THE ROLE OF THE MONOCLONAL B LYMPHOCYTOSIS IN THE ETIOLOGY OF CHRONIC LYMPHOCYTIC LEUKEMIA

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Abstract: Chronic lymphocytic leukemia (CLL) is among the most common types of leukemia. Recent studies suggest that a population of clonal B cells with the phenotype of CLL, can be detected in the general population, a condition now designated as monoclonal B-cell lymphocytosis (MBL). Although all cases of CLL appear to be preceded by MBL, the majority of individuals with MBL will not develop a hematologic malignancy. The biological characteristics and clinical implications of MBL appear to differ based on whether it is identified during the diagnostic evaluation of lymphocytosis or incidentally discovered through screening of individuals with normal lymphocyte counts as part of research studies using highly sensitive detection methods. In this paper, we provide a state of the art review on the nomenclature, diagnosis and the role of MBL in the etiology of CLL.

Keywords: CLL, etiology, MBL

Rezumat: Leucemia limfatică cronică (LLC) este printre cele mai frecvente forme de leucemie. Studii recente sugerează că o populație de celule B clonală cu fenotip de LLC poate fi detectată în rândul populației generale, definită acum ca limfocitoză monoclonală cu celule B (MBL). Deși toate cazurile de LLC par să fie precedate de MBL, majoritatea persoanelor cu MBL nu vor dezvolta o boală malignă hematologică. Caracteristicile biologice și implicațiile clinice ale MBL par să difere la cei identificați în timpul investigații unei limfocitoze descoperite întâmplător față de cei cu un număr de limfocite normal încluși în screening, ca parte a studiilor de cercetare folosind metode foarte sensibile de detectare. În această lucrare, oferim o actualizare a nomenclaturii, diagnosticului și rolului MBL în etiologia LLC.

Keywords: LLC, etiologie, MBL

Cuvinte cheie: etiologie, MBL

Scientific article of bibliographic nomenclature, diagnosis and the role of MBL in the etiology of CLL. The role of the monoclonal B lymphocytosis in the etiology of chronic lymphocytic leukemia.

SCIENTIFICAL ARTICLE OF BIBLIOGRAPHIC NOMENCLATURE, DIAGNOSIS AND THE ROLE OF MBL IN THE ETIOLOGY OF CLL

Chronic lymphocytic leukemia (CLL), the most common form of leukemia among older adults in western countries, accounting for around 30% of all leukemias, though in a proportion of cases it can present with lymphadenomegaly with a limited peripheral blood involvement (defined as “Small Lymphocytic Lymphoma” - SLL).

The etiology of CLL is mostly unknown, though older age, Caucasian race and family history of malignancy or other lymphoproliferative disease have consistently been recognized as risk factors for CLL (1), indicating a genetic and familial predisposition in the pathogenesis of the disease. Chronic infectious or noninfectious prolonged self-antigenic stimulation is potentially relevant for the onset and progression of CLL.

Monoclonal B cell lymphocytosis with CLL-like phenotype is frequently recognized in the peripheral blood of otherwise healthy individuals, suggesting a potential etiological role in the pathogenesis of CLL. There are studies on CLL cases, both with mutated and unmutated genes, that show evidence of CLL clone up to 3 years before leukemia. (2)

DEFINITION OF MBL

Criteria for diagnosis of chronic lymphocytic leukemia have been recently changed, the absolute number of monoclonal B cells were replaced by the total number of lymphocytes. When the number of clonal B-cell with characteristic CLL phenotype in peripheral blood is higher than 5000/ml it is CLL, less than 5000 monoclonal B cells / ml, with characteristic CLL phenotype in the absence of lymphadenopathy, organomegaly, cytopenias or disease-related symptoms has to be defined as monoclonal B-cell lymphocytosis (MBL), an newly diagnosed entity. (3) Multiparametric flow cytometry has become widely spread way, so that detection of leukemic cells does not raise problems.

For the MBL diagnosis the following criteria have been proposed: (4)

1. Monoclonal B-cell population in the peripheral blood with characteristics:
   a. report k: λ ≥ 3:1, or
   b.>25% of B cells lacking or expressing low-level surface immunoglobulin (slg), or
   c. a disease-specific immunophenotype.
2. the monoclonal B-cell population is stable over a three-month period.
3. Exclusion criteria:
   a. lymphadenopathy and organomegaly, or
   b. associated autoimmune/infectious disease, or
   c. B-lymphocyte count> 5.000 / ml, or
   d. any other diagnostic feature of a chronic lymphoproliferative disease with B cell. A paraproteine associated with MBL should be evaluated independently.
4. Subclassifications:
   a. CD5+CD23+; together with low levels of CD20, CD79b, and slg corresponds to a CLL immunophenotype.
   b. CD5+CD23+/-; with moderate level of CD20 and CD79b expression corresponds to an atypical CLL immunophenotype.
   c. CD5-; corresponds to a lymphoproliferative disease other than...
CLL. MBL with CLL phenotype has a very high prevalence in healthy first-degree relatives of affected individuals in CLL families. The risk for detection of MBL with CLL phenotype in CLL families fourfold in comparison with the general population and for young adults aged 16-40 years, the relative risk is 17-fold. (5) The average age of onset in familial CLL is approximately 10 to 20 years earlier than in sporadic CLL, due to an inherited abnormality that increases susceptibility to development of CLL at a much earlier age than the general population, increasing the risk CLL within the family as a whole.

MBL and senescence of the immune system

Aging brings progressive decline of humoral immunity, the elderly show an increased morbidity and mortality because of infectious diseases. Aging individuals tend to produce less diverse antibodies because of limited IGHV gene usage and a lower incidence of somatic hypermutations. Not only changes in the T-cell compartments but also changes in the B-cell compartments could account for the defects in the immune system observed in older individuals. The presence of B-cell monoclonal expansions may also concur to this phenomenon.

MBL clones show a rather heterogeneous phenotype of monoclonal B cells, being both CD5+ and CD5–, but also with different levels of CD20 expression, reflecting the physiological aspects of immune senescence.

MBL clone expansion could not be linked with any latent viral infection, but might be dependent on some sort of persistent antigenic stimulus. In the case of B lymphocytes, could be considered also the action of self-antigens. Chronic and sustained activation may then be a prerequisite for the progression to malignant tumors, following a nondispensable oncogenic hit.

Biological similarity between MBL and CLL

The debate continues about whether MBL cells are truly neoplastic or reflect a normal counterpart of CLL. Experimental methods, phenotypic characterization, molecular and cyogenetic analysis of cells have been recently performed, so helped to shed some light.

Phenotype. Most cases of MBL express the same markers for the routine diagnostic CD5, CD20, CD23, and CD79b as typical CLL. This shows an extremely close association between protein expression profile of CD5 +23+ MBL from people with a normal blood cells and CLL (6), confirming the close biological relationship between the two entities.

Microarray Profiling. Using this approach, it can easily distinguish MBL from the normal B cells and the results suggest that LEF1 gene is a common feature of CLL and MBL. (7)

IGHV genes in MBL. Recent studies have approached the relationship between MBL and CLL by IGHV gene analysis. There were no significant differences in IGHV gene use between CLL-like MBL cases with a normal blood count and those with an absolute lymphocytosis. Most of CLL-like MBL (80-85% of cases), using mutated IGHV genes, 100% homologous to the corresponding germ line gene. The mutated cases used predominantly are IGHV3-07, IGHV3-23, IGHV3-30 or IGHV4-34 and IGHV4-59/61 genes, which are also frequently expressed by mutated CLL cases and rarely by unmutated CLL. (8)

The CLL-phenotype MBL show the same biased usage of IGHV genes that characterized of indolent CLL, but this can be seen also in normal B lymphocytes from elderly donors.

Clonal selection versus clonal diversification. Unmutated CLL/MBL had a higher degree of intraclonal variation than mutated CLL. Intraclonal heterogeneity is a frequent occurrence in both MBL and CLL. Clonal heterogeneity is either independent of, or inversely related to, the Ig mutation status, demonstrating that both mutated and unmutated CLL have undergone somatic hypermutation. The mechanisms of disease progression in MBL/CLL are based on the selection process under the action of an antigen. (9)

FISH. There is no specific chromosomal translocation associated with CLL, but a 13q14 deletion is detected in the leukemic cells from over 50% of CLL patients and it is associated with a good prognosis. Trisomy 12 and deletion of 11q and/or 17p are also common in CLL; the latter two abnormalities confer a poor prognosis. The chromosomal abnormality most closely associated with CLL is readily detectable in the CLL-phenotype MBL cells found in individuals with a normal blood count. The presence of markers of poor prognosis in MBL raises questions, suggesting a more close resemblance to CLL.

Clinical similarities between MBL and CLL. Some studies (10) show that MBL patients have a low probability of early progression, with no patients requiring treatment or dying of CLL-related causes after a median 2.5-year follow-up.

Predicting outcome in MBL patients is unlikely to be possible using conventional prognostic markers. Lymphocyte doubling time is uninformative because CLL-phenotype cells usually do not represent the majority of lymphocytes. CLL cell CD38 expression does not predict outcome, and initial data suggest that most patients with progressive disease have mutated IGHV genes. (11) The reason for the lack prognostic power of CD38 is not clear and requires further study, especially as some patients have an aggressive disease course. The rate of progression to a stage requiring treatment is 1% per year, disease progression show no plateau over time, indefinite periodic monitoring may be indicated and the majority of deaths are due to unrelated causes of these disease.

CONCLUSIONS

Monoclonal proliferation of B lymphocytes (defined MBL) can be detected in an increasing number of healthy individuals, depending on the progressive improvements in the flow-cytometric technique. Most MBL cells originate from the CD5+ B-cell pool and represent a minority of circulating B lymphocytes in humans. An extended phenotype associated with microarray analysis; clearly show a close resemblance between MBL and CLL.

This phenotypic similarity, together with the presence of monoclonality and the increased frequency among the male population, suggests the possibility that MBL may be considered in some respect a preleukemic phase of CLL. (12)

Despite the prevalence of MBL in the population at least 100-fold higher than that of CLL and monoclonality may be just a sign of the senesence process of the normal immune system, MBL may be a sort of normal counterpart of CLL, for which neoplastic transformation is not the inevitable fate but rather a rare event.

The critical question whether a biological relationship between MBL and CLL have not a final answer. The first clinical studies with longer follow-ups are demonstrating a yearly progression to CLL requiring chemotherapy of approximately 1% and rarity of the evolution into a life-threatening disease. Further biological studies are needed to clearly identify those cases that are at higher risk of progression, thereby needing a periodic monitoring and to avoid lengthy and expensive follow-ups for the enormous number of people carrying MBL, who will never develop any leukaemic disease.
BIBLIOGRAPHY


