Published in final edited form as:

Clin Lymphoma Myeloma. 2009 March ; 9(1): 23–26. doi:10.3816/CLM.2009.n.004.

Genetic and immune-related factors in the pathogenesis of lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia

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Abstract

There are emerging data to support a role for genetic and immune-related factors in the pathogenesis of lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia. In this paper, we review our recently published large population-based studies using data from Sweden and from U.S. Veterans and proposed mechanisms and pathways underlying our observations. We also talk about future directions for new studies designed to increase our current knowledge and to define underlying biological mechanisms of our findings. Finally, based on novel insights on this topic, we discuss clinical implications and provide perspective on the relevance of these data for patient counseling and clinical follow-up.

Keywords

Lymphoplasmacytic lymphoma; Waldenström's macroglobulinemia; lymphoproliferative malignancies; MGUS; familial aggregation; susceptibility; immune-related; hepatitis C virus; autoimmune disease; rheumatoid arthritis

INTRODUCTION

Lymphoplasmacytic lymphoma (LPL)/Waldenström's macroglobulinemia (WM) is a non-Hodgkin lymphoma (NHL) subtype characterized by small B-lymphocytes, plasmacytoid

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Presented in part (as two oral presentations: "Risk of lymphoproliferative disorders in relatives of Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma patients", by Dr. Kristinsson; and "Chronic immune stimulation and subsequent Waldenström's macroglobulinemia", by Dr. Landgren) at the 5th International Workshop on Waldenström's Macroglobulinemia (IWWM), Stockholm Sweden, October 15–19, 2008.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

SY Kristinsson and O Landgren initiated this work and wrote the report. All authors read, gave comments, and approved the final version of the manuscript.

lymphocytes, and plasma cells, usually involving bone marrow, lymph nodes, and spleen.^{1, 2} WM can be distinguished clinically from LPL on the basis of a detectable monoclonal (IgM) immunoglobulin spike in serum.¹ Also, using fluorescent in situ hybridization analysis, LPL tumor cells have frequent t(9;14)(p13;q32) translocations, while WM tumor cells appear to be diploid or near diploid and often have deletions of 6q21.³

In the general population, LPL/WM is a very rare disease, accounting for only 1–2% of all hematological malignancies, reflected in an incidence rate of 3 to 4 cases per million people per year.^{4, 5} Although the underlying mechanisms are unclear, males and whites are at higher risk of developing LPL/WM.^{4, 5} The median age at diagnosis is around 70 years,⁶ and median survival varies greatly based on disease stage, co-morbidity, and given therapy.^{7, 8} Based on long-term follow-up data from the Mayo Clinic, a personal history of the precursor condition monoclonal gammopathy of undetermined significance (MGUS) of the IgM class, is associated with an average 1–1.5% annual risk of developing WM.⁹ Although it has been evident for some time that there is heterogeneity among IgM MGUS patients and that the actual risk of WM most likely varies greatly, we still lack reliable biological predictors of outcome. Future work is needed to define molecular markers which can be applied to predict lymphomagenesis for individual IgM MGUS patients.

Currently, the causes of LPL/WM are unknown; however, there are emerging data to support a role for genetic and immune-related factors in the etiology of LPL/WM. In this paper, we review our recently published population-based studies based on data from Sweden and from U.S. veterans as well as other relevant findings. The implications of these studies are discussed with respect to the mechanisms and pathways underlying both autoimmunity and lymphoma. Furthermore, we discuss the future directions including a combination of population-based and molecular studies, which are needed to better define underlying biological mechanisms. Finally, we address clinical implications and provide perspective on the relevance of these data for patient counseling and clinical follow-up.

GENETIC FACTORS

The first report on familiarity in WM was published in 1962,¹⁰ and since then a number of multiply affected families, as well as case-control and cohort studies, have been published showing familial clustering of LPL and WM.^{11–15} Recently, Treon et al. characterized clinicopathological patterns of familial disease in a clinic-based series of 257 WM patients and found that 19% of the patients had at least one first-degree relative affected with WM or another B-cell disorder.¹⁵ We recently performed a large study, including 2,144 LPL/WM patients (1,539 WM [72%] and 605 LPL [28%]) diagnosed in Sweden, 8,279 population-based matched controls, and linkable first-degree relatives of patients (n = 6,177) and controls (n = 24,609).⁶ In our study, we found first-degree relatives of LPL/WM patients had a significantly increased risk of developing LPL/WM, other subtypes of NHL (including chronic lymphocytic leukemia; CLL), and MGUS, compared to first-degree relatives of controls. However, we found no excess risk of multiple myeloma or Hodgkin lymphoma (HL).

Together with previous studies,^{16–18} our findings support a role for shared common susceptibility genes that predispose to LPL/WM and certain lymphoproliferative disorders. We observed similar excess risk among parents, siblings, and offspring, which favors the operation of dominant or co-dominant gene effects, rather than recessive genes. There are a number of gene candidates that could be causing susceptibility to LPL/WM and related conditions. For example, polymorphisms in lymphomagenesis, immune function and DNA repair genes have been found to be associated with an elevated risk of CLL¹⁹, HL²⁰, and NHL.²¹ Recently, we performed the first genomewide linkage analysis of families at high risk for WM. In that study, we included 11 high-risk WM families (a total of 122 individuals, including 34 WM patients

and 10 IgM MGUS patients) that were informative for linkage.¹³ The strongest evidence of linkage was found on chromosomes 1q and 4q when patients with WM and with IgM MGUS were both considered affected. Other locations suggestive of linkage were found on chromosomes 3 and 6. Future work is needed to identify gene(s) that modulate susceptibility to WM and LPL.

Genetic anticipation is a term that refers to an earlier age at onset or increasing severity of a disease in successive generations. Trinucleotide repeat expansions explain anticipation in some Mendelian neurodegenerative diseases such as Huntington's disease.²² Epigenetic changes and abnormalities in telomeres have also been suggested as possible mechanisms that may contribute to anticipation in some diseases.²³ Anticipation has been widely investigated in complex diseases. In their clinical series, Treon et al. reported that WM patients with a familial history of WM (n=13) or a plasma cell disorder (MGUS, n=5; multiple myeloma, n=8) were diagnosed at a younger age and with greater bone marrow involvement than sporadic WM cases.¹⁵ In our large population-based study, we found that offspring of LPL/WM patients were diagnosed with LPL/WM at an earlier age than the parent group. However, offspring of controls with LPL/WM had a similar age at diagnosis as offspring of cases indicating that this difference is likely due to differences in follow-up time between generations and not explained by earlier diagnosis in children of parents with LPL/WM. This is consistent with our earlier studies showing no anticipation after correcting for bias in follow-up times.^{17, 24} These observations highlight the need to be cautious when interpreting familial aggregation patterns with regard to age of onset and consider the potential influence of so called "truncation" bias (i.e. the offspring generation is not followed up as long as the parent generation).²⁵

IMMUNE-RELATED FACTORS

A few studies have reported evidence of somatic immunoglobulin gene mutations, suggesting that the WM cells originate from B cells that have undergone repeated antigenic stimulation and selection in the germinal centers of lymphoid follicles.^{26, 27} Until recently, only a few smaller epidemiological studies had been conducted to assess the role of chronic antigenic stimulatory conditions in relation to risk of developing LPL/WM. For example, in a hospital-based study including 65 WM patients and 213 hospital-based controls, personal history of autoimmune disease was not associated with subsequent risk of developing WM.¹²

Interestingly, WM patients were more likely than controls to have first-degree relatives with a history of pneumonia, diphtheria, rheumatic fever, and diabetes mellitus. An exploratory evaluation of immunologic profiles revealed that relatives of two WM cases had IgM MGUS and about 40% had diverse immunologic abnormalities.¹² More recently, we conducted two large nationwide studies based on U.S. veterans designed to explore the role of antigenic stimulation in the pathogenesis of WM. In the first study, including 146,394 patients infected with hepatitis C virus (HCV) and 572,293 controls,²⁸ we found that HCV infection confers a 20–30% increased risk of NHL overall and a 3-fold higher risk of WM. In the second study, we assessed WM risk in relation to a variety of chronic immune stimulatory conditions among 4 million U.S. veterans and among 361 patients with WM with up to 27 years of follow-up, we found a 2- to 3-fold elevated risk of WM in individuals with a personal history of an autoimmune disease and notably elevated risks associated with hepatitis, human immunodeficiency virus, and rickettsiosis.²⁹ In the latter study, we also evaluated whether a personal history of allergy was associated with the risk of developing WM. However, based on small numbers, we found no statistical association (relative risk=1.03; 95% confidence interval 0.67–1.60) between allergic conditions and subsequent WM risk.²⁹

Importantly, one has to keep in mind that autoimmunity and exogenous antigens are not mutually exclusive. For example, monoclonal rheumatoid factors react with the Fc portion of IgG to form mixed cryoglobulins; but there is also a strong association with HCV in these

patients. Similarly, patients with chronic cold agglutinin disease have monoclonal IgM antibodies targeted to antigens on red cells; however, these specificities may be related to bacterial lipopolysaccharide. Future studies designed to clarify biological causes of observed cross-reactivity patterns might provide clues to the etiology and pathogenesis of WM.

Taken together, our results support a role for chronic immune stimulation in lymphomagenesis and WM. Future work is needed to uncover underlying mechanisms of the observed associations between immune-related conditions and the excess risk of developing lymphoma.³⁰ Figure 1 shows the suggested basic steps in the development of WM.³¹

CLINICAL IMPLICATIONS

It is important to put these novel insights regarding risk factors for LPL/WM development into a clinical context. As discussed above, there is convincing evidence that first-degree relatives of LPL/WM patients are at increased risk of developing LPL/WM and certain types of lymphomas (including NHL and CLL).^{6, 15} However, because of the low baseline risk of LPL/WM and other lymphoproliferative malignancies in the general population, the absolute risk for a relative of a LPL/WM patient to develop LPL/WM or another lymphoproliferative malignancy is still very low. For example, the National Cancer Institute SEER program estimates that 2.05% of people born today will be diagnosed with NHL at some time during their lifetime.³² One can still question whether there is an advantage for prevention or early detection for a relative knowing that they are at increased risk for LPL/WM. Currently, early detection of LPL/WM is not likely to affect outcome since asymptomatic LPL/WM is typically not treated. Although relatives of LPL/WM cases are at increased risk for developing MGUS,⁶ the average transformation rate from MGUS to WM is only about 1–1.5% per year.⁹ These characteristics of LPL/WM make it quite different from common solid tumors, such as colon cancer,³³ where early detection of the tumor or precursor can affect survival. Instead, while relatives of patients with LPL/WM can be informed that have a higher risk of developing LPL/WM and other lymphomas (compared to family members of unaffected individuals), it should be emphasized that the absolute risk for developing LPL/WM and other hematologic malignancies is very low, there is no treatment for early lesions, and thus no increased medical surveillance is necessary at this time.

The observation that immune-related and inflammatory conditions are associated with an excess risk of developing WM and other lymphomas may also have clinical implications regarding the treatment of those conditions. Indeed, it has been suggested in some, but not all, prior studies, that autoimmune disease therapy (such as methotrexate and TNF-alpha blocking agents) might play a role in the development of subsequent lymphoma.^{34–36} Some studies have reported spontaneous lymphoma regression in rheumatoid arthritis (RA) patients following removal of methotrexate therapy.^{37, 38} Others have found that lymphomas occurring following transplantation are more likely to be of aggressive subtypes and are thought to be due to immunosuppression and subsequent re-activation of Epstein-Barr virus (EBV).³⁹ Overall, the literature on the role of immunosuppression and EBV in RA-related lymphomas is controversial.^{35, 37} New therapeutic agents blocking TNF-alpha clearly benefit patients with RA and other autoimmune conditions. The monoclonal antibody rituximab, which is effective for treatment of RA,⁴⁰ is a commonly used treatment for lymphomas; thus, one would not expect it to increase risk for subsequent lymphoma, however there is no available data on that topic. From a clinical perspective, we need to conduct a careful pretreatment evaluation and long-term surveillance of our patients receiving therapy for autoimmune diseases while keeping in mind that the absolute lifetime risk of LPL/WM is very low. Thus, although the relative risk of LPL/WM is elevated for individual patients affected by immune-related conditions, the public health impact of these findings is small.

Overall, these insights might trigger complex medical considerations and imply ethical dilemmas. As treating physicians, we need to handle this information with care and provide and counsel our patients with clinically relevant information.

FUTURE DIRECTIONS

Emerging data support a role for germline susceptibility genes in the causation of LPL/WM and other lymphoproliferative disorders.⁶ In a genomewide linkage analysis of families at high risk for WM, evidence of linkage was found on chromosomes 1q and 4q.¹³ At the same time, there is evidence to support a role for immune-related conditions in the development of LPL/WM.^{26–29} Future studies are needed to identify susceptibility gene(s) and define the role of immune-related conditions, and their interaction, in the etiology of LPL/WM. Given the fact that LPL/WM is a very rare disease, there is a clear need for international collaboration to advance the research field further.

Furthermore, we need to explore the role of immune-related conditions in the development of LPL/WM by incorporating molecular and laboratory components to validate diagnoses and evaluate more biologically homogeneous groupings of autoimmune disorders. Other areas of interest might be to study the impact of intervention (e.g. molecular markers of lymphoproliferation in HCV infected individuals undergoing HCV treatment) and to investigate prospectively the natural history and pathogenesis of autoimmune disorders in individuals who subsequently develop LPL/WM. Finally, we need to better define the role of immune-related conditions on prognosis and survival in LPL/WM as this may have clinical implications for the treatment of LPL/WM patients with autoimmune conditions.

Future studies designed to assess the underlying mechanisms of our recently defined associations might not only improve our understanding of LPL/WM pathogenesis. They could also have a direct influence on clinical lymphoma management by leading to more informed risk assessments of novel autoimmune drugs that might be involved in lymphomagenesis.

Acknowledgments

This research was supported by grants from the Swedish Cancer Society, Stockholm County Council, the Karolinska Institutet Foundations, and the Intramural Research Program of the NIH, NCI.

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Figure 1.

The normal steps in B-cell maturation. WM is considered to originate from cells that have been through the process of somatic hypermutation at the lymph node but have not yet undergone isotype class switching. Both genetic susceptibility and sustained antigenic stimulation, which can be observed during autoimmunity and chronic infection, constitute risk factors for WM development. (Adapted from Ghobrial et al, Lancet Oncol 2003.)³¹