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ORIGINAL ARTICLE

Serum levels of cytokines and prevalence of autoantibodies in lymphoma patients and their prognostic value

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Summary

Purpose: *Recent studies have shown that cytokines and autoantibodies that have an important role in pathogenesis of lymphoma can be used as prognostic markers. In this study, we aimed to determine the prognostic significance of a large panel of serum cytokines and compare them with a control group, and also to see for any relationship with known classical prognostic factors, the frequency of autoantibody positivity and autoimmune phenomena in patients with untreated non Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL).*

Methods: *For cytokine studies blood samples were obtained in the morning after fasting for at least 8-12 h. We used empty tubes for serum and EDTA-containing tubes for plasma samples. Blood samples were then transferred to laboratory in 5-10 min, plasma and sera were separated by centrifugation, and stored at -75 ºC until assayed. Then, all sera were warmed to room temperature. All the cytokine levels were studied with Panomics Company Procarta™ Human Cytokine multiplex kits.*

Results: *In lymphoma patients INF-γ was related with thyroglobulin antibody positivity and IL-6 with direct Coombs positivity. IL-6 was the most important cytokine connected with lymphopenia and B symptoms in lymphoma patients. IL-1ß, INF-γ, IL-2 and IL-4 were markers associated with poor prognosis in HL. At least one autoantibody was positive in 50% of NHL and HL patients. At least one antiphospholipid antibody (APA) was positive in 26% of NHL and 38% of HL patients.*

Conclusion: *TNF-α and IL-6 are poor prognostic factors that may be included in the International Prognostic Index (IPI). To understand the effects of autoantibodies in the prognosis of HL and NHL, long-term patient follow-up studies are required.*

Key words: *autoantibodies, cytokines, lymphoma, prognosis*

Introduction

Various clinical and laboratory parameters have been defined and are used in the prognostic definition of NHL and HL [1,2]. Recent studies have shown that cytokines that have an important role in the pathogenesis of lymphoma can be used as prognostic markers. Cytokines associated with poor prognosis are IL-2, IL-4, IL-6, IL-8, IL-10, sIL-2R, TNF-α and sTNF-R2 in aggressive NHL; and IL-6, IL-10, IL-13, TNF-α, sTNF-RI in HL [1-9].

Not all lymphoma patients have a malignant clone [10]. There are autoimmune diseases that develop in relation with autoantibodies or foreign antibodies. In a study the median survival was shorter in autoantibody-positive NHL patients than in the negative ones [10]. NHL patients with high levels of APAs have a shorter life expectancy. APAs are shown to be independent prognostic markers for NHL patients [11,12].

There is only a limited number of studies investigating the relationship between autoantibody positivity and cytokine levels in lymphoma patients. In this study, we aimed to determine a large panel of serum cytokine levels including IL-1ß, IL-2, IL-4, IL6, IL-10, IL-13, IL-17, INF-γ, GM-CSF and TNF-α, their prognostic significance, comparison with a control group, relationship with known classical prognostic factors, the frequency of autoantibody positivity and autoim-

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mune phenomena in patients with NHL and HL and evaluate the relationship of cytokines and autoantibodies in untreated NHL and HL patients.

Methods

Patients and controls

This study was performed between April 2006 - October 2007 in the Hematology Division of Osmangazi University Medical Faculty Internal Medicine Department. Eskisehir Osmangazi University Faculty of Medicine ethics committee gave approval (2007/236-382) and informed consent including necessary explanations were obtained from all patients in this study. The study included a total of 54 lymphoma patients (38 NHL and 16 HL) who were newly diagnosed, untreated and had not used steroids in the last month. A control group included 26 healthy individuals, not taking any medication, not having any acute or chronic disease and not having fever in the last week.

Patients receiving chemotherapy and having used steroids in the last month were excluded from the study. In the control group people taking any medication, having any acute or chronic disease or having fever in the last week were excluded from the study.

Clinical and laboratory evaluations

Antinuclear antibodies (ANA), anti-dsDNA, extractable nuclear antigen (ENA) panel, lupus anticoagulant, anticardiolipin antibody (ACA)-IgG and IgM, thyroid function tests, antithyroglobulin antibodies, antimicrosomal antibody, antiparietal antibody, p-and c-antinuclear cytoplasmic antibodies (ANCA), hepatitis B and C, and direct-globulin tests were performed. In all cases, the blood samples were taken in the morning after fasting for at least 8-12 h. Routine tests were performed immediately. For cytokine studies blood samples were obtained in the morning after fasting for at least 8-12 h. We used empty tubes for serum and EDTA containing tubes for plasma samples. As soon as blood samples were put into tubes they were transferred to laboratory in 5-10 min, plasma and sera were separated by centrifugation at 3000 rpm, +4 ºC, for 10 min and stored at -75 ºC until assayed.

Then all sera were warmed to room temperature. IL-1ß, IL-2, IL-4, IL6, IL-10, IL-13, IL-17, INF-γ, GM-CSF and TNF-α cytokine levels were studied with Panomics Company Procarta™ Human Cytokine multiplex kits. ANA were evaluated by immunofluorescence microscopy. Anti-dsDNA, ACA-IgG, and IgM were evaluated with the ELISA method in Grifols Triturus analyzer (Barcelona, Spain). Lupus anticoagulant was evaluated with coagulometric method by using ACL Top analyzer using interleukin kits.

Statistics

For statistical evaluation of the findings of this the study the SPSS for Windows, version 15.0, was used. A p value of <0.05 was considered statistically significant at 95% confidence interval. Quantitative variables were expressed as mean ± standard deviation (SD). Assumptions of normality were tested with the Shapiro Wilk test. We used parametric tests for data with normal distribution, and non-parametric tests for data with non-normal distribution. Student's t-test, Fisher's exact test, and Mann-Whitney U test were used for comparison of two independent groups. Chi-square was used for analysis of cross tables. Spearman's correlation coefficients were used to determine the relationships between the variables.

Results

Of the 54 patients 38 (70%) had NHL (19 female, 19 male) and 16 (30%) HL (6 female,10 male). The mean patient age was 53.7±17.1 years (range 18-90). It was 60.6 ± 13.9 years (range 25-90) for NHL patients, and 37.5±12.4 years (range 18-65) for HL patients. The control group included 26 healthy individuals (10 female,16 male) with mean age 48.6±5.3 years (range 40-63). When serum cytokine levels of the control group and lymphoma patients were compared, the evaluated cytokine levels (TNF-α, IL-2, IL-6,IL-1 ß, INF-γ, IL-4, IL-10, IL-13, IL-17 and GM-CSF) were higher in the patient group, but only serum IL-6 (median 2.86 pg/ml; range, undetectable to 18.01 pg/ml), TNF-α (median 2.35 pg/ml; range, undetectable to 26.41 pg/ml) and INF-γ (median 12.95 pg/ml; range, undetectable to 384.39 pg/ml) showed statistically significant differences between these groups (p<0.001, p<0.01 and p<0.05, respectively). Cytokine levels in the control group were IL-6 (range undetectable to 1.45 pg/ml), TNF-α (range undetectable to 1.28 pg/ml), INF-γ (range, undetectable to 30.01 pg/ml).

When ACA-IgG and IgM antibody levels were compared between lymphoma patients and the control group both ACA-IgG and ACA-IgM were found higher, but only ACA-IgG [IgG→antiphospholipid units/ml (gpl/ml)] 10.09±8.16 was significantly higher compared with the control group (3.29±2.31; p<0.001). IL-2 levels were significantly higher in lymphoma patients with arthralgia (Fisher's exact test, p <0.05).

Hemoglobin and albumin levels were significantly lower in NHL patients having high levels of IL-6 (p<0.01, p<0.001 respectively). Positive correlation with high levels of IL-6 was found with beta-2 microglobulin, ESR, CRP, lymphopenia, hypogammaglobulinemia, advanced stage and high IPI score and poor ECOG performance status in NHL patients (p<0.05, p<0.05, p<0.001, p<0.01,

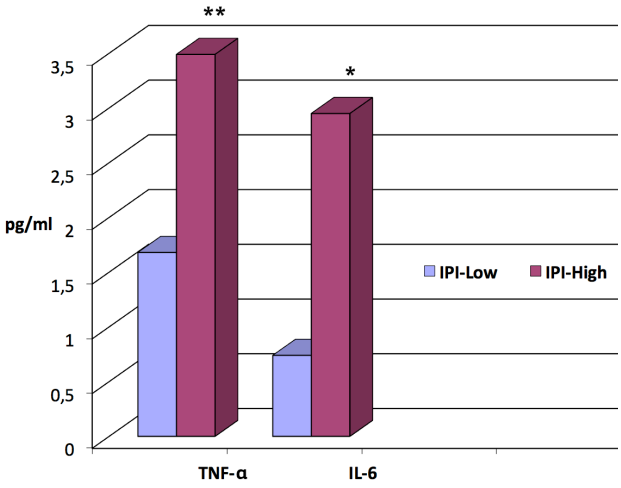

Figure 1. Serum IL-6 and TNF-α levels in non-Hodgkin's lymphoma patients with International Prognostic Index (IPI) high-risk and low-risk groups (* p <0.05, ** p <0.01).

p<0.05, p<0.01, p<0.05, p<0.001 respectively).

In NHL patients with high levels of TNF-α, anemia and high IPI score TNF-α levels were statistically significant high (p<0.05, p<0.001).

Also in NHL patients with high levels of INF-γ, HCV-positive patients were more frequently seen (p<0.05).

In NHL patients with hypogammaglobulinemia high levels of IL-6 and IL-17 and high levels of CRP were found (p<0.05, p<0.001, p<0.05, respectively).

NHL patients with high LDH levels were found to have more advanced stage, poor ECOG performance status, high IPI scores and higher relapse rates (p<0.05, p<0.05, p<0.001, p<0.05, p<0.01, respectively).

In NHL patients with high beta-2 microglobulin levels, high IL-6 levels (p<0.05) and increased mortality rates were found (p<0.001).

When patients were evaluated in terms of the IPI score, the cytokines TNF-α and IL-6 were higher in those with elevated IPI group (Figure 1); in NHL patients with high ESR, CRP, LDH, beta-2 microglobulin levels, advanced stage, poor ECOG performance status, advanced age, higher number of involved extra-nodal sites, lower albumin and hemoglobin levels, the IPI score was significantly higher. In these patients the relapse and mortality ratios were significantly higher (p<0.05 for both).

The percentage of B symptoms seen in patients with NHL and HL were also high in both groups (76% and 75%, respectively). Table 1 shows the relationship between B symptoms and INF-γ, TNF-α, IL-1β and IL-6.

In HL patients with high levels of TNF-α, hypogammaglobulinemia was more frequently seen (p<0.05).

Also, in HL patients significant correlation was detected between serum IL-2 level and IL-1ß, INF-γ, IL-4 and IL-10 (p<0.01, p<0.01, p<0.01, p<0.01, respectively); also, hepatitis B positivity and relapse rate were statistically significant when correlated with serum IL-2 levels (p<0.01 for both).

In HL patients with anemia, elevated ESR, CRP, hypoalbuminemia, positive direct Coombs, and IL-6 were significantly higher (p <0.05, p <0.05, p<0.01, p <0.05, p <0.01, respectively).

When absolute lymphocyte counts of lymphoma patients were grouped into 2 categories (0-1000 and > 1000/ml), significantly higher IL-6 and LDH levels were found in patients with absolute lymphocyte count of <1000 (p<0.01, p<0.05, respectively).

No lymphoma patient had positive ANA, anti-dsDNA and ENA panel. Fifty percent of NHL and HL were positive for at least one of the autoantibodies.

The most frequent autoantibodies in patients with NHL was direct Coombs (27%), followed by the lupus anticoagulant (21%). The most frequently detected autoantibody in patients with HL was lupus anticoagulant (36%), followed by direct

Table 1. Comparison of serum INF-γ, TNF-α, IL-1β and IL-6 levels with the control group in relation to B symptoms in Non-Hodgkin's lymphoma and Hodgkin's lymphoma patients

Lymphoma	*INF-γ*	*TNF-α*	*IL-1β*	*IL-6*
Non-Hodgkin lymphoma	6/38 (16%)	15/38 (40%)	2/38 (5%)	23/38 (61%)
B symptoms (+) (29/38)	3/6	13/15	1/2	20/23
B symptoms (-) (9/38)	3/6	2/15	1/2	3/23
Hodgkin lymphoma	1/16 (6%)	2/16 (13%)	1/16 (6%)	6/16 (38%)
B symptoms (+) (12/16)	0/1	1/2	0 /1	5/16
B symptoms (-) (4/16)	1/1	1/2	1 /1	1/16
Control	0/26	0/26	0/26	0/26
x^2, p	<0.05	<0.001	>0.05	<0.01

Table 2. Autoantibodies, hepatitis and hypogammaglobulinemia in Hodgkin lymphoma and Non-Hodgkin lymphoma patients

Hodgkin lymphoma Number of positive patients, (%)		*Non-Hodgkin lymphoma Number of positive patients, (%)*	
ANA (N=15)	0 (0)	ANA (N=38)	0 (0)
Anti DNA (N=15)	0 (0)	Anti -dsDNA (N=38)	0 (0)
ENA panel (N=15)	0 (0)	ENA panel (N=38)	0 (0)
Lupus anticoagulant (N=14)	5 (36)	Lupus anticoagulant (N=38)	8 (21)
Anticardiolipin IgG (N=15)	1 (6.6)	Anticardiolipin IgG (N=37)	4 (10.8)
Anticardiolipin IgM (N=15)	1 (6.6)	Anticardiolipin IgM (N=37)	2 (5.4)
Direct coombs (N=15)	5 (33)	Direct coombs (N=37)	10 (27)
Antiparietal antibody (N=15)	1 (6.6)	Antiparietal antibody (N=35)	3 (8.6)
Hepatitis sAg (N=16)	1 (6.3)	Hepatitis B Ag (N=38)	3 (7.9)
Hepatitis C (N=16)	0 (0)	Hepatitis C (N=38)	1 (2.6)
Antithyroglobulin (N=13)	0 (0)	Antithyroglobulin (N=33)	5 (15.2)
Antimicrosomal antibody (N=13)	2 (15.4)	Antimicrosomal antibody (N=33)	3 (9.1)
Hypogammaglobulinemia (N=15)	2 (13)	Hypogammaglobulinemia (N=37)	5 (14)

Table 3. Autoimmune diseases in Hodgkin lymphoma and Non-Hodgkin lymphoma patients

Diseases	*Non-Hodgkin lymphoma*		*Hodgkin lymphoma*	
	N (%)	*F/M*	*N (%)*	*F/M*
Autoimmune thyroiditis (hypo, hyperthyroidism)	5 (13)	3/2	2 (12)	0/2
Immune thrombocytopenia	1 (2.6)	1/0	0	
Direct Coombs-positive autoimmune hemolytic anemia	7 (18)	5/2	5 (33)	2/3
Chronic Hepatitis	4 (11)	1/3	1 (6.6)	1/0
Pernicious anemia	3 (8.6)	1/2	1 (6.6)	0/1
ANCA-positive (vasculitis)	2 (5.3)	2/0	0	
Systemic lupus erythematosus	0		0	
Rheumatoid arthritis	0		0	
Ulcerative colitis	0		0	
Sjögren's syndrome	0		0	
Polimyalgia rheumatica	0		0	
Chronic urticaria	0		0	
Psoriasis	0		0	

F/M: females/males

Table 4. Characteristics of anticardiolipin antibodies and/or lupus anticoagulant positive patients

Characteristics	*Antiphospholipid antibodies*	
	Positive patients (N=16)	*Negative patients (N=38)*
Age average.(range)	63 (28-70)	53.4 (18-90)
F/M	9/7	16/22
Type of lymphoma, N(%)		
HL	6 (38)	10 (26)
NHL	10 (62)	28 (74)
Clinical stage, N (%)		
I/II	6 (38)	17 (45)
III/IV	10 (62)	21 (55)
Thrombosis, N (%)	0 (0)	1 (3)

HL: Hodgkin's lymphoma, NHL: non-Hodgkin's lymphoma, F/M: females/males

Coombs (33%). Autoantibodies and their frequency in HL and NHL patients are shown in Table 2.

In terms of the presence of a relationship between cytokine levels and autoantibodies, INF-γ was significantly higher in thyroglobulin antibody-positive patients and IL-6 was significantly higher in direct Coombs-positive patients ($p<0.05$, $p<0.01$, respectively).

Autoimmune diseases seen in patients and their rates are displayed in Table 3.

The percent of patients with at least one positive APA including lupus anticoagulant, ACA-IgG and IgM antibodies was 26% in NHL and 38% in HL patients. None of these positive patients experienced any thromboembolic event (Table 4).

Discussion

It is known that interleukins have an important role in the pathogenesis of lymphoma, are potential markers for the growth of tumor cells, and when compared with healthy subjects serum cytokine levels are higher in HL and NHL patients [1,3,8,9], a fact that was also confirmed in our study.

In the present study, we found high IL-6 levels of B symptom positive lymphoma patients. We found an association between the IL-6 levels and lymphopenia, and also found higher frequencies of hypoalbuminemia and hypogammaglobulinemia in the group with high IL-6 levels. Kurzrock and colleagues found that serum IL-6 levels were higher in B symptom positive lymphoma patients in their study [9]. This finding suggests that IL-6 is one of the most important cytokines responsible for lymphopenia and B symptoms.

Elevated serum IL-6 levels in patients with aggressive NHL were shown to be correlated with B symptoms, high serum beta 2 microglobulin and LDH levels, bulky disease, advanced Ann Arbor stage, poor performance status, advanced age (>60 years) and poor IPI score [8,13]. Shorter disease free survival and overall survival in NHL patients with high serum IL-6 levels was also observed [3,8]. In conclusion, our results showed that elevated serum IL-6 levels in patients with NHL were correlated with high serum beta-2 microglobulin levels, Ann Arbor advanced stage, poor performance status, advanced age and poor IPI score.

In a study, advanced stage and B symptoms positive HL patients had high serum levels of IL-6 associated with shorter survival [9]. We could not show this correlation, but, in contrast with the literature, in our study we showed relationship between IL-6 and direct Coombs positivity.

Our findings showed that IL-6 could be considered as an additional prognostic factor in HL and NHL patients, and their follow-up is going on to register disease free and overall survival.

We found higher serum levels of IL-2 in patients with NHL. However, we did not find any correlation among IPI, B symptoms and advanced stage of disease. In serum of untreated NHL patients IL-2 may be detected at higher levels than in healthy controls [1,14]. Serum IL-2 levels of patients with high IPI score are higher than in patients with low IPI score and this correlation indicates that IL-2 may be used as a criterion of poor prognosis [1]. According to our study, IL-2 levels were higher in NHL patients but not enough to affect prognosis. In contrast, we found higher IL-2 levels in HL patients which were accompanied with significantly higher relapse rate. This suggests that IL-2 may be a good marker for monitoring relapse in HL patients.

In the present study increased relapse rates in HL patients were correlated with high serum levels of IL-1ß, INF-γ and IL-4, advanced stage, and more than 2 extranodal involvement sites. In one study of 32 patients with HL and 28 with NHL, only 3 patients (8%) had higher IL-1ß, 15 patients (37%) had higher TNF-α, 20 patients (35%) had higher IL-6, but no patients had higher IFN-γ [9]. In this study, in HL patients we found high levels of INF-γ in one patient (6%), TNF-α in 2 (13%) patients, IL-1ß in one (6%) patient and IL-6 in 6 (38%) patients. In 38 NHL patients, we found high levels of INF-γ in 6 (16%) patients, TNF-α in 15 (40%) patients, IL-1ß in 2 (5%) patients and IL-6 in 23 (60%) patients. Elevation of IL-10 in patients with HL is an already poor prognostic factor [2]. In the present study we found additional poor prognostic factors (IL-1β, INF-γ, IL-2 and IL-4).

If we look at the relationship between autoantibodies and lymphoma, the positivity of autoantibodies in HL and NHL patients was 50%. ANA, anti-dsDNA, and ENA panel were not positive in any patient. In the NHL patient group, direct Coombs positivity was the most common (27%), while in the HL patient group lupus anticoagulant positivity (36%) was the most common.

A higher prevalence of autoantibodies, such as ANA or anti-phospholipid antibodies was observed in NHL, but usually without clinical manifestations [15]. In a study including 64 NHL patients, sera of 25 (39%) patients displayed one or more of direct Coombs, indirect Coombs, platelet autoantibodies and lupus anticoagulant positivity; on the other hand, in autoantibody positive patients the median survival was shorter compared with autoantibody negative patients. In the literature direct Coombs positivity ratio of NHL patients ranges between 14 and 28% [10,16]. Direct Coombs positivity of our patients was similar to other studies in NHL patients, and much higher in HL patients. To be able to comment on patient

survival according to autoantibody positivity, long-term patient follow-up is required.

While some of autoantibody positive patients manifest clinical autoimmune phenomena, some others may display immune hematological phenomena. In one study of 626 patients with NHL, autoantibodies could be detected in 14% of the patients; 8% of these patients exhibited clinical autoimmune phenomena and 6% showed immune hematological phenomena [17]. In our study we found autoimmune thyroiditis in 13%, immune thrombocytopenia in 2.6%, chronic hepatitis in 11%, and direct Coombs positive autoimmune hemolytic anemia (AIHA) in 18% of NHL patients. In HL patients we observed autoimmune thyroiditis in 12%, chronic hepatitis in 6.3%, and direct Coombs-positive autoimmune hemolytic anemia in 33%. None of the patients had clinical findings of Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, ulcerative colitis or polymyalgia rheumatica. In NHL patients direct Coombs positivity was 27%, clinical AIHA 18%, prevalence of thyroid autoantibodies 24.3%, and thyroiditis 13%. In HL patients direct Coombs positivity was 33%, clinical AIHA 33%, prevalence of thyroid autoantibodies 15.4%, and thyroiditis 12%. Autoantibodies can exist without causing any autoimmune disease. We do not know whether autoantibody positivity occurred before or after the development of lymphoma, so we cannot comment on this issue. Whether autoantibody-positive or autoantibody-negative patients will develop lymphoma could be answered with long-term follow up.

It has been shown that there was a good positive correlation between lupus anticoagulant, anticardiolipin antibodies, serum anti-β2 glycoprotein-1 and thromboembolic complications [18]. With or without thromboembolic events, many NHL patients have been reported to have ACA or lupus anticoagulant [19]. The incidence of antiphospholipid antibodies in the sera of patients with NHL is about 27-40% [11,12,20]. Survival of NHL patients who are antiphospholipid antibody-positive at diagnosis is shorter compared to negative patients. The presence of antiphospholipid antibodies in patients with aggressive NHL is considered to be an independent poor prognostic factor [12,21]. At least one of the antiphospholipid antibodies including lupus anticoagulant, ACAIgG and IgM antibodies positivity was found in 26% of the NHL patients and in 38% of the HL patients. Compared to relevant studies the rate we achieved was similarly high, and interestingly it was higher in HL compared with NHL patients. Anticardiolipin antibody-positive patients had more advanced disease in comparison with negative patients, thus high anticardiolipin antibody at advanced stage may support its use as a poor prognostic marker. Research to assess the impact on survival of patients with antiphospholipid antibody positivity continues. In addition, thromboembolic events were not detected in any of the antiphospholipid antibodies positive patients. This result may imply that different mechanisms are involved in patients who are antiphospholipid antibody positive and have thromboembolic episodes, and prophylactic use of low molecular weight heparin for the prevention of thrombosis in lymphoma patients may be suggested.

There are many studies on the relationship between cytokines and autoimmune diseases [21]. In our study we found high levels of IL-2 in patients with arthralgia. In our thyroglobulin antibody-positive lymphoma patients INF-γ levels were significantly high and this finding suggests that INF-γ is an effective cytokine in the development of thyroiditis. We also found significantly high levels of IL-6 in direct Coombs positive lymphoma patients. Based on this finding we could argue that lymphoma cells may produce IL-6 and that this cytokine can increase the plasma cell population in these patients.

Conclusion

In lymphoma patients INF-γ is responsible for thyroglobulin antibody positivity; IL-6 is responsible for direct Coombs positivity and is the most important cytokine responsible for lymphopenia and B symptoms in lymphoma patients. TNF-α and IL-6 are poor prognostic factors that may be included in the IPI. IL-1ß, INF-γ, IL-2 and IL-4 are markers associated with poor prognosis in HL.

At least one autoantibody was positive in 50% of NHL and HL patients, but to understand their effect on prognosis long-term follow-up is required.

At least one antiphospholipid antibody was positive in 26% of NHL and 38% of HL patients, therefore they can be regarded as poor prognostic marker that can be used in lymphoma prognosis.

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