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Evolution of a Precursor

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Many investigators had previously noted collections of CLL-like cells in various clinical settings and reported their observations with colorful descriptors (1) but their precise clinical, population, and phenotypic characteristics were poorly understood. A unifying nomenclature was lacking before 2005 when a group of international investigators forged the terminology and definition of Monoclonal B-Cell Lymphocytosis or “MBL” and consolidated the observations available at that time (2).

As is often the case in science, this permitted rapid progress. Today an increasing number of reports document a steadily expanding understanding. The following are now well-appreciated:

MBL is more common in the elderly and in high-risk B cell malignancy (CLL) kindreds;

MBL precedes virtually all cases of CLL (3);

MBL has strong parallels with MGUS and myeloma as a B-cell precursor (4);

“Low count MBL” with a normal absolute B-cell count has limited potential to progress to CLL (5);

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As some basic features came into focus, further issues have arisen and are controversial. Studies are needed to answer the following questions:

How do the molecular features of MBL alter during progression to CLL and what precisely are the features of MBL that indicate likely progression to CLL? For example, the immunoglobulin repertoire in MBL is different from CLL (for example, Vh 1–69, commonly observed in CLL is lacking in MBL) and the stereotyped heavy chain receptors observed in as many as 30% of CLL cases are present in far fewer MBLs (6–9).

What is the etiologic origin of MBL? Does it derive from a dysregulated antigen response or is it induced by some extrinsic environmental or infectious insult? Although no extrinsic risk factors for CLL are established, several are suspected and highly controversial, including, for example herbicides (Agent Orange?) and radiation. While every population studied exhibits a male excess of CLL, in MBL the gender difference is less pronounced and further study is needed to understand if there is a real dichotomy by gender and if so what it implies about progression.

Is the pattern of ethnic variation similar to CLL? Examining the frequency of MBL in diverse geographic and ethnic settings is a future priority (10–12).

Does MBL share the genetic susceptibility increasingly well documented for CLL in both population samples (13, 14) and in families (15,16)?

What are the “borders” of MBL? On the “high” side, MBL merges with CLL. What is the most precise definition of MBL on the ‘border’ with CLL (17)?

On the “low” side or the border with the “normal” state, MBL has been divided into “low count” and “high count “ based on the projected likelihood of progression (6,7). How should the definition be refined to reflect these distinctions? What features distinguish MBL that progresses from that likely to remain benign? Some studies suggest the ALC is more important than total clonal B cells (7) and further work is needed to settle this.

Some rarer subgroups (CD20 bright, CD5–) have been defined (1,2,18). Should these be modified in an eventual refinement of the MBL definition?

What immunophenotyping protocols should be used for standard clinical documentation and what is recommended for research investigation? The approach selected depends in part, on how frequent MBL is in the general population (9,13,14) and how it varies in key subgroups such as families (15,16)? Although the reported age-adjusted population prevalence has been consistent, altered protocols predictably result in detection of lower (19) or higher (20) rates.

What clinical studies if any are indicated when MBL is identified and what are the ethical considerations for research when someone is identified with MBL (8,21,22)?

Is the prevalence of MBL also elevated in relatives of individuals with other blood and lymph cancers such as Waldenstrom’s or NHL? Do the B cell precursor states MBL and MGUS share characteristics, for example elevated levels of free light chains?

The study of MBL offers the opportunity to identify the earliest changes and sets the stage for a new assault on its key molecular, genetic and etiologic features. Prospective observation of MBL cases may reveal the earliest molecular alterations that permit progression to CLL. Furthermore, such studies may offer an opportunity for early treatment.

Refining the understanding of MBL and CLL in high risk kindreds will allow dissection of the genetic architecture of CLL in relation to the larger group of lympho-proliferative malignancies. The precursor is much more common than CLL and so it offers a more efficient way to investigate early but potentially critical steps toward developing disease.

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