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Case Report

B-Cell Prolymphocytic Leukemia: Two Case Reports and Review of the Literature

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Abstract: B-cell prolymphocytic leukemia is a very rare mature B-cell leukemia occurring in elderly people diagnosed when prolymphocytes comprise more than 55% of the lymphoid cells in peripheral blood. Its evolution is most often aggressive. We report here the cases of two patients with clinical signs dominated by splenomegaly associated with significant hyperlymphocytosis. Their blood smears revealed extensive prolymphocyte invasion suggesting Prolymphocyte leukemia confirmed by immunophenotyping. Both purine analogues and monoclonal antibodies have shown promoting results, however, allogeneic hematopoietic stem cell transplantation remains the only therapeutic means allowing a lasting response. However, it is reserved for young patients with compatible donors. A good understanding of the pathogenesis and a better integration of the molecular data of this hemopathy open the way to the use of new targeted therapies. Prolymphocyte leukemia is a very rare, complex, and often aggressive, mature lymphoid hemopathy. The mean age of onset is 65 years with a predominance of males. We report here the case of a patient with splenomegaly and severe lymphocytosis in whom the smear showed an invasion of 90% of prolymphocytes suggesting Prolymphocyte leukemia confirmed by immunophenotyping.

Keywords: B cell prolymphocytic leukemia, lymphoproliferative syndromes, diagnosis, treatment, case report.

INTRODUCTION

B-cell prolymphocytic leukemia (B-PLL) is a rare mature B-cell lymphoid hemopathy with a mostly aggressive clinical course. It is a very rare and complex mature B lymphoid hemopathy affecting the elderly with a generally unfavorable prognosis.

Before it was first described as a distinct disease entity in the 1970s, prolymphocytic leukemia was considered a variant of chronic lymphocytic leukemia, but without typical clinical manifestations, and then secondarily individualized as a distinct entity, with its own clinical, morphological, phenotypic, and cytogenetic features.

Therapeutic proposals are modest and currently based on purine analogues and monoclonal antibodies, and allogeneic hematopoietic stem cell transplantation is the only therapeutic strategy to achieve a durable response. Advances in the understanding of the pathogenesis of these entities open the way to the use of promising new targeted therapies.

We report two observations of patients followed for de novo prolymphocytic leukemia type B, illustrating the diagnostic, therapeutic and evolutionary particularities of this subtype of hemopathy.

PATIENTS AND OBSERVATIONS

Observation N1

This is a 71-year-old diabetic patient with 15 years of hypertension who consulted for a heaviness of the right hypochondrium in a context of altered general condition and night sweats. Clinical examination revealed splenomegaly 5 cm from the left costal margin and firm and mobile adenopathies located in the cervical region.

The biological assessment revealed a hyperleukocytosis at 352000/mm3 associated with an aregenerative normocytic anemia at 11g/dl without

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thrombocytopenia and an accelerated sedimentation rate at 100 mm the first hour.

Blood protein electrophoresis was normal. Liver and kidney function tests were normal. Viral serologies, HIV, viral hepatitis B and C and TPHA - VDRL were negative.

The blood smear stained with May Grünwald Giemsa (MGG) showed a 70% invasion by atypical monomorphic lymphoid cells twice the size of lymphocytes, with regular nuclei and dense chromatin, often nucleated, and weakly basophilic cytoplasm in favor of prolymphocytic leukemia (figure 1) with the presence of 25% lymphocytes and 10% neutrophils. The myelogram showed a rich marrow, infiltrated by 53% of cells identical to those found in the peripheral blood. In addition, there was hypoplasia of the erythroblastic and granular lineages.

The osteomedullary biopsy had shown significant infiltration by cells of similar morphology to those found in the myelogram analysis, with absence of myelofibrosis.

Flow cytometry showed a monotypic B lymphoid population, CD19+, CD20+, CD22+, partial CD5, CD23-, strong FMC7+ and strong CD79b+. The Matutes score was 1, did not argue for chronic lymphocytic leukemia.

The patient was put on monthly courses of the COP protocol: Cyclophosphamide 600mg/m2, Vincristine 1.2mg/m2 and prednisone 60mg/m2). After the second course, the patient presented with a left parietal ischemic stroke, secondary to a hypertensive peak (200/120mmHg) and blood hyperviscosity with a concomitant white blood cell count >100000/mm3. He had retained a sequential right brachial monoparesis and Broka's aphasia. The re-evaluation performed after the 6th course of COP.

The evolution was marked by a decrease in the white blood cell count and the disappearance of adenopathies, but with persistent splenomegaly. We noted a therapeutic escape after the 8th treatment, with the appearance of hepatomegaly, anemia at 7g/dl, thrombocytopenia at 60,000/mm3, re-increase of the white blood cell count, and the onset of renal insufficiency and tumor lysis syndrome after the second cycle. The patient died and the overall follow-up time was 1 year and 4 months.

Observation N2

A 65-year-old patient, type 2 diabetic on metformin, was referred for major hyperlymphocytosis with anemia and thrombocytopenia.

Clinical examination revealed mucocutaneous pallor and splenomegaly 8 cm from the left costal margin, without palpable peripheral adenopathies with a few subcutaneous nodules of the scalp.

The initial blood count revealed white blood cells at 730,000/mm3 with an anemia of 5 g/dl normocytic aregenerative and thrombocytopenia at 26,000/mm3. The blood smear stained with May Grünwald Giemsa (MGG) showed 93% invasion by prolymphocytic cells with 5% lymphocytes and 2% neutrophils. The myelogram showed a rich marrow, infiltrated by 90% of cells identical to those found in the peripheral blood.

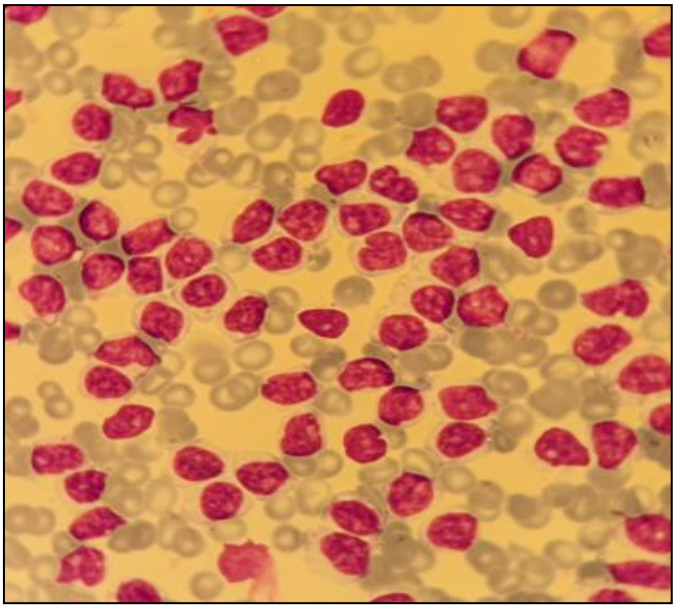

Figure 1: (x 100) MGG-stained blood smear: presence of medium-sized prolymphocytes with a high nucleo-cytoplasmic ratio, regular nucleus sometimes notched, with dense chromatin with prominent nucleolus, and low basophilic cytoplasm

Immunophenotyping revealed a monotypic B lymphoid population with CD19+, partial CD5+, CD23+, CD43+, FMC7+, CD79b+, CD20+ (high intensity), expressing a lambda light chain of moderate intensity in favor of B-PLL.

Cytogenetic analysis revealed a complex karyotype with clonal chromosomal abnormalities of number including: monosomy of chromosome 10, monosomy of chromosome 15, monosomy 20, and of structure including: a derivative of chromosome Y, a derivative of chromosome 9, a deletion of the long arm of chromosome 11 and a derivative of chromosome 12. Fluorescence in situ hybridization (FISH) showed a deletion of the P53 locus on the short arm of chromosome 17 at 17p13 and of the ATM2 locus on the long arm of chromosome 11 at 11q22.3. The P53 mutation searched by PCR was positive.

The thoraco-abdomino-pelvic CT scan revealed a supra- and subdiaphragmatic polyadenopathy and a nodular splenomegaly of 18 cm. The rest of the workup was unremarkable (renal and hepatic functions, viral serologies for hepatitis B, C and HIV, TPHA-VDRL).

The patient was initially started on obinutuzumab and bendamustine, with an initial decrease of more than 50% in WBCs. However, there was a rapid re-escalation of WBCs at week 3 of treatment. The patient then received ibrutinib at a dose of 420mg/d.

Progression was marked by a moderate decrease in WBCs, but also in platelets. During the second cycle of ibrutinib, the patient developed a progression of lymphocytosis with profound thrombocytopenia and massive brain hemorrhage. Unfortunately, he died a few days later.

DISCUSSION

B-cell prolymphocytic leukemia was originally described by Catovsky *et al*., and Galton et al. in the 1970s as a variant of chronic lymphocytic leukemia [4]. It is a rare disease, representing less than 1% of chronic lymphoproliferative syndromes (cLPS) [1]. The average age of onset is 65 years with a male predominance [5].

The signs of the disease are often not pathognomonic. To confirm the diagnosis, a multidisciplinary approach including clinical, cytological, immunophenotypic, cytogenetic and molecular data is required.

Patients classically present with enormous splenomegaly (more than 80% of cases), with little or no adenopathy [6]. A frank hyperleukocytosis (>100 G/L) is almost constant, associated with a massive lymphocytosis. Anemia and thrombocytopenia are not uncommon, especially in cases of extensive bone marrow invasion [7, 8]. The blood smear is an important element to orient the diagnosis. According to the French-American-British (FAB) classification and the World Health Organization (WHO) 2016, the smear objectifies an invasion of more than 55% by circulating prolymph B cells [9] having as cytological features, an increased cell volume of up to twice the size of a mature lymphocyte, a rounded nucleus, a prominent nucleolus, condensed chromatin, and a low basophilic cytoplasm. Unlike splenic marginal zone lymphoma and Hairy Cell Leukemia, there are no cytoplasmic projections [6]. The myelogram shows a significant bone marrow infiltration with the persistence of variable hematopoiesis, as in our patient [2].

Lymphocyte immunophenotyping is an essential diagnostic tool. It allows to differentiate B-PLL from other cPLS. Malignant B lymphocytes strongly display CD19, CD20, CD22, CD79b and FMC7 antigens, as well as the surface immunoglobulin IgM +or- IgD. CD23 is usually absent and CD5 is expressed in only 30-65% of cases. The Matutes score is classically between 0 and 1, exceptionally 2 [2, 5, 6]. Tumor cells expressing cyclin D1 represent a variant of mantle cell lymphoma [10]. The search for cyclin D1 expression in case of CD5 positivity allows to rule out the leukemia variant of mantle cell lymphoma. In our patients, the Matutes score was 1 in the first case and 2 in the second, in agreement with the data in the literature.

B-PLL are often associated with a complex karyotype (>3 chromosomal abnormalities) [1, 10]. The most recurrent chromosomal abnormalities include translocations involving the MYC gene (t(8;14)(q24; q32), t(2; 8)(p11; q24), t(8; 22) (q24; q11), and overexpression of C-MYC), suggesting a major role for this oncogene in the pathogenesis of B-PLLs. More recently, fluorescent in situ hybridization techniques have demonstrated deletions of the 11q23 (RB1), 17pl 3 (TP53) regions [1]. Exon sequencing has revealed recurrent mutations in TP53 genes. The variable regions of the immunoglobulin heavy chains (IGVH) are mutated in more than 50% of cases [1]. One of our patients presented with a complex karyotype, a deletion of regions 11q23, 17p13 and a mutation of the TP53 genes. Recently, a prognostic model has been proposed taking into account MYC and 17p status. This model identifies three risk groups: low risk (no MYC abnormality), intermediate risk (MYC abnormality without del17p) and high risk (MYC abnormality and del17p) [1].

Regarding therapeutic management, there are currently few published data on studies of small case series. We still do not have results from randomized clinical trials [5]. Currently, there are few data available regarding therapeutic management and the results that can be expected from it. The published studies concern small case series and there are no randomized clinical

trials. Published data have shown that the use of rituximab immunotherapy combined with fludarabine and cyclophosphamide or bendamustine chemotherapy in patients without TP53 abnormalities induces complete remissions of more than 5 years. For patients with TP53 mutation, other treatments such as alemtuzumab are proposed, given the primary resistance they develop to standard therapy. Recently, the BTK inhibitor (ibrutinib) has shown promising results, especially in patients with del17p. Targeting MYC may be an additional option in the therapeutic arsenal [1, 3]. Currently, allogeneic hematopoietic stem cell transplantation remains the only promising therapeutic option for achieving a long-term response [5]. However, it is reserved for young patients with compatible donors.

CONCLUSION

B-cell LPL is a rare and complex disease whose therapeutic management remains a challenge. The analysis of these cases confirms the difficulty of the diagnosis of this pathology whose clinical evolution is aggressive. Its diagnosis is based on a complete biological exploration using morphological, immunophenotypical, cytogenetic and molecular studies. Hematopoietic stem cell allografting is, to date, the only promising therapeutic strategy to obtain a long-term response.

Conflicts of Interest: The authors declare no conflicts of interest.

REFERENCES

1 Chapiro, E., Pramil, E., Diop, M. B., Roos-Weil, D., Dillard, C., Gabillaud, C., ... & Nguyen-Khac, F. (2019). Genetic characterization of B-cell prolymphocytic leukemia: a prognostic model involving MYC and TP53. *Blood, The Journal of the American Society of Hematology*, *134*(21), 1821-1831.

2 Rabhi, S., Amrani, M., Khammar, Z., Khibri, H., Lamchachti, L., Ouazzani, M., ... & Bono, W. (2011). Leucémie Prolymphocytaire De Phénotype B De Mauvais Pronostic. *Maroc Médical*, *33*(3), 212-215.

3 Collignon, A., Wanquet, A., Maitre, E., Cornet, E., Troussard, X., & Aurran-Schleinitz, T. (2017). Prolymphocytic leukemia: new insights in diagnosis and in treatment. *Current oncology reports*, *19*(4), 1-11.

4 Galton, D. A. G., Goldman, J. M., Wiltshaw, E., Catovsky, D., Henry, K., & Goldenberg, G. J. (1974). Prolymphocytic leukaemia. *British Journal of Haematology*, *27*(1), 7-23.

5 Bellal, M., & Damaj, G. (2019). Leucémies prolymphocytaires. *Hématologie*, *25*(3), 163-168.

6 Nguyen-Khac, F. (2006). Leucemie Prolymphocytaire B. *Rev Francoph des Lab*, 379, 45-47.

7 Krishnan, B., Matutes, E., & Dearden, C. (2006, April). Prolymphocytic leukemias. In *Seminars in oncology* (Vol. 33, No. 2, pp. 257-263). WB Saunders.

8 Dungarwalla, M., Matutes, E., & Dearden, C. E. (2008). Prolymphocytic leukaemia of B-and T-cell subtype: a state-of-the-art paper. *European journal of haematology*, *80*(6), 469-476.

9 Bennett, J. M., Catovsky, D., Daniel, M. T., Flandrin, G., Galton, D. A., Gralnick, H. R., & Sultan, C. (1989). Proposals for the classification of chronic (mature) B and T lymphoid leukaemias. French-American-British (FAB) Cooperative Group. *Journal of clinical pathology*, *42*(6), 567-584.

10 Ruchlemer, R., Parry-Jones, N., Brito-Babapulle, V., Attolico, I., Wotherspoon, A. C., Matutes, E., & Catovsky, D. (2004). B-prolymphocytic leukaemia with t (11; 14) revisited: a splenomegalic form of mantle cell lymphoma evolving with leukaemia. *British journal of haematology*, *125*(3), 330-336.

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