INTRODUCTION

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. Since the first recognition by Gordon et al\textsuperscript{1} in 1982, several other authors have mentioned cases reporting new data, such as anomalies in chromosome 3 and polyclonal increase 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 cells 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.
B-CELL POLYCLONAL LYMPHOCYTOSIS IN A WOMAN WITH BONE MARROW INVOLVEMENT BY BREAST CANCER CELLS

Lymphocytes; platelet count 106 x 10⁹/L; LDH 1,747 IU; total/direct bilirubin 0.10/0.07 mg/L; reticulocyte count showed 181 x 10⁹/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
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rearrangement of t(11;14)BCL1/IgH was negative (Figure 2B)\textsuperscript{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\textsuperscript{9}/L, 65% of which were lymphocytes; platelet count 179 x 10\textsuperscript{9}/L. Once again, the flow cytometric characterization of lymphocytes confirmed the expansion of polyclonal B-cells (CD19\textsuperscript{+}, CD20\textsuperscript{+}, CD23\textsuperscript{+} 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)\textsuperscript{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\textsuperscript{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 \textsuperscript{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 bineuleated 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 \textsuperscript{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 \textsuperscript{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 \textsuperscript{17}. In this way, the PPBL could be mentioned in next hematologic malignancies classification \textsuperscript{18}. Furthermore, to interpret lab results of these genetic variants correctly, it is necessary a continuous learning upgrading of the oncologist in this field \textsuperscript{19}.

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**CONFLICT OF INTEREST:**

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