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Scientific Comment

Monoclonal B-cell lymphocytosis[☆]



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Chronic B-cell lymphocytic leukemia (B-CLL) represents 0.9% of all new cancers. It is estimated that there will be almost 15 000 new cases and 4600 deaths due to CLL in 2015 in the USA.¹ The median ages at diagnosis and death are 71 years and 80 years, respectively.¹ The criteria that define the diagnosis of B-CLL include the presence of at least 5×10^6 B lymphocytes/L with the peculiar CLL phenotype, persisting in the peripheral blood for at least 3 months.²

Monoclonal B-cell lymphocytosis (MBL) is characterized by an expansion of circulating clonal B lymphocytes, totaling less than 5×10^9 /L in individuals without any symptoms or signs of a lymphoproliferative disease.^{3,4} Three categories of MBL have been recognized: CLL-like MBL, atypical CLL-MBL, and CD5-negative MBL. Seventy-five percent of all cases are CLL-like MBL, and present the same phenotype as CLL (CD5, CD19, CD23 and CD20^{dim}, with low surface immunoglobulin expression).^{3,4} Moreover, the clonal B cells in CLL-like MBL share similar chromosomal abnormalities with B-CLL.

A recent systematic review reported frequencies of MBL ranging from <1% to 18.2%.⁵ This wide variation reflects different study populations (general population, blood donor population, outpatients from clinics and relatives of CLL patients – familial cases or sporadic cases) and the sensitivity of the multiparameter flow cytometry employed (two or three

color antibody-fluorochrome combinations or four to eight color antibody-fluorochrome combinations). Furthermore, it is well established that the prevalence increases with age. In a recent study in Spain, 608 healthy individuals were evaluated with an eight-color antibody panel. The overall prevalence of MBL was 14%; it was around 5% in under 60-year-old individuals, 17.5% in individuals between 60 and 69 years old, and reached 75% in ages >89 years.⁶ High frequencies of MBL (12–18%) have been observed among first-degree relatives of familial CLL patients, defined as a family with at least two first-degree relatives with CLL. However, long-term follow-up studies of the MBL individuals identified among relatives of familial CLL patients are still lacking.^{7,8}

MBL can be further classified as ‘high-count MBL’ or ‘low-count MBL’ depending on the number of circulating B cells (the size of the clone). One accepted cut-off to distinguish between these two categories is 5×10^9 /L clonal B cells.^{4,9} High-count MBL is also called ‘clinical MBL’ because it is often detected during an investigation of lymphocytosis. The median number of B cells is around 3×10^9 /L, and 95% of the cases present more than 4.5×10^9 lymphocytes/L. The risk of progression to CLL is around 1% per year.¹⁰ In contrast, in low-count MBL almost 95% of the cases have less than 1.0×10^9 /L clonal B cells and have a low risk of progression to CLL.¹¹ Of note, this condition

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[☆] See paper by Matos et al. on pages 292-5.

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is rarely found in the clinical practice, since high-sensitivity techniques are required for its detection.⁹

Some authors have argued that low-count MBL might not be an actual pre-leukemic state, reflecting instead immune senescence or persistent antigen stimulation. One study, in particular, compared the immunogenetic profile of low-count and high-count CLL-like MBL with early stage CLL (Rai stage 0). They found that high-count MBL was similar to CLL Rai stage 0, while low-count MBL was not.¹²

Although virtually all CLL cases evolve from CLL-like MBL,¹³ not every individual with CLL-like MBL has the same risk of progression to CLL. So far, the number of clonal B lymphocytes is the only well-established factor correlated with the likelihood of transformation to CLL.⁹ Two studies showed that B-cell counts at presentation below 1.2×10^9 or 1.9×10^9 /L predicted a stable course, while counts over 3.7×10^9 /L predicted rising lymphocyte numbers over time.^{14,15} Further studies are needed to determine other biological factors associated with a higher risk of progression.⁹

In their first report in 2009, while studying 167 first-degree relatives of sporadic (non-familial) CLL patients, Matos et al. reported an overall prevalence of 4.1%, reaching 15.6% in over 60-year-old individuals.¹⁶ The authors suggested that, as the prevalence in older relatives of sporadic CLL patients was similar to that reported among relatives of familial CLL patients, the risk of MBL might be similar and also susceptibility for the development of CLL. In the present study, the authors have analyzed the long-term outcome of five out of the seven individuals with MBL.¹⁷ All had presented with low-count MBL. After a median follow-up of 7.6 years, no progression to CLL was observed, and the size of the clones remained stable. These results are in line with previous studies in CLL-like MBL detected in the general population.

In conclusion, current evidence does not support systematic laboratory monitoring of low-count MBL individuals to detect progression; clinical and laboratory monitoring is only recommended in high-count MBL. Also for the latter group, open questions remain regarding biological factors that could predict the risk of progression, and whether its distinction from CLL Rai stage 0 based on the arbitrary threshold of 5×10^9 /L has any biological or clinical significance.

Conflicts of interest

The authors declare no conflicts of interest.

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