 cm in diameter in the right axilla, and diffuse pleural effusion in the right hemithorax. The hematological examination of the blood revealed anemia, biochemical parameters were normal. Excisional biopsy from the mass was performed and histological examination showed CD20 positive DLBCL. Bone marrow biopsy examination was normal. Cytological examination of the pleural fluid was negative for lymphoma infiltration. She was treated with 375 mg/m^2 rituximab (R) along with CHOP

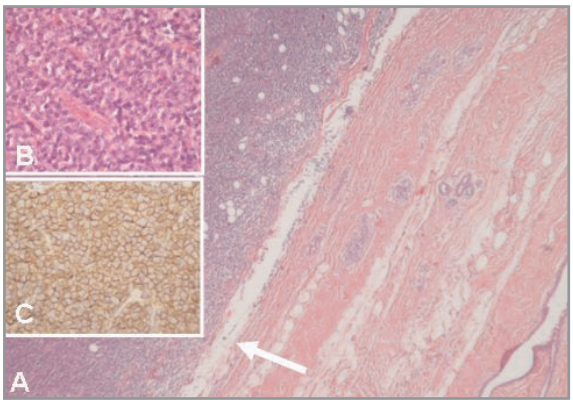

Figure 1. Marginal zone B-cell lymphoma infiltrating the breast tissue. A, The border of the neoplastic lymphoid infiltrate and uninvolved breast tissue. Arrow: the expanding margin of the infiltration (H&E, x4). B, Diffuse pattern of small lymphocytic infiltration (H&E, x40). C, CD20 expression of neoplastic cells (CD20, immunoperoxidase, DAB, x40).

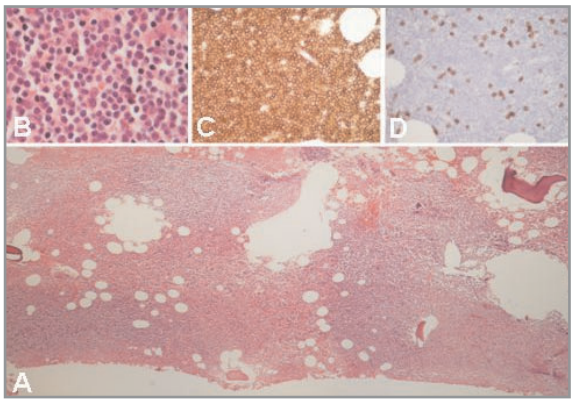

Figure 2. Marginal zone B-cell lymphoma infiltrating the bone marrow (same case as Fig. 1). A, The focal and interstitial pattern of infiltration (H&E, x4). B, Predominantly lymphocytic infiltration (H&E, x40). C, CD20 expression of neoplastic cells (CD20, immunoperoxidase, DAB, x40). D, CD3 expression of neoplastic cells (CD20, immunoperoxidase, DAB, x40).

chemotherapy. After 8 cycles of R-CHOP chemotherapy she achieved CR. She has been under out-patient follow-up for four years without relapse.

CASE 4

A 23-year-old woman was admitted with a painless lump in the left breast and the left neck appearing just after terminating pregnancy. On physical examination, the lump in the upper outer quadrant of the left breast was found to be painless and immobile. There was no skin retraction, nipple discharge or peau d'orange appearance. There were conglomerated LAPs on both sites of the supraclavicular area and in the left axilla. Hematological and biochemical examination of the blood including lactate dehydrogenase (LDH) level were normal. A fine needle aspiration biopsy from the lump of left breast confirmed the diagnosis of peripheral T-cell lymphoma. Bone marrow biopsy was normal. CT of the whole body showed the presence of bilateral paratracheal LAPs, in addition to left axillary, bilateral supraclavicular LAPs, and a mass in the upper outer quadrant of the left breast measuring 10x15 cm. The patient had received 5 cycles of CHOP chemotherapy but the tumor showed resistance to treatment. Then, she was treated with 6 cycles of mechloretamine, vincristine, procarbazine, prednisone (MOPP) chemotherapy followed by mantle radiotherapy with total dose of 3600 cGy, and achieved CR. Two years after the CR she relapsed with the left cervical and supraclavicular LAPs. Breast mass was not detected at relapse. Four cycles of salvage chemotherapy containing chlorambucil, vinblastine, procarbazine, prednisone was given to the patient. Unfortunately, the patient died of disease progression two months after the last chemotherapy and 4 years after the first admission.

CASE 5

A 47-year-old woman was referred to our hematology unit with a mass in the right breast and right neck noticed during self examination 15 days before admission. Mammography of both breasts showed the presence of 4 different masses the largest measuring 5x3.5cm in the upper outer quadrant of the right breast. Multiple LAPs were detected with CT in bilateral axillary, cervical and supraclavicular areas. CT analysis also confirmed the presence of multiple LAPs making packages in mediastinum and abdomen. She underwent partial mastectomy and masses were all extracted. Pathological and immunohistochemical analysis revealed a marginal zone non-Hodgkin's lymphoma (Figure 1). She has had night sweats for a year, but denied fever and weight loss. Physical examination of the patient revealed bilateral supraclavicular, cervical and axillary LAPs, and scars due to the operation in right breast. Bone marrow examination showed lymphoma infiltration with immunohistochemical staining (CD20+, CD45RO-, CD5-, CD23-, TdT-, cyclin D1-, CD10-) suggesting a B-cell marginal zone lymphoma (Figure 2). The di-

agnosis of a stage IV-B marginal zone NHL according to Ann Arbor clinical staging system was established. After 6 cycles of CHOP chemotherapy, residual lymphoma infiltration in the bone marrow still remained. Treatment of the patient continued with 2 cycles of etoposide, solumedrol, high-dose cytosine arabinoside, cisplatin (ESHAP) chemotherapy regimen and she achieved complete remission. However, 6 months later, bone marrow examination showed lymphoma infiltration once again. Bulky abdominal mass was also detected with CT analysis at the same time. Radiotherapy at a dose of 5000 cGy to paraaortic LAPs in abdomen was administered. After the last therapy CT examination of the neck, thorax and abdomen were all normal. She received 4 cycles of rituximab (375 mg/m^2) and dexamethasone, high-dose cytosine arabinoside, cisplatin (DHAP) chemotherapy. Residual lymphoma infiltration in bone marrow was detected in every bone marrow biopsy examination. She is alive with disease for six years, taking low-dose oral chlorambucil, and rituximab infusions once in every up to 8 cycles.

DISCUSSION

Clinicopathologic features and treatment outcomes of 5 women with breast lymphomas diagnosed and followed-up in Ege University Adult Hematology Unit were evaluated retrospectively. Median age of patients was 47 years (range 23-65 years) representing the literature's information; the median age of patients diagnosed with breast lymphoma either primary or secondary is between 40 and 67 years, but the range is broad. These tumors can appear in teenagers or patients in their 90's, but the peak age incidence is during the six decade.[3,8-10]

Extranodal NHL accounts for 10-48% of all NHL cases. Commonly involved extranodal sites include the stomach, tonsils, lungs, adenoids, skin, small intestine, and testis.[1,3,8,11,12] Lymphoma involving the breast is very rare. The rarity of the breast lymphoma may be related to the relatively small amount of lymphoid tissue present in the breast as compared to the gut or lung in which primary lymphomas are much more frequent.[8,11-14] All published series reported an overwhelming female predominance.[3,8,9] It has been reported that right breast is involved more common than the left breast.[3,13,15] Bilateral breast involvement at presentation or relapse in the contralateral breast is found very rarely, less than 10% of cases with breast lymphoma. It was also noted that bilateral breast involvement at presentation usually is observed during pregnancy.[4,5,8,9,16] In the present small case series, bilateral breast involvement with lymphoma was not seen at presentation or relapse. Three patients have had right sided and 2 patients have had left sided masses. Pregnancy-related breast lymphoma was noticed in Case 4 but mass was present in the left breast, and involvement of contralateral breast was not detected even at relapse.

The clinical presentation of the lymphomas involving the breast, either primary or secondary, is difficult to differentiate from other breast neoplasms.[4,11,13,17] However, some particular patterns guide towards the diagnosis of breast lymphoma has been noted in the literature; breast lymphomas tend to be larger at diagnosis than the breast cancers and rapid enlargement of breast mass is described.[2,4,7,13,18,19] Skin retraction, nipple discharge, erythema, local heat, peau d'orange appearance are uncommon signs in breast lymphomas.[4,7,8,13,20] The radiological appearance on mammography usually shows well defined borders, absence of microcalcifications and spiculations favors the diagnosis of lymphoma. All the clinical and radiological characteristics mentioned above may overlap and the diagnosis of lymphoma relies only on histology.[1,7,14,21] Most of breast lymphomas are of B-cell type, T-cell type is uncommon. Diffuse large B-cell lymphoma appears to be the most common subtype ranging from 40 to 70% of breast lymphoma series.[3,7,13,18-20] The frequency of the low-grade lymphomas of the mucosa associated lymphoid tissue (MALT) type varies among recent reports from 8.5 to 35%.[2,14,22,23] One of the patients in our small series is a peripheral T-cell lymphoma and 4 of the cases are B-cell lymphomas; 2 are DLBCLs, 1 is a diffuse small B-cell lymphoma, and the last patient is a marginal zone lymphoma, showing broad differences in histology. All the patients in this study had masses in their breast exceeding 2 cm in diameter at diagnosis. Systemic B symptoms due to lymphoma such as night sweats, weight loss, and fever rarely reported in published small series.[11,20] Only Case 4 had night sweats as systemic symptom among our patients. Cutaneous edema, erythema were seen in 2 women (Case 1 and 3). Symptoms which were mostly seen in breast cancers, like nipple discharge and peau d'orange appearance, were not seen in any of pa-

tients. Radiological appearances of breast masses were also in accordance with the literature.

Diagnosis of all cases made with surgical excision either partial mastectomy or biopsy extraction. Fine needle aspiration biopsy (FNAB) was not instituted in our patients in contrary to last publications which advocate FNAB cytology might achieve accurate diagnosis in more than 90% of NHLs.[8,24-27]

Because of its rarity, there is no uniform approach for the treatment of malignant lymphoma involving the breast. Treatment modalities of breast lymphomas vary from surgery alone, to surgery followed by radiotherapy, to combination chemotherapy followed by irradiation. Previous reports have recommended the surgery as standard treatment. The surgical treatments also differ from simple mastectomy to radical mastectomy with axillary lymph node dissection.[3,11,15,20] At present, combined chemotherapy especially anthracycline-based chemotherapy with or without irradiation after the diagnosis with biopsy is preferred instead of surgery.[4,11,20,28-30] In many series, treatment is similar to that given systemic lymphoma related to histology; thus high-grade lymphomas such as DLBCL should be treated with combined chemotherapy usually an anthracycline-based protocol including rituximab with or without radiotherapy; whereas MALT lymphoma may be treated with local excision and/or radiotherapy as other indolent localized lymphomas.[3,4,11,13,22] The clinical efficacy of rituximab, a monoclonal anti-CD20 chimeric antibody, was first demonstrated in follicular lymphomas. Then, the use of the antibody has been extended to various B-cell lymphomas such as DLBCL, mantle-cell lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma.[31] In less frequent lymphomas, the role of rituximab has not been extensively studied. In two studies in patients with gastric extranodal marginal zone lymphoma (MZL) who treated with single-agent rituximab, the overall response (OR) rate and the complete response (CR) rate were 64-77% and 29-46%, respectively.[31,32] Single-agent rituximab resulted in an OR rate of 80% in 20 patients with primary non gastric extranodal MZL.[33] In a recent study, combination therapy with rituximab and fludarabine in first line was evaluated in 22 patients with gastric lymphoma and extragastric MALT lymphoma. The OR and CR rate were reported as 100% and 90% at the end of the treatment, respectively (34). Twenty-six patients with MZL who treated with combination therapy with rituximab and fludarabine were enrolled another phase II study. The overall response rate was 85%, with 54% complete responses.[35]

The prognosis of the lymphomas involving the breast either primary or secondary have been reported as poor; 5-year survival rates of 9 to 85% were reported in different series.[3,11,36,37] Primary mass size, histological grade, international prognostic index (IPI) risk score, stage according to Ann Arbor system, distant sites of involvement determine the prognosis as other systemic lymphomas.[3,8,13] Some of the recently published series raised a question about the relatively high possibility of dissemination of the lymphoma to unusual sites such as central nervous system (CNS) ranging from 14-21%.[6,38,39] But, some other series didn't find any CNS recurrence.[7,11,15,20,40]

Only one (Case 5) out of five patients in our small series was admitted with the disseminated disease, and Cases 1, 2, and 3 can be classified as primary breast lymphoma (PBL) according to Wiseman and Liao's definition.[7] Case 4 had ipsilateral neck involvement of lymphoma, remained outside the definition, and accepted as secondary breast lymphoma (SBL) in spite of being stage II according to Ann Arbor classification. We didn't see CNS infiltration either at presentation or relapse. Two patients underwent partial mastectomy preserving the majority of breast tissue. Patient with DLBCL (Case 2) treated with local radiotherapy after mastectomy and followed-up in CR for 2 years. Other patient (Case 5) with marginal zone breast lymphoma who underwent radical mastectomy, the lymphoma was resistant to all the applied treatments including anthracycline-based combined chemotherapy followed by radiotherapy. She has been followed-up with disease for 6 years. Two patients (Case 1 and 3) treated with 8 cycles of CHOP chemotherapy and achieved CR, remained in remission for 9 and 3 years, respectively. Patients who had pregnancy related peripheral T-cell breast lymphoma of stage II-E (Case 4) received combined anthracycline-based chemotherapy, and local radiotherapy. Two years after the first CR, the disease relapsed, in spite of salvage chemotherapy she died of disease progression.

In conclusion, we have described the five women with lymphoma including breast; 3 of them having

primary, 2 of them having secondary breast lymphomas. At a median follow-up of 5 years, all 3 patients with primary disease achieved CR, and remained in CR for median 3 years. Prognosis and treatment results were not different from the other lymphomas with the same histopathological classification. Primary breast lymphomas (PBLs) according the described criteria[7] are stage I and II, so having good prognosis compared to secondary breast lymphoma are inevitable. According to our observation, the treatment modalities of lymphomas involving the breast should not be different than the other lymphomas with the same stage and histological classification.

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