Monoclonal B-cell lymphocytosis (MBL)

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Continuous research and targeted examinations of blood and bone marrow result in various diagnostic recommendations for patients with monoclonal b-cell lymphocytosis.

Diagnostic recommendation

Method	Anticoagulant	Recommendation
Cytomorphology	EDTA	mandatory
Immunophenotyping	EDTA or Heparin	mandatory
Chromosome analysis	Heparin	no
FISH	EDTA or Heparin	optional
Molecular genetics	EDTA or Heparin	optional

Definition and characteristics of monoclonal b-cell lymphocytosis

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, Vardi 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 monoclonal b-cell lymphocytosis, monoclonal b-cell lymphocytosis is very rare in people under 40 years of age (Rawstron et al. 2002). Men have a 1.5-2 times higher risk of developing monoclonal b-cell lymphocytosis 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 monoclonal b-cell lymphocytosis 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, monoclonal b-cell lymphocytosis is one of the mature B-cell neoplasm and is classified here as chronic lymphatic leukemia (CLL). Depending on the phenotype, monoclonal b-cell lymphocytosis is classified into three categories: CLL type, atypical CLL type, and non-CLL type. The most frequent type of monoclonal b-cell lymphocytosis is the CLL type with about 75% of all cases.

MBL WHO Classification 2017 (Swerdlow et al. 2017)

Mature B-cell neoplasm
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 monoclonal b-cell lymphocytosis 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 monoclonal b-cell lymphocytosis 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: monoclonal b-cell lymphocytosis subtype and immunophenotype

MBL subtype	Immunophenotype
CLL type	$CD19^+$, $CD5^+$, $CD20^{dim}$
atypical CLL type MBL	$CD19^+$, $CD5^+$, $CD20^{bright}$
No CLL type (CD5-)	$CD19^+$, $CD5^-$, $CD20^{bright}$

Chromosome analysis

Corresponding to the similarity to CLL, monoclonal b-cell lymphocytosis shows chromosomal abnormalities, which are also observed in CLL. The most frequent are heterozygous and homozygous 13q deletions (44%), 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 monoclonal b-cell lymphocytosis exist. As in CLL, clonal B-cell receptor rearrangements are also found in monoclonal b-cell lymphocytosis. A mutated *IGHV* status is found in 75-90% of monoclonal b-cell lymphocytosis 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 monoclonal b-cell lymphocytosis, 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 (sole 13q deletion, mutant *IGHV* status or normal karyotype, trisomy 12) are found more frequently in MBL than in CLL (Lanasa 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 ZAP70 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 eta 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: $<1.2x10^9/l$). 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: $>3.7x10^9/l$) progress to CLL every year (Rossi et al. 2009, Shanafelt et al. 2010, Shim et al. 2013, Vardi et al. 2013).

Monoclonal b-cell lymphocytosis - Recommendation

Depending on the leukocyte value, patients with monoclonal b-cell lymphocytosis 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 monoclonal b-cell lymphocytosis or CD5-negative monoclonal b-cell lymphocytosis, an examination every 6-12 months is recommended (Rawstron et al. 2009, Shanafelt et al. 2010).

References

You can find the corresponding references here:
https://www.mll.com/en/diagnostic-offer/mature-b-cell-neoplasms/monoclonal-b-cell-lymphocytosis-mbl.html#references