Abstract

Monoclonal B-lymphocytosis (MBL) is defined as the presence of a population of monoclonal B-cells with a peripheral blood absolute B-cell count below 5 x 10^9/L and no lymphadenopathy, splenomegaly or other features diagnostic of lymphoma. The majority of MBL cases have a phenotype associated with Chronic Lymphocytic Leukaemia (CLL) but increasing information is becoming available about other types of MBL. In population studies using high sensitivity flow cytometry, MBL may be detectable in more than 10% of adults aged over 60 and clinical progression is rare. In cohorts of hospital patients, MBL is a premalignant condition with approximately 1% of cases developing progressive disease per year.

Introduction

The incidence of Chronic Lymphocytic Leukaemia (CLL) has more than doubled over the last century but early diagnosis does not appear to result in improved survival and there is increased anxiety, surprisingly greater even than for other cancer diagnoses, because of the uncertain outcome. In addition to increased surveillance, the detection of B-lymphoproliferative disorders is also affected by the diagnostic technology available. Using basic cytometry it is possible to detect monoclonal B-cells in nearly 1% of adults in the general population and in 3-5% of adults using more sensitive cytometry. The availability of such technology in routine laboratories, coupled with a greater propensity for referring individuals with a slight lymphocytosis for laboratory investigations, led to an increasing number of individuals being identified as having circulating monoclonal B-cells but not meeting the criteria for a lymphoproliferative disorder. This in turn led to the development of diagnostic criteria for MBL which were intended to designed to provide a framework for assessing clinical significance and investigating the underlying pathology of B-lymphoproliferative disorders by identifying biological factors present at the earliest stages of disease.

MBL in population studies: association between prevalence and assay sensitivity

Studies into the prevalence of MBL in the general population are summarised in Table 1. The prevalence of CLL-type MBL in the general population has increased from 0.6% in early studies using basic flow cytometry, through to 12% in studies using the highest sensitivity techniques. There has been a more modest change in the proportion of individuals in the population reported to have a CD5-negative MBL and even high sensitivity studies detect CD5-negative MBL in only 2.3% of adults. Furthermore, studies including assessment of CD10 expression on monoclonal B-cells report no cases of CD5-negative MBL co-expressing CD10 and most CD5-negative MBL have a phenotype more consistent with marginal zone lymphoma. This is surprising given the relatively high prevalence of detecting the t(14;18) translocation in the peripheral blood of healthy individuals.

The biological relationship between MBL and associated B-lymphoproliferative disorders

For CLL-type MBL there is evidence on several levels that the cells are neoplastic. Extensive studies of protein expression confirm that the phenotype of the abnormal B-cells is consistent with CLL and different to any other normal B-cell population even for cases with very low levels of...
abnormal B-cells. Chromosomal abnormalities consistent with CLL, notably the 13q14 deletion affecting mir-15a/16-1 which is reported to cause CLL, are detected in CLL-type MBL even in cases where the neoplastic B-cells represent <10 cells per μL. The underlying genetic factors responsible for development of CLL also result in an increased susceptibility to CLL-type MBL as shown in CLL families. The immunoglobulin gene usage is restricted in CLL and many cases use closely homologous (stereotype) complementarity determining regions. Similar immunoglobulin gene usage is seen in CLL-type MBL cases from hospital clinic series but different usage is seen in individuals with a very low (<10 cells per μL) CLL cell count. Together the data indicate that there is a common genetic background and set of chromosomal abnormalities that lead to the development of both CLL-type MBL and CLL but that specific immunoglobulin receptor genes are required for expansion of CLL cells above a very low level.

Similar data is not available for other types of MBL. As noted above, MBL with a germinal centre phenotype has not been reported. CD5+CD23- MBL occurs in clinic series but is very rare in population studies. CD5-negative MBL typically has a phenotype consistent with marginal zone lymphoma or lymphoplasmacytic lymphoma and although clonal genetic abnormalities are detectable there are limited data available on underlying genetic factors associated with susceptibility or oncogenesis.

The clinical relationship between MBL and associated B-lymphoproliferative disorders

Pre-diagnostic monoclonal B-cell populations are detectable up to 6.4 years prior to diagnosis of CLL in most (44/45) cases. However, only a limited number of cases with CLL-type MBL show progressive disease at a rate of approximately 1% per year. In the studies from the UK and Italy a B-cell count at presentation below 1,200 per mm$^3$ or 1,900 per mm$^3$ respectively predicted a subsequently stable lymphocyte count, whereas a presentation B-cell count above 3,700 per mm$^3$ or 4,000 per mm$^3$ respectively predicted a higher probability of a subsequently rising lymphocyte count.

The B-cell count predicted treatment-free survival in the Mayo series but not in the UK and Italian studies. There is some evidence that an increased presentation B-cell count as a continuous variable is associated with poorer overall survival whereas an increased T-cell count is associated with an improved overall survival. In addition to the risk of progression requiring therapy, it is possible that individuals with CLL-type MBL who have higher CLL cell counts may have greater suppression of normal B-cell activity resulting in an increased susceptibility to infection. In the Leeds series of patients with clinically identified MBL (i.e. all with B-cell counts below 5,000 per mm$^3$), a B-cell count above $3.2 \times 10^9/L$ was the optimal cut-off point for predicting overall survival. In the Mayo clinic series, which included both patients with MBL as well as Rai stage 0 CLL, a B-cell threshold of $11 \times 10^9/L$ optimally predicted overall survival.

Outcome for population studies is generally not known, either because of limited follow-up time or because the studies were performed in an anonymised fashion for ethical reasons. Initial data indicates that the five-year outcome, in terms of overall survival and risk of infections, is not different for individuals with a detectable MBL population but a normal blood count.

Clinical series of non-CLL MBL cases are infrequent. However, CD5-negative and CD5+CD23-B-lymphoproliferative disorders are more likely to have significant tissue or bone marrow infiltration with lower levels of peripheral involvement. In our unpublished experience, cases initially diagnosed through peripheral blood investigation, fewer than 5% of CLL-type MBL will have significant bone marrow or tissue disease detected within one year.

Table 1: Reported prevalence of CLL-type and CD5-negative MBL in population studies.

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Flow Cytometry</th>
<th>MBL Prevalence</th>
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<tbody>
<tr>
<td></td>
<td>Source</td>
<td>Median age (range)</td>
</tr>
<tr>
<td>U.S. residential population</td>
<td>53 (40-78)</td>
<td>1926</td>
</tr>
<tr>
<td>U.K. hospital outpatients</td>
<td>57 (40-90)</td>
<td>910</td>
</tr>
<tr>
<td>Italy primary care</td>
<td>74 (65-98)</td>
<td>500</td>
</tr>
<tr>
<td>U.K. hospital outpatients</td>
<td>74 (60-80)</td>
<td>1520</td>
</tr>
<tr>
<td>Italy residential population</td>
<td>55 (18-102)</td>
<td>1725</td>
</tr>
<tr>
<td>Spain primary care</td>
<td>62 (40-97)</td>
<td>608</td>
</tr>
</tbody>
</table>
of diagnosis compared to 20-25% for CD5-negative and CD5+CD23+ MBL and therefore full investigation, including bone marrow biopsy, may be indicated for individuals with non-CLL type MBL.

Conclusions

Monoclonal B-cell Lymphocytosis is a common finding in elderly adults in the general population and is also an increasingly common condition identified through routine hospital investigations. There is a clear biological relationship between the cells detected in healthy adults and those in clinically recognised cases, and MBL can be considered to be a pre-malignant condition. Although progression is rare, the development of impaired immunity is a more significant issue. The clinical impact and healthcare outcomes are closely associated with the MBL type as well as the absolute numbers of abnormal cells and the length of time that the abnormal cells have been present.

References

6. Rawstron, A.C. et al. Monoclonal B lymphocytes with the characteristics of "indolent" chronic lymphocytic leukemia are present in 3.5% of adults with normal blood counts. Blood 100, 635-9 (2002).

