An unusual presentation of secondary involvement of B-cell chronic lymphocytic leukemia. A case report

Fausto Famà¹, Valeria Barresi², Giuseppe Giuffrè², Paolo Todaro², Sergio Mazzei¹, Angelo Vindigni¹, and Maria Gioffrè-Florio¹

¹Division of General Surgery, and ²Division of Diagnostic Cytopathology, Department of Human Pathology, University of Messina, Italy

ABSTRACT

Extramammary tumors rarely metastasize to the breast. The commonest tumors to metastasize in breast tissue are lymphoproliferative diseases, melanoma, lung cancer and gynecological malignancies.

Primary breast lymphoma has been reported in the literature with a maximum percentage of about 0.5% of all breast malignancies, while secondary localizations of lymphomas in the breast are less well studied in the literature than primary ones.

The authors report a rare case of a secondary localization of B-cell chronic lymphocytic leukemia to the breast in which the diagnosis was obtained by histopathology and immunohistochemistry and further confirmed by molecular data.

This occurrence must be considered in the differential diagnosis of a breast lump so that the primary hematological disease can be adequately treated and the correct type of breast surgery performed.

Introduction

Metastatic breast involvement by extramammary tumors is rare. Breast metastases represent about 2% of all neoplastic mammary lesions¹. The most frequent tumors to metastasize in breast tissue are lymphoproliferative diseases, melanoma, lung cancer and gynecological malignancies (uterus and ovary)²⁻⁷. According to the literature, lymphomas show an incidence of 0.07% as secondary breast localization, accounting for about 17% of all malignancies metastatic to the breast⁸. Some cases of lymphomas with involvement of the breast have been reported in the literature; the most frequent were 2 types of B lymphomas: follicular lymphoma and diffuse large B-cell lymphoma⁹. B-cell chronic lymphocytic leukemia rarely involves the breast⁹.

We report a case of recurrent B-cell chronic lymphocytic leukemia with a metastatic breast localization.

Case report

A 45-year-old nulliparous woman was under our observation for breast screening. The patient recalled no significant diseases in her personal history. Clinical examination revealed a small retroareolar palpable lump in the left breast, not superficially or deeply fixed, measuring approximately 1 cm in diameter; no enlarged lymph nodes were found. Laboratory values were as follows: white blood cells 18.7 x 10⁹/L (72.3% lymphocytes); platelets 338 x 10⁹/L; hemoglobin 13.2 g/dL. No liver or spleen enlargement was found despite the lymphocytosis.

Mammography revealed a nodular area (diameter 6-8 mm) with irregular margins and without microcalcifications, which did not show up in the previous radiographic check-up (Figure 1). Ultrasonography confirmed the presence of a hypo-anechoic lump with a maximum diameter of 5 mm (Figure 2). Ultrasound-guided fine-needle aspiration cytology...
ogy was performed. The cytological smears were routine-
ly stained with Papanicolaou and May-Grunwald Giemsa.
Examination revealed hypocellularity with few typical
ductal cells and lymphocytes that were isolated or
grouped in microaggregates; these lymphoid cells were
characterized by hyperchromatic nuclei and absence of
nucleoli (Figures 3A and B).

Figure 1 - Craniocaudal mammogram shows a retroareolar lump
of 6-8 mm in diameter with spiculated margins.

Figure 2 - Ultrasound findings of a hypo-anechoic lesion of 5 mm.

Figure 3 - Cytological examination. A) Typical ductal cells and iso-
lated lymphoid cells (Papanicolaou stain, magnification ×160). B) Lymphocytes with hyperchromatic nuclei were grouped in mi-
croaggregates (May-Grunwald Giemsa stain, magnification ×320).
Since the number of cells in the smears was insufficient to obtain a certain diagnosis of secondary lymphoma or leukemia, the patient underwent a retroareolar lumpectomy (diameter 6 mm) with clear margins. A periareolar superior approach and translocation of the areola was performed. The wound was closed with a fine subcuticular absorbable suture (5.0 poliglecaprone).

Peroperative histological examination showed isolated lymphoid aggregates invading the breast stroma (Figure 4). These aggregates were made up predominantly of small lymphocytes with hyperchromatic nuclei and scanty cytoplasm, prolymphocytes, and paraimmunoblasts. The mitotic rate was low. No cytarchitectural alterations in the breast tissue were found.

After this morphological observation the hypothesis of autoimmune or proliferative lymphoid disease was tested. A deeper inquiry into the patient’s medical history revealed a previous undefined hematological disorder. Therefore immunohistochemical analysis (by CD5, CD23, CD20 and CD79α) was performed on 5-µm-thick breast sections, with evident immunoreactivity of lymphoid elements. Moreover, to better define the lesion, a bone marrow biopsy was performed.

The microscopic findings showed bone marrow hypercellularity with an interstitial multifocal lymphoid infiltrate mainly represented by elements of small dimension, with coarse chromatin and scanty cytoplasm. A reticulum stain showed an increased meshwork. The bone marrow residual rate was about 80%. Immunohistochemically, the CD79α-CD20-CD23-CD5 immunopositivity of these cells suggested a diagnosis of B-cell chronic lymphocytic leukemia.

This diagnosis was further confirmed by the molecular data obtained by polymerase chain reaction (PCR), in which a monoclonal rearranged band of the immunoglobulin heavy chain (IGHV) genes was found. Nucleotide sequencing analysis showed a germline locus IGHV4-34 rearrangement with a somatic hypermutation rate of 7.6%, in accordance with immunohistochemical ZAP-70 protein negativity.

Discussion

Breast cancer is the first cause of death from malignancy in women\textsuperscript{10,11}. Extramammary tumors rarely metastasize to the breast\textsuperscript{11}. A correct diagnosis of secondary breast lumps may be hard to make. Breast metastases from extramammary neoplasms (carcinomas, sarcomas, melanomas and hematological cancer) have been reported in the literature\textsuperscript{2-5,10-14}. Tumor spread to the breast may be found after diagnosis of the primary neoplasm, but a secondary breast lump is sometimes the first disease manifestation\textsuperscript{15}.

A single superficial lump, not painful and not fixed and without skin or nipple changes like the one in our report is the most frequent clinical presentation of a secondary neoplastic breast localization\textsuperscript{16-19}. As extramammary tumors do not involve the ducts, nipple retraction, skin dimpling, and nipple discharge are rare\textsuperscript{20}. Lymph node involvement has been variably documented\textsuperscript{21}. Mammographic and ultrasound findings are unspecific and do not allow differentiation between primary and secondary breast lesions. Well-defined masses without microcalcifications are more suggestive of secondary lesions such as the present case\textsuperscript{22}. A diagnosis can be obtained only by fine-needle aspiration cytology or histopathology.

Cytological examination suggests lymphoid proliferation in the presence of single uniform cells with condensed chromatin and scanty cytoplasm associated with a lack of 3-dimensional epithelial aggregates, as in our case. Nevertheless, a differential diagnosis between metastatic breast lumps and intraparenchymal lymph nodes (presenting heterogeneous characteristics), reactive lymphoid infiltrates, amelanotic melanomas, medullary carcinomas, lobular carcinomas and poorly differentiated ductal carcinomas is needed\textsuperscript{6}. A definitive diagnosis may be obtained only by specimen histology showing lymphoid proliferation with typical cytarchi-
tectural findings like aggregates and an undamaged breast gland structure.

In the event of breast metastases related to hematological disease, immunohistochemistry is necessary for cell typing, classification, postsurgical treatment, and in particular the identification of B-lymphocytes characterized by CD79α-CD20 immunopositivity. In our case, the cellular monoclonality revealed by PCR allowed the immunophenotype to be identified and CD23-CD5 immunoreactivity finally suggested a diagnosis of B-cell lymphocytic leukemia. The immunohistochemical findings in the examined breast tissue were consistent with those of the bone marrow biopsy. All histocytopathological and immunohistochemical data taken together allowed us to exclude a diagnosis of high-grade lymphoma.

B-cell chronic lymphocytic leukemia metastasizing to the breast has been infrequently reported in the literature. This possibility must be considered in the differential diagnosis of a breast lump to avoid unnecessary mastectomy and ensure proper treatment of the primary hematological disease. In our report, a favorable prognostic evaluation was obtained by mutational analysis of the IGHV genes and immunohistochemistry for ZAP-70 protein.

References