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Primary diffuse large B-cell non-Hodgkin lymphoma of the breast in an elderly woman: case report and review of literature

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Summary. Primary non Hodgkin's lymphomas of the breast is a rare disease representing 0.38-0.70% of all non Hodgkin's lymphomas (NHL), 1.7-2.2% of all extranodal NHL and only 0.04-0.5% of all breast tumors. We report a case of an old woman with a primary diffuse large B-cell NHL of the breast who is still alive and disease free after 10 years since the end of treatment with a R-CHOP regimen followed by radiotherapy on residual disease. A review of the literature is also presented.

Key words: breast, primary non Hodgkin lymphoma

Introduction

Primary non-Hodgkin lymphoma of the breast is a rare disease, which represents about 0.38 to 0.70% of all NHL, 1.7 to 2.2% of all cases of extranodal NHL and only 0,04-0.5% of all breast cancers (1-6).

In literature about 700 cases of primary breast NHL (7, 8) have been reported so far. However their incidence is growing. Aviles (9) recently presented a review of 96 patients and the International Extranodal Lymphoma Study Group (IELSG) registered 204 cases (10). Female are the most affected, being primary male breast involvement reported only in rare cases (4, 11,12). The incidence peaks in the fifth and sixth decade of life (5, 8,13).

In 1972, Wiserman and Liao (14) have established the fundamental criteria for the diagnosis of primary lymphoma of the breast: 1) removal of breast tissue enough for a proper pathologic evaluation; 2) close association between breast tissue and lymphomatous infiltrate; 3) exclusion of systemic involvement of lymphoma or previous extra mammalian lymphoma. The ipsilateral axillary lymphadenopathy does not exclude the diagnosis of primary lymphoma of the breast. Although lymphomas represent the largest group of secondary breast cancers, a secondary involvement of the breast in an elsewhere arising lymphoma is a rare occurrence (15).

The most common histological type of primary breast lymphoma is B-cells. T Lymphoma is more rare and anaplastic large T-cell Lymphomas have a higher incidence in women with silicone implants (16-19). The diffuse large B-cell type is the most common B-cell lymphoma, constituting up to 53% of cases (20).

A mucosal-associated lymphoid tissue neoplasm (MALToma) is less frequently observed despite its incidence has increased in recent years since the first description of Lamovec and Jancar in 1987 (21). Burkitt's lymphoma is rare, typically occurs in young women and shows a very aggressive course (16).

Since the first description in 1893 there have been substantial advances in diagnostics and therapeutics of the primary breast NHL. However many controversial issues are still present, mainly concerning the diagnostic and therapeutic conduct. This paper describes the case of a patient with a primitive breast NHL and pre-

sents a review of the most controversial aspects in the diagnostic and therapeutic field.

Case report

In July 2005, a female patient aged 77, came to our attention because of a massive swelling in the upper-outer quadrant of the right breast which had lasted for several weeks (Figure 1).

Family and physiological anamnesis showed no risk factors for breast cancer. Clinical anamnesis recorded no major diseases. On clinical examination, our patient had a massive swelling of an area of about cm 9 per cm 6 which adhered to the underlying plans located in the outer quadrants of the right breast. Overlying skin looked hyperemic with an "orange peel" appearance. The clinical features simulated a carcinomatous mastitis.

Mammography and breast ultrasound were not specific. Serum lactate dehydrogenase (LDH) was within normal range. No systemic symptoms were recorded.

The patient underwent a biopsy of the breast lesion. Histological examination showed a lymphoma consisting of diffuse large peripheral B lymphocytes, immunologically typed as CD20+.

Total body computed tomography and CT-PET showed no further localization of lymphoma. Bone marrow biopsy was negative for systemic involvement.

The patient was administrated with 6 cycles of chemo-immunotherapy, according to the R-CHOP scheme (Rituximab - cyclophosphamide, doxorubicin, vincristine, prednisone).

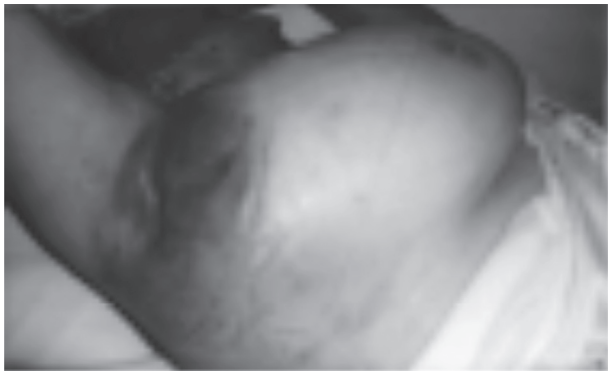

Figure 1. Neoplasms at first clinical examination

A CT/PET at the end of chemo-immunotherapy showed residual disease in the right armpit. Therefore the patient underwent radiation therapy on the right armpit reaching the total dose of 40 Gy in 20 sessions.

A CT/PET revaluation, performed 3 months after completion of radiation therapy, showed a complete remission of malignant disease which it is still maintained about 10 years after the end of treatment.

Discussion and conclusions

Primary NHL of the breast is a rare disease, especially if diagnosis complies with the necessary features as shown above in order to define the primitive mammary origin (14). Because of its features our case can be definitely classified as a primary lymphoma of the breast.

Breast lymphomas are supposed to originate from intramammary lymph nodes and/or periductal and perilobular lymphoid tissue. The low lymphocyte population in this organ justifies the low incidence of cases.

The majority of patients come to clinical observation for the appearance of an asymptomatic unilateral palpable mass. At onset ipsilateral axillary adenopathy is present in 30-40% of cases (14). A higher incidence of lesions in the right breast has been reported but so far no explanation has been proposed for this side preference (22). A bilateral simultaneous presentation at diagnosis is found in approximately 10% of cases (23, 24). Systemic symptoms such as fever, weight loss and night sweats are uncommon findings (2).

The primary lymphoma of the breast is difficult to differentiate from classic carcinoma in preoperative diagnostic phase. Mammography and breast ultrasound are not specific for the diagnosis of lymphoma. Therefore, the diagnosis of breast lymphoma can be obtained performing a cytological examination, for which literature reports a diagnostic accuracy of 86% (25). Greatest diagnostic accuracy is achieved with a needle biopsy (core biopsy) or excisional biopsy. Regardless of histologic type, the lymphomatous cells tend to widely affect the breast parenchyma with infiltration of ductal-lobular structures that are recognizable only in the periphery of the lesion.

After a diagnosis of primary lymphoma of the breast has been histologically confirmed, it is mandatory to perform an accurate staging of the disease for prognostic and therapeutic purposes.

Our patient was subjected to common laboratory tests (including the dosage of lactate dehydrogenase), to total body computed tomography and CT/PET, bone marrow biopsy, all of which were negative for systemic involvement.

The classification of Ann Arbor is the most frequently used in primary NHL of the breast (Table 1). However the International Prognostic Index (Table 2) has proved to be prognostically more accurate than the Ann Arbor staging, allowing the identification of different prognostic sub-groups within the same histological variety (26).

At present a uniform approach to the treatment of primary breast lymphoma is not available. Mastectomy has no indication since lymphomas are in most cases highly chemo and radioresponsive. The treatment is that of systemic lymphomas of the same histological type. Low degree malignant Lymphomas can be treated with a simple excisional biopsy and/or radiotherapy. High-grade malignant lymphoma should be treated with chemotherapy with or without radiation therapy.

Patients with diffuse large B-cell, as in this case, have to start with anthracycline-containing chemotherapy associated to rituximab. The randomized study of the French Groupe d'Etudes des Lymphomes de l'Adulte (GELA) (27) compared 8 cycles of CHOP (cyclophosphamide, adriamycin, vincristine, prednisone) and 8 cycles of CHOP + rituximab (R-CHOP) in 399 patients aged between 60 and 80 years. After a follow-up of 10 years, the addition of rituximab to the CHOP scheme has improved progression-free survival and overall survival of 6%, and disease-free survival for patients with complete remission of 22%. Their conclusions is similar to that of the Mayo

Table 1. Ann Arbor staging for lymphomas[1]

Stage I	Involvement of a single lymph node region (I) or lymphoid structure (eg, spleen, thymus, Waldeyer's ring) or extranodal structure (I_E)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or involvement of limited contiguous extralymphatic organ or tissue (II_E).
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III) which may include the spleen (III_S) and/or limited contiguous extralymphatic organ (III_E) or site (III_{ES})
Stage IV	Multiple or disseminated foci of involvement of extralymphatic organs or tissues and/or lymphatic involement

[1] All stages are further divided on the basis of the absence (A) or presence(B) of the following systemic symptoms: fever >38°C, drenching sweats and/or unexplained weight loss of greater than 10% of body weight over 6 months). Itching alone is not considered a systemic symptom

Table 2. International Prognostic Index (IPI): adverse risk factors of survival at 5 years

Adverse risk factors: (all patients)	Adverse risk factors: patients younger than 60 years of age
Age >60 years	Stage III/ IV (Ann Arbor)
Stage III/IV (Ann Arbor)	Performance status ≥1 (ECOG)
Performance status ≥2 (ECOG)	Serum LDH >normal
Number of Extranodal site >1	

IPI (all patients)	IPI score	Complete Response (%)	Relapse-Free Survival at 5 years (%)	Overall Survival at 5 years (%)
Low	0 o 1	87	70	73
Low intermediate	2	67	50	51
High intermediate	3	55	49	43
High	4 o 5	44	40	26

Clinic group (28), in which the addition of rituximab, administered simultaneously or successively to CHOP, provides a benefit of 30% in terms of progression-free survival at approximately two years. Therefore, in absence of contraindications such as severe heart problems, the use of R-CHOP regimen is strongly recommended in all patients with diffuse large B-cell.

Radiotherapy is indicated when PET scan at the end of R-CHOP chemo-immunotherapy shows a single site residual disease that can be irradiated, as in the reported case. The Canadian group retrospective evaluation (29) of 196 patients treated with 6 cycles of R-CHOP and radiotherapy to PET residues confirmed the advantage of that regimen. Patients who were irradiated showed the same progression free rate at 3 years as patients in complete remission (PET negative) after R-CHOP. The efficacy of R-CHOP regiment plus radiotherapy on residual disease in old patients is also confirmed in our woman who is still alive and free from progression 10 years after completing the treatment.

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