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Precursors to Lymphoproliferative Malignancies

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Abstract

We review monoclonal B-cell lymphocytosis (MBL) as a precursor to chronic lymphocytic leukemia and monoclonal gammopathy of undetermined significance (MGUS) as a precursor to plasma cell disorders. These conditions are present in the general population and increase with age. These precursors aggregate with lymphoproliferative malignancies in families suggesting shared inheritance. MBL and MGUS may share some of the same risk factors as their related malignancies but data are limited. While these conditions are characterized by enhanced risk for the associated malignancy, the majority of individuals with these conditions do not progress to malignancy. A key focus for current work is to identify markers that predict progression to malignancy.

I. Introduction, definition, and history

Hematologic neoplasms are classified according to the cell lineage. The use of the term “precursors” with respect to these malignancies includes a broad range of conditions. We will focus on the precursors that are pre-malignant lymphoproliferative conditions. We will discuss monoclonal B-cell lymphocytosis (MBL) as a precursor to chronic lymphocytic leukemia (CLL) and monoclonal gammopathy of undetermined significance (MGUS) as a precursor to multiple myeloma (MM) and Waldenström macroglobulinemia (WM). Lymphoid malignancies show significant familial aggregation (1-5). Many studies of MBL and MGUS have been conducted in the setting of high risk families; these have shown the co-aggregation of the precursors with their related malignancies (6, 7). In addition, CLL, WM, and other lymphomas often aggregate together in families suggesting that they may share common etiologic pathways. Moreover, expression studies have shown that WM is more closely related to CLL than either of them are related to MM (8) although one study showed that each subtype could be distinguished (9). To date, such studies that directly compare these B-cell lineage diseases are limited. Genetic, epidemiologic and molecular studies of MBL and MGUS provide opportunities to elucidate disease mechanisms and define common etiologic pathways.

a. MBL

MBL is detected by multi-color flow cytometry of lymphocytes and is defined as a monoclonal B-cell population with cell surface markers consistent with CLL in an individual that does not meet the criteria for CLL. These monoclonal populations were first noted in studies of unaffected relatives in families segregating for CLL (10). A large cross-sectional study was started in 1995 to evaluate by flow cytometry individuals living near hazardous waste sites in the U.S. compared to controls. This study found evidence of an MBL phenotype in several individuals, the prevalence being significantly higher in those

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living near the hazardous waste sites (11). Other researchers described monoclonal B-cell findings in different clinical settings and for a number of years there was no standard nomenclature or definition. In 2005, the International Familial CLL Consortium published diagnostic criteria for MBL (12). Briefly, diagnosis requires detection of a monoclonal B-cell population with overall kappa:lambda ratio of $> 3:1$ or $<0.3:1$, or $> 25\%$ of B cells lacking or expressing low level surface immunoglobulin, and with a disease specific immunophenotype. The monoclonal population must be stable. Other lymphoproliferative disorders or symptoms indicative of CLL must be excluded. The B-lymphocyte count must be less than $5 \times 10^9/L$. MBL clones are classified similarly to CLL clones (i.e., by immunophenotype) into the following three subtypes: 1) CLL-like: CD5+23+ (vast majority) 2) atypical CLL : CD5+23- and 3) non-CLL like: CD5- (12).

b. MGUS

Essential monoclonal gammopathy was first described by Waldenström in 1960 following his observation of abnormal narrow bands in the serum of apparently healthy individuals tested by serum protein electrophoresis (13). Although this observation was also termed “benign”, Kyle introduced the term “monoclonal gammopathy of undetermined significance (MGUS)” in 1978 after documenting that asymptomatic patients with monoclonal protein are at higher risk of developing a variety of malignant and non-malignant conditions, including multiple myeloma, Waldenström macroglobulinemia, and amyloidosis, among others (14). Following three decades of research, three distinct clinical subtypes of MGUS have been defined: non-IgM MGUS, IgM MGUS and light-chain MGUS. In 2003, consensus definitions were developed for non-IgM MGUS and IgM MGUS by the International Myeloma Working Group (IMWG) and the International Workshop for Waldenström Macroglobulinemia (IWWM), respectively. The definitions of these two entities overlap substantially. MGUS is defined as the presence of a serum monoclonal protein with concentration $<3g/dL$, less than 10% infiltration of the bone marrow by plasma (non-IgM MGUS) or lymphoplasmacytic (IgM MGUS) cells, and the absence of constitutional symptoms, anemia, lymphadenopathy, hepatosplenomegaly or other symptoms related to the clonal process (15) (16). In 2010, the IMWG revised its diagnostic criteria such that non-IgM MGUS is defined as the presence of serum M protein $< 3 g/dL$, fewer than 10% clonal plasma cells in the bone marrow, and absence of end-organ damage characterized by hypercalcemia, renal insufficiency, anemia or lytic bone lesions (the ‘CRAB’ criteria) (17). Recently, researchers have proposed criteria to identify the precursor entity for light-chain multiple myeloma, termed light-chain MGUS, which is defined by an abnormal kappa-lambda free light chain ratio, elevation of free light chain level, and absence of an identifiable monoclonal heavy chain band on serum immunofixation (18).

Not all non-malignant monoclonal gammopathy, however, is of undetermined significance. Patients may have symptoms due to their specific monoclonal protein in the absence of morphological evidence of a bone marrow infiltrate or symptoms related to tumor burden. Thus, patients who have an IgM monoclonal protein together with specific symptoms attributable to the IgM (for example, cryoglobulinemia or autoimmune phenomena such as peripheral neuropathy or cold agglutinin disease) have been proposed to represent a clinically distinct subset, termed “IgM-related disorders” (16). Similarly, renal deposition of any immunoglobulin type represents another recently proposed clinical subgroup (19). Patients in these subsets often require treatment to manage the immunoglobulin-related symptoms, and care should be taken to distinguish them from true MGUS patients, who lack end-organ involvement.

II. Epidemiology and Etiology

a. MBL

Several studies have shown that the prevalence of MBL in the general population depends on age and the method of detection (20-24) (25) (26). For example, as more cells are screened by flow cytometry, the chance of detecting a monoclonal population increases. Thus, the population prevalence ranges from 3-12% among individuals over age 40 and 5-20% among individuals over age 60. In addition, the criteria for diagnosis of CLL have recently changed to require a B-cell count of at least $5 \times 10^9/L$ where previously the diagnosis required a total lymphocyte count of $5 \times 10^9/L$ (27). Thus, some individuals who would previously have met criteria for CLL are now diagnosed as MBL. We and others have reported that MBL is significantly more frequent among individuals who are members of high risk CLL families compared to those in the general population (6, 28, 29). We recently reported a study of 505 first-degree relatives of CLL patients representing 140 high risk families (28). Overall, 17% of relatives were diagnosed to have MBL consistent with earlier data based on smaller samples and substantially larger than the 3-7% rate in the population using similar methodology. The probability of developing MBL by age 90 was 61%. Consistent with CLL patterns, males had a significantly higher prevalence than did females. These family studies imply a shared inherited risk for CLL and MBL. Molecular studies have shown that MBL cells have similar chromosome abnormalities and other genetic markers as do CLL cells suggesting that these chromosome aberrations occur early in the development of MBL/CLL. One study reported that MBL clones found in individuals from high risk CLL families had similar molecular characteristics as indolent CLL (30). Ongoing studies are being conducted to determine whether MBL is present in families at risk for other types of non-Hodgkin lymphoma at a higher rate than in the population.

From an epidemiologic perspective, MBL has strong parallels with CLL being associated with age, gender and family history of CLL. However, as with CLL, the etiologic origin is unknown. It may derive from a dysregulated antigen response or induced by some currently unknown environmental or infectious factor. While no extrinsic risk factors for CLL are established, there is some evidence for herbicides and emerging evidence for radiation exposure (31, 32). Whether or not these factors are associated with MBL is unknown. Several SNPs that were identified from GWAS studies as being associated with CLL have also been shown to be associated with MBL (33, 34). Additional genetic and environmental studies will help clarify these relationships.

b. MGUS

Similar to MBL, MGUS is a common premalignant conditions, with overall prevalence rates among adults ranging from 0.05% to 6.1% (35-39) (40). Accurate and generalizable prevalence estimates for MGUS have been elusive because study methodologies vary considerably (41). Although large scale studies have been conducted in Olmstead County to establish the prevalence of MGUS among adults, many questions remain. Other population-based studies are limited, evolving laboratory methods enable more sensitive detection of monoclonal proteins, and not all studies have stratified data by age, race, gender, or immunoglobulin type; each of these variables is believed to have important implications for prevalence and possibly outcome. Thus, studies that report higher prevalence (35, 38, 42, 43) tend to employ the most sensitive methods in populations enriched for persons aged 50 years and above. Despite these limitations, however, consistent trends have emerged. From studies in predominantly white populations, the overall crude estimate of MGUS is 3.2% in individuals older than 50 years. Studies in whites and some Asian populations have shown that MGUS is strongly dependent upon age (36, 38, 44-46), with prevalence increasing nearly 4-fold between ages 50 and 80. However, this age-dependence is less clear in smaller

populations in Africa and Thailand (43, 47). Similarly, males appear to be at increased risk compared to females in most studies, with a male to female ratio ranging from 1.3 to 1.8. Race and ethnicity also appear to play a key role. We and others have documented 2- to 3-fold increased prevalence in African Americans and African blacks compared to whites (42, 43, 48). In contrast, studies in Asian (46, 47, 49) and Mexican (50) populations suggest that prevalence of MGUS in these groups may be lower compared to whites, but this needs further study. In addition, there is a clear association of MGUS with family history of MGUS or myeloma (5, 51-53). Together, these data strongly suggest a role for genetic susceptibility in the pathogenesis of MGUS.

Epidemiological data regarding other risk factors for MGUS are sparse and somewhat inconsistent, and confirmatory studies for many potential exposures are lacking. MGUS has been associated with certain occupations, including farmers and industrial workers (39). Occupational exposures to aromatic hydrocarbons, asbestos, fertilizers, paints, pesticides, petroleum products and radiation have been implicated (54, 55). In a recent study, increased risk of MGUS was confirmed among pesticide applicators (56). Tobacco (57) and obesity (in females) (58) have also been associated with higher risk for MGUS, but these observations require confirmation. Immune factors may also play a role in MGUS susceptibility. Infections, including human immunodeficiency virus-Type 1 and hepatitis C virus, have been inconsistently associated with MGUS in small series. Immunosuppressive therapy may also confer increased risk. In terms of genetic risk factors, one study of 388 MGUS patients and matched controls found 1/3 SNPs that had been previously identified from a GWAS study of MM to be associated with MGUS (59).

III. Natural History

a. MBL

MBL can be stratified by the absolute B-cell count into “low count” (normal ALC) and “clinical” (lymphocytosis present) MBL. The majority of patients identified from the general population have low count MBL. Several studies have conducted follow-up in MBL patients. The actual cut-off to define clinical MBL varies among studies but those with clonal B-cell count $> 2 \times 10^9/L$ tend to have increasing B-cell counts over time although the risk of progression to CLL requiring treatment is still low, approximately 1-2% per year for those with elevated B-cell counts. One study found that in a clinical MBL population, B-cell count and CD38 status predicted time to treatment (60). In addition, overall survival of MBL patients who were CD38+ was significantly shorter than age and sex matched controls (61). This is consistent with CD38 predicting more aggressive CLL. One study reported a higher rate of hospitalization for infections in both MBL and CLL patients than in controls (62). Studies have shown that the risk of progression for low count MBL is rare. One population study, with an average follow-up time of 34 months, reported that 90% of CLL-like clones, but somewhat lower proportion of atypical and CD5- MBL clones, persisted over time (63). It is unknown whether MBL individuals who are members of high risk CLL families have a higher chance to progress. Continued follow-up of these individuals is needed. A study by Landgren et al. (64) ascertained individuals from a cohort who developed CLL and had available biospecimens preceding their diagnosis. They reported that MBL preceded virtually all cases of CLL. Thus, MBL is likely to be a critical state in the pathway to CLL but only a small proportion of MBL patients will ever progress to CLL.

b. MGUS

Studies in a defined cohort have shown that MGUS consistently precedes the development of multiple myeloma (58, 65). There are different patterns of progression, ranging from a long stable MGUS phase to a rapidly evolving MGUS phase having a relatively short latent

period prior to diagnosis of myeloma. The average risk of progression to malignancy is approximately 1.0% and 1.5% per year for patients with non-IgM (66) and IgM MGUS (66, 67), respectively. Several factors influence the rate of progression, including the level of the monoclonal protein, the immunoglobulin isotype, the percentage of bone marrow plasma cells and the presence of polyclonal hypogammaglobulinemia (68). Serum free light chain (sFLC) analysis has been proposed as a method to assess malignant clonal expansion, and inclusion of information about the sFLC ratio further improves prognostic models (69). Non-IgM MGUS most frequently progresses to multiple myeloma, but occasionally other lymphoproliferative disorders develop instead. Similarly, Waldenström macroglobulinemia is the most common malignant outcome for IgM MGUS, but patients are also at risk to develop other B-cell neoplasms, such as chronic lymphocytic leukemia or other non-Hodgkin lymphoma (70). However, the majority of MGUS patients never progress and die from unrelated causes (71).

While MGUS patients are by definition asymptomatic, they may be subject to increased morbidity and mortality (71, 72). Emerging evidence documents increased risk of hypercoagulability/venous thrombotic disease (42, 73-76) and osteoporosis/fractures (72, 77-79) in MGUS patients, and biomarkers associated with these conditions may have prognostic implications for subsequent progression. MGUS patients have also been found to report certain infections more frequently, but it is unclear whether susceptibility to these infections is related to an underlying immune dysfunction or is a consequence of MGUS-induced immune defects.

In contrast to MBL patients who progress to CLL but do not need treatment, MGUS patients who progress to MM are more likely to need therapy. Consensus guidelines for the clinical management of MGUS have been proposed (80). Current recommendations suggest dividing patients into low- and high-risk groups based on the isotype and size of the monoclonal protein (Low risk: serum IgG < 1.5 g/dL or IgA or IgM < 1.0 g/dL; high-risk: serum IgG 1.5 g/dL, IgA or IgM 1.0 g/dL, or IgD or IgE at any level). Low-risk patients can be monitored every 3 – 4 months for the first year then every 6-12 months, depending on their clinical course, laboratory results, and comorbidities. High-risk patients should be monitored more frequently, every 3 – 4 months, indefinitely. Laboratory studies that are useful for monitoring include serum protein electrophoresis, quantitative immunoglobulins, sFLC (if available at diagnosis), complete blood count, creatinine, urea, electrolytes, and calcium.

Future Challenges: screening, prognosis, prevention—Table 1 compares MBL and MGUS for key features discussed in this review. For both MBL and MGUS, the risk of progression to a disease needing treatment is low and no early intervention is shown to prevent progression for either condition. Thus, there is no benefit for screening of the general population. MGUS patients with less than 10% infiltration of the bone marrow by lymphoplasmacytic cells have an overall survival similar to that of the general population (81), so patients diagnosed with MGUS should be reassured and care should be taken to not misclassify them as having a malignancy. One exception to the general rule not to screen for MBL is in the case of prospective bone marrow donors. It has been shown that MBL clones can be transmitted through bone marrow transplantation indicating that such individuals should be excluded as donors (82). To date, there has been no discussion of the theoretical risks due to MGUS for candidate marrow donors and recipients.

Accurate risk stratification for both MGUS and MBL is a major goal. For MGUS, the scope of the problem is indicated by the existence of at least two major risk stratification models that utilize different sets of criteria (69, 83). Future research should focus on the identification of 1) biomarkers that will facilitate the development of individualized risk profiles and 2) molecular markers that will provide insights into the biology of progression

and potentially provide therapeutic targets. Such studies should be coupled with prospective well-designed epidemiologic investigations to provide additional information about risk factors for MGUS development and progression. Progression does not seem to be a consequence of a discrete molecular event. Many of the somatic events that characterize myeloma and Waldenström macroglobulinemia can be seen in the MGUS phase, suggesting that progression results from the accumulation of sequential, or possibly overlapping, oncogenic events. We need better understanding of the microenvironment, epigenetics, and bone metabolism.

Longitudinal studies with serial follow-up of individuals with these conditions are needed to answer many questions. Among them, do the exposures associated with the malignancies also predict the precursor condition or progression from the precursor to malignancy? Which somatic, germline and chromosome abnormalities characterize the precursor, and what is the evolution that precedes frank malignancy? To obtain these answers, it is expected that integrated investigations involving genomic (GWAS, expression, chromosome, methylation, etc.), environmental (questionnaire complemented with cytokine and metabolomics characterization), and clinical follow-up will be needed. Since both these malignancies involve B cells, comparisons of 'normal' B-cells and 'pre-malignant' plasma or CD19/CD20/CD5 cells may offer special opportunities to evaluate serial alterations that may predict progression. As is the case in many complex diseases and the majority of cancer, no single genetic or exposure event fully characterizes cancer, so coordinated and repeated study in defined populations with a rich epidemiologic, clinical and biospecimen resource will be required to unravel the puzzle. But since progression is uncommon, co-ordination of efforts in consortia will prove necessary to identify sufficient numbers of patients.

High risk families with B-cell malignancies provide another powerful opportunity to characterize etiology and progression of MGUS and MBL since close relatives of patients are at substantially increased risk (compared to the population) for developing a precursor condition. Long term follow-up studies of relatives with MGUS and MBL will help define molecular determinants of progression. In our studies of families ascertained for either multiple cases of CLL or multiple cases of WM, we have found that cases of CLL and WM (and other lymphomas) often occur among closely related individuals in the same family. One such example is shown in Figure 1. Studies of both MGUS and MBL in such families provide a unique opportunity to discover and dissect common pathways leading to different B-cell malignancies.

Given that both MBL and MGUS uniformly precede malignancy, chemoprevention strategies are an area of keen interest. Both MGUS and MBL patients have a low probability of progressing to a clinical disease and thus chemoprevention would only be a goal for those who could be determined to be at high risk for developing aggressive disease. The opportunity to prevent or delay the development of the disease outcomes provides a compelling rationale to optimize risk stratification and identify potential therapeutic targets in MBL/MGUS patients. Ideally, chemoprevention trials would employ effective agents with low/no toxicity in high-risk patients. When such agents do become available in the future, these patients should be treated only on clinical trials. In the meantime, efforts should focus on defining high-risk cohorts and standardizing eligibility and response criteria.

In summary, while there are some predictors of progression for MBL and MGUS, but are no reliable markers that predict the risk of progression for individual patients. Molecular studies are underway to be able to better predict who will progress and thus should be followed more closely. Large scale genomic methods are being applied to CLL, WM, MM and many other cancers in order to discover the somatic changes leading to malignancy. As more of

these studies are applied to precursor states, it will be possible to define the critical pathways determining the progression of normal to clonal to malignant B-cells.

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Figure 1.
Pedigree with multiple B-cell malignancies

Characteristics of MBL and MGUS

Table 1

	Population Prevalence and Age	Gender	Risk Factors	Ethnic differences	Clinical correlates	Molecular Features	Rate of Progression	Determinants of Progression
MBL	3-12% over age 40 5%-17% over age 60	Males>Females	Family history of CLL Chemical exposures	Unknown	Increased risk of infections	Similar chromosome findings as in CLL	Clones persist over time 1-2%/yr requiring treatment(if lymphocytosis present)	B-ALC > 2000 CD38+
MGUS	3.2% over age 50 Increasing with age	Males>Females	Obesity, Occupation, Family history of MGUS, MM	Blacks>Caucasians>Asian	Increased risk of fractures, thrombosis	Similar somatic events as MM & WM	1-2%/yr	Size of monoclonal protein Type of monoclonal protein Degree of bone marrow infiltration sFLC