

Monoclonal B-cell lymphocytosis

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Monoclonal B-cell Lymphocytosis (MBL) is considered as a premalignant state and has given great impulse in the field of hematology for further understanding the various pathways involved in the lymphomagenesis from the B-cell precursor states to overt lymphoproliferative disorders. The International Familial Chronic Lymphocytic Leukemia (CLL) consortium experts in 2005 defined this condition as circulating B-cell count less than $5 \times 10^9/L$ in an apparently healthy individual in the absence of signs and symptoms of an overt B-lymphoproliferative disorder [1]. This threshold of 5×10^9 B-lymphocytes/L was adopted in the new (International Workshop on Chronic Lymphocytic Leukemia) IWCLL 2008 criteria and in updated (World Health Organization) WHO 2016 classification for CLL diagnosis. MBL cases are further classified according to the immunophenotypic profile as:

CLL-like MBL: Sharing the characteristic immunophenotype of CLL, characterized by CD19 and CD5 concomitant expression, low levels of surface immunoglobulin (sIg), dim CD20 expression, CD23 positivity;

Atypical CLL MBL: Expressing CD5 together with bright CD20 expression and/or lack of CD23 expression;

CD5 negative (or Non-CLL) MBL: Lacking CD5 expression [2].

CLL-LIKE MBL

With the recent use of high-sensitivity flow cytometry techniques, CLL-like expansions have been consistently detected in different geographical and demographical settings. The prevalence of CLL-like expansions can range between 3.5%-12% of healthy individuals older than 40 years, higher among male subjects and increases with aging, being detected in up to 50%-75% of people >90 years. The frequency of MBL is significantly higher in first-degree relatives of CLL patients indicating a familial predisposition. Single-nucleotide polymorphisms in about 6 normal genes, associated with familial CLL, have now been demonstrated to confer increased risk of developing MBL as well. Besides, MBL has been linked to infections like hepatitis C virus and in pneumonia patients [3]. CLL-like MBL shows a bimodal distribution in clonal B-cell count. The lower peak condition, named as low-count MBL (LC-MBL), is characterized by CLL-like B cells $< 0.5 \times 10^9/L$ in the peripheral blood, is usually found in population screening studies performed for research purposes and carries a negligible risk of transformation to CLL. CLL-like B cells $\geq 0.5 \times 10^9/L$, is labeled as high-count MBL (HC-MBL), is usually detected in the clinical setting and carries a risk of progression into CLL of 1%-2% per year. With regards to cytogenetic and molecular abnormalities, specific immunoglobulin gene rearrangements, frequently observed in patients with CLL, such as *IGHV* 4-34, 3-23, and 1-69, are underrepresented or absent in subjects with LC-MBL but are comparable in HC-MBL. The frequency of *IGHV*-mutated cases is also significantly higher in individuals with LC-MBL than in subjects with HC-MBL or CLL. Moreover, whereas at least 25% of patients with CLL and 22% of subjects with HC-MBL demonstrate stereotyped complementarity determining region 3 sequences, these are present in 5% of individuals with LC-MBL. Cases of LC-MBL are also enriched with genetic abnormalities typically associated with more favorable prognosis in CLL, such as deletion 13q. Novel mutations, such as *NOTCH1* and *SF3B1*, described in 10% and 15% of patients with CLL, respectively, appear to be extremely rare in MBL, including HC-MBL [3]. Hence, it can be observed that the progression of

MBL to CLL probably involves multiple pathophysiologic mechanisms including critical gene mutations and micro-environmental stimulation along with a CLL-prone genetic background. HC-MBL is closely related to CLL-Rai 0. Hence, whether HC-MBL should or should not remain an entity separate from Rai 0 CLL and, if a separate entity, what threshold should be used to segregate the 2 conditions, is a topic of concern. The answer to this is based on the clinical implication for patients, such as having an impact on survival. Various studies concluded that a B-cell threshold of $10 \times 10^9/L$ was the best predictor of overall survival and can guide for managing the case of HC-MBL and Rai 0 CLL. Accurate clinical assessment of lymphadenopathy is essential when evaluating individuals with MBL, because the presence of lymphadenopathy would suggest the diagnosis of SLL rather than MBL. Moreover, development of lymphadenopathy appears to be a common pattern of progression among individuals with MBL. Current approach is to classify individuals with the incidental discovery of a CLL phenotype infiltrate in a normal-sized lymph node (eg, 1.5 cm), normal blood counts, and no other nodes >1.5 cm in size as nodal MBL and those with any enlarged lymph nodes (≥ 1.5 cm) as SLL [3]. Bone marrow examination is not required for the establishment of MBL diagnosis. Only few studies have recently evaluated the histopathological and immunohistochemical findings of bone marrow biopsies in MBL cases. The median percentage of bone marrow infiltration was 28% (range, 5%-85%). The pattern of infiltration was interstitial or mixed (nodular and interstitial) in the majority of the cases. There was no correlation between the extent of BM infiltration and the absolute number of peripheral blood monoclonal B cells [4]. Clinicians usually face difficulty on how to inform and follow up an individual with a diagnosis of MBL. The most sensible strategy, for the HC-MBL cases, is to reassure them that MBL is not a malignant entity and that the risk of progression to CLL is low, but not negligible, indicating a yearly hematologic consultation with a complete blood cell count and physical examination. For LC-MBL, which is identified in general population studies after the application of high-sensitivity flow cytometry methods, the risk of progression to CLL is very low, if any. Based on these data, it would be appropriate not to inform individuals for having MBL and not to prompt any monitoring.

MBL OTHER THAN CLL-LIKE

This category includes atypical CLL (CD5 positive, CD20 bright and/or lacking CD23 expression) and CD5 negative (non-CLL) MBL. These conditions comprises 20% of MBL cases, prevalence ranges between 1% and 2.5% and are less affected by aging in comparison to CLL-like MBL. CD5(-) MBL displays features consistent with a marginal zone origin. The cutoff value of less than $5.0 \times 10^9/L$ CD5(-) clonal B cells cannot be applied in non-CLL-like MBL, since in contrast to CLL, there is not currently a defined entity to include cases with more than $5.0 \times 10^9/L$ CD5(-) clonal B cells. The term clonal B-cell lymphocytosis with marginal zone features (MZ-CBL) can better describe non-CLL-like cases with clonal B-cell lymphocytosis, irrespective of the absolute number of clonal B cells, and it may be regarded as a provisional entity, probably under the name of "primary bone marrow marginal zone lymphoma." [4] The majority of MZ-CBL present an indolent and stable clinical course. Nevertheless, a proportion of such cases may progress into an overt lymphoma, usually SMZL. Finally, further studies are required in order to better define this entity.

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