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ORIGINAL ARTICLE

The prevalence and significance of autoantibodies in patients with non-Hodgkin's lymphoma: are they correlated with clinicopathological features?

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Summary

Purpose: *It is well known that an association exists between the pathogenesis of lymphomas and autoimmune diseases. Autoantibodies are detected at higher frequency in lymphoproliferative diseases, but neither the precise role of the immune system nor the cause of this is comprehensively understood. In this study we evaluated the presence and significance of some autoantibodies for patients with non-Hodgkin's lymphoma (NHL).*

Methods: *150 patients with NHL who had either newly diagnosed disease, or active disease being under chemotherapy or were disease-free during follow-up, were analyzed. The frequency of autoantibodies and the relationship between autoantibodies and several clinicopathological factors were evaluated.*

Results: *The majority of the patients (50%) had diffuse large B-cell lymphoma (DLBCL). Thirty-two patients (21.4%) were newly diagnosed, 81 (54%) had active disease and were receiving chemotherapy and 37 (24.6%) were disease-free and followed-up. Fifty-one patients (34%) had stage IV disease. Antinuclear antibodies (ANA) were found in 7 (4.7%) patients, perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) in 10 (6.7%), anti dsDNA in 1 (0.7%), anti ssDNA in 16 (10.7%), anti Jo-1 in 3 (2%), anti-scleroderma antibody (anti Scl-70) in 4 (2.7%), and rheumatoid factor (RF) in 85 (56.7%) patients. No c-ANCA positivity was found. The mean levels of anti Jo-1 (p=0.028), anti ssDNA (p=0.014), c-ANCA (p=0.015), ANA (p=0.026) and RF (p=0.046) were significantly higher in cases with DLBCL compared to patients with non-DLBCL. In addition, in patients with newly diagnosed NHL the mean levels of anti Scl-70 (p=0.023), anti Jo-1 (p=0.017), and RF (p=0.046) were significantly higher than the other patient groups. No significant correlation was detected between the presence of autoantibodies and other clinicopathological factors.*

Conclusion: *Our results show that the frequency of autoantibodies is high in NHL patients, especially in DLBCL and newly diagnosed cases. Autoantibodies may be helpful for the diagnosis of autoimmune diseases, but regular and long follow-up is needed in NHL patients with high levels of autoantibodies.*

Key words: autoantibodies, autoimmunity, chemotherapy, diffuse large B-cell lymphoma, non-Hodgkin's lymphoma

Introduction

Many reports indicate that both increased and decreased immune function may result in lymphoid malignancies [1-4]. Different types of chronic immune stimulation may end to the development of NHL, including Burkitt's lymphoma in Epstein-Barr virus (EBV) infection [5] and B-cell lymphoma in Sjögren's syndrome [6], due to immune dysregulation, activation of B and T cells, and the generation of a wide range of pathogenic autoantibodies [7,8]. Moreover, in autoimmune diseases there is dysregulated lymphocytic reactivity against self-antigens and the production of autoantibodies, leading to damage of the targeted tissue, such as joints and skin [6].

Accumulated data indicate that the different autoantibodies are found in high levels in lymphoproliferative disease, but neither the precise role of the immune system nor the cause of this is comprehensively understood. However, a relationship between these autoan-

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tibodies and antitumor immunity is assumed by some authors [4,9].

In the present study, we investigated the frequency and significance of some autoantibodies for patients with NHL. In addition, the association of these autoantibodies and related autoimmunity with clinicopathological features in patients with NHL were also analyzed.

Methods

A total of 150 patients with NHL diagnosed at Dr Lutfi Kirdar Kartal Education and Research Hospital, between June 2009 and November 2010, were evaluated. All patients were staged according to the Ann Arbor staging system by clinical and radiological studies. Patients were categorized into 3 groups: those with newly diagnosed disease, those receiving chemotherapy, and those being disease-free during their follow-up. Before or after treatment, patients were asked about the presence of specific signs or symptoms related to autoimmune diseases. In addition, development of joint pain or swelling, arthritis, mucosal dryness, persistent rashes and morning stiffness, myalgia, diarrhea, mouth ulcers, genital ulcers were recorded.

The clinicopathological characteristics of the patients such as age at diagnosis, gender, clinical stage, performance status, presence of B symptoms, histopathological subtype, grade (high or low), chemotherapy and total treatment cycles, radiation therapy details, and response to treatments were obtained from the patients' charts after written informed consent had been obtained from patients or their relatives. Patients who had insufficient disease information were excluded from data analysis.

Collection of serum samples

Fifteen milliliters of venous blood were collected from 150 patients with NHL and centrifuged at 4000 g for 10 min to obtain serum within 1.5 h after blood sampling. All serum samples were stored at –80° C until evaluation. Serum ANA, c-ANCA, p-ANCA, anti Scl-70, anti dsDNA, anti ssDNA, anti Jo-1, RF, C-reactive protein (CRP), lactate dehydrogenase (LDH) levels and erythrocyte sedimentation rate (ESR) were measured and mean values were compared.

Analysis of autoantibodies

ELISA kit (Trinity Biotech, USA) was used to detect the p-ANCA (myeloperoxidase), anti Scl-70, anti dsDNA and anti Jo-1. Each ELISA kit was designed to detect IgG, IgM and IgA antibodies to antigens related to the kit. Values ≤0.90 ELISA units (EU)/mL were characterized as negative, 0.91-1.09 EU/mL as suspicious and ≥ 1.10 EU /mL as positive. All suspicious results were reanalyzed. ANA were detected by ELISA (Trinity Biotech kit, USA). Values <1.0 EU/ml were characterized as negative, while values >1.0 EU/mL were accepted as positive. c-ANCA (anti proteinase-3) was detected by ELISA (IMMCO Diagnostics kit, USA). Antibodies to proteinase-3 antigen were identified using this method. Values ≤ 20 EU/mL were interpreted as negative, 20-25 EU/mL as suspicious and ≥ 25 EU/mL as positive. All suspicious results were confirmed after reanalysis. RF was analyzed using ELISA (IMMCO Diagnostics kit, USA) that could detect IgA, IgG and IgM class RF. Values< 20 EU/mL were interpreted as negative, and those > 20 EU/mL as positive. Aida (Autoimmune Diagnostic Assays, Germany) ELISA kit was used to determine anti-ssDNA. It was designed for the measurement of IgG class autoantibodies directed against ssDNA. Values <16 EU/mL were accepted as negative, 16-24 EU/mL as suspicious and > 24 EU/mL as positive. All suspicious results were restudied. All values were recorded as both qualitative and quantitative.

Blood samples for ESR were collected into Vacuplus-ESR tubes containing sodium citrate (3.2% sodium citrate: blood ratio 1:4). ESR was measured continuously via infrared sensors on ESR-30 analyzer (normal range 6-12 cm/h). CRP was analysed by immunonephelometry on Dade Behring BN 2 nephelometer (normal range 0-5 mg/dL). LDH was photometrically measured by enzymatic colorimetric assay method on Roche Hitachi Modular P analyzer (normal range ranges 240-480 mg/dL).

Statistical analyses

Statistical analyses were performed using SPSS 13.0 software (SPSS Inc., Chicago, IL, USA). Descriptives of the parameters were quoted as mean ± SD (standard deviation) and 95% confidence interval (95% CI). Parameters non-normally distributed were compared with Mann-Whitney U and Kruskal-Wallis tests. The relationship between autoantibodies and patient groups was analyzed by the chi-square test and Fisher's exact test. All p values were two-sided and p values ≤ 0.05 were considered statistically significant.

Results

Sixty-five patients (43.3%) were women and 85 (56.7%) men, with median age 56 years (range 17-87). The majority of the patients (n=75; 50%) had DLBCL histology. Other histologies included 26 patients (17.3%) with small lymphocytic lymphoma (SLL), 12 (8%) with follicular lymphoma, 6 (4%) with mantle cell lymphoma, 6 (4%) with Burkitt's lymphoma, 9 (6%) with extra marginal-zone lymphomas (EMZL), 3 (2%) with T-cell lymphoma, 4 (2.7%) with primary CNS lymphoma and 9 (6%) with other rare histologies. According to the Ann Arbor staging system, 39 (27.4%) patients were classified as stage I, 31 (20.6%) as stage II, 27 (18%) as stage III as and 51 (34%) as stage IV. Sixty-six (44%) of the patients had B symptoms at diagnosis. According to the categorization of patients into 3 groups, the majority of them (n=81; 54%) had active disease when receiving chemotherapy, 32 (21.4%) were newly diagnosed and 37 (24.6%) were disease-free during their follow-up. Patient and disease characteristics are shown in Table 1.

No patient had family history of autoimmune diseases. Only 9 (6%) patients had a history of arthritis localized bilaterally in wrist and ankle before treatment. Of these 9 patients only 2 with NHL had a history of RA. Arthralgia was the most common symptom (23.3% of the patients) before chemotherapy, while the most common symptoms or findings were oral aphthae (25.3%) and xerostomia (22%) during treatment, possibly related to chemotherapy or to radiotherapy. Furthermore, xerostomia was the most frequent symptom both before

Table 1. Patient and disease characteristics

Characteristics	*N (%)*
All patients	150 (100)
Age, years, median (range)	56 (18-87)
≤50	56 (37.3)
>50	96 (62.7)
Gender	
Male	85 (56.7)
Female	56 (43.3)
Histopathologic type	
Diffuse large B-cell lymphoma	75 (50)
Small lymphocytic lymphoma	26 (17.3)
Follicular lymphoma	12 (8)
Mantle cell lymphoma	6 (4)
Burkitt's lymphoma	6 (4)
EMZL	9 (6)
T-cell lymphoma	3 (2)
Primary CNS lymphoma	4 (2.7)
Others	9 (6)
Ann Arbor stage	
I	39 (27.4)
II	31 (20.6)
III	27 (18)
IV	51 (34)
B symptoms	
Present	66 (44)
Absent	84 (56)
Disease groups	
Newly diagnosed	32 (21.4)
Currently treated	81 (54)
Follow-up after treatment	37 (24.6)

EMZL: extra marginal-zone lymphomas, CNS: central nervous system

and during treatment. No relationship between the presence of rheumatological symptoms or findings and autoimmune diseases was found (p>0.05). Table 2 shows the distribution of rheumatological symptoms or findings before and after chemotherapy or before and during treatment.

Of the patients, 126 (84%) disclosed positivity for one or more autoantibodies. Seven (4.7%) patients showed ANA positivity, while p-ANCA positivity was detected in 10 (6.7%) patients. In addition, 4 (2.7%) patients with positive anti Scl-70, 1 (0.7%) with positive anti dsDNA, 16 (10.7%) with positive anti ssDNA, 3 (2%) with positive anti Jo-1 and 85 (56.7%) with positive RF were detected. No c-ANCA positivity was found. Table 3 shows the qualitative distribution of autoantibodies in patients with NHL. Mildly elevated CRP levels were detected in 38 (25.3%) patients, while elevated CRP levels were found in 25 (16.7%). ESR was determined as mildly elevated in 36 (24%) patients and as elevated in 22 (14.7%). The LDH levels were high in only 41 (27.3%) patients. Distribution of CRP, ESR and LDH levels are summarized in Table 4.

After the patients were divided into 2 groups according to the histopathological subtype (DLBCL vs. non-DLBCL), the quantitative levels of autoantibodies, CRP, ESR and LDH were compared. The mean levels of anti Jo-1 (p=0.028), anti ssDNA (p=0.014), c-ANCA (p=0.015), ANA (p=0.026) and RF (p=0.046) were significantly higher in cases with DLBCL compared to patients with non-DLBCL (Table 5).

No significant relationship was detected between mean levels of autoantibodies and the presence of B symptoms, age (≤50 vs. >50 years) and the other clini-

Table 2. Distribution of rheumatological symptoms or findings before treatment, after chemotherapy or in both periods in patients with NHL

Symptoms or findings	*Before treatment N (%)*	*After chemotherapy N (%)*	*Both periods N (%)*
Arthritis	9 (6)	–	–
Arthralgia	35 (23.3)	–	–
Morning stiffness and pain	21 (14)	–	–
Generalized myalgia	6 (4)	4 (2.7)	21 (14)
Muscle weakness	4 (2.7)	6 (4)	14 (9.3)
Xerostomia	15 (10)	33 (22)	34 (22.7)
Xerophthalmia	4 (2.7)	8 (5.3)	17 (11.3)
Oral aphthae	16 (10.7)	38 (25.3)	9 (6)
Oral aphthous ulcers	1 (0.7)	3 (2)	5 (5.3)
Genital aphthae	3 (2)	4 (2.7)	1 (0.7)
Genital ulcers	1 (0.7)	1 (0.7)	1 (0.7)
Photosensitivity	1 (0.7)	1 (0.7)	8 (5.3)
Photophobia	2 (1.3)	1 (0.7)	13 (5.7)

Table 3. Qualitative distribution of autoantibodies in patients with NHL

Autoantibodies	*Positive N (%)*	*Negative N (%)*
ANA (IU/mL)	7 (4.7)	143 (95.3)
p-ANCA (IU/mL)	10 (6.7)	140 (93.3)
c-ANCA (IU/mL)	–	150 (100)
Anti dsDNA (IU/mL)	1 (0.7)	149 (99.3)
Anti ssDNA (IU/mL)	16 (10.7)	134 (89.3)
Anti Jo-1 (IU/mL)	3 (2)	147 (98)
Anti Scl (IU/mL)	4 (2.7)	146 (97.3)
RF (IU/mL)	85 (56.7)	65 (43.3)

For abbreviations see text

Table 4. Distribution of CRP, ESR and LDH levels in patients with NHL

Parameters	*Mildly elevated N (%)*	*Elevated N (%)*	*Normal N (%)*
CRP (mg/L)	38 (25.3)	25 (16.7)	87 (58)
ESR (mm/h)	36 (24)	22 (14.7)	92 (61.3)
LDH (U/L)	41 (27.3)	–	109 (72.7)

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, LDH: lactate dehydrogenase

Table 5. Quantitative distribution of antibodies and CRP, ESR and LDH levels in patients with NHL according to histopathology

Parameters	*DLBCL mean±SD*	*Non-DLBCL mean±SD*	*p-value*
ANA (IU/mL)	0.75±0.34	0.39±0.41	0.026*
p-ANCA (IU/mL)	0.47±0.25	0.50±0.38	0.632
c-ANCA (IU/mL)	1.34±0.76	1.19±0.89	0.015*
Anti dsDNA (IU/mL)	0.28±0.14	0.26±0.18	0.107
Anti ssDNA (IU/mL)	12.2±8.7	10.1±8.7	0.014*
Anti Jo-1 (IU/mL)	0.31±0.23	0.29±0.33	0.028*
Anti Scl (IU/mL)	0.31±0.24	0.30±0.31	0.166
RF (IU/mL)	32.0±30.6	30.0±27.3	0.535
CRP (mg/L)	21.6±19.6	26.9±20.5	0.892
ESR (mm/h)	34.1±27.5	30.7±28.2	0.148
LDH (U/L)	452.8±251.4	427.3±166.4	0.801

*Statistically significant, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, LDH: lactate dehydrogenase, RF: rheumatoid factor, DLBCL: diffuse large B-cell lymphoma, SD: standard deviation. For the rest of the abbreviations see text

copathological factors (p>0.05). The mean levels of anti Scl-70 (p=0.023), anti Jo-1 (p=0.017), RF (p=0.046), CRP (p=0.001), ESR (p=0.022) and LDH (p=0.028) were significantly higher in patients who had newly diagnosed NHL (Table 6).

Only 2 patients had a history of RA before the diagnosis of NHL. However, when clinical signs and findings related to autoimmune diseases and the results of autoantibodies were analyzed at the end of the follow-up period, none of the patients with positive autoantibodies developed autoimmune disease.

Discussion

Chronic immune stimulation such as *Helicobacter pylori* infection, Sjögren's syndrome or coeliac disease may initiate NHL [5,6]. Therefore, altered expression of autoantibodies is to be expected in NHL. It has been documented that different autoantibodies, such as ANA [10] or lupus anticoagulants [11], anti ssDNA and anti-histones [12,13] are prevalent in lymphoid malignancies. In the present study, we found that 126 (84%) patients with NHL disclosed positivity for one or more autoantibodies. Of the patients, 85 (56.7%) had positive RF, while no c-ANCA positivity was detected. In addition, elevated CRP levels were found in 25 (16.7%) patients, ESR was elevated in 22 (14.7%) patients and LDH levels were high in only 41 (27.3%) patients. Also, the mean levels of anti Jo-1, anti ssDNA, c-ANCA, ANA and RF were significantly higher in cases with DLBCL compared to non-DLBCL. Furthermore, the mean levels of anti Scl-70, anti Jo-1, RF, CRP, ESR and LDH were significantly higher in patients with newly diagnosed NHL.

Different autoimmune conditions including autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, autoimmune neutropenia, different dermatological syndromes, thyroid abnormalities and musculoskeletal abnormalities have been reported in association with hematological malignancies [6,9]. It is known that autoimmune diseases and lymphocytic malignancies are bidirectionally related and lymphomas develop more frequently in the course of autoimmune diseases. In addition, signs and symptoms of autoimmune diseases occur in the course of lymphoma [6]. The relationship between immune dysregulation and the development of lymphomas has been documented and different types of chronic immune stimulation may also lead to development of NHL by immune dysregulation, activation of B and T cells, and the generation of a wide range of abnormal autoantibodies may be related with malignant transformation [6-8]. Different autoantibod-

Table 6. Quantitative distribution of antibodies and RF CRP, ESR and LDH levels in patients with NHL according to the patient groups

Parameters	*Group 1 n=32 mean±SD*	*Group 2 n=37 mean±SD*	*Group 3 n=81 mean±SD*	*p-value*
ANA (IU/mL)	0.42±0.33	0.43±0.37	0.70±0.27	0.905
p-ANCA (IU/mL)	0.54±0.33	0.42±0.22	0.50±0.35	0.447
c-ANCA (IU/mL)	1.37±0.92	1.23±0.77	1.19±0.82	0.531
Anti dsDNA (IU/mL)	0.31±0.16	0.29±0.15	0.25±0.16	0.026*
Anti ssDNA (IU/mL)	10.4±8.1	10.1±8.0	11.9±8.3	0.189
Anti Jo-1 (IU/mL)	0.33±0.28	0.32±0.14	0.29±0.19	0.017*
Anti Scl (IU/mL)	0.32±0.19	0.31±0.21	0.30±0.23	0.023*
RF (IU/mL)	36.7±30.7	33.2±27.7	27.7±19.6	0.046*
CRP (mg/L)	37.9±29.6	6.7±4.5	27.0±19.5	0.001*
ESR (mm/h)	46.6±26.5	25.8±14.9	29.7±20.8	0.022*
LDH (U/L)	477.2±301.2	376.3±144.3	454.5±192.7	0.028*

Group 1: newly diagnosed patients, Group 2: patients on follow-up after treatment, Group 3: currently treated with chemotherapy, *Statistically significant. For abbreviations see footnote of Table 5

ies are biological indicators of autoimmunity and are found at a higher frequency in lymphomas, but neither their precise role nor the cause of this condition is fully understood [3,4,14]. On the other hand, autoantibodies are produced in systemic autoimmune diseases and they can serve as indicators of autoimmune diseases, which may occur before the onset of clinical signs and findings. These autoantibodies are not specific for autoimmune diseases and they can be produced in different clinical conditions, as well as in some healthy people. A high titer of ANA is significant for connective tissue diseases, but ANA positivity is found in 10-15% of healthy people over the age of 65 years [15].

Guyomard et al. [10] evaluated 347 patients with NHL before any specific treatment and 213 controls with respect to ANA positivity and found that ANA positivity was significantly higher in patients with NHL (19%) compared to the control groups (5.6%; $p<0.001$). In addition, the frequency of ANA positivity was high in follicular and mantle cell lymphomas. During follow-up, 7 patients were diagnosed with typical autoimmune diseases. Timuragaoglu et al. [16] analyzed the autoimmune phenotype of 64 patients with NHL. In 39% of the patients positivity for one or more autoimmune markers was determined. The authors reported that 7 patients displayed ANA positivity, but no significant relationship was found between ANA positivity and any clinical features in NHL patients. In the present study, we detected ANA positivity in 7 (7%) patients, which was lower compared with previous reports [10,16]; however, the mean ANA levels in patients with DLBCL were significantly higher compared with non-DLBCL. In addition, our study included newly diagnosed patients, similarly to the study of Guyomard et al. [10], but no significant differences were found between our 3 patient groups according to the mean ANA levels.

Swissa et al. analyzed 84 patients with Hodgkin's lymphoma (HL) and 55 patients with NHL 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 ELISA [4] and found that anti ssDNA was positive in 16 patients with NHL and in 4 patients with HL, the difference being significant ($p<0.01$). The frequency of anti RNP and anti Sm antibodies in lymphoma patients were significantly higher compared with healthy controls, while no significant difference was found with respect to the other autoantibodies between lymphoma patients and healthy controls. In our study, we detected anti dsDNA positivity in only 1 patient and anti ssDNA positivity in 10.7% of the patients. The frequencies of anti dsDNA and anti ssDNA positivity were low, in contrast to the study of Swissa et al. [4], but the mean anti ssDNA levels in DLBCL patients were significantly higher than in patients with non-DLBCL.

In our study, 126 patients (84%) showed positivity for autoantibodies, and 85 (67.5%) of them displayed RF positivity. Only 2 patients had a history of RA before the diagnosis of NHL, and at the end of follow-up period RA was developed in an additional 2 patients. The majority of our patients were over 50 years of age and this factor might influence RF positivity. Positivity of the remaining autoantibodies was detected in 41 (27.3%) patients. In their study Altintas et al. found 28.5% positivity for autoantibodies in NHL patients receiving treatment [17]. Our findings were thus compatible with their results. However, these authors analyzed only patients receiving chemotherapy, whereas we included patients with newly diagnosed or active disease during chemotherapy or being disease-free during follow-up. Twenty-nine of 41 patients who had positive autoantibodies were with active disease and under treatment. Therefore, it could be argued that treatment might trigger autoantibodies positivity because of increased autoimmunity in lymphoproliferative disorders. On the other hand, the mean levels of anti Scl-70, anti Jo-1 and RF were significantly higher in patients who had newly diagnosed NHL, in contrast to the study of Altintas et al. [17].

In a study conducted by Timuragaoglu et al. the authors found mildly elevated levels of autoantibodies in patients with low grade and disseminated NHL [16]. In the current study, we detected that the mean levels of anti Jo-1, anti ssDNA, c-ANCA, ANA and RF were significantly higher in cases with DLBCL compared to patients with non-DLBCL. In their analysis Guyomard et al. also found that ANA levels were especially high in follicular and mantle cell lymphomas [10]. Our findings were not similar to their results. In our study, 50% of the patients had DLBCL histology, but follicular and mantle cell lymphoma patients comprised only 12% of NHL patients and this might influence our results.

The small sample size and short follow-up time of our study could be considered as significant limitation and might have influenced these results. Moreover, this study did not include healthy controls. Although our results should be confirmed by prospective studies, we believe that they contribute to the literature because the study included NHL patients who had newly diagnosed NHL, active disease under chemotherapy or were disease-free during follow-up.

In conclusion, our study shows that the frequency of autoantibodies is high in patients with NHL. In addition, the mean levels of anti Jo-1, anti ssDNA, c-ANCA, ANA and RF were significantly higher in cases with DLBCL compared to patients with non-DLBCL. Also, the mean levels of anti Scl-70 and anti Jo-1 were sig-

nificantly higher in patients who had newly diagnosed NHL. Although NHLs are associated with autoimmunity, the present study showed no manifestation of autoimmune disease, irrespective of elevated autoantibodies. Autoantibodies may be helpful for the diagnosis of autoimmune diseases, but regular and long follow-up is warranted in NHL patients with elevated autoantibodies. Prospective studies including healthy controls are necessary to shed light to these contradictory results.

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