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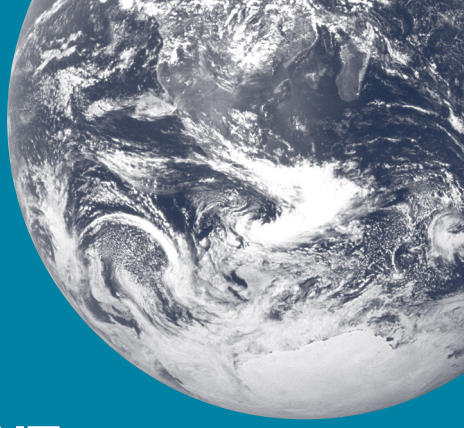

B-CELL POLYCLONAL LYMPHOCYTOSIS IN A WOMAN WITH BONE MARROW INVOLVEMENT BY BREAST CANCER CELLS

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Abstract – *Persistent polyclonal B-cell lymphocytosis (PPBL) is a rare entity of unknown origin usually observed in smoking women, characterized by binucleated B-lymphocytes and a specific clinical course. We described a case of an "atypical" form of PPBL in a no smoking woman suffering from bone marrow involvement by breast cancer cells with concomitant circulating polyclonal B-lymphocytes without augmenting in serum polyclonal IgM levels. No cytogenetic abnormalities were found. To date, it is not clear whether a PPBL may represent a response to a bone marrow involvement of breast cancer or a pre-neoplastic reality, preceding the emergence of a predominant clone. Recently, because of the natural history of PPBL remain unclear and unclassifiable in the current hematological malignancies, these patients need to undertake a careful long-term follow-up.*

KEYWORDS: *Breast cancer cells, B-cell polyclonal Lymphocytosis, Analytical validations.*

INTRODUCTION

Persistent polyclonal B-cell lymphocytosis (PPBL) is a rare entity of unknown origin usually observed in smoking women, characterized by binucleated lymphocytes and a favorable clinical course. Since the first recognition by Gordon et al[1] in 1982, several other authors have mentioned cases reporting new data, such as anomalies in chromosome 3 and polyclonal increase in serum IgM levels [2-9]. The PPBL entity is not said as distinctive hematological malignancy in the current WHO 2016 classification [10].

Here, we report a case of PPBL with atypical lymphoid characteristics of a no smoking female patient presenting mononucleated PPBL without an increase in serum IgM levels and chromosome aberrations.

CASE PRESENTATION AND METHODS

A 55-year-old woman, with ductal carcinoma of the left breast, underwent to wide breast local excision and axillary lymph nodes dissection. Post surgery, she received adjuvant chemotherapy regimen including epirubicin, followed by cyclophosphamide, methotrexate and 5-fluorouracil, at standard doses. After scheduled chemotherapy (six courses), she continued with tamoxifen, discontinued in the next

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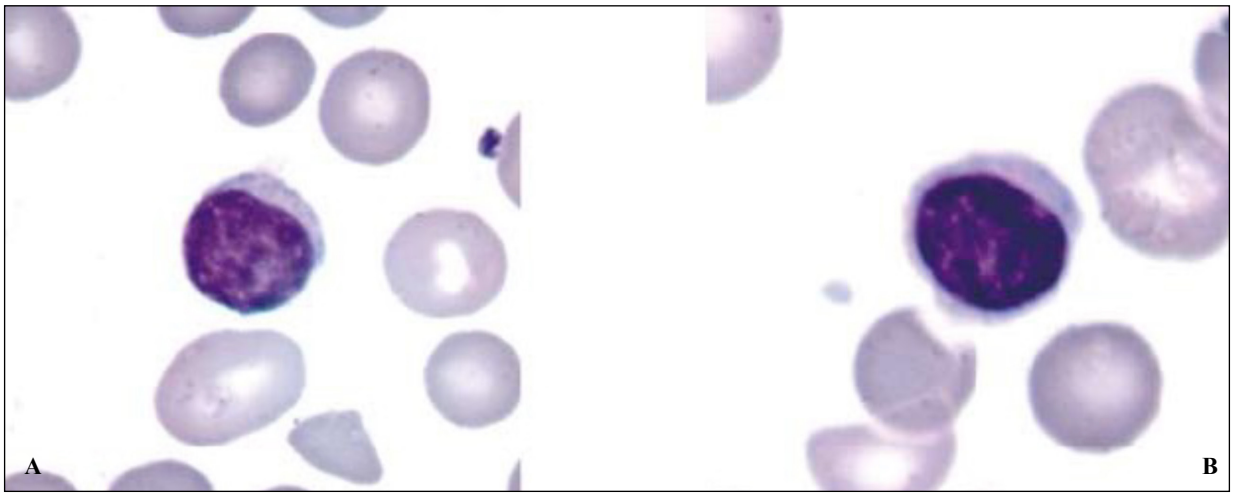

Fig. 1. *A*, Peripheral blood thin glass showed polychromasia, normoblasts with elliptocytes and some dacryocytes while lymphocytes were found as mature appearing. *B*, In bone marrow biopsy, there were several aggregates of mature mononucleated mostly B-lymphocytes.

three months because of a transitory ischemic attack occurred. Pharmacogenomics panel assay was performed to define individual metabolic genetic profile [11,12]. Letrozole was then given as an alternative anti estrogen receptor. Other comorbidities are diabetes mellitus and hypertension. After three years of letrozole maintenance, cervical nodes and a right axillary node involvement in breast cancer were found and the patient required therapy with intravenously docetaxel for six courses with partial remission of the disease. Because of disease progression, orally capecitabine for nine courses was given, with a partial response, followed by orally Exemestane maintenance therapy [13]. The patient experienced weakness, platelet reduction (50 x 10^9/L) with spontaneous gingival bleeding, anemia (Hb 1.11 g/L) and lymphocytosis (WBC 14.2 x 10^9/L; 65% of which were lymphocytes) along with a rise in neoplastic markers (CA15.3 and MCA). A peripheral blood cell count performed 20 days later showed again anemia (Hb 0.86 g/L), a further rise in WBC count (24.2 x 10^9/L; 54% of which were lymphocytes) and also a platelet count recovery (101 x 10^9/L). In light of this, exemestane was stopped and the patient underwent a re-evaluation of her breast cancer and hematological alterations as well.

At hospital admission (after four years from breast surgery), physical examination showed lateral-cervical lymphoadenopaties and hepatomegaly confirmed by total body Computed Tomography (CT) and abdominal Ultrasound (US) scans. The patient referred weakness and nightly fever revealed. Finally, a whole body bone CT scans technetium 99m-based method was not able to find areas of abnormally increased activities using a node biopsy.

Laboratory findings: Hb was 0.85 g/L; MCV 95.6 fL; WBC count 30.1 x 10^9/L, 60% of which lymphocytes; platelet count 106 x 10^9/L; LDH 1,747 IU; total/direct bilirubin 0.10/0.07 mg/L; reticulocyte count showed 181 x 10^9/L. Renal function, iron status and coagulation tests were also found normal, serum IgG 0.14 mg/L; IgA 42.1 mg/L; IgM 10.9 mg/L. Finally, the detection of the liver viral pathogens load (HBV and HCV) was negative.

A peripheral blood thin glass showed polychromasia, normoblasts with elliptocytes and some dacryocytes while lymphocytes were found as mature appearing (Figure 1A). Bone marrow aspiration yielded a hypocellular specimen with very few cells, some of which were found as large mononucleated non-hemopoietic cells. In fact, bone marrow biopsy showed diffuse infiltration of epithelioid cells (breast cancer metastasis) with abundant eosinophilic, sometimes vacuolated cytoplasm morphologically similar to those present in the primary breast cancer. The neoplastic cells were immunohistochemically positive to cytokeratin 7(CK7) and focally to gross cystic disease fluid protein 15(GCDFP15). In the examined bone marrow biopsy, there were also two small nodular aggregates of mature mononucleated mostly B-lymphocytes (Figure 1B). The flow cytometric analysis of peripheral blood and bone marrow samples showed B-cell lymphocytosis with representation of both kappa and lambda light chains, while T-cell and NK-cell number were found normal (CD3+ -, CD5+, CD10+, CD19+ +, CD20+ +, CD22+ +, CD23+ +, CD10+ , CD37+ +, FMC7+ +, HLA-DR+ +, CD38+ +, CD11c+ -, Kappa+ 27 %, Lambda+ 15 %). Polyclonality of B-cells was also demonstrated by means of the molecular detection of immunoglobulin heavy chain gene IgH V-D-J rearrangement (Figure 2A). The detection of the

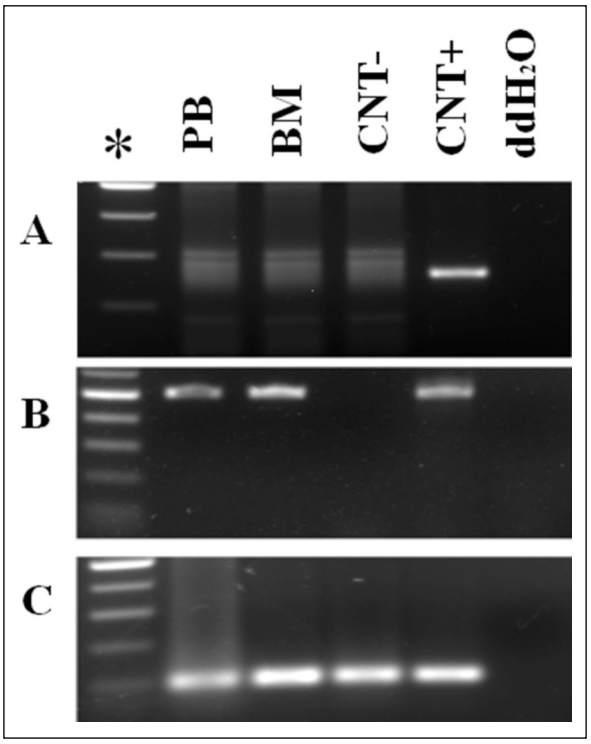

Fig. 2. *A*, Rearrangement of the immunoglobulin heavy chain (IgH) gene for framework region 2 (FR2) of the variable region, according to the manufacturer's instructions of "Ampli set B Kit (Dia-Chem, Naples, Italy)". *B*, Rearrangement of the BCL1/IgH. 0.5 microgram of DNA sample was amplified in two step (first Round and nested-PCR) by specific primers, that cover a Major Breakpoint Region (MBR) in BCL2 gene in forward. *C*, Albumin reference gene amplification was performed to evaluate the quality PCR-Grade DNA source.

rearrangement of t(11;14)BCL1/IgH was negative (Figure 2B)[14]. Cytogenetic analysis showed a normal karyotype in all 20 metaphases analyzed. The patient was treated with vinorelbine as salvage therapy.

After one cycle of therapy, lymphocytosis and anemia persisted: Hb 9.8 g/dL; MCV 104.46 fL; WBC 18.9 x 10^9/L, 65% of which were lymphocytes; platelet count 179 x 10^9/L. Once again, the flow cytometric characterization of lymphocytes confirmed the expansion of polyclonal B-cells (CD19+, CD20+, CD23+ etc.). Finally, the patient died after one month post- vinorelbine, because of a disease progression with the central nervous system and liver involvement by breast cancer cells.

DISCUSSION

Sometimes, a polyclonal lymphocytosis may be associated with an infectious disease of viral origin or secondary to drug reactions. In these cases, a transient T-lymphocytosis is commonly observed in Breast Associated Implant Anaplastic Large Cell Lymphomas (BAI-ALCL)[15]. On the contrary, a persistent B-cell expansion is usually related to B-cell chronic lymphoproliferative disorder in leukemic phase. In this latter, monoclonality of neoplastic B-cells is easy to demonstrate by means of flow cytometry or molecular biology. However, a rare entity, firstly described in 1982 by Gordon et al[1] in three adult smoking women with binucleated polyclonal B-cell lymphocytosis, must be taken into account. Since then, the so-called PPBL, usually affecting young or middle-aged smoking women, has been reported by several investigators [2-11].

Despite unknown origin, the clinical picture of this syndrome is characterized by a polyclonal B-cell lymphocytosis due to the expansion of morphologically binucleated lymphocytes and a polyclonal increase in serum IgM levels.

The patients are usually asymptomatic and the clinical course is right without calling for treatment.

Anomalies in the chromosome 3, such as +ins(3), with or without premature chromosome condensation in 79% of cases, chromosome instability in 67,5% with various clonal and non clonal chromosomal abnormalities, such as del(6q), +8 or del(11q), were also documented in the largest cytogenetic investigation on PPBL [16]. Also, the same authors, confirmed the benign clinical course of PPBL showing that cytogenetic abnormalities persisted after stopping tobacco use, thus suggesting no apparent relationship between cigarette smoking and documented ATR amplification gene [16].

Finally, we believe that the validation of the robust methods able to detect markers to address costly this rare lymphocytosis allows to integrate this information in a personalized approach [17]. In this way, the PPBL could be mentioned in next hematologic malignancies classification [18]. Furthermore, to interpret lab results of these genetic variants correctly, it is necessary a continuous learning upgrading of the oncologist in this field [19].

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Ethical Committee:
The study was conducted according to the Institutional requirements and Helsinki Declaration.

Informed Consent:
All participants in this study signed the informed consent

Conflict of Interest:
Dr. Santorelli is a consultant and speaker for Allergan, Inc. (Irvine, CA). The other authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article. Others Authors have no conflicts of interest to declare

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