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Biclonal B-Chronic Lymphocytic Leukemia: A rare Case Report with Review of Literature

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Authors' contributions

This work was carried out in collaboration among all authors. Author BS designed the study, author SFJ performed the statistical analysis, wrote the protocol and author BS, SFJ wrote the first draft of the manuscript. Author BS and US managed the analyses of the study. Authors SFJ and TA managed the literature searches. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia is a neoplasm composed of monomorphic small mature B cells that co-express CD5, CD23 and one type of immunoglobulin light chain either kappa or lambda, which is necessary for the diagnosis. Here, we report a case in a 65 year woman with morphological diagnosis of B-Chronic Lymphocytic Leukemia. On flowcytometry analysis, immunoglobulin light chain restriction was not apparent as B cells expressed both kappa & lambda light chains without a clear monotypic population. Sequential gating on flowcytometry revealed two monoclonal B-cell populations and helped in identification of this rare case of biclonal disease in chronic lymphocytic leukemia (CLL).

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1. INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a well-characterized B-cell chronic lymphoproliferative disorders with high prevalence in older adults. The annual incidence rate is about 5 cases per 100,000 populations, and dramatically increases with age, to as many as > 20 cases per 100,000 individuals aged > 70 years. The median patient age at diagnosis of CLL is approximately 70 years, but can also present in younger adults [1].

Well established Criteria for the diagnosis of CLL include the presence of peripheral blood monoclonal B-lymphocytosis (>5 × 109/L) with less than 55% prolymphocytes along with co-expression of CD5 and CD23 with either kappa or lambda light chain restriction which explain the monoclonality and remains the main stream of diagnosis [2].

Abnormal circulating B-cell express pan B-cell markers CD19, dim CD20 and CD22. They also expressed CD5, CD23, CD43 and CD200. CD10 is negative and FMC-7 usually negative or weakly expressed in these cases.

In our institute, found a unique case of CLL which show features of biclonal pattern of immunoglobulin light chain expression with typical CLL phenotype. Till date in best of our knowledge only few cases were published so far.

2. CASE HISTORY

A 65 year women presented in outpatient department with complaints of generalized weakness, fever and pain in lower limb, since two to three months. Clinical examination revealed bilateral inguinal lymphadenopathy. There was no organomegaly.

Hemogram revealed hemoglobin 11.5g/dl (13-17g/dl), total leucocytes count- 85.40x10^9/l (4.0-10.0x10^9/l), platelet count 182 x10^9/l (150-410x10^9/l). Peripheral blood smear prepared and stained with Leishman stain. Manual differential count performed which include lymphocytes 86%, neutrophils 10%, eosinophils 1% and monocytes 3%. Peripheral smear divulged lymphocytosis with morphologic features suggestive of CLL. The lymphocytes were small with round nuclear contour and scant cytoplasm. Prolymphocytes were very occasional (<5%) and background showed smudge cells. Hence, impression was made of chronic lymphoproliferative disorder (CLPD) with feature of CLL. Flowcytometric immunophenotyping (FCI) was advised to confirm the diagnosis of CLL. Bone marrow examination was advised however not performed (patient denied invasive procedure).

FCI was performed on peripheral blood with using standard stain lyse wash technique. Comprehensive six color antibody panel for CLPD on CANTO II from BD was performed. Data were collected and analyzed using CD19 vs. side scatter based gating strategy on Diva software.

FCI analysis of peripheral blood revealed 69.7% abnormal B-lymphoid cells which were small in size with expression of CD5 (homogenous bright), CD20 (heterogeneous dim to moderate), CD22 (homogenous dim), CD23 (homogenous bright), CD200 (homogenous moderate) with co-expression of CD5 and CD23. There were very dim heterogeneous expression of CD11c however negative for CD10, CD103, CD123, CD38 and sIgG. Surprisingly gated B‑lymphoid cells expressed both kappa as well as lambda light chains restriction, apparently give a polyclonal pattern. As light chain restriction by flowcytometry in mature B-cell population confirms monoclonality and suggests malignancy; however in present scenario, dual κ and λ expressing CLL resulting in failure to make a CLL diagnosis. Thus, although abnormal B cell phenotype was registered, but misguiding event was existence of both light chain expression in this case.

Two distinct CD5/CD19 positive CLL clones were separated by flowcytometry, based on bimodal expression of CD79b (moderate homogenous). The CD79b positive and CD79b negative fractions harbored completely different light chain restriction, favor biclonal population over sub-clone. Rest of the antigen expression was uniform without evidence of separate population.

Major subset (85% B-lymphoid cells) showed CD79b negativity, IgM positivity along with dim KAPPA light chain restriction and other minor subset (15% B-lymphoid cells) showed dim CD79b positivity along with dim LAMBDA light chain restriction (Fig. 1).

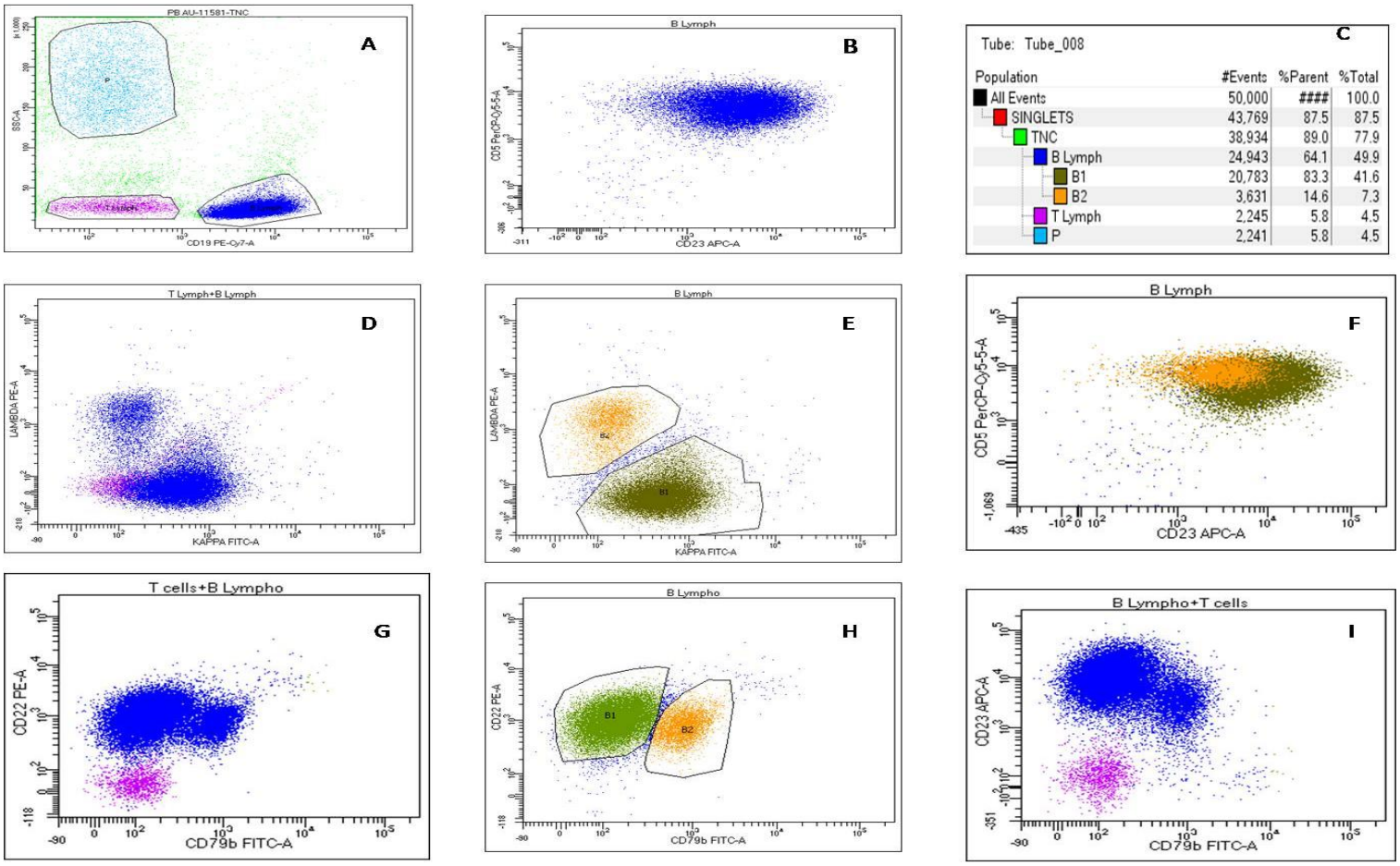

Fig. 1 (A-I). Positivity along with dim LAMBDA light chain restriction

Thus, different antigen intensity of CD79b, IgM, and light chain expression with sequential gating plays a pivotal role to arrive a more precise and an accurate diagnosis despite of apparently misleading expression of light chains (kappa as well as lambda).

Molecular (IGHV) and cytogenetic (13q deletion, trisomy 12) studies were also advised (for molecular confirmation of biclonality but it was not done in our case due to financial constraints), as IGHV genes are mutated in 50- 70% of cases and unmutated in 30-50%. The most common cytogenetic alterations are deletions in 13q14.3 (miR-16-1 and miR15a; present in -50% of cases) and trisomy 12 or partial trisomy 12q13 (present in -20%) [1].

The overall clinical profile, hematological findings and flowcytometric analysis led to the diagnosis of a rare biclonal B-chronic lymphocytic leukemia with Rai stage I. No active treatment was initiated at this time and patient was put on conservative management but subsequently lost to follow up.

3. DISCUSSION

B-cell chronic lymphoproliferative disorders (B-CLPDs) are a heterogeneous group of diseases that result from the proliferation and accumulation of mature-appearing aberrant B lymphocytes arrested at a given stage of differentiation. B-CLPDs are generally believed to result from the monoclonal expansion of a single transformed B lymphocyte [3].

CLL is commonly seen in elderly patients with expression of pan B-cell marker CD19, dim CD20 and CD22 with co-expression of CD5 and CD19 as well as CD5 and CD23. Along with expression of either kappa or lambda surface light chain immunoglobulin restriction.

B-cell or T-cell clonal expansion for the diagnosis is demonstrated by two methods, i.e., molecular assay or flowcytometric immunophenotyping (FCI). FCI is easy, widely available and traditionally used for the confirmation of clonal proliferation of B-cells. Normal and reactive B-cell populations show the expression of both kappa and lambda light immunoglobulin chains usually with ratio of 2–4:1 [4]. However, some time mere calculation of light chain ratios can be misleading. Here, we presented a case demonstrating phenotypically abnormal B cell population typical for CLL with rare appearance of both kappa and lambda light chain restriction in two different B-cell population and this was clear from flowcytometry since applied gating was sequential. Significant absolute lymphocyte with appropriate morphologic feature of CLL and typical immunophenotyping, all this together sequential gating prompted us to think about biclonal CLL with review of literature.

Gonzalez-Campos et al. [3] reported one case of biclonal CLL among 130 (0.7%) CLL patients by FC IPT [5]. Sanchez et al. [3] Reported two or more B-cell clones in 12/353 (3.4%) typical CLL and in 4/29 (13.8%) atypical CLL patients by FC IPT [3]. The largest study by Kern et al. [6] identified 76 patients with biclonal CLL (1.4%) in a cohort of 5523 CLL cases by FC IPT [6]. Ghodke et al reported two cases out of 194 CLL cases [4].

Molecular genetic analysis of two different gated population (kappa and lambda populations) further aid in identification of biclonality. The literature reveals del 13q (62.2%) is most frequent cytogenetic abnormality followed by trisomy 12 which is 15.9% in biclonal CLL cases [6]. However this was not done in presented case due to financial constraints.

Multiparametric flowcytometry helped in identification of the rare case of biclonal disease in chronic lymphocytic leukemia (CLL). Hence, this case highlights the importance of morphology of the blood smear and the comprehensive immunophenotyping panel to arrive at a precise diagnosis.

Biclonal CLL is a clinically significant entity as it has a progressive disease course which may require prompt treatment with close follow up. Incidence of splenomegaly and death rate is also relatively higher. Along the course of disease some of them may loss the biclonality and convert into monoclonal CLL [3].

4. CONCLUSION

Biclonal CLL is not well characterized. Only handful of cases has been reported so far. It is very important to create awareness about its existence to avoid misdiagnosis as only light chain ratios can be misguiding. The fact that the patient discussed here had significant absolute lymphocyte and typical immunophenotyping of CLL which drove our attention. But cases with low level of CLL clone type need careful attention with molecular and cytogenetic study.

Morphology of the blood smear and comprehensive immunophenotype panel is

important with proper sequential gating, which will aid in precise diagnosis of biclonal CLL with its actual incidence & prognosis.

CONSENT

We have added the Consent Disclaimer in the revised paper. The revised paper is attached herewith this mail for your kind perusal. Kindly check the revised paper.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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