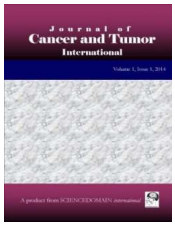

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Primary Breast Lymphoma: A Study of 9 Cases

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aim: Non-Hodgkin's primary lymphoma of the breast is rare. These tumors represent 0.04 to 0.52% of malignant breast pathology, 2.2% of extranodal lymphoma and 0.4% of all non-Hodgkin's lymphoma. Clinical and radiological aspects show no special characteristics. The aim of our study is to report the epidemiological, clinical and therapeutic features of patients with primary breast lymphoma.
Patients and Methods: This is a retrospective study including 9 patients with primary non-Hodgkin's lymphoma of the breast treated at the institute Salah Azaiez from 2000 to 2013. This sample includes 1 case of follicular lymphoma, 1 case of large T-cell lymphoma and 7 cases of large B-cell lymphoma.
Results: The average patient age was 50 years, ranging from 30 to 76 years. The sex ratio was 0.11 (1 man/8 women). The average consultation time was 3 months (5 days-8 months). The median follow-up period was 43 months (4-192 months).Six patients were older than 60 years; one had disseminated disease and was diagnosed with stage III Ann Arbor classification. All tumors were architecturally diffuse. The overall survival was 100% at one year and 75% at 3 years. Seven

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patients achieved complete remission after initial treatment, and one relapsed after 2 months. Among the 7 cases of large B cell lymphoma, two cases resulted from the transformation of follicular lymphoma. The average processing time was 17 months.
Conclusion: Primary breast lymphoma is often diagnosed in the late stages of the disease. Treatment should be rapidly implemented. The 5-year survival of stage I of the Ann Arbor classification is higher than that for stage II.

Keywords: Breast cancer; non-Hodgkin's lymphoma; histology; immunohistochemistry.

1. INTRODUCTION

Primary breast lymphoma can affect one or both breasts. Lymphomatous proliferation should be highly associated with breast tissue, and the diagnosis of an extra-mammary lymphoma must be excluded except in the presence of ipsilateral axillary lymphadenopathy.

Wiseman and Liao first defined primary breast lymphoma according to four criteria [1]: The close anatomic proximity of mammary and lymphomatous tissue; the absence of a previous diagnosis of an extra-mammary lymphoma; the lack of evidence of disseminated disease (except for the ipsilateral axillary nodal involvement); and an adequate quality of the histopathological specimen.These criteria are still widely accepted.

Primary breast lymphoma represents only 0.04 to 0.52% of breast malignancies, 2.2% of extranodal lymphomas and 0.4% all non-Hodgkin's lymphoma [2,3]. We propose to study the clinical, radiological, histological and immunohistochemical characteristics, as well as the treatment and results, of non-Hodgkin's primary lymphoma of the breast.

2. PATIENTS AND METHODS

This is a retrospective study including 9 patients with primary non-Hodgkin's lymphoma of the breast treated at the institute Salah Azaiez from 2000 to 2013.

Data on patient characteristics, management procedures and disease evolution were collected from medical records and information sheets. This study concerns patients with a pathologic diagnosis of breast lymphoma. Patients with an extra-mammary location have been excluded from the study. In all patients, the pathological diagnosis was established on excisional biopsy or mastectomy specimen. Original hematoxylin-eosinstained sections and formalin-fixed, paraffinembedded tissue were available in all cases. Extensive immunohistochemical studies using a large pannel of antibody (B marker (CD20), T marker (CD3), CD30, CD45, CD15, vimentin, CD10) were performed.

3. RESULTS

The average age of the patients was 50 years, ranging between 30 and 76 years of age. The study population was predominantly female: eight patients were female, and only one patient was male (sex ratio: 0.14) (Table 1). In our study, three patients had a history of breast pathology: One had a history of an in situ ductal carcinoma, and two patients had a history of primary breast follicular lymphoma that became diffuse large cell lymphoma B after 2 years and 10 months. One patient had a family history of infiltrating ductal carcinoma reported in a paternal aunt and a cousin. Three patients were already postmenopausal for 10, 15 and 21 years, whereas 5 patients were still of childbearing age. One of our patients had been taking hormonal contraception for seven years. One of our patients, aged 30 years old, was five months pregnant at the time of the breast lymphoma diagnosis.

Patients had mammary masses, increased breast volume and signs of skin inflammation at the time that the primary breast lymphoma was discovered. This pathology occurred on the right side in 3 patients, the left side in 5 patients, and bilaterally in only one patient. The average clinical size of the primary breast lymphoma was 6.4 cm, with a maximum of 15 cm. the tumor diameter measured more than 5 cm in 3 patients. The ipsilateral axillary lymph nodes were palpated in 5 patients. In a patient with left axillary lymph nodes, the clinical examination revealed a supraclavicular lymphadenopathy. The histological exam identified a reactional node in all cases.

Mammography was performed by using a Lorad M3 unit in 6 patients and was followed by an ultrasound examination. The average tumor size revealed by mammography was 40.5 mm,

ranging from 10 to 70 mm. The mammographic aspects that were observed included the following: A poorly circumscribed opacity with indefinite and irregular contours or a spiculated dense center, a dense heterogeneous and irregular mass and a retraction and thickening of the superficial skin planes.

Table 1. Patients' characteristics

Characteristics	Total number of patients
Numbers	9
Sex, Male /Female	1/8
Age	
Median (range) years	50(30-76)
Type of primary breast lymphoma	
Large B cell lymphoma	7
Follicular lymphoma	1
T cell lymphoma	1
Lymphoma stage	
I/II	8
III/IV	1
Treatment	
Surgery	7
Chemotherapy alone	5
Chemotherapy +radiotherapy	4
Overall Survival at 5 years	42%
Progression free survival at 5 years	24%

The observed ultrasound aspects included the following: A hypoechoic irregular mass, a multilobulated mass or a rounded supra areolar opacity, heterogeneous hypoechoic, surrounded by a hyperechoic halo interrupting the glandular architecture and hypervasculature on color Doppler. Magnetic resonance imaging (MRI) was performed in only two patients and showed a spiculated lesion with polycyclic limits. This lesion was hypointense on T1-weighted MRI, isointense on T2-weighted MRI. The scan of the male patient showed contiguous right axillary lymph nodes of 2 to 4 cm in diameter, a large multilobed right parieto-axillary mass of 11 cm and a multinodular splenomegaly.

In our study, 8 patients had localized stages (I + II) at diagnosis, and 1 patient had the disseminated stage (stage III) of primary breast lymphoma (Table 1).

The study of primary breast lymphoma involved 7 cases of large B-cell lymphoma, a case of follicular lymphoma and a case of large T-cell lymphoma (Fig. 1, Fig. 2). The immunohistochemical study allowed us to confirm the diagnosis of non-Hodgkin's lymphoma and to eliminate other diagnoses. We used a large panel of antibodies: B marker (CD20), T marker (CD3), CD30, CD45, CD15, vimentin, and CD10. In 7 cases, the IHC results showed a diffuse and intense labeling of anti-CD20 (Fig. 3). In one case, the tumor cells had diffusely expressed anti-CD3. In one case, we found a diffuse expression of anti-CD20 and CD10. Five patients underwent chemotherapy treatment alone, and four had chemotherapy with radiotherapy. Surgery was performed in 7 cases. Five patients had a lumpectomy with axillary dissection, and 2 had a Patey type surgery. Sixty-six percent of operated patients underwent neoadjuvant chemotherapy with 6 cycles of R-CHOP (Rituximab 375 mg/m^2, Cyclophosphamide 750 mg/m^2, Adriablastine 50 mg/m^2, Vincristine 1.4 mg/m^2 and Prednisone 60 mg/m^2) every 3 weeks. Progression-free survival was 43% at 3 years and 24% at 5 years. The median follow-up of our patients was 41 months, ranging from 1 to 159 months. Overall survival was 60% at 3 years and 42% at 5 years (Table 1).

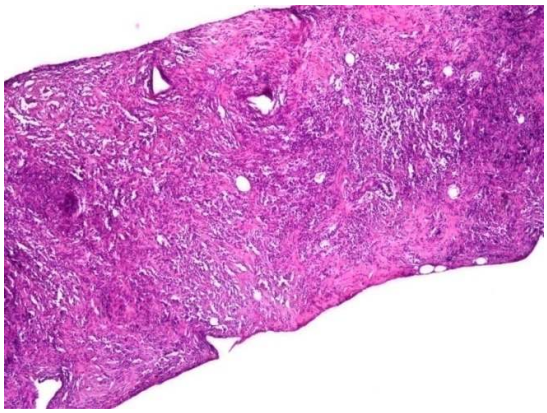

Fig. 1. Core needle biopsy sample in a 28-year old female showing breast tissue widely infiltrated by a diffuse large B-cell lymphoma (H&E x40)

4. DISCUSSION

Primary breast lymphoma is most common in women with a median age of between 50 and 60 years [4,5]. Men are rarely affected by this condition, with only a few cases described in the literature [6]. We found that 8 of 9 patients were female.

Primary breast lymphoma is also a tumor common in elderly women [2,3]. However, some authors have reported a median age of 28 years

in 15% of pregnant women or during breast-feeding [7]. In our study, a patient with diffuse large B cell lymphoma was 30 years old and was 5 months pregnant.

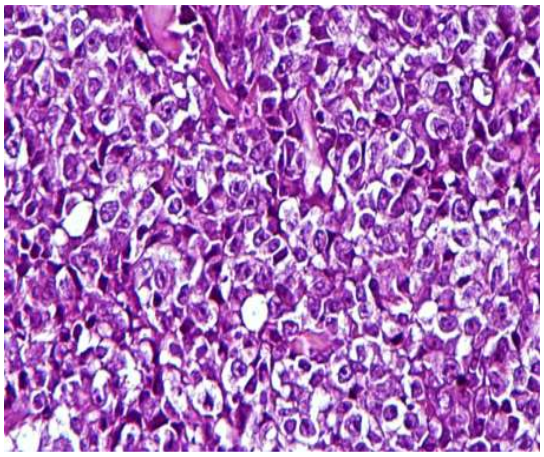

Fig. 2. Core biopsy high power magnification (H&E x 200) in a 28-year old female showing large atypical cells with one to three nuclei peripheral nucleoli

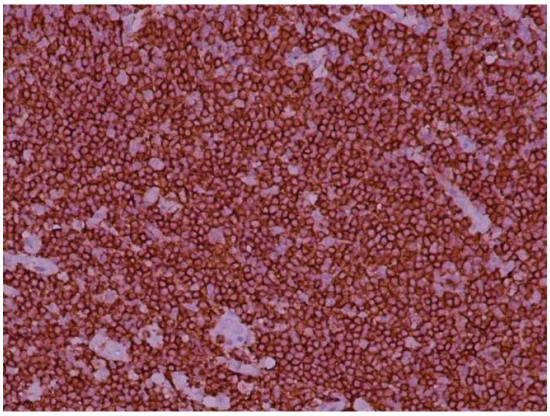

Fig. 3. Diffuse large B-cell lymphoma in a 28 year old female (the same case described in Figs. 1 and 2): cells intensively and diffusely expressing anti-CD20 antibody (Immunohistochemical evaluation x100)

The association between lymphoma and pregnancy is being described at an increasing rate, and some authors have found that it is more commonly reported than the association between pregnancy and carcinoma. Thus, we can suggest that hormonal disturbances are likely to play a role in inducing the proliferation of lymphoma [7].

Primary breast lymphoma is often unilateral. In 18% of cases, it is bilateral; and it can be simultaneous (12%) or sequential (6%) [8,9]. Primary breast lymphoma is almost always revealed under initial examination for a breast tumor with an inflammatory mastitis [2]. Axillary lymph nodes were found in 20-40% of cases [10].

The primitive characterization of breast lymphoma is based on clinical investigation. Indeed, we should eliminate secondary invasion of the breast during the natural evolution of non-Hodgkin's lymphoma [11].

The imaging characteristics of non-Hodgkin's lymphoma are non-specific. Mammograms often show a well-defined mass with a homogeneous density and benign appearance, resembling a cyst, a fibroadenoma or a phyllodes tumor. Less frequently, the lymphoma has the appearance of mastitis with diffuse increased breast density or an ill-defined or spiculated-contoured mass [12].

Rarely is a suspicious aspect of malignancyobserved, but there is never optimal opacity or microcalcifications [10].

Ultrasound presentation is not specific and usually presents as a hypoechoic and homogenous mass with regular contours. Rarely is the appearance of mastitis observed on ultrasound. The discrepancy between an alarming clinical presentation and a reassuring mammography may suggest the diagnosis [10].

The standard histological examination leaves little doubt in the case of medullary and anaplastic carcinoma, whereas the diagnosis of lymphoma is often difficult [13,14]. The difficulty may be absolved by a histological and immunohistochemical study of paraffin sections [15].

The most frequently observed type of lymphoma in the literature is diffuse large B-cell lymphoma (45% to 80%), particularly in localized forms,whereasfollicular lymphoma appears more frequently in disseminated forms. All histological types have been described. Lymphoma of the MALT type marginal zone is common (0-44%), and Burkitt's lymphoma is often associated with bilateral involvement [16]. In our study, no cases of Burkitt's lymphoma were identified, which may be related to a particular geographical distribution of this type of lymphoma [13,14].

The management strategies for primary breast lymphoma vary broadly, from surgical

interventions to combination chemotherapy and radiotherapy. However, there is no up to date standard guideline for the treatment of primary breast lymphoma. Mastectomy for primary breast lymphoma is not well-supported because it results in neither improved survival nor a reduced risk of recurrence. Several studies have recommended that surgery should be offered for diagnostic purposes only and that minimally invasive surgery is the preferable option because extensive surgery may carry a high risk of morbidity. Additionally, axillary dissection adds no therapeutic advantage [17].

At present, the early stages of primary breast lymphoma can be successfully treated with combination therapy, in which the CHOP regimen is the most common chemotherapeutic agent. Several investigators have recommended a treatment regimen involving combination chemotherapy with or without radiation therapy [17].

The prognosis of diffuse large B-cell lymphoma is poor. Among 215 cases whose outcomes were known, Prevot [18] notes that more than half of the patients died within a period ranging from 4 days to 178 months after diagnosis. Baltali estimated the 5-year survival rate to be 30% to 50% [19]. The histological type and clinical stage of the disease are the two main prognostic factors. Indeed, the risk of death is nearly double for patients with primary breast lymphoma stage II versus stage I [20].

5. CONCLUSION

Primary lymphoma is a very rare pathology. If symptoms do not respond to treatment, histological sampling is imperative. Treatment should be implemented quickly. Indeed, the five-year survival for stage I Ann Arbor classification is better than that for stage II.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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