Monoclonal B-cell lymphocytosis; not the same as B-cell chronic lymphocytic leukaemia

Maya Svenningsen[1], Laura L. Herborg[1], Peter Hokland[1, 2] & Maja Ludvigsen[1, 2]

ABSTRACT

INTRODUCTION: Depending on the location and the extent of disease, mature B-cell disorders can be divided into benign monoclonal B-cell lymphocytosis (MBL), chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL). Whereas SLL is characterised by its location outside the blood stream, MBL is distinguished from CLL by a monoclonal B-cell count below 5 × 10^9/l. Due to its low tendency to transform into CLL, correct diagnosis of MBL is essential. We hypothesised that this might not always be the case.

METHODS: This study includes data on monoclonal B-lymphocyte count based on diagnostic flow cytometry from patients diagnosed in the period from 1 January 2011 to 31 December 2016 at the Department of Haematology, Aarhus University Hospital, Denmark. A total of 69 patients had less than 5 × 10^9/l monoclonal B-cells with a CLL-like immunophenotype in peripheral blood. All cases were classified based on the 2008 WHO criteria and evaluated according to the clinical diagnosis of CLL, MBL or SLL in the medical records. A total of 24 of the 69 patients were classified as MBL.

RESULTS: In the study cohort, 12 (50%) patients classified as MBL were diagnosed accurately with MBL, whereas nine (38%) were diagnosed with CLL.

CONCLUSIONS: The findings of this study indicate that a sizeable fraction of MBL patients are diagnosed inaccurately with CLL, even after the introduction of the MBL diagnosis.

FUNDING: The Danish Cancer Society.

TRIAL REGISTRATION: not relevant.

Monoclonal B-cell lymphocytosis (MBL), B-cell chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL) are clonal B-cell expansions. Whereas CLL is characterised by lymphocytosis, SLL is found in lymph nodes and bone marrow. Both usually run an indolent course, but are, by definition, neoplastic diseases. MBL, in turn, is a benign or pre-neoplastic condition to CLL. Although one study showed that practically all cases of CLL are preceded by MBL [1], only 1-2% of MBL patients develop CLL per year [2, 3].

According to the 2008 World Health Organization (WHO) criteria, the diagnosis of CLL presupposes the presence of at least 5 × 10^9/l monoclonal B-cells in peripheral blood (PB) or a lower monoclonal B-cell count along with disease-related symptoms and/or cytopenias. The SLL diagnosis presupposes the presence of less than 5 × 10^9/l monoclonal B-lymphocytes in PB in combination with lymphadenopathy and/or splenomegaly as well as a positive histopathologic evaluation of a lymph node biopsy. Contrary to this, the diagnosis of MBL presupposes less than 5 × 10^9/l monoclonal B-lymphocytes in PB and simultaneous absence of disease-related symptoms, cytopenias, lymphadenopathy and splenomegaly [4].

With the 2016 WHO classification update, the diagnostic criteria for MBL and CLL were altered. The diagnosis of CLL in patients with a monoclonal B-lymphocyte count below 5 × 10^9/l in combination with cytopenias and/or disease-related symptoms has been retracted [5]. Consequently, according to the 2016 WHO criteria, a monoclonal B-lymphocyte count below 5 × 10^9/l in PB is diagnostic for MBL regardless of whether the patient is cytopenic and/or experiencing symptoms [5].

The diagnosing of patients with CLL, SLL and MBL in the clinic is complex, even when following the WHO criteria. Thus, this may lead to an inaccurate diagnosis which is potentially harmful for these patients. Given the relatively new definition of MBL, there are concerns as to whether patients with MBL are accurately diagnosed or given a malignant diagnosis of CLL. We hypothesised that starting out with flow cytometry data from a large haematological laboratory might be a valid approach to evaluating this question. Thus, the aim of this study was to determine the fraction of accurately diagnosed patients with MBL.

METHODS

In this study, monoclonal B-lymphocyte count data are based on diagnostic flow cytometry from patients diagnosed at the Department of Haematology, Aarhus University Hospital, Denmark. In total, 579 patients fulfilled the inclusion criteria of being diagnosed in the Central Denmark Region between 1 January 2011 and 31 December 2016 and having had monoclonal B-lymphocyte count data obtained from their PB samples. These cases were identified by a database diagnosis code of either CLL or MBL in the Haemodiagnostic Laboratory database (**Figure 1**).

Out of the 579 cases, 500 were excluded due to a

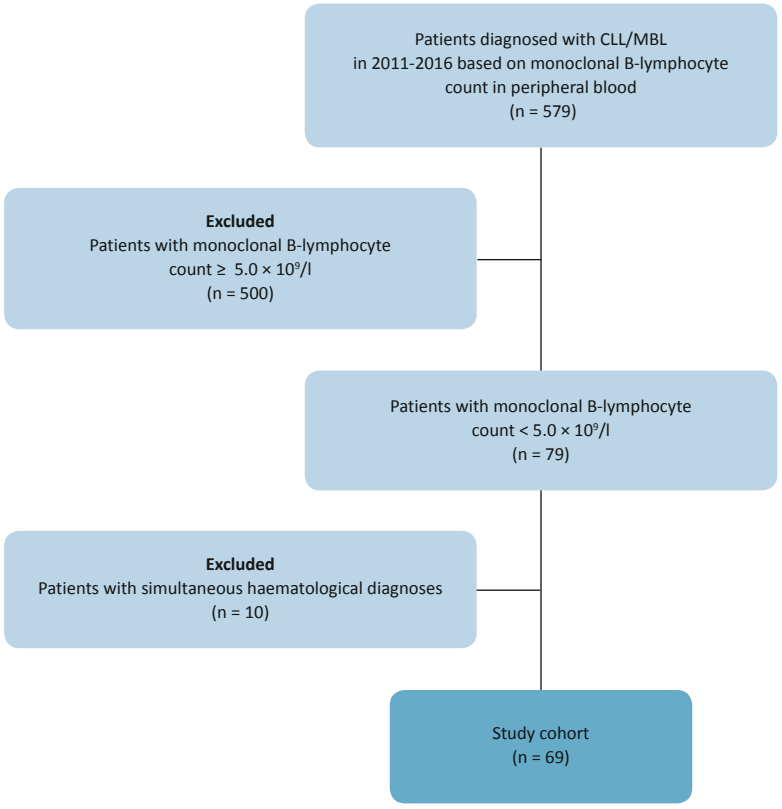
ORIGINAL ARTICLE

1) Department of Haematology, Aarhus University Hospital
2) Department of Clinical Medicine, Aarhus University, Denmark

Dan Med J 2017;64(12):A5431

FIGURE 1

Flow chart of patient inclusion and exclusion.



CLL = B-cell chronic lymphocytic leukaemia; MBL = monoclonal B-cell lymphocytosis.

monoclonal B-lymphocyte count of 5 × 10^9/l or above (n = 79). The medical records of the 79 cases were examined systematically, and ten cases were excluded due to haematological double diagnoses (n = 69). Thus, 69 cases were included in the study cohort. Clinico-pathological data for the 69 patients were obtained from medical records, i.e. date of diagnosis, age, sex, clinical diagnosis, pathology results, symptoms and/or cytopenia at the time of diagnosis, lymphadenopathy and/or splenomegaly at the time of diagnosis. All diagnoses are from before January 2017 when the new WHO 2016 criteria were published, and hence based on the 2008 WHO criteria [4]. This study was approved by the Danish Data Protection Agency (no. 1-16-02-603-16).

Trial registration: not relevant.

RESULTS

The medical records of 69 patients included in the study cohort with a monoclonal B-lymphocyte count below 5 × 10^9/l were reviewed and the patients were classified according to the 2008 WHO criteria [4]. Of the 69 patients, 24 were classified as MBL, 34 as SLL based on biopsies from lymph nodes (n = 32), skin (n = 1) or tonsils (n = 1), and seven were classified as CLL due to disease-related symptoms or neutropenia. The remaining four patients could not be classified due to lymphadenopathy and absence of lymph node biopsies (n = 2) or missing data about symptoms (n = 2).

Of the 24 patients classified as MBL, 12 (50%) were diagnosed with MBL, nine (38%) with CLL, two (8%) with CLL/MBL, and one (4%) had no haematological diagnosis (**Figure 2**). Out of the nine MBL-classified cases who were diagnosed with CLL, three were described as mild (n = 1), low-risk (n = 1) or incipient (n = 1). The SLL and CLL-classified cases were also examined, and none were diagnosed with MBL.

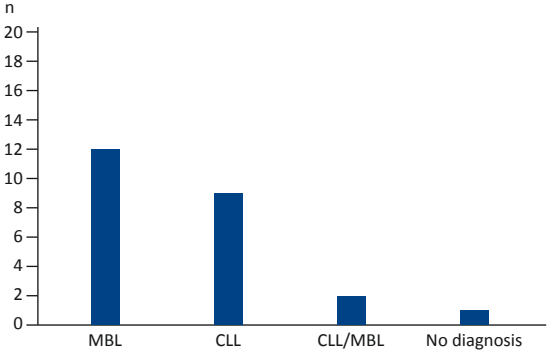
The average time from flow cytometry to clinical diagnosis of MBL-classified cases was 15 days (range: 7-46 days).

DISCUSSION

This study examined whether patients with a monoclonal B-lymphocyte count below 5 × 10^9/l were diagnosed correctly according to the 2008 WHO criteria. We found that 50% of MBL-classified cases were diagnosed correctly. An additional 8% were diagnosed with MBL/CLL. Importantly, even in the setting of a university department of haematology, 38% of the MBL-classified cases were inaccurately diagnosed as CLL. Moreover, in a third of these cases, the CLL diagnosis was described as mild, incipient or low-risk. This indicates that some of the treating physicians resolved to using extenuating adjectives in relation to a CLL diagnosis, when the patient did not actually fulfil the criteria. By inference, this meant that some patients were diagnosed with a malignant disease rather than being informed that they had a

FIGURE 2

Clinical diagnosis given to patients classified with monoclonal B-cell lymphocytosis by the 2008 World Health Organization criteria (N = 24).



CLL = B-cell chronic lymphocytic leukaemia;
MBL = monoclonal B-cell lymphocytosis.

precursor to a malignant disease, and notably where progression rates to overt disease are only 1-2% [2, 3]. Thus, patients with MBL, who are diagnosed with CLL may become unnecessarily concerned, since the diagnosis of CLL can cause anxiety as well as emotional and psychological distress [6].

Showing that only 50% of the MBL-classified cases were diagnosed with MBL, the above results suggest that the 2008 WHO criteria are not optimally implemented for clinical use. In fact, the recent WHO 2016 classification criteria may be less complex for distinguishing between MBL, SLL and CLL as the diagnosis is based on monoclonal B-lymphocyte count and lymph node status solely. A flow chart outlining the diagnosis according to the WHO 2016 criteria has been devised (**Figure 3**) [5]. One reason for inaccurate diagnosis of MBL patients seemed to be the use of total leukocyte count rather than monoclonal B-lymphocyte count. Thus, out of the nine MBL-classified patients who were diagnosed with CLL, two were diagnosed with CLL based on a total leukocyte count above 5 × 10^9/l. Consequently, stressing the point that the diagnosis should be based on the monoclonal B-lymphocyte count in current guidelines may also reduce the number of inaccurately diagnosed patients.

These findings are from a specialised lab with extensive experience with the diagnosis of malignant blood disorders. However, as will be seen, such findings must be related to total leukocyte counts and the actual fraction of B-cells within this compartment in order to obtain the correct absolute count of monoclonal B-cells. Thus, lymphocytosis, irrespective of where it is detected, be it in the setting of primary health care or hospital departments, entails a clear danger that the patient may be given a malignant diagnosis, which can cause distress and result in futile follow-ups in specialised departments.

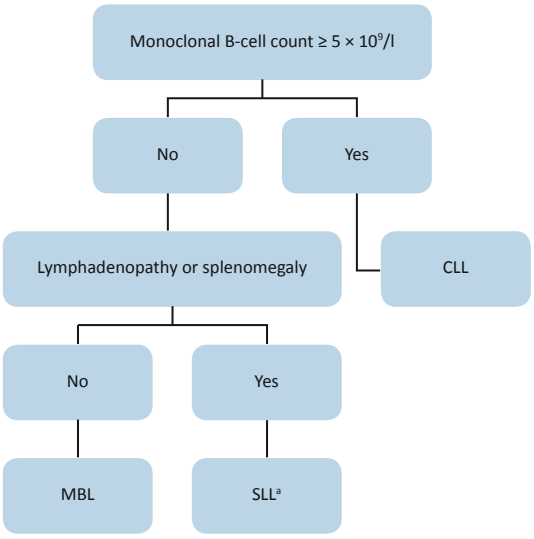
While it is important not to cause distress by diagnosing MBL patients with CLL, it is also important to correctly identify all patients with CLL, as they need closer monitoring and possibly treatment. None of the SLL or CLL cases classified in accordance with the WHO 2008 criteria were diagnosed with MBL in this study.

As the average time from flow cytometry to clinical diagnosis was only 15 days, it seems unlikely that any patients should have progressed from MBL to CLL before the clinical diagnosis was made. Furthermore, all medical records were examined for progression and only one patient had flow-cytometry-verified progression to CLL after approximately two years.

Some limitations apply to our study. First, the cohort was limited to 69 patients among whom only 24 cases classified as MBL. Furthermore, some (n = 127) samples in the total cohort lacked monoclonal B-lymphocyte count as well as total leukocyte count. Total leukocyte count was then found from another blood sample ± 1 week from the flow cytometry testing and multiplied by the monoclonal B-lymphocyte fraction. Consequently, borderline cases with a monoclonal B-lymphocyte count around 5 × 10^9/l may have been falsely classified as MBL rather than CLL.

FIGURE 3

Flow chart of the diagnosis of B-cell chronic lymphocytic leukaemia (CLL), small lymphocytic lymphoma (SLL) and monoclonal B-cell lymphocytosis (MBL) based on the 2016 World Health Organization criteria.



a) Diagnosis requires histopathological evaluation of lymph node.

CONCLUSIONS

This study showed that only approximately half of patients with MBL were diagnosed correctly. Furthermore, no patient with CLL/SLL in the cohort was inaccurately diagnosed with MBL, thus suggesting that the risk of overlooking malignant disease is minimal. The issue, then, is how to avoid diagnosing MBL patients with a malignant disease. Two points are especially relevant in this context: 1) avoiding the emotional distress experienced when receiving a malignant diagnosis and, 2) avoiding a frequent follow-up regime in secondary healthcare. To achieve this, the present study proposes two initiatives: 1) a flow chart outlining the diagnosis of CLL, MBL and SLL based on the WHO 2016 criteria and 2) stressing the fact that in current guidelines the diagnosis of MBL depends on the monoclonal B-cell count rather than the total leukocyte count. The implementation of the 2016 criteria may also simplify the diagnosis of clonal B-cell expansions compared with the more complex 2008 criteria. These data are of equal importance to primary care providers and hospital staff.

CORRESPONDENCE: *Maja Ludvigsen.* E-mail: majlud@rm.dk

ACCEPTED: 26 October 2017

CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk

LITERATURE

1. Landgren O, Albitar M, Wanlong M et al. B-cell clones as early markers for chronic lymphocytic leukemia. N Engl J Med 2009;360:659-67.
2. Rawstron AC, Bennett FL, O'Connor SJ et al. Monoclonal B-cell lymphocytosis and chronic lymphocytic leukemia. N Engl J Med 2008;359:575-83.
3. Shanafelt TD, Kay NE, Rabe KG et al. Brief report: natural history of individuals with clinically recognized monoclonal B-cell lymphocytosis compared with patients with Rai 0 chronic lymphocytic leukemia. J Clin Oncol 2009; 27:3959-63.
4. Hallek M, Cheson BD, Catovsky D et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008;111:5446-56.
5. Hsi ED. 2016 WHO Classification update-What's new in lymphoid neoplasms. Int J Lab Hematol 2017;39:14-22.
6. Shanafelt TD, Bowen D, Venkat C et al. Quality of life in chronic lymphocytic leukemia: an international survey of 1482 patients. Br J Haematol 2007; 139:255-64.