Autoimmunity and Lymphoma: A Brief Review

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Abstract

The relationship between the immune system and both Hodgkin’s (HL) and Non-Hodgkin’s (NHL) lymphomas is a complex bidirectional process which has fascinated researchers and clinicians for many years. Lymphomas of all types are known to be associated with autoimmune paraneoplastic manifestations, and conversely are recognized in increased frequency in patients with pre-existing autoimmune diseases. This review briefly surveys this two-way process whereby lymphomas induce autoimmune dysfunction, and autoimmune system dysfunction induces lymphomagenesis. An emphasis on the clinical manifestations of these disorders is presented along with a brief overview of the pathophysiologic mechanisms involved.

Autoimmune Paraneoplasia

Autoimmune phenomenon is common in patients with lymphoproliferative disorders. One of the most prevalent autoimmune manifestations is the higher than normal prevalence of autoantibody production in these individuals. Swissa and colleagues found that more than one third of lymphoma patients produced one or more of several autoantibodies typically associated with systemic autoimmune diseases, an incidence significantly higher than in normal controls. Furthermore, the frequency of autoantibody production was greater in individuals with NHL than those with HL. Among the autoantibodies detected were those directed against single stranded DNA (ssDNA), ribonucleoprotein (RNP), Smith antigen (Sm), Sjogrens antigens (SSA and SSB) and cardiolipin [1]. Sthoeger, et al. revealed that CLL patients secrete or can be made to synthesize monoclonal antibodies against self ssDNA, double stranded DNA (dsDNA), and Immunoglobulin G (IgG) [2]. Similarly, Guyomard and associates found a significantly higher percentage of NHL patients had detectable antinuclear antibodies (ANA) than normal controls (19% vs. 6%), with a marked prevalence in follicular and mantle cell lymphoma subgroups [3]. In a similar study Timuragaoglu found a 39% incidence of autoimmune markers in NHL patients including direct and indirect antiglobulin tests, antiplatelet antibodies, ANA, anti-native DNA, antiphospholipid antibodies and lupus anticoagulant. The presence of autoimmune phenomenon was more common in male patients and antiglobulin and antiplatelet antibodies were associated with autoimmune hemolytic anemia and thrombocytopenia respectively [4].

Although the presence of autoantibodies may be clinically significant, the majority of these patients do not display clinical autoimmune symptoms. However, many lymphoma patients do have concomitant autoimmune diseases. In a study of 940 lymphoma patients Varoczy and colleagues found a 7.6% incidence of autoimmune disease in NHL patients, and 8.6% of HL affected individuals. The most common diagnosis was Sjogren’s syndrome, but other associated autoimmune diseases included skin diseases, thyroiditis, polymyositis, scleroderma, rheumatoid arthritis (RA), vasculitis, autoimmune hepatitis, autoimmune hemolytic anemia (AIHA), systemic lupus erythematosis (SLE) and more. Although in NHL cases most (70%) autoimmune diseases preceded the onset of lymphoma, in HL the autoimmunity developed mainly after the treatment of malignancy [5]. However, the presence of autoantibodies alone does not appear to affect the prognostic outcome in these individuals [2-3,6].
Common clinical autoimmune manifestations in lymphoma patients are hematologic disorders, particularly autoimmune hemolytic anemia (AIHA). In addition to AIHA, Evan’s syndrome, pure red cell aplasia and autoimmune thrombocytopenia (ITP) have been described. These are primarily seen in patients with NHL although they are well described in HL as well [7-9]. A specific incidence of AIHA is difficult to estimate due to the heterogeneity of lymphoma subtypes but appears to range from 3-5% with many more individuals exhibiting a positive direct antiglobulin test without anemia. The incidence appears to be greater in marginal cell lymphoma with an incidence of about 10%, and in affected individuals with T-cell histology [10]. Immune thrombocytopenia and Evan’s syndrome in comparison occur in less than 1% of NHL patients [11]. Anti-lymphoma treatment seems to be more effective than traditional therapy including steroids or immunoglobulin, and more importantly the presence of these manifestations may herald a worse overall prognosis [10-12].

The underlying mechanism may vary between entities and patients. While the origin of antibodies causing AIHA in CLL is controversial, in NHL the antibody may be clonal and produced by the lymphoma cells. For example, in cold autoimmune hemolytic anemia the malignant clone secretes monoclonal IgM antibodies directed against i or I antigen on red blood cells. Another potential mechanism is demonstrated in patients with angioimmunoblastic T-cell lymphoma who have an increased incidence of autoimmune phenomena due to reduced number and activity of T regulatory cells (Treg) [13,14]. Moreover, autoimmune phenomenon in NHL may occur before or upon diagnosis, during or after treatment [10].

**Association of Lymphoma and Systemic Autoimmune Diseases**

Patients suffering from autoimmune diseases have been recognized to be at increased risk of developing NHL in for a number of years. Most clearly evident in individuals with rheumatoid arthritis (RA), Sjogren’s disease (SjS) and systemic lupus erythematosus (SLE) an association with other autoimmune disorders such as celiac disease and scleroderma (SS) has been demonstrated in some studies. Several recent large population-based studies have confirmed this association.

Smedby and colleagues conducted a population-based case-control study in Denmark and Sweden consisting of 3,055 NHL patients and a similar number of matched controls who were surveyed for a history of autoimmune and chronic inflammatory diseases. Their results demonstrated that the risk of all NHL was increased in association with RA, primary SjS, SLE, and celiac disease [15].

In second report Smedby and colleagues performed a pooled analysis of self-reported autoimmune conditions and risk of NHL and subtypes, including 29,423 participants in 12 case-control studies. They found that risk of NHL is increased in SjS, SLE, AIHA, ITP, psoriasis and in older patients with celiac disease [16].

An even larger study incorporating the U.S. Surveillance, Epidemiology and End Results (SEER)-Medicare data base of 44,350 lymphoma patients and more than 120,000 population-based controls revealed an increased risk of diffuse large B-cell lymphoma in RA- and SjS-affected individuals. T cell lymphomas were found to be associated with AIHA, psoriasis, discoid lupus erythematosus and celiac disease. Marginal zone lymphoma was found at increased risk in patients with SjS, SLE, and AIHA [17].

In a meta-analysis of 20 studies Zintzaras and colleagues found a high risk of NHL development in patients with scleroderma, moderate risk for individuals with SLE, and lower risk for those suffering from RA [18]. In a prospective study of 2,105 subjects with new onset inflammatory polyarthritis followed for a median of 8.4 years, a doubling of the risk of lymphoma was found with higher incidences occurring in those individuals with rheumatoid factor positivity and in those treated with methotrexate [19]. In contrast, an attempt to demonstrate an increased risk of NHL in patients with a family history of systemic autoimmune diseases showed a modest and non-significant increase [20].

An increased incidence of HL has also been reported with several systemic autoimmune diseases. In a recent large population-based case-controlled study in Denmark and Sweden, Landgren and colleagues evaluated the historical association between 7,476 case subjects with HL and compared these with more than 18,000 matched control subjects, and more than 86,000 first degree relatives of case and control subjects. According to their analysis a statistically significant increased risk of HL was associated with personal histories of several autoimmune conditions, primarily those characterized by systemic involvement. These included RA, SLE, SS, sarcoidosis and ITP. A weaker association was found with autoimmune diseases in which more organ-specific involvement is characteristic including primary biliary cirrhosis (PBC) and Wegener’s granulomatosis. In addition, a statistically significant increased risk of HL was also associated with family histories of sarcoidosis and ulcerative colitis further suggesting a shared susceptibility for these conditions [21].

Data from the U.S. Surveillance Epidemiology and End Results (SEER)-Medicare database also demonstrated an association between HL and both systemic and discoid lupus erythematosus as well as RA. This study was perhaps more limited than the Scandinavian study due to the older age of individuals and the relatively smaller number of HL versus NHL patients [17]. In a multisite cohort study of 9547 SLE patients by Bernatsky and as-
ties and increased risk of HL was also demonstrated [22]. Autoimmunity was associated with a significantly elevated risk only for MC Hodgkin’s Lymphoma (HL), no significant associations were found with NS HL. A long latency was seen from the date of autoimmune diagnosis to the date of MC HL (mean time = 15.4 years) suggesting that long-term chronic immune stimulation may play a role in the induction of MC HL [23].

**Immunosuppressive Therapy and Lymphoma**

An association between immunosuppressive therapies used in the treatment of autoimmune diseases has long been suspected to play a role in the development of lymphomas in these individuals. Mostly studied in RA, development of lymphoma is increased by the use of cyclophosphamide and equivocal with respect to azathioprine. Although methotrexate has been associated with certain cases of “reversible lymphoma” which disappear with drug discontinuation, epidemiologic studies have failed to demonstrate an increased risk beyond what is expected in RA alone [24].

Of more recent interest is the possible association of newer biologic agents, particularly those directed against tumor necrosis factor (TNF), and the onset of malignancies including lymphomas. While some studies have detected a possible increased lymphoma risk with use of biologic agents [25,26], large population-based studies have failed to demonstrate an increased risk with use of anti-TNF drugs [24,27-29]. Therefore, the prevailing opinion is that immunomodulatory biologic agents do not appear to increase the risk of lymphoma development.

**Autoimmunity and Lymphomagenesis**

The possible mechanism by which autoimmunity could be related to the risk of developing lymphoma has been the subject of investigation for more than 50 years. Initial theories focused on the similar proliferative processes of lymphocytes that characterize both autoimmunity and hematologic malignancies [30]. Goodnow in a recent review described the pathways and genes likely to be involved in both autoimmune diseases and lymphomas. According to his analysis both disease types are the consequence of multistep processes that eliminate the checkpoints that inhibit uncontrolled B-cell growth, including uncontrolled growth of autoimmune lymphocytes. These processes are likely to involve both inherited and somatic mutations of the genes involved in these pathways. The most prominent example is the finding that somatic and germ line Fas mutations, are associated with both autoimmune diseases and lymphomas in mice and in humans. These mutations dysregulate apoptosis, enhance lymphoid hyperplasia thus inducing both the autoimmune and malignant lymphoproliferative processes (Autoimmune lymphoproliferative syndrome-ALPS) [31].

Hansen and colleagues summarized the possible mechanisms for progression of autoimmune diseases to lymphomas, including how specific dysregulation and hyperactivity of B-cells associated with autoimmune diseases and impaired T-cell function may lead to lymphomagenesis. They emphasize that the more intense disease activity and/or longer duration of disease might indicate a higher risk of lymphoma development [32].

A comprehensive picture of the major immune-related factors thought to contribute to lymphomagenesis is presented by Goldin and Landgren [33]. In their model, autoimmunity may lead to both over-stimulation and defective apoptosis of B-cells. Secondary inflammation due to autoimmune stimulation can also promote these processes. Patients with celiac disease caused by antibodies to gliadin may develop enteropathy T cell lymphoma. Several infections have been associated with lymphoma development including Hepatitis C, Epstein Barr virus and certain bacteria are likely to operate through some of these same pathways. Infection with *Helicobacter* induces synthesis of antiparietal antibodies and MALT lymphoma.

In patients with gastric autoimmunity cytolytic T cells, that cross-recognize different epitopes of *H. pylori* proteins and H+K+-ATPase autoantigen, infiltrate the gastric mucosa and lead to gastric atrophy via long-lasting activation of Fas ligand mediated apoptosis and perforin-induced cytotoxicity. Gastric T cells from MALT lymphoma exhibit defective perforin- and Fas-Fas ligand-mediated killing of B cells, with consequent abnormal help for B-cell proliferation Antibacterial treatment cures cases with early lymphoma [34].

Hepatitis C virus induces mixed cryoglobulinemia and B-cell lymphoma. Genetic factors predisposing to both autoimmune diseases and lymphomas may also play a substantial role. The suppressive/immunomodulatory function of CD4+CD25+Foxp+ regulatory T (Treg) cells is crucial for the maintenance of immune homeostasis, which helps to prevent autoimmunity and reduce the inflammation induced by pathogens and environmental insults.

Some studies have found a reduced or normal frequency of Treg cells in autoimmune disorders like SLE and early rheumatoid arthritis (RA) also defective *in vitro* suppressive function of human Tregs appears to be a common feature of autoimmune diseases. From the other side in hematologic malignancies, up-regulation of CD25 Treg cells was found in Hodgkin disease, Non-Hodgkin lymphoma and multiple myeloma. Moreover, some subtypes of T-cell lymphoma cells exhibit a Treg phenotype. In NHL, Treg cells attenuated CD8 T-cell function, thereby protected lymphoma cells from cytotoxic activity. However, in some entities lymphoma cells are killed by Treg cells. In these cases, lower number of Treg cells explain both autoimmunity and severity of lymphoma [13,14].

Human Tregs can exhibit functional plasticity beyond...
converting between various suppressive Treg subsets. Human Treg plasticity may play roles in the dysfunction of Tregs in autoimmune diseases and enhancement of lymphoma. Immune suppression presented in the entity of common variable immune deficiency (CVID) displays high incidence of autoimmune phenomena (28.6%) lymphoma (8.2%) and secondary malignancy (7%). Interestingly IVG replacement didn’t protect against non-infectious and malignant complications [35].

Summary

In conclusion, although NHL and HL and other hematologic malignancies may present with autoimmune paraneoplastic manifestations, the relationship between these disorders is a two-way street with similar pathogenic mechanisms predisposing to the development of both autoimmune and lymphoproliferative disorders. Continued epidemiologic studies and basic immune and genetic investigations are needed to further clarify this complex bi-directional process.

References


