SECONDARY INVOLVEMENT OF BREASTS BY FOLLICULAR LYMPHOMA

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Abstract  Metastatic lesions involving the breast are exceptional; hematolymphoid neoplasias rank second as per their frequency in case series reported in the literature with a prevalence of 0.04% to 1.6% when considering all malignant breast tumors and reaching an annual incidence of 0.07%, mainly accounted for by secondary lymphomas. Eighty percent of them are diffuse, large B cells lymphomas (DLBCL), followed by follicular lymphoma and marginal zone lymphoma. This case is about a 60 year-old woman with a diagnosis of follicular lymphoma, who presented with a right perirenal mass and ipsilateral retroperitoneal and inguinal lymph nodes, whose clinical status progressed during the treatment with unusual secondary involvement of both breasts by hematolymphoid neoplasia. The biological behavior of the condition was evaluated to understand the pathophysiological mechanisms; this was done analyzing clinical, histologic and prognostic factors that led to a definitive staging, which was key to select the individualized therapy following the clinical practice guidelines based on scientific evidence, with a positive impact on the patient’s medical progress.

Key words: follicular lymphoma, breasts, BCL-2, metastasis

Clinical case

A 60 year-old woman came to the clinic reporting bilateral, fast-growing mammary nodules that caused mild breast...
tenderness. She had a pathologic history of follicular lymphoma diagnosed 12 months before, which presented as a $6.5 \times 5$ cm mass, right perirenal location, associated to right retroperitoneal and inguinal lymph nodes, without bone marrow infiltration.

In the paraclinical testing hemoglobin level was 12.5 mg/dL and lactate dehydrogenase (LDH) level was 205 u/L. It was initially staged as IIE of the Lugano classification and low risk according to the Follicular Lymphoma International Prognostic Index (FLIPI). The chemotherapy protocol was started with rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP), then maintenance with rituximab 375 mg/m² every 8 weeks with partial response.

In the current physical exam, a nodular lesion was palpated in the lower inner quadrant of the right breast, firm consistency, slightly tender to the touch, with no evidence of skin changes or nipple retraction. Two masses were found in the left breast, located in the upper outer quadrant and the lower outer quadrant with morphological features similar to those described in the contralateral breast.

A bilateral mammogram was obtained, which reported the presence of a nodule in the right breast, with smooth edges and clear boundaries, while in the left breast radiopaque and circumscribed nodules were noted; both lesions were categorized IVB according to the Breast Imaging Reporting and Data System (BI-RADS), and interpreted as suspicious findings (Fig. 1). In the ultrasound a 4.5 cm micro lobulated, heterogeneous mass was defined in the right breast and two similar nodules in the left breast measuring 1.2 cm in diameter, average. No axillary lymphadenopathies were identified.

An ultrasound-guided trucut needle biopsy was performed and pathology reported infiltration of the mammary stroma by monotonous and diffuse small lymphoid cell population with no angioinvasion. The axillary lymph nodes' biopsy reported tumoral involvement. Immunohistochemistry markers were run and showed tumor cells positive for CD45, CD20, CD10, BCL2, BCL6, and negative for CKAE1/AE3 and CD56. The rate of cellular proliferation expressed as a Ki-67 proliferative index (PI) is 8% (Fig. 2). The diagnosis was defined as bilateral breast and axillary lymph nodes involvement by follicular non-Hodgkin B cell lymphoma histological grade LF1 and stage IV in the Lugano classification. Second line treatment ensued with rituximab-bendamustin protocol, 4 cycles, resulting in significant tumor cytoreduction and currently in the consolidation phase with rituximab 375 mg/m² every 12 weeks, without bone marrow infiltration or new masses in positron emission tomography scan, or clinical characteristics evidencing its transformation to diffuse large B cells lymphoma (DLBCL).

Written informed consent was obtained from the patient for the publication of this case report and its accompanying images.
Discussion

Follicular lymphoma (FL) is generally an indolent B cell lymphoproliferative condition of transformed follicular center B cells. Its clinical characteristics are diffuse lymphadenopathy, cytopenias, bone marrow infiltration, splenomegaly, and less commonly extranodal involvement. The extranodal localization may appear in any anatomical position sharing similar characteristics regarding morphology, immunophenotype, and genetics with nodal lesions, however, this location is associated to an unfavorable outcome.

The infiltration by FL in the breast may be primary or secondary, the latter being the most common clinical presentation, requiring for the diagnosis the previous confirmation of a generalized extra-mammary hematolymphoid neoplasia, as noted in our patient, who presented with a retroperitoneal mass, lymph nodes and subsequently bilateral breast involvement. Besides the clinical course, the diagnostic images may also help differentiate between primary and secondary lesions, since more frequently multiple and bilateral tumor lesions are found in secondary breast lymphomas, seen in the diagnostic images of this case.

From a pathophysiological perspective, follicular lymphoma is characterized by clonal, diffuse proliferation of germinal center B lymphocytes, specifically centrocytes and centroblasts, 85% of which present the (14;18) (q32;q21) translocation resulting in the fusion gene IGH-BCL2, associated to the overexpression of the B-cell leukemia/lymphoma 2 (BCL2) which induces the apoptosis blockade.

Based on clinical factors, the patient was categorized according to the size of the tumor with the Lugano classification, which considers the involvement of one or two lymphatic regions in the limited phase (stages I and II), it adds the letter E when an organ outside the lymphatic system is affected, while the advanced phase (Stages III and IV) involves lymphatic regions on both sides of the diaphragm, and is diffuse in extra lymphatic organs. The patient was initially staged IIE due to the presence of the retroperitoneal mass and the involvement of lateral right retroperitoneal and inguinal lymph nodes, and subsequently in the tumor progression phase she was defined as stage IV, given the bilateral infiltration of the breasts.

To consider the patient’s prognosis as low risk at the time of the diagnosis, a combination of clinical variables was used, which together belong to the Follicular Lymphoma International Prognostic Index (FLIPI), in order to estimate the overall survival (OS) and subsequently, with FLIPI-2 establish disease-free survival, after introducing the therapy with anti CD20 monoclonal antibodies. The criteria used for the assessment were: older than 60 years of age, hemoglobin levels in peripheral blood lower than 12 g/dl, identification of Ann Arbor stage III and IV (currently modified in the Lugano System), high serum LDH values, and the number of nodes involved higher than 4. With these criteria the categorization is as low risk (score 0-1), intermediate (score 2) and high risk (≥ 3), estimating
91%, 78% and 53% OS at 5 years, respectively for each of the categories. The histologic characteristics of the tumor cells were analyzed to establish the morphologic classification as LF1, considering the number of centroblasts per high-power field: LF1 less than 6 centroblasts; LF2 from 5 to 15 centroblasts; LF3A more than 15 centroblasts and LF3B exclusive representation of centroblasts. This histologic grading system is relevant from the prognostic perspective since the scientific literature has shown that grade LF3B presents an aggressive clinical course with a higher risk of becoming DLBCL, while survival in grades LF1-3A exceeds 12 years.

Staging with the above-described parameters led to the selection of the right treatment algorithm according to the National Comprehensive Cancer Network (NCCN) guidelines proposed for FL. Thus, for stages I or II and histologic grade LF1-3A the recommendation includes radiotherapy in the affected site (ISRT) with curative intent. However, in the presence of large intra-abdominal and mesenteric lesions, first-line therapy with anti CD20 monoclonal antibodies is indicated (obinutuzumab or rituximab) plus CHOP chemotherapy, leading to disease-free survival rates reported in the literature at three years of 68%. Given the partial response to treatment and disease progression to Stage IV and the identification of large bilateral breast tumors, the treatment indications were assessed and following the NCCN guidelines, the second-line treatment was initiated with the rituximab + bendamustine scheme and consolidation with 375 mg/m² rituximab doses every 12 weeks, with satisfactory response so far.

In conclusion, this case is an exceptional presentation of follicular lymphoma due to its bilateral breast extranodal location, where understanding the biological behavior of the pathology, through the analysis of clinical, histologic and prognostic factors, allowed for the final staging. This was relevant for individualized therapy selection according to the clinical practice guidelines based on scientific evidence, with a positive impact on the medical progress of the patient.

Conflict of interest: None to declare

References