Serum IL-13 levels at diagnosis and remission in children with malignant lymphoma

Derya Özyörük[1], Gülsan Yavuz[1], Handan Dinçaslan[1], Emel Cabı-Unal[1], Nurdan Taçyıldız[1], Deniz Karataş[2], Figen Doğu[2], Aydan İkincioğulları[2]

Divisions of [1]Pediatric Oncology and [2]Pediatric Immunology, Department of Pediatrics, Ankara University Faculty of Medicine, Ankara, Turkey. E-mail: dozyoruk@yahoo.com

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SUMMARY Özyörük D, Yavuz G, Dinçaslan H, Cabı-Unal E, Taçyıldız N, Karataş D, Doğu F, İkincioğulları A. Serum IL-13 levels at diagnosis and remission in children with malignant lymphoma. Turk J Pediatr 2016; 58: 246-253.

Interleukin (IL)-13 has been reported to have a role in the pathogenesis of lymphoma through recent molecular studies predominantly in adult patients. As malignant lymphomas in children differ from adult counterparts in terms of histology and response to treatment, we aimed to determine the serum IL-13 levels of patients with lymphoma; its relation with clinical-laboratory parameters and to look for any correlation of serum IL-13 levels with different prognostic factors in children. Twenty-eight patients with malignant lymphoma and 20 age-matched healthy controls were included in the study. The median serum IL-13 level at diagnosis (range 0.59-68 pg/ml, median 3.40 pg/ml) was higher than that in remission (range 0.14-12.2 pg/ml, median 1.60 pg/ml) in the HL group ($p<0.05$). Remarkably, median serum IL-13 level of patients with nodular sclerosis at diagnosis was higher than those with mixed-cellularity ($p<0.05$) and declined to normal limits during remission ($p<0.05$). In Burkitt's lymphoma (BL) subgroup, the median (range 2.94-154 pg/ml, median 4.5 pg/ml) was high and declined to normal levels during remission (range 0.55-11.30 pg/ml, median 1.57 pg/ml) and the difference was significant ($p<0.05$). In terms of prognostic factors, serum IL-13 levels were found to be associated with white blood cells counts only in HL group. Although the number of patients is limited in our study, we found that the serum IL-13 levels exhibit variances in different histopathologic groups. IL-13 might have a role in histopathogenesis of lymphoma, but seems to have no prognostic significance. Nevertheless, more molecular studies are needed to evaluate the pathogenesis of HL.

Key words: malignant lymphoma, cytokines, interleukin-13, Hodgkin's lymphoma, non-Hodgkin's lymphoma.

Hodgkin lymphoma (HL) differs from other malignant lymphomas in that tumors are composed mainly of benign reactive cell and just a minority of malignant cells that are called Hodgkin and Reed-Sternberg (H-RS) cells. H-RS cells produce and secrete a wide variety of cytokines such as interleukin-1 (IL-1), IL-5, IL-6, IL-9, tumor necrosis factor-alpha, macrophage colony-stimulating factor, transforming growth factor-beta and less frequently, IL-4 and granulocyte colony-stimulating factor. These various cytokines seem to be responsible for sclerosis, tissue eosinophilia, and B symptoms including fever, night sweats and weight loss and so on in HL patients[1,2]. Recently, IL-13 has been identified as an autocrine growth factor for H-RS cells[2-4]. It is a pleiotropic immune regulatory cytokine and is predominantly produced by activated Th2 cells and regulates the humoral response by driving the proliferation and survival of B cells and triggers immunoglobulin class switching [5-7]. On the other hand, taking into account that IL-13 acts in B-cell proliferation and Reed-Sternberg cells originate from germinal center B lymphocytes, it has been hypothesized that IL-13 might play a role proliferation of H- RS cells and even can act as an autocrine factor. The first molecular

studies related to IL-13 started about 10 years ago. In 1999, Kapp et al.[3] have reported IL-13 expression in patients with nodular sclerosis-HL. In 2001, Oshima and colleagues[2] also showed IL-13 and IL-13 R α 1 expression in HL cell lines and the researchers suggested that IL-13 could be an autocrine growth factor for RS cells and also for formation of fibrosis. Also, Skinnider et al.[4] reported that IL-13 and IL-13 receptor are frequently expressed by H-RS cells of HL. Despite the fact that IL-13 was found to be commonly expressed by H-RS cells, only 10% HL patients had detectable levels of IL-13 present in the serum [8].

Non-Hodgkin lymphoma (NHL) is usually high grade with different pathologic, immunologic and clinical features in children. There is limited study about IL-13 in NHL in the literature. Skinnider et al. showed IL-13 expression by immunohistochemistry in a small proportion of patients with NHL, in 2001[4].

So far, the studies regarding serum Interleukin (IL)-13 in patients with malignant lymphoma have been conducted predominantly in adult patients. It is well known that malignant lymphomas in children differ from adult counterparts in terms of histology and response to treatment. Therefore, in the present study, we aimed to determine the serum IL-13 levels of patients with different histopathologic types of malignant lymphoma; its relation with clinical-laboratory parameters and to look for any correlation of serum IL-13 levels with different prognostic factors in childhood.

Material and Methods

Twenty-eight ML patients (12 HL and 16 NHL) who were diagnosed at Ankara University Pediatric Oncology Department between 2008 to 2011 and 20 healthy children were included in the study. Diagnosis of ML was performed by histopathological and immunophenotyping studies on samples collected through lymph node biopsies in addition to cytologic and/or flow cytometric analysis of ascites or pleural effusion. Staging was carried out for all patients clinically according to the Ann Arbor system for HL patients and St-Jude staging system for NHL patients[9]. In each patient complete medical history taking and physical examinations were performed. In addition to that, complete blood cell counts, erythrocyte sedimentation rates (ESR), serum lactate dehydrogenase levels (LDH) and biochemical parameters, Epstein-Barr Virus (EBV) serology (VCA IgM and IgG) were determined. Bone marrow biopsy and aspiration, and imaging studies like 18-fluorodeoxyglucose positron emission tomography (FDG-PET) and computed tomography of the chest, abdomen, and pelvis were performed [10]. In ML patients, criteria for remission are based on treatment protocols that have been used according to their histopathological type. The study was approved by the Research Ethics Committee of Ankara University. Informed consent was obtained from all patients and volunteers. All study procedures were in accordance with the Helsinki Declaration of 1975. The serum samples of patients with ML were collected at diagnosis and in remission (within 3 months after the end of treatment). The children, with no history of chronic disease like allergy, asthma, parasitosis or malignancy, who were admitted to the hospital for their periodic health control or immunization program and were accepted as healthy children to the control group and their blood samples were also obtained for determination of the serum IL-13 levels. All samples which were collected from ML patients and control group were stored at -80° C until they were studied.

Patients' Characteristics

There were 12 HL patients (5 female, 7 male) with a median age of 12.5 years (range: 4-17.5 years). The demographic characteristics, histological subtypes, clinical stages, clinical-laboratory findings and serum IL-13 levels of each patient with HL are shown at Table I. Of these patients, 50% (n: 6/12) had nodular sclerosis and 50% (n:6/12) had mixed-cellularity histology. Five patients (41%) had stage I-II and 7 patients (59%) had Stage III-IV disease. Six patients (50%) had B symptoms. Anti- EBV VCA IgG was found to be 100% (n: 12/12) positive in patients with HL.

There were 16 NHL patients (9 female, 7 male) with a median age of 10 years (range: 2-17 years). The demographic characteristics, histological subtypes, clinical stages, clinical-laboratory findings and serum IL-13 levels of each patient with NHL are shown at Table II. Of these patients, 31% (n: 5/16) had Burkitt's lymphoma, 43% (n: 7/16) had non-Burkitt's

Table I. Clinical, Laboratory Characteristics and Serum IL-13 Levels of Patients with HL

Patients No	Sex	Age (year)	Histologic Subtypes	Stage	B Sx	White blood cell (/mm^3)	ESR (mm/h)	LDH (ıu/l)	Anti-VCA IgG	LMP-1	IL-13 level (pg/ml) at diagnosis	IL-13 level (pg/ml) in remission
1	F	14	NS	II	B	4.200	105	356	+	+	0.59	1.12
2	M	17	NS	IV	B	32.000	124	382	+	-	68	0.76
3	F	9	NS	II	A	4300	58	388	+	+	4.67	1.60
4	M	17	NS	IV	A	12.800	80	386	+	+	6.41	3.90
5	M	14	NS	III	A	4.800	6	212	+	+	3.40	1.60
6	M	17.5	NS	IV	B	25.900	134	386	+	+	10.5	8.20
7[a]	M	9	MC	III	A	7.000	82	423	+	+	3.04	3.65
8	F	13	MC	II	B	6.400	100	636	+	+	2.74	-
9	M	6	MC	IV	B	8.700	145	4181	+	+	1.65	1.18
10	F	4	MC	II	A	9.700	80	476	+	+	19.1	12.2
11	F	11.5	MC	III	A	8.100	30	168	+	+	3.4	2.82
12	M	12	MC	II	B	4.200	16	415	+	+	2.8	0.14

a: Ataxia telangiectasia; ESR: erythrocyte sedimentation rate; F: female; HL: Hodgkin's lymphoma; LDH: lactate dehydrogenase level; ; LMP-1: latent membrane protein; M: male; MC: mixed cellularity; NS: nodular sclerosis; Sx: symptoms;

Table II. Clinical, Laboratory Characteristics and Serum IL-13 Levels of Patients with NHL

Patients No	Sex	Age (year)	Histologic subtypes	Stage	White blood cell (/mm^3)	ESR (mm/h)	LDH (ıu/l)	Anti-VCA IgG	IL-13 level (pg/ml) at diagnosis	IL-13 level (pg/ml) in remission
1	M	6	BL	III	14,900	18	1570	+	26.0	1.57
2	F	3	BL	III	9,300	54	1620	+	2.94	0.55
3 [a]	M	13	BL	IV	15,400	20	376	-	154	11.3
4	M	5	BL	II	9,300	80	379	+	4.56	2.23
5	F	15	BL	IV	10,100	4	5918	+	3.16	0.70
6	F	10	B NHL	II	10,000	130	1200	-	1.53	0.12
7	F	7	B NHL	IV	6,200	100	606	-	2.74	0.10
8	F	9.5	B NHL	II	5,200	54	534	+	1.14	10.2
9 [b]	M	14	B NHL	IV	8,700	17	10 000	+	17.7	0.56
10	F	13	B NHL	III	3,400	86	187	-	2.00	0.50
11	F	11.5	B NHL	IV	5,600	10	343	+	2.97	0.11
12	M	4	B NHL	IV	8,400	86	1528	+	0.97	52.3
13	M	10	T NHL	III	10,700	53	1778	+	0.64	4.44
14	F	11	T NHL	IV	20,000	30	289	+	9.00	0.11
15	M	15	T NHL	IV	210,000	46	2698	+	3.56	21.3
16	F	13	T NHL	IV	36,000	80	816	+	0.13	2.36

a: relapsed Burkitt's lymphoma; b: Primary mediastinal large B cell lymphoma; BL: Burkitt's lymphoma; B NHL: non Burkitt's B-cell non Hodgkin's lymphoma; ESR: erythrocyte sedimentation rate; F: female; HL: Hodgkin's lymphoma; LDH: lactate dehydrogenase level; ; LMP-1: latent membrane protein; M: male ;MC: mixed cellularity; NS: nodular sclerosis; Sx: symptoms; T NHL: T-cell non-Hodgkin's lymphoma

B-NHL (mature B cell) and 25% (n:4/16) had T-NHL (lymphoblastic lymphoma). Three (18%) patients had stage I-II, 13 patients (82%) had stage III-IV disease. Anti- EBV VCA IgG positivity rate was found to be 80% (n: 4/5) in patients with Burkitt's lymphoma, 57% (n:

4/7) in patients with non-Burkitt's B-NHL and 100% (n: 4/4) in patients with T-NHL.

There were 20 healthy children (9 female, 11 male) with a median age of 10 years (range: 2-17 years) in control group.

Determination of serum IL-13 levels

Serum IL-13 concentrations of samples were determined by enzyme-linked immunosorbent assay (ELISA) (Bender Med Systems, human IL-13 ELISA instant kit, Vienna, Austria) using 96-well microplates in accordance with the manufacturer's instructions and each serum sample was tested twice. IL-13 levels were determined with the microplate reader set to the wavelength of 450 nm. IL-13 levels were expressed as picogram per milliliter (pg/ml). According to the information provided by the manufacturer of the ELISA kit, the lower detection limit for IL-13 was determined to be 0.99 pg/ml (mean of 6 independent assays).

Statistical Analysis

Data analysis was performed using SPSS 17.0 for Windows statistical program. The Wilcoxon Rank test was used to compare the levels of serum IL-13 at diagnosis and during remission. The Mann-Whitney U test and Student- t test were used to compare the levels of serum IL-13 in patients with ML and control group, where appropriate. Spearman Rank correlation test was conducted to assess any correlations between serum levels of IL-13 with laboratory parameters (hemoglobin, WBC, platelet, LDH, ESR), EBV status and clinical stages. P values of <0.05 were considered to be significant.

Results

HL group has higher median serum IL-13 levels at diagnosis (range 0.59-68 pg/ml, median 3.40 pg/ml) compared to that of control group (range 0.04-5.14 pg/ml, median: 1.60 pg/ml) and the corresponding difference was significant ($p<0.05$) (Table III). Remarkably, difference was especially more prominent in NS subgroup ($p<0.05$) On the other hand, there was no difference between MC subgroup with control. The level of IL 13 during remission of both subgroups was similar to control group (Table III, IV, V). No correlation was found between serum IL-13 levels and gender, B symptoms, clinical stages, previous EBV infections (positive vs negative), hemoglobin, ESR, or LDH at diagnosis in patients with HL ($p>0.05$). A positive correlation was found only between serum IL-13 levels and white blood cell (WBC) count in HL group (r: 0.702; $p<0.05$).

We determined different results in patients with NHL (Table IV). The median serum IL-13 level at diagnosis was higher compared to that of control group, but difference was not significant. In Burkitt's lymphoma subgroup, the high level at diagnosis (range: 2.94-154 pg/ml, median 4.5 pg/ml) declined to normal levels during remission (range: 0.55-11.30 pg/ml, median 1.57 pg/ml) and the difference was as significant ($p<0.05$) as in the NS subgroup. The highest serum IL-13 level (154 pg/ml) belongs to the patient with relapsed BL (Table II, number 2). In non-Burkitt's B-NHL, except for one patient diagnosed with primary mediastinal large B-cell lymphoma (Table II, number 9),

Table III. The Comparison of the Serum IL-13 Levels in Hodgkin's and non-Hodgkin's Lymphoma Patients at Diagnosis with the Control Group 's

GROUPS	Serum IL-13 levels		P values
	At diagnosis	Control group	
	range (pg/ml)	range (pg/ml)	
HL	0.59-68 (median:3.40)	0.04-5.14 (median:1.60)	*0.03
NS	0.59-68 (median:5.50)	0.04-5.14 (median:1.60)	*0.03
MC	1.65-19.10 (median:3.04)	0.04-5.14 (median:1.60)	0.24
NHL	0.13- 154 (median:2.95)	0.04-5.14 (median:1.60)	0.11
BL	2.94-154 (median:4.5)	0.04-5.14 (median:1.60)	*0.02
BNHL	0.97-17.7 (median:2)	0.04-5.14 (median:1.60)	1.00
T NHL	0.13-9 (median:2.1)	0.04-5.14 (median:1.60)	0.63

*P<0.05: Statistically significant; BL: Burkitt's lymphoma; B NHL: non Burkitt's B-cell non Hodgkin's lymphoma; MC: mixed cellularity; NS: nodular sclerosis; T NHL: T-cell non-Hodgkin's lymphoma

the median IL-13 level at diagnosis was similar to the level in remission and control group. Differently, in T-NHL group, low median IL-13 level at diagnosis increased during remission but not up to a significant degree. In NHL group, the level of IL-13 during remission of all three subgroups was not found different from control group (Table III, IV, V). No correlation was found between serum IL-13 levels and clinical–laboratory findings.

Discussion

Increased cytokine levels can contribute to the clinical and pathological features of malignant lymphomas. Several studies have demonstrated that the RS and surrounding cells release a wide variety of cytokines and chemokines responsible from different clinical and histological presentations of HL, survival and proliferation of RS cells. To understand the role of these cytokines and the employed signal transduction pathways will allow the development of new treatment models in the future[4,11-15].

To the best of our knowledge, serum IL-13 levels of patients with HL had been evaluated previously in two studies. Both studies were conducted in adult patients with HL and to this date, there is no study related with pediatric HL in the literature. In the first study, Fiumara et al.[8] have measured serum levels of IL-13 in 108 adult patients with newly diagnosed HL. Of these patients, 70% had nodular sclerosis histology and 36% were in clinical stage III-IV of the disease. Thirty-one patients (28%) had B symptoms. Only in 11(10%) of the 108 patients had detectable levels of IL-13 (range, 34 to 82 pg/ml). Among them, 3 patients with the highest IL-13 levels had nodular sclerosis histology. Serum IL-13 level was not correlated with gender, disease stage, histological subtype, bulky disease, or presence of extranodal involvement. The authors have suggested that this lack of correlation may simply be due to the small number of patients who were found to have elevated serum IL-13 levels. They have also studied IL-13 levels in serum samples from 31 patients with relapsed HL. In this group, 28 patients had nodular sclerosis histology and 3 had unclassified histologies. Five (16%) of 31 patients had elevated IL-13 levels. Recently, Gaiolla et al.[15] studied IL-13 levels from sera of 27 adult patients with HL (23 nodular sclerosis, 3 mixed-cellularity, 1 lymphocyte predominant HL). The researchers reported that the serum IL-13 levels were undetectable and in this line suggested that IL-13 might be acting predominantly at the tumor microenviroment level, possibly at very low concentrations and with a short range of action[15].

In contrary to the literature findings mentioned above, serum IL-13 levels were at detectably high levels in patients with NS in our study when compared to healthy controls. We speculate that the decreased serum IL-13 levels at the end of treatment might be related to the elimination of the RS and the variant cells which serve as a source of IL-13 in NS subgroup. Accordingly,

Table IV. The Comparison of the Serum IL-13 Levels in Hodgkin's and non-Hodgkin's Lymphoma Patients at Diagnosis and in Remission

GROUPS	Serum IL-13 levels		p values
	At diagnosis	In remission	
	range (pg/ml)	range (pg/ml)	
HL	0.59-68(median:3.40)	0.14-12.2(median:1.60)	*0.01
NS	0.59-68 (median:5.50)	0.76-8.24 (median:1.60)	*0.04
MC	1.65-19.10 (median:3.04)	0.14-12.20 (median:2.82)	0.22
NHL	0.13- 154 (median:2.95)	0.10-52(median:1.10)	0.23
BL	2.94-154 (median:4.5)	0.55-11.3 (median:1.57)	*0.04
B NHL	0.97-17.7 (median:2)	0.10-52.3 (median:0.50)	0.73
T NHL	0.13-9 (median:2.1)	0.11-21.30 (median3.40)	0.59

*P<0.05: Statistically significant; HL: Hodgkin's lymphoma; NS: nodular sclerosis; MC: mixed cellularity; NHL: non Hodgkin's lymphoma; BL: Burkitt's lymphoma; B NHL: non Burkitt's B-cell non-Hodgkin's lymphoma ; T NHL: T-cell non-Hodgkin's lymphoma

Table V. The Comparison of the Serum IL-13 Levels in Hodgkin's and non-Hodgkin's Lymphoma Patients in Remission with the Control Group 's

GROUPS	Serum IL-13 levels		p values
	In remission	Control group	
	range (pg/ml)	range (pg/ml)	
HL	0.14-12.2(median:1.60)	0.04-5.14(median:1.60)	0.67
NS	0.76-8.24 (median:1.60)	0.04-5.14(median:1.60)	0.79
MC	0.14-12.20 (median:2.82)	0.04-5.14(median:1.60)	0.71
NHL	0.10-52(median:1.10)	0.04-5.14(median:1.60)	0.74
BL	0.55-11.3 (median:1.57)	0.04-5.14(median:1.60)	0.86
B NHL	0.10-52.3 (median:0.50)	0.04-5.14(median:1.60)	0.49
T NHL	0.11-21.30 (median3.40)	0.04-5.14(median:1.60)	0.43
ML	0.10-52 (median:1.60)	0.04-5.14(median:1.60)	0.14

HL: Hodgkin's lymphoma; NS: nodular sclerosis; MC: mixed cellularity; NHL: non Hodgkin's lymphoma; BL: Burkitt's lymphoma; B NHL: non Burkitt's B-cell non-Hodgkin's lymphoma ; T NHL: T-cell non-Hodgkin's lymphoma; ML:Malignant lymphoma

a simultaneous 18-fluorodeoxyglucose positron emission tomography (FDG-PET) study, which is accepted as an objective evaluation of response to chemotherapy16, was consistent with remission status in our study. Furthermore, all Hodgkin's lymphoma patients achieved long-term remission and they are still alive. On this basis, we believe that IL-13 might have an important role in histopathogenesis especially of NS-HL, but we do not think it has a prognostic importance in Hodgkin's lymphoma. Nevertheless, there are few patients (6) with NS histology to conclude from the present study, but much less in adult series as well. In the literature, controversial results had been reported related to IL-13 expressions, indicating the variations in different histological subgroups of HL. Oshima et al.[2] has determined higher expressions of IL-13 in nodular sclerosis than in mixed-cellularity subtype. In addition, the same study figured out IL-13 R α 1 protein expression in fibroblasts nodular sclerosis subtype. They reported that IL-13 could be responsible of fibrosis, a characteristic feature of nodular sclerosis. On the other hand, Skinnider and coworkers[4] found no difference in terms of IL-13 and IL-13R α 1 expression between morphological types of HL. In the latter study, the authors concluded that this result might be due to the scarce number of mixed-cellularity type patients in their study in comparison to patients with nodular sclerosis.

White blood cell count ≥11,500/mm^3 is considered to be associated with a poor prognosis in patients with HL[10]. In our study, the serum IL-13 levels were associated with high WBC counts in HL group. We noticed that the patients with high WBC counts have also high serum IL-13 levels (Table I, number 2 and 6). In addition to higher white blood cell counts, B symptoms, advanced stage, male gender, nodular sclerosis histology, and bulky mediastinal involvement are considered as poor prognostic-factors [15-19].

In our study, we obtained different results in patients with NHL. Interestingly, in Burkitt's lymphoma subgroup, the high levels at diagnosis declined to normal levels during remission and the difference was significant ($p<0.05$). In non-Burkitt's B-NHL subgroup, except for one patient with primary mediastinal large B-cell lymphoma who achieved long-term remission by Rituximab-EPOCH treatment, IL-13 levels were similar to those in control group. So far, the studies regarding IL-13 in patients with NHL are generally insufficient; if at all exist, in pediatric literature. Skinnider et al.[14] reported that IL-13 expression in non-Hodgkin lymphoma is uncommon. Despite there were no Burkitt's lymphoma cases in their study group, they found that IL-13 expression was negative in diffuse large B cell lymphoma (n: 8). Guiter et al.[20] did not detect any IL-13 receptor α 1 and α 2 chain expressions in Burkitt's lymphoma B cells. On the other hand, in T-NHL subgroup which consists of lymphoblastic lymphoma histology, low median IL-13 level at diagnosis had increased during remission in present study, but the difference was insignificant. Skinnider

et al.[14] demonstrated IL-13 expression in 2 of 5 anaplastic large cell lymphoma cases, one of 5 T cell-rich B cell lymphoma cases and in one of 5 unspecified type peripheral T cell lymphoma cases. Although IL-13 from Th2-type cells suppresses induction of antigen-specific Th1 immunity in a T-cell lymphoma[21], we suggest that increased IL-13 level might be resulted from generation of naive thymic T cells and increased Th2 type cell activity following the elimination of malignant T- cells in timic tissue after chemotherapy.

The primary mediastinal large B-cell lymphoma and nodular sclerosis-type Hodgkin's disease with a mediastinal mass are common clinical features. Transcriptional analysis has demonstrated increased expression of the IL-13 receptor α 1 dependent genes in primary mediastinal large B-cell lymphoma[20]. Consistent with the literature, an above-mentioned patient who was diagnosed to have primary mediastinal large B-cell lymphoma had high serum IL-13 level at diagnosis in a similar manner to patients with NS-HL.

The relationship of Epstein-Barr Virus with ML, especially with BL and HL, has been studied by serological, epidemiological and molecular studies. It had been shown that Epstein-Barr Virus plays an important role in pathogenesis of HL [22-24]. Moreover, Tsai and colleagues[25] have determined a relationship between IL-13 and the EBV ZTA protein in both cell lines as well as EBV infected lymphoblastoid cell lines and suggested a contribution of the increased expression of IL-13 in HL's pathogenesis. Formerly, we had determined a previous EBV infection rate of approximately 90% in patients with HL and BL treated in our center[26,27]. In the present study, we have identified a previous EBV infection rate of 100% for HL and 80% for BL. Based on our results, we suggest that both IL-13 and EBV are associated with pathogenesis of lymphoma with no prognostic significance.

In conclusion, we figured out that the serum IL-13 levels exhibit variances in different histopathologic groups. Although the number of patients is limited in our study, our findings suggest that IL-13 might have a role in histopathogenesis of lymphoma in light of the information that the expression of IL-13, IL-13Rα1 in tumor tissue and its relation with signal transduction pathways in previous literatures, but seems to have no prognostic significance. Nevertheless, more molecular studies are needed to evaluate the pathogenesis of HL.

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