The Dual Association between Lymphoma and Autoimmunity

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ABSTRACT: Autoimmune rheumatic diseases and lymphocytic malignancies are related and this association is bidirectional. Lymphomas occur more frequently in the course of autoimmune disease and autoimmune rheumatic manifestations occur in the course of lymphocytic malignancies. An increased incidence of malignant lymphocytic diseases is present in patients with rheumatoid arthritis, systemic lupus erythematosus, Sjögren’s syndrome, and autoimmune thyroid disease. Descriptions of lymphocytic malignancies among other autoimmune rheumatic diseases have been published. In some patients, the malignant disease is diagnosed months or years before the appearance of the rheumatic disease. © 2001 Academic Press

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INTRODUCTION

The association of immune dysregulation and lymphoma was heightened by the early observations of lymphoma incidence in solid organ transplant patients receiving immunosuppressive drugs. Individuals with inherited or acquired immune dysregulation also have an increased risk of lymphoma. In this setting the association of lymphoma with acquired diseases mediated by cellular immune dysregulation has become of increasing interest because it may speak to the mechanisms of lymphomagenesis in general. A book discussing the interplay of cancer and autoimmunity has detailed these relationships (1). Here we review the studies associating the rheumatic diseases with lymphoma frequency.

RHEUMATOID ARTHRITIS

There is a 1.5- to 8.7-fold increased risk of lymphocytic malignancies in patients with RA compared to the general population (2–5). In a population-based study of 840 patients with cancer found in a cohort of 11,683 Swedes with a diagnosis of rheumatoid arthritis, the relative risk of lymphoma was found to be 1.52 (1.2–1.9) (2). In a study of 20,699 Danish patients with RA, the risk of lymphoma was 1.7 (1.5–2.0) (3). A higher relative risk of lymphoma was reported among men (RR = 10.9) and women (RR = 6.9) with RA (2, 5) and among men with Felty’s syndrome (RR = 8.05) (6). These reports suggest that men with more severe disease have a higher risk of lymphoma but the former may reflect the higher risk of lymphoma in men compared to women in the general population without rheumatic diseases (Table 1).

EFFECT OF THERAPEUTIC AGENTS USED IN RHEUMATOID ARTHRITIS

Cytotoxic drugs used to treat RA may contribute to the development of malignancies. Azathioprine has been suggested to play a role in the increased risk of hematological malignancies (7, 8). Silman et al. followed a group of 202 RA patients treated with azathioprine for a period of 20 years and compared them with a matched group of RA patients, who were not treated with...
this agent (7). Four cases of lymphoproliferative cancers occurred in a group of 202 RA patients treated with azathioprine for a period of 20 years compared with two in the control group (7). This represented an increased risk of lymphoma of 1 case per 1000 patient years of azathioprine treatment. The authors further compared the lymphoma rates with the incidence in the general population, and calculated a fivefold increase in the RA group not receiving azathioprine compared with a 10-fold increase in the azathioprine-treated group. Other studies did not support an association between the use of cytotoxic drugs and the increased frequency of malignancy (9, 10).

Immunosuppressive or cytotoxic drugs are also used in other autoimmune rheumatic diseases, and their deleterious effect may be through induction of chromosomal abnormalities or by facilitating the development of latent chronic infection with EBV and other related viruses. An alternative mechanism could be through malignant transformation of the lymphocytic clones and their expansion as a result of all the immunogenetic mechanisms involved in the pathogenesis of the autoimmune diseases. Genetic predisposition can be based on evidence of a family history or specific HLA-gene association, both of which have been reported in autoimmune diseases, but not in association with lymphoma. A more plausible alternative is the existence of an immunological predisposition for developing malignancies in patients with autoimmune diseases. It appears that the immune dysregulation plays a role in the pathogenesis of autoimmunity and cancer. So far, no satisfactory explanation has been proposed for the increased risk of cancer in autoimmune diseases.

The use of cyclosporin A, and tumor necrosis factor-α inhibitors in the treatment of autoimmune rheumatic diseases has been associated with anecdotal descriptions of development of lymphocytic as well as other types of malignancy. However, there are no data to support an increased risk of lymphoma in these settings. The rates of malignancies are within the expectation for the population involved. Most of the data regarding the risk of neoplasms in patients treated with cyclosporine A derive from transplant recipients while there is little information regarding this issue in patients with autoimmune rheumatic disorders.

### SJÖGREN’S SYNDROME

Primary Sjögren’s syndrome has been shown to be associated with an increased risk of lymphoproliferative diseases (RR = 44), the highest incidence among the autoimmune diseases (11, 12). The onset of the lymphoma may be preceded by angioimmunoblastic lymphadenopathy or pseudolymphoma (13). Sjögren’s syndrome is considered a link between autoimmune and lymphoproliferative diseases. Most lymphomas occurring in patients with Sjögren’s syndrome, are of B-lymphocyte origin, although most cells infiltrating the salivary glands are T cells. The lymphoma risk has been associated especially with extra-glandular features such as splenomegaly, lymphadenopathy, pulmonary infiltrates, renal insufficiency, hypergammaglobulinemic purpura, leukopenia and raised levels of serum β2-microglobulin (14, 15).

Retrospective studies of the incidence of lymphoma in patients with Sjögren’s syndrome yield rates ranging from 1 to 10%. The wide range of variation probably relates to differences in diagnostic criteria and length of follow-up. An epidemiological study showed a standardized incidence ratio of 2.2 for non-Hodgkin’s lymphoma in RA of 4.5 for secondary Sjögren’s syndrome, and of 8.7 for primary Sjögren’s syndrome (16). The study cohort was composed of 676 Finnish pa-
tients with primary Sjögren’s disease, 709 with secondary Sjögren’s syndrome, and 9469 with RA. Younger onset Sjögren’s disease was at a higher risk for developing an associated lymphoproliferative diseases (12, 17).

SYSTEMIC LUPUS ERYTHEMATOSUS

The suggestion that patients with systemic lupus erythematoses (SLE) are at an increased risk of developing lymphoma stems from animal models of SLE, notably the (NZB/NZW)F1 and MRL/lpr mice, that spontaneously develop malignant lymphoma and monoclonal macroglobulinemia (18), and from case reports of patients with SLE who developed lymphoma. Various centers over the world have confirmed the increased risk in large series of SLE patients. Non-Hodgkin’s lymphoma was shown to be significantly increased in SLE patients. The SIR ranged from 5.2 to 44 (19–21). One study identified 24 cancers in 23 SLE patients during 7,233 patient-years follow-up in a cohort of 724 SLE patients followed prospectively for 24 years (19). Although the overall estimated risk for cancer was not increased in this cohort, a 4.1-fold increased risk for hematologic malignancies was observed as a result of the increased frequency of non-Hodgkin’s lymphoma. Furthermore, the increased risk of lymphoproliferative malignancies was found to be unrelated to disease severity or extent of involvement of organ systems (19–23).

Occasional reports of lymphocytic malignancies, especially lymphoma, have been published in association with other autoimmune rheumatic diseases such as scleroderma and myositis and in patients with anti-phospholipid antibody syndrome (24).

VASCULITIS

Approximately 5% of patients with vasculitis have a related malignancy: about two-thirds of them having a hematological malignancy and one-third a solid tumor (25). A study of a long-term experience in one center, demonstrated 12 patients in whom malignancy and vasculitis were recognized within a 12-month period. The most common form of vasculitis was cutaneous leukocytoclastic vasculitis, with 6 of the 12 patients, having lymphoproliferative or myeloproliferative disorders (26). The authors note the importance of the failure of the vasculitis to respond to effective conventional therapy, as a major diagnostic clue.

POTENTIAL MECHANISMS INVOLVED IN CANCER AND AUTOIMMUNITY

Various postulates as to the underlying mechanisms involved in the development of cancer in association with autoimmune rheumatic diseases have been made over the years. These include a common etiologic agent for both diseases, exogenous factors including the use of cytotoxic or immunosuppressive agents, genetic factors favoring a common genetic susceptibility, and immunoregulatory disturbances of the immune system. Some investigators have attributed autoimmune disease-associated lymphoma to chronic stimulation of lymphocytes, which may increase the likelihood of initiating mutations (27, 28).

Another hypothesis suggests the possibility that autoimmunity is basically an antineoplastic process (29). The author suggests that individuals suffering from autoimmune diseases have inherited foci of prematurely aging cells. These damaged cells adapt to challenges by transforming into cancer cells. As long as they have not fully transformed, the cells will continue to signal “danger” to the immune system. The outcome of this response of the immune system to incipient neoplasia varies with the degree of tumor-proneness or resistance of the individual. The author postulates that tumor-proneness and immunity are linked polygenic traits and proposes that HLA-linked autoimmune diseases constitute “chronic hypersensitivity syndromes” representing the antineoplastic immunity, the humoral manifestation of which is the increase in autoantibodies usually found in cancer patients.

AUTOIMMUNITY IN LYMPHOMA

The other end of the spectrum of the interrelationships between lymphatic malignancies and autoimmune rheumatologic disorders includes the
A wide range of autoimmune features that may occur in the course of the lymphoma. These manifestations are at times the first clue to the existence of a hematologic malignancy and may be either due to direct invasion of malignant cells into joints or muscles, or due to a wide range of paraneoplastic syndromes, including classic autoimmune rheumatic diseases (30). The musculoskeletal manifestations of lymphoma include bone pain, which is the most common feature, as well as monoarthritis, polyarthritis, and spinal cord involvement. Cutaneous T-cell lymphoma may present with a chronic nonerosive polyarthritis. Furthermore, these patients may generate autoantibodies against various autoantigens, the clinical significance of which is unclear. Further studies are needed to determine whether those autoantibodies have a diagnostic value and prognostic significance and/or if they can be used to monitor response to a specific antineoplastic therapy. These patients may first present to the rheumatologist.

Tumor associated autoantibodies may bind a variety of antigens including tissue-specific antigens, membrane receptors, tissue restricted antigens, and nuclear proteins. P53 is probably the most widely studied tumor suppressor protein. P53 may become immunogenic among patients with malignancy (31), and is associated with the P53 gene missense mutation. Anti-P53 antibodies have been found in the sera of 21% of patients with B-cell lymphoma (32).

Onconeural antigens are normally identified in the nervous system, but they may be expressed in neoplasia via gene activation or repression. The generation of anti-onconeural antibodies among patients with a malignancy, may result in the development of paraneoplastic neurological syndromes (33, 34). The sera of patients with Hodgkin’s disease and cerebellar degeneration react with the Tr antigen, a new onconeural antigen localized in the Purkinje cells (35, 36).

A variety of autoimmune rheumatic disease-associated autoantibodies have been demonstrated in lymphocytic malignancies and other cancers.

Eighty-four patients with Hodgkin’s lymphoma and 55 with non-Hodgkin’s lymphoma were studied for the presence of autoantibodies to ssDNA, dsDNA, poly(I), poly(G), cardiolipin, histones, RNP, Sm, Ro, La, and the common anti-DNA idiotype (16/6), using an ELISA (37–39). Anti-ssDNA antibodies were detected in the sera of 23.8% of the patients with lymphomas. Anti-RNP and anti-Sm antibodies were found in 21.7 and 20% of the patients, respectively, significantly more than in the controls. No significant difference in the incidence of other autoantibodies examined was when lymphoma patients were compared to healthy subjects. Monoclonal antibodies derived from patients with hematological malignancies, including lymphoma, were found to bind DNA, Sm, RNP, Ro, La, I-Ag, histones, actin, myosin, and others (37, 40–42).

AUTOIMMUNE PARANEOPLASTIC SYNDROMES AND LYMPHOMA

Numerous autoimmune phenomena have been reported in association with hematological and nonhematological malignancies. These features may be regarded as paraneoplastic syndromes or syndromes that cannot be explained by the local effects of the tumor.

Autoimmune hemolytic anemia is the most common autoimmune syndrome found in association with cancer, and is characterized by autoantibodies against red cells leading to an increased rate of destruction of these red blood cells. B-cell lymphomas and leukemias are the malignancies most frequently associated with autoimmune hemolytic anemia, as a result of elaboration of both warm and cold anti-red cell antibodies (43, 44). Glucocorticoid therapy is less efficacious in paraneoplastic autoimmune hemolytic anemia compared to the idiopathic form (45). A study of 501 patients with non-Hodgkin’s lymphoma confirmed that patients who did not develop autoimmune hemolytic anemia had a better overall survival and median survival compared to those who did develop the autoimmune hemolysis (46). The autoimmune hemolytic anemia was a precursor of the malignant lymphoproliferative disorder in some of these patients (47). Among a cohort of 107 patients diagnosed with idiopathic or a secondary autoimmune hemolytic anemia, 19 developed a malignant lymphocytic disorder. Ad-
vanced age, an underlying autoimmune disease, and the presence of a serum gammopathy, were risk factors for future development of the lymphocytic neoplasm in these patients (47).

The mechanisms of the autoimmune hemolytic process secondary to malignancy are unknown but several hypotheses have been suggested: release of tumor-associated antigens inducing antibodies that cross-react with red cell antigens, production of autoantibodies by the tumor itself in the case of B-cell lymphomas, and immune complex adsorption on the membrane of the red cells (45).

Anti-platelet antibodies and autoimmune thrombocytopenia have been associated with lymphoproliferative diseases, especially Hodgkin’s disease. This type of thrombocytopenia has a poor response to glucocorticoids (48, 49). Possible mechanisms leading to the thrombocytopenia, include cross-reaction between a tumor-associated and platelet antigens, or immune complex adherence to platelet membranes (48).

Autoimmune neutropenia is a rare paraneoplastic condition, described occasionally in association with Hodgkin and non-Hodgkin lymphomas. The neutropenia has been related to IgG autoantibodies directed against leukocytes and its precursors in the bone marrow (50–52).

Paraneoplastic neurologic syndromes occur rarely in association with neoplasia. They are triggered by activation of autoimmune mechanisms, specifically generation of anti-onconeural autoantibodies. Motor, sensory, or autonomic peripheral neuropathy may occur. The motor peripheral neuropathies, associated with generation of anti-Hu antibodies, include the Guillain–Barré syndrome which occurs primarily in patients with Hodgkin lymphoma, and anterior horn cell neuropathy occurring in patients with lymphoma. Hodgkin lymphoma has also been associated with subacute cerebellar degeneration and the anti-Yo antibody (type I anti-neuronal antibodies), with ataxia and ocular dysmotility and the anti-Ri antibody (type IIb anti-neuronal antibodies), and with the Isaac’s syndrome associated with the anti-potassium-sensitive channel antibodies (53–57). There are reports also of the stiff-person syndrome associated with Hodgkin’s lymphoma (58, 59).

Paraneoplastic syndromes can involve the kidneys, including membranous nephropathy manifested by nephrotic syndrome and minimal change glomerulopathy. Rapidly progressive glomerulonephritis as well as focal and segmental glomerulonephritis do also occur. Patients with lymphoproliferative neoplasia, mainly with Hodgkin’s disease frequently develop nephrotic syndrome with histological features of minimal change glomerulopathy. Focal and segmental glomerulonephritis have been described in patients with T cell lymphoma (60).

Cutaneous leukocytoclastic vasculitis has been described as a paraneoplastic syndrome associated with lymphoproliferative diseases, as well as with other malignancies, especially in patients over 50 years of age (61, 62).

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