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What Causes Waldenström's Macroglobulinemia: Genetic or Immune-Related Factors, or a Combination?

Sigurdur Y. Kristinsson¹, Ola Landgren²

¹Department of Medicine, Division of Hematology, Karolinska University Hospital Solna and Karolinska Institutet, Stockholm, Sweden

²Medical Oncology Branch, Center for Cancer Research, National Cancer Institute, NIH, Bethesda, MD

Abstract

Population-based studies suggest a role for chronic immune stimulation and genetic factors in the causation of lymphoplasmacytic lymphoma (LPL)/Waldenström's macroglobulinemia (WM). In this review we summarize and discuss our current understanding on etiology and pathogenesis of LPL/WM. We also highlight on gaps in the literature and propose future directions for population-based and molecular studies designed to expand our knowledge and uncover biological underpinnings of identified associations. Further, we address clinical implications and provide perspective on the relevance of these data for patient counseling and clinical follow-up.

Introduction

Lymphoplasmacytic lymphoma (LPL)/Waldenström's macroglobulinemia (WM) is a distinct B-cell disorder characterized by small B-lymphocytes, plasmacytoid 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

LPL/WM is a very rare disease, with an incidence rate of 3 to 4 cases per million people per year, and with a higher incidence in males and whites.³ The strongest risk factor for WM is the precursor condition monoclonal gammopathy of undetermined significance (MGUS) of the IgM class, which is associated with an average 1%–1.5% annual risk of developing WM.

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Address for correspondence: Sigurdur Yngvi Kristinsson, MD, Department of Medicine Division of Hematology, Karolinska University Hospital Solna, SE-171 76 Stockholm, Sweden, Fax: 46-8-31-82-64; sigurdur.kristinsson@karolinska.se.

Author Contributions

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

Conflict of Interest Statement

The authors have no conflict of interest to declare.

Currently, the causes of LPL/WM are poorly understood; however, there are emerging data to support a role for immune-related factors and genetic in the etiology of LPL/WM, which will be reviewed in this paper.

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.^{5–6} Until recently, only a few 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.⁷ Interestingly, WM patients were more likely than controls to have first-degree relatives with a history of pneumonia, diphtheria, rheumatic fever, and diabetes mellitus, with relatives of 2 WM cases having IgM MGUS and about 40% had diverse immunologic abnormalities.⁷ We conducted 2 large nationwide studies based on US veterans designed to explore the role of antigenic stimulation in the pathogenesis of WM. In the first study, including 146,394 individuals infected with hepatitis C virus (HCV) and 572,293 controls,⁸ 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 based on 4 million US veterans; 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.⁹ In a recent study based on 2470 LPL/WM patients, 9698 matched controls, and almost 30,000 first-degree relatives of cases and controls from Sweden, we analyzed whether personal or family history of a wide range of autoimmune, infectious, allergic, and inflammatory conditions were associated with LPL/WM.¹⁰ An increased risk of LPL/WM was associated with a personal history of the following autoimmune diseases: systemic sclerosis, Sjögren's syndrome, autoimmune hemolytic anemia (both warm and cold type), polymyalgia rheumatica, and giant cell arteritis. An increased risk of LPL/WM was associated with a personal history of the following infectious diseases: pneumonia, septicemia, pyelonephritis, sinusitis, herpes zoster, and influenza. Interestingly, an increased risk of LPL/WM was associated with a family history of Sjögren's syndrome, autoimmune hemolytic anemia, Guillain-Barré syndrome, cytomegalovirus, gingivitis and periodontitis, and chronic prostatitis.¹⁰

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.

Taken together, our results support that chronic immune stimulation plays a role in the pathogenesis of LPL/WM. Our findings that both personal and family history of Sjögren's

syndrome or autoimmune hemolytic anemia were associated with increased risk of LPL/WM indicate that there might be some shared (genetic, environmental, or both) susceptibility for these conditions. Future work is needed to uncover underlying mechanisms of the observed associations between immune-related conditions and the excess risk of developing WM.¹¹

Genetic Factors

A number of multiply affected families, as well as case-control and cohort studies, have been published showing familial clustering of LPL and WM.^{7, 12–13} In a clinic-based series of 257 WM patients, 19% of the patients had at least 1 first-degree relative affected with WM or another B-cell disorder.¹³ We recently performed a large study, including 2144 LPL/WM patients diagnosed in Sweden, 8279 population-based matched controls, and linkable first-degree relatives of patients (n = 6177) and controls (n = 24,609).¹⁴ We found that first-degree relatives of LPL/WM patients had a significantly increased risk of developing LPL/WM, other subtypes of NHL and MGUS, compared to first-degree relatives of controls.

Together with previous studies,^{15–17} 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. In a questionnaire-based study on 103 WM patients and 272 unaffected relatives from 35 multiple-case WM and 46 mixed WM/related B-cell disorders kindred and 28 sporadic WM patients, familial WM patients were more likely than unaffected relatives to report a history of autoimmune disease and infections. Familial WM patients were also more likely to report exposure to farming, pesticides, wood dust, and organic solvents compared with unaffected family members.¹⁸ These results are in accordance with our previous results from Sweden.¹⁰

There are a number of gene candidates that could be causing susceptibility to LPL/WM and related conditions.^{19–21} Recently, the first genome-wide linkage analysis of 11 high-risk WM families found the strongest evidence of linkage on chromosomes 1q and 4q.¹² 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.

Clinical Implications

The observation that immune-related and inflammatory conditions are associated with an excess risk of developing WM and other lymphomas may have clinical implications regarding the treatment of those conditions. It has been suggested in some studies that the treatment of autoimmune disease might play a role in the development of subsequent lymphoma.^{22–23} Pretreatment evaluation and long-term surveillance of our patients receiving therapy for autoimmune diseases is recommended, 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.

The fact that first-degree relatives of LPL/WM patients are at increased risk of developing LPL/WM and certain types of lymphomas is interesting from a pathogenetic point of view, however, on a clinical note, one has to keep in mind that baseline risk of LPL/WM and other lymphoproliferative malignancies is very low in the general population. Consequently, despite the observed increased relative risk among first-degree relatives of LPL/WM patients, the absolute risk for a relative of a LPL/WM patient to develop LPL/WM or another lymphoproliferative malignancy still remains very low. In addition, at present time early detection of LPL/WM is not likely to affect outcome since asymptomatic LPL/WM is typically not treated, and no increased medical surveillance is necessary at this time.

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.¹⁴ 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.

There is also need to better define the role of immune-related conditions in the development of LPL/WM by incorporating molecular and laboratory and evaluate more biologically homogeneous groupings of autoimmune disorders. Other areas of interest might be to study the natural history and pathogenesis of autoimmune disorders in individuals who subsequently develop LPL/WM. In addition, 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.

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