Autoimmune Disease Is a Risk Factor for the Development of Non-Hodgkin's Lymphoma

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ABSTRACT. ***Objective.*** To investigate the relationship of prior autoimmune disease to the development of non-Hodgkin's lymphoma (NHL).

Methods. Patients with NHL (n = 278) seen from 1993 to 2002 were compared with a group of patients with other hematological disorders (controls, n = 317) seen at the same time. All patients were questioned about prior autoimmune disease. Comparisons between NHL patients and controls were based on analysis of a 2×2 table of counts using Fisher's exact test. Analysis of the effect of autoimmune disease on NHL status, controlling for other risk factors, was performed using logistic regression.

Results. Thirty-six (13%) NHL patients had a prior autoimmune disease compared to 5% of controls (p = 0.001). Sixty-nine percent of NHL patients with a prior autoimmune disease were female compared to 43% without a prior autoimmune disease, and this was similar in control patients, 69% and 48%, respectively. Twenty percent of all women with NHL had a history of autoimmune disease compared to 7% of women in the control group (p = 0.001). Nineteen of the NHL patients with autoimmune disease (56%) received immunosuppressive treatment compared to 5 (38%) in the controls.

Conclusion. Autoimmune disease may account in part for the increase in NHL, especially in women. (J Rheumatol 2005;32:1884–7)

Key Indexing Terms:
AUTOIMMUNE DISEASE NON-HODGKIN'S LYMPHOMA EPIDEMIOLOGY

The incidence of non-Hodgkin's lymphoma (NHL) has increased dramatically over the last 20 years[1]. This is most evident in the population over 60 years of age[2]. The reasons for this are likely to be multifactorial and may include a diminution of immune surveillance that occurs with aging. The use of immunosuppressive drugs to control autoimmune diseases decreases immune surveillance and may thereby increase the likelihood of developing NHL[3].

NHL is the malignancy with the greatest increase in frequency in autoimmune disease[4,5]. Rheumatoid arthritis (RA), Sjögren's syndrome (SS), and dermatomyositis are the autoimmune diseases that have been most frequently studied in relation to malignancy. Kinlen reported a 9.7-fold increase of NHL among patients with RA after immunosuppressive therapy, and a 2.5-fold increase in the absence of such treatment[6].

We reviewed the records of our patients with NHL with and without a history of autoimmune disease, and compared them with patients seen during the same time period without NHL. Our goal was to determine the incidence of autoimmune disease in our patients with NHL.

MATERIALS AND METHODS

All patients seen by the senior author (JC) from 1993 to 2002 form the basis of this report. All patients are questioned at their initial consultation about exposure to drugs, toxins, smoking, radiation, etc., as well as any history of malignancy or autoimmune disease. They are questioned a second time when they are asked to consent to have their sera frozen and stored under a unique patient number. This and other information forms part of a computerized data base that has been in place for more than 10 years.

All pathology specimens were reviewed by a hematopathologist using the Revised European American Lymphoma classification system and/or the World Health Organization classification. Patients with NHL were staged using the Ann Arbor staging system[6A]. We compared the NHL patients with another group of patients with other hematological disorders (controls) seen in the same time period (chronic lymphocytic leukemia 90, Hodgkin's 69, multiple myeloma 24, acute myelocytic leukemia 21, myelodysplasia 16, hairy cell leukemia 16, monoclonal gammopathy of undetermined significance 10, thrombocythemia 10, thrombotic thrombocytopenic purpura 9, chronic lymphocytic leukemia 9, and other patients 43). Patients with RA met the criteria of the American College of Rheumatology[7].

Patients with RA, SS, polymyalgia rheumatica, scleroderma, and systemic lupus erythematosus (SLE) were treated by a rheumatologist. The patient with chronic urticaria was diagnosed and treated by an immunologist. The patients with inflammatory bowel disease were treated by a gastroenterologist. The diagnosis of uveitis was made by an ophthalmologist. Thyroid antibodies were present in all patients with autoimmune thyroid disease. Patients with a history of an autoimmune disease were questioned

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for the date of diagnosis and type of treatment. For patients with a history of autoimmune disease, relevant autoimmune tests were performed.

This study was approved by our institutional review board.

Statistical analysis. Comparisons between the NHL patients and controls were based on analysis of a 2 × 2 table of counts using Fisher's exact test. Analysis of the effect of autoimmune disease on NHL status controlling for other risk factors was performed using logistic regression. Analyses were performed using SAS (revised), and all tests and confidence intervals were 2 tailed, at nominal 0.05 level.

RESULTS

There were 278 patients with NHL and 317 patients in the control group. Patients' demographic data are shown in Table 1. Thirty-six (13%) of the NHL patients had an autoimmune disease prior to or at diagnosis of NHL compared to 5% of the controls (p = 0.001). One hundred three (43%) NHL patients without a prior autoimmune disease were female compared to 25 (69%) of those with a prior autoimmune disease. The findings were similar in the control group. Twenty percent of all women with NHL had a history of autoimmune disease compared to 7% of women in the control group (p = 0.001). The median age of the NHL patients was similar: 63 and 63.5 years, respectively, for those without and with a history of autoimmune disease. The median age of the control population was younger, 52 years.

A logistic regression was performed to evaluate simultaneously the effects of sex, age, and autoimmune disease on disease status (NHL vs other). Even adjusting for age and sex, autoimmune disease was significantly more likely to be associated with NHL, with an odds ratio of 2.6 (95% confidence interval 1.4–4.9). Thus, for patients of the same age and sex, patients with autoimmune disease are about 2.6 times more likely to have NHL than controls. The median time from autoimmune disease to the diagnosis of NHL was 10 years; it was 14 years in the control group. Table 2 lists the autoimmune diseases seen.

The 2 most frequent disorders in NHL patients were RA and autoimmune hypothyroidism. Two patients had both SS and Graves' disease. In the control group the most common autoimmune diseases were autoimmune hypothyroidism and inflammatory bowel disease. Tables 3 and 4 show the laboratory findings. All patients with Hashimoto's and/or Graves' disease who were tested had thyroid antibodies. Ten of 32 (31%) of the NHL autoimmune patients had a monoclonal protein compared to 30 of 190 (16%) of the other NHL patients. There were 4 control autoimmune patients with a monoclonal protein, 2 with multiple myeloma, and 2 with a monoclonal gammopathy of undetermined significance. The NHL autoimmune patients were more likely to have had a prior "rheumatologic" disease.

Corticosteroids had been given to 50% of the NHL patients and 34% of the controls. No other immunosuppressive treatment was given to the controls, whereas 8 of the NHL patients received additional immunosuppressive treatment: 3 received 6-mercaptopurine, 3 methotrexate (MTX), one azathioprine, one chlorambucil, 3 gold, and one cyclosporine (p = 0.002).

DISCUSSION

Autoimmunity was first recognized in the early 1950s. Complex autoimmune disease exhibits a lack of tolerance to self-antigens, whereby autoreactive lymphocytes and/or antibodies of the adaptive immune system mount an inflammatory response against various tissues and systems within an individual. The response may be organ-specific, such as Graves' disease, autoimmune hypothyroidism, and inflammatory bowel disease (IBD), or non-organ-specific, such as SLE or RA[8-10]. Together, autoimmune diseases are estimated to be prevalent in 4%–5% of the general population, with most showing a female predominance[11].

The subject of malignancy in autoimmune disease is inseparable from an important hypothesis of cancer etiology, namely impaired immune surveillance. It has become clear that immune surveillance operates, not against all human malignancies, but against a restricted range of neoplasms. NHL is the commonest malignancy related to autoimmune disease[12]. RA affects mainly middle-aged women. NHL is the commonest malignancy associated with RA. This may be related to impaired immune surveillance, chronic immune activation, and/or the use of immunosuppressive drugs. SS, which has a female preponderance, as does RA, commonly occurs in association with other autoimmune diseases[5,13,14]. NHL is a known complication of this disorder. It is postulated that chronic B cell stimula-

Table 1. Findings at diagnosis in NHL patients and controls.

	NHL		Control	
	AIMD, n (%)	Non-Autoimmune n (%)	AIMD n (%)	Non-Autoimmune n (%)
No. of patients	36 (13)	242 (87)	16 (5)	301 (95)
Median age, yrs	63.5 (—)	63 (—)	59 (—)	52 (—)
Female	25 (69)	103 (43)	11 (69)	146 (48)
Extranodal disease	21 (58)	105 (43)	NA (—)	NA (—)
Family history of AIMD	7 (19)	12 (5)	0 (0)	10 (3)

AIMD: autoimmune disease. NA: not applicable.

Table 2. Autoimmune diseases seen in NHL patients and controls.

Autoimmune Disease	NHL, n (%)	Control, n (%)	Female NHL, n (%)	Female Control, n (%)
Rheumatoid arthritis	7 (19)		5 (71)	
Autoimmune hypothyroidism	7 (19)	4 (25)	4 (57)	3 (27)
Graves' disease	4 (11)	3 (19)	3 (75)	2 (18)
Inflammatory bowel disease	4 (11)	4 (25)	3 (75)	2 (18)
Polymyalgia rheumatica	3 (8)	2 (13)	3 (75)	2 (18)
Sjögren's syndrome	2*		2 (100)	
Gluten enteropathy	2 (5.5)		2 (100)	
SLE	1 (2.7)		1	
Scleroderma	1 (2.7)		1	
Polyarteritis nodosa	1 (2.7)		1	
Uveitis	1 (2.7)	1 (6)		
Chronic urticaria	1 (2.7)		1	
AIHA	2 (5.6)	1 (6)		1 (9)
ITP		1 (6)		1 (9)
Psoriasis	1 (2.7)		1	
Pemphigus	1 (2.7)		1	

* Patients also had Graves' disease. SLE: Systemic lupus erythematosus, AIHA: autoimmune hemolytic anemia, ITP: idiopathic thrombocytopenic purpura.

Table 3. Antibody studies in NHL patients and controls.

Autoimmune Disease	Antithyroid Antibodies				Rheumatoid Factor				Other			
	NHL		Control		NHL		Control		NHL		Control	
	No. Tested	No. Positive	No. Tested	No. Positive	No. Tested	No. Positive	No. Tested	No. Positive	No. Tested	No. Positive	No. Tested	No. Positive
Autoimmune hypothyroidism	7	7	2	2								
Graves' disease	3	3	1	1	1	1						
Rheumatoid arthritis	1	1	1	1	5	4						
Polymyalgia	2	1							1 gran[ab]*	1		
IBD	2	0										
SLE									1 ACA	1		
AIHA			1	1					Coombs' +	2	Coombs' +	1
Pemphigus									Antiparietal +	1		

* Granulocyte antibody. IBD: inflammatory bowel disease, SLE: Systemic lupus erythematosus, ACA: anticardiolipin antibody, AIHA: Autoimmune hemolytic anemia.

Table 4. Monoclonal protein in autoimmune patients with NHL.

Disease	IgG kappa		IgM kappa		Other	
	No. Tested	No. Positive	No. Tested	No. Positive	No. Tested	No. Positive
Autoimmune hypothyroidism	7	1	7	0	IgA kappa	1
Graves' disease	2	0	2	1		
Rheumatoid arthritis	6	0	6	0		
Polymyalgia	3	0	3	1		
IBD	3	0	3	0	IgG lambda	1
Urticaria	1	0	1	1		
AIHA	2	0	2	2		
Psoriasis	1	1				
Pemphigus	1	0	1	1		

IBD: inflammatory bowel disease; AIHA: autoimmune hemolytic anemia.

tion eventually results in the production of a malignant clone. NHL of the thyroid almost always occurs in patients with a history of autoimmune hypothyroidism[15]. There has been a dramatic increase in the incidence of NHL[2]. This is especially the case in the population over 60 years of age. These patients commonly present with extranodal disease[16]. NHL has a male predominance. Autoimmune disease, on the other hand, has a female predisposition, occurring mainly in middle-aged or elderly women. The mean age at diagnosis of autoimmune hypothyroidism is 60 years[17]. RA affects women roughly 2 times more often than men. SS affects mainly middle-aged women[18]. Twenty percent of the women with NHL in our study had a history of autoimmune disease. Autoimmune disease may account, in part, for the increase in NHL in women. We found that for patients of the same age and sex, patients with NHL were 2.6 times more likely to have had a prior autoimmune disease than other patients. In our series, 13% of our patients with NHL had a history of autoimmune disease compared to 5% of the controls ($p = 0.001$). They were predominantly female. Of note, one of our control patients first seen in 1996, a woman with autoimmune hemolytic anemia and a monoclonal gammopathy of undetermined significance, developed an indolent NHL in 2003.

About half of the autoimmune NHL patients had had a prior rheumatologic disease and these patients were more likely to have received immunosuppressive drugs. Corticosteroids were given to 50% of the NHL patients and 34% of the controls. There were 7 patients with a history of RA who developed NHL. One received nonsteroidal antiinflammatory drugs and one corticosteroids. Four others received at least 2 additional treatments including gold (n = 3), MTX (n = 3), and azathioprine (n = 1). There were 8 patients with prior IBD, 4 controls, and 4 NHL patients. One control underwent small bowel resection and the other 3 were treated with azulfidine, 5-ASA, and prednisone, respectively. One NHL patient received no specific treatment. All 3 other patients received corticosteroids and in addition 2 received 6-mercaptopurine and one also received cyclosporine. More importantly, only the NHL autoimmune patients received other immunosuppressive treatment. The median time to their development of NHL was 10 years.

It has become common to use potent immunosuppressive drugs in patients with refractory autoimmune diseases. Some patients are being treated with immunosuppressive drugs earlier in their disease course in an effort to prevent disabling sequelae.

Autoimmune disease occurs predominantly in women, some of whom are receiving ever more potent immunosuppressive therapy, which may increase their risk of developing NHL.

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