Monoclonal B-cell lymphocytosis (MBL)

Status: May 2020

Diagnostic recommendation

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<thead>
<tr>
<th>Method</th>
<th>Anticoagulant</th>
<th>Recommendation</th>
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<tr>
<td>Cytomorphology</td>
<td>EDTA</td>
<td>mandatory</td>
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<tr>
<td>Immunophenotyping</td>
<td>EDTA or Heparin</td>
<td>mandatory</td>
</tr>
<tr>
<td>Chromosome analysis</td>
<td>Heparin</td>
<td>no</td>
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<tr>
<td>FISH</td>
<td>EDTA or Heparin</td>
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<tr>
<td>Molecular genetics</td>
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</table>
**Definition and characteristics**

If a small population of circulating monoclonal B-cells (<5 x 10^9/L) can be detected in peripheral blood in otherwise healthy individuals, this is called monoclonal B-cell lymphocytosis (MBL). This is considered a precursor of chronic lymphocytic leukemia (CLL) and shows parallels in various areas (Shanafelt et al. 2010, Vardal et al. 2013, Kern et al. 2012).

With the exception of families with a high incidence of CLL, in which 10% of all individuals develop MBL, MBL is very rare in people under 40 years of age (Rawstron et al. 2002). Men have a 1.5-5 times higher risk of developing MBL than women (Shim et al. 2013). The incidence rises with increasing age for both sexes from ~2% in the 40-59 age group to over 5% in people over 60 (Kern et al. 2012). Thus, the frequency of MBL at age is 100 times higher than that of CLL (Fazi et al. 2011).

**Classification of the monoclonal B-cell lymphocytosis**

According to the WHO classification, 2017, MBL is one of the mature B-cell neoplasms and is classified here as chronic lymphatic leukemia (CLL). Depending on the phenotype, MBL is classified into three categories: CLL type, atypical CLL type, and non-CLL type. The most frequent type of MBL is the CLL type with about 75% of all cases.

**MBL WHO Classification 2017 (Swerdlow et al. 2017)**

**Chronic Lymphocytic Leukemia (CLL)**

Monoclonal B-cell lymphocytosis (MBL): CLL type, atypical CLL type, non-CLL type

CLL type MBL is further subdivided into a low-count (0.5 x 10^9/L) and a high-count (>0.5 x 10^9/L) form according to the size of the monoclonal B-cell population in peripheral blood. In the low-cell variant, progression into CLL is rare. The life expectancy corresponds to that of the normal population, which is why regular follow-ups are not recommended. In contrast, the high-cell MBL shows very similar phenotypic and (molecular) genetic characteristics as a CLL at Rai stage 0, so that regular annual follow-ups are recommended. The risk of progression into CLL is 1-2% per year (Fazi et al. 2011; Rawstron et al. 2008).

**Monoclonal B-cell lymphocytosis – Diagnostics**

**Cytomorphology**

The blood count usually shows mild leukocytosis with proliferation of mature lymphocytes, whose monoclonality must be proven by immunophenotyping. A bone marrow puncture is not necessary; it does not provide additional diagnostic or prognostic results.

**Immunophenotyping**

**Immunophenotype similar to CLL**

The immunophenotype in MBL usually corresponds to that of CLL and is divided into three subgroups (Shim et al. 2013, Rawstron et al. 2012) (see Table 1).

**Table 1: MBL subtype and immunophenotype**

<table>
<thead>
<tr>
<th>MBL subtype</th>
<th>Immunophenotype</th>
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<tbody>
<tr>
<td>CLL type</td>
<td>CD19+, CD5-, CD20^dim</td>
</tr>
<tr>
<td>atypical CLL type MBL</td>
<td>CD19+, CD5+, CD20^bright</td>
</tr>
<tr>
<td>Non CLL type (CD5-)</td>
<td>CD19+, CD5-, CD20^bright</td>
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</table>

**Chromosome analysis**

Corresponding to the similarity to CLL, MBL shows chromosomal abnormalities, which are also observed in CLL. The most frequent are heterozygous and homozygous 13q deletions (94%), but also alterations such as trisomy 12 and 17p deletions have been detected (Fazi et al. 2011, Kern et al. 2012). This examination is not indicated for the low cell CLL type MBL.

**FISH**

For the atypical CLL type MBL and the non-CLL type MBL (CD5-) the presence of t(11;14)(q13;q32) should be investigated by FISH to exclude mantle cell lymphoma.

**Molecular genetics**
Currently, no molecular markers specific for MBL exist. As in CLL, clonal B-cell receptor rearrangements are also found in MBL. A mutated IGHV status is found in 75-90% of MBL and thus more frequently than in CLL. The somatic mutations typical for CLL in the genes NOTCH1, SF3B1, ATM and TP53 are also found at MBL, but with lower frequency than in CLL. These analyses are not indicated for classical MBL.

**Prognosis of monoclonal B-cell lymphocytosis**

**Genetic prognostic factors not yet well studied**

The genetic background of MBL is not yet as well understood as in CLL, where cytogenetic abnormalities are an important prognostic parameter after FISH analysis. Parameters that are associated with a favorable or intermediate risk profile in CLL (e.g., 13q deletion, mutant IGHV status or normal karyotype, trisomy 12) are found more frequently in MBL than in CLL (Janasa et al. 2011, Kern et al. 2012). On the other hand, 11q- and 17p deletions, IGH translocations as well as TP53 mutations and a positive ZAP-70 status (>20% of cells), which are known to be prognostically adverse in CLL, are found less frequently in immunophenotyping in MBL than in CLL (Rossi et al. 2009, Kern et al. 2012). A correlation between certain chromosomal abnormalities and an earlier transition into CLL has not been described so far, but the prognostically unfavorable changes correlate with a shorter time to treatment (Fazi et al. 2011, Kern et al. 2012, Vardi et al. 2013).

A progression from a low-count MBL to a high-count MBL and CLL is extremely rare. However, especially women with low-count MBL showed an increased risk of death due to infections. This could be a marker that low-count MBL impairs the immune system (Criado et al. 2018).

Approximately 1-2% of the "high-count" MBL develop into CLL per year. Recent studies have shown that mutations in the driver genes occur with the same frequency in both MBL and CLL, with the exception of mutations in NOTCH1, TP53 and XPO1, which are less frequent in MBL. Mutations can be detected at an early stage of MBL and are associated with a shorter time to need for therapy (Barrio et al. 2017).

**Clinical course depends on lymphocyte count at diagnosis**

The clinical course of MBL appears to depend on whether MBL is detected during the clarification of lymphocytosis or is randomly identified during screening of individuals with relatively low lymphocyte counts ("low-count" MBL, lymphocytes: <1.2x10^9/μl). While there is only a very low risk of progression to CLL if low-count MBL is detected, about 1-2% of cases with high-count MBL (especially CLL-like MBL; lymphocytes: >3.7x10^9/μl) progress to CLL every year (Rossi et al. 2009, Shanafelt et al. 2010, Shim et al. 2013, Vardi et al. 2013).

**Recommendation**

Depending on the leukocyte value, patients with MBL of the CLL type, similar to patients with early stage CLL, should have a detailed blood test once a year in addition to the medical history. For patients with CLL-atypical MBL or DBS-negative MBL, a lymphocyte count MBL and further examination every 6-12 months is recommended (Rawstron et al. 2009, Shanafelt et al. 2010).

**References**

You can find the corresponding references here: