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What does it mean I have a monoclonal B-cell lymphocytosis?: Recent insights and new challenges

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ABSTRACT

Monoclonal B-cell lymphocytosis (MBL) is defined as a laboratory abnormality where small ($< 5 \times 10^9$/L) clonal B-cell populations are detected in the peripheral blood of otherwise healthy subjects. According to the immunophenotype, MBL is labeled as chronic lymphocytic leukemia (CLL)-like (75% of cases), atypical CLL, and CD5-negative. Concentration of clonal B cells differentiates low- (LC) and high-count (HC)-MBL ($<$ or $\geq$ 0.5×10^9/L, respectively). Thanks to technical improvements, we are able to identify CLL-like clonal B-cell populations at increased frequency with age, but we are still far from understanding its relationship with clinically overt CLL. LC-MBL, requiring high-throughput screening technique to be identified in population studies, seems to be a bird of a different feather and several hints suggest that LC-MBL is related to aging and/or chronic antigenic stimulation. Immunogenetic, cytogenetic and genetic data support the notion that HC-MBL, usually identified in the clinical setting, is a premalignant condition and, based on biological parameters, it is frequently difficult to differentiate it from early stage CLL. The rapid improvement and widespread availability of cutting-edge technology, in particular next-generation sequencing (NGS), raises hope that we are getting closer to unveiling the fundamental nature of MBL and CLL and how they are related to each other.

1. Introduction

The defined syndrome of monoclonal B-cell lymphocytosis (MBL) recently celebrated its tenth birthday in 2015, as the first consensus panel guidelines adopting the current diagnostic criteria were published in 2005 [1]. Though being recognized as a distinct entity, MBL remains heterogeneous and complex in its essence and significance. That notwithstanding, the huge progress made in the past 10 years in defining and understanding its pathogenesis should not be underestimated, thanks to widespread availability and use of multiparameter flow cytometry, the technical improvement of genome sequencing and the information derived from mouse models. As "with great power comes great responsibility", we have now the chance to clarify the essence of MBL as well as its potential relationship with chronic lymphocytic leukemia (CLL). In this review we thoroughly review our current knowledge about MBL focusing our attention on the most relevant open issues and unanswered questions.

2. What we know

2.1. Outlining the roots: history and definitions

Monoclonal B-cell lymphocytosis is defined as a laboratory abnormality where *small* clonal B-cell populations are detected in the peripheral blood of otherwise *healthy* subjects. In this setting *small* was considered below 5×10^9 clonal B cells per liter and *healthy* means that no signs or symptoms of lymphoproliferative disorders or autoimmune diseases are reported [1,2]. Based on the name of this entity, a usual misconception is that people with MBL should also have an abnormality in terms of increased number of lymphocytes at a routine white blood cell count. This is definitely not the rule and indeed the term *lymphocytosis* should be referred to the B lymphocytes only and in particular it indicates that the diagnosis should be suspected when there is an increase of "*monoclonal B lymphocytes*", virtually absent in healthy individuals. The criteria for MBL diagnosis are intertwined with the changes in CLL diagnostic criteria, as the 2005 consensus guidelines [1] have been subsequently adopted by the World Health Organization (WHO) [3] and the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) [4]. MBL is further classified according to two different parameters: the immunophenotypic profile and the size of the B-cell clone [1,2].

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