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Original Article

Mast Cell Counts and Microvessel Density Expressions in Hodgkin's Lymphoma and Reactive Lymphadenopathy in Children

Çocuklarda Hodgkin Lenfoma ve Reaktif Lenfadenopatilerde Mast Hücre Sayısı ve Mikrovessel Dansite Ekspresyonları

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ABSTRACT

Objective: Mast cells (MCs) have been shown to make a significant contribution to both normal and tumor-associated neo-angiogenesis. The aim of this study is to analyse the relationship between microvessel density (MVD) and MCs in tissues of children with Hodgkin's lymphoma (HL) and reactive lymphadenopathy (RL).

Method: This retrospective study was conducted with 29 newly diagnosed HL patients and 30 patients with RL. MCs and microvascular density expressions were studied immunohistochemically in the tissues obtained from formalin-fixed and paraffin embedded blocks of archival specimens in our clinic.

Results: The mean MC count in HL was higher compared to the RL group ($p<0.001$). MVD expression in HL was lower than RL ($p<0.001$). In RL group, MC counts were correlated with MVD expression ($r=-0.055$, $p>0.05$). MC counts in nodular sclerosis subgroup were higher compared to mixed cellularity subgroup ($p<0.05$). In HL group, MC counts were positively correlated with age and nodular sclerosis histology, and negatively correlated with serum lactate dehydrogenase enzyme levels. Microvascular density expressions were positively correlated with advanced stages.

Conclusion: Our data suggest that MCs may have limited contribution to angiogenesis in childhood HL rather than RL group.

Keywords: Hodgkin lymphoma, mast cell, microvessel density

ÖZ

Amaç: Mast hücrelerinin (MH) hem normal hem de tümörle ilişkili neo-anjiyogenezde önemli bir katkı sağladığı gösterilmiştir. Bu çalışmanın amacı, Hodgkin lenfoma (HL) ve RL'li çocukların dokularındaki mikrovessel dansite (MVD) ve MH arasındaki ilişkiyi incelemektir.

Yöntem: Bu retrospektif çalışma, HL tanısı konmuş 29 hasta ve 30 RL'li hasta ile yapıldı. Kliniğimizde formolinle fikse ve parafine gömülü arşiv bloklarından elde edilen dokularda MH ve mikrovasküler dansite ekspresyonu immünohistokimyasal olarak çalışıldı.

Bulgular: HL'de ortalama MH sayısı RL grubuna göre daha yüksekti ($p<0,001$). HL'de MVD ekspresyonu RL'den daha düşüktü ($p<0,001$). RL grubunda, MH sayısı MVD ekspresyonu arasında korelasyon vardı, HL grubunda ise yoktu. Nodüler skleroz alt grubunda MH sayısı, miks sellüler alt grubuna göre daha yüksekti ($p<0,05$). HL grubunda, MH sayısı, yaş ve nodüler skleroz histolojisi ile pozitif korelasyon gösterdi ve serum laktat dehidrojenaz enzim seviyeleri ile negatif korelasyon gösterdi. Mikrovasküler dansite ile ileri evreler arasında pozitif korelasyon saptandı.

Sonuç: Verilerimiz, RL grubunun aksine, MH'nin çocukluk çağı HL'sinde anjiyogeneze sınırlı katkısının olabileceğini düşündürmektedir.

Anahtar kelimeler: Hodgkin lenfoma, mast hücre, mikrovasküler dansite

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INTRODUCTION

Angiogenesis is defined as a formation of new blood vessels and occurs in both physiological and pathologic conditions such as embryonic development, wound healing and cancer. The progression of solid tumors and hematologic malignities are associated with their degree of angiogenesis [1]. In several studies, mast cells (MCs) have been shown to make a significant contribution to both normal and tumor-associated neo-angiogenesis through secreting several factors including vascular endotelial growth factor, basic fibroblast growth factor, transforming growth factor-B, tumour necrosis factor-α, interleukin-8, histamine, tryptase, matrix metalloproteinase-9, and heparin [2-4]. First study regarding the association between MCs and induction of tumor angiogenesis was reported in MC deficient mice, which displayed slow angiogenesis, and recovery after local reconstitution of MC. In the last two decades, the association between MCs and angiogenesis has been displayed in several tumors, such as hemangioma, carcinomas, lymphomas and multiple myeloma, but the studies in pediatric Hodgkin's lymphoma (HL) and reactive lymphadenopathy (RL) are scarce in the literature [5-10]. The aim of this study is to analyse the relationship between microvessel density (MVD) and MC in HL and RL tissues of childhood.

MATERIALS and METHODS

Patients Characteristics

This retrospective study was conducted to analyse retationship between angiogenesis and MCs in tissues of HL and RL in children. A total of 29 newly diagnosed HL patients and 30 patients with RL who had undergone excisional lymph node biopsy as a control group were enrolled into the study. Ages of the patients with HL varied between 4 and 17 years, mean age was 10 years [standard deviation (SD) ±4.4 years] and 68% (n=20) of them were males. In the RL group, ages varied between 1 and 18 years, mean age was 7.8 years (SD ±4.7 years) and 68% (n=20) of them were females. Any statistically significant difference was not found between mean ages of the groups (p>0.05) (Table 1).

The tissues were obtained from formalin-fixed, paraffin-embedded blocks of the archival specimens of our clinics. Diagnosis of HL was performed by histopathological and immunophenotyping studies according to the World Health Organization classification of samples collected through excisional lymph node biopsies. Staging was carried out according to the Ann Arbor system for HL patients. Diagnostic work-up included physical examination, abdominal and cervical ultrasound, thoracic and abdominal computerized tomography scans, and bone marrow biopsies. The demographic and clinical data of the patients were retrospectively obtained from the files. Patients' age, gender, histopathologic subgroups, stages, B-symptoms, bulky involvement and laboratory parameters were recorded. This study was approved by the Research Ethics Committee of the Ankara Children Hematology and Oncology Training and Research Hospital (approval number: 2015-059). There was no conflict of interest for the present study.

Table 1. Demographic and clinical features of patients with Hodgkin's lymphoma and reactive lymphadenopathy

	HL	RL	p
Age (years)	4-17 y (median: 10 y)	1-18 y (median: 7.8 y)	p<0.05
Gender			
Male	20/29	10/30	-
Female	9/29	20/30	-
B-symptoms			
Positive	12/29	-	-
Negative	17/29	-	-
Histopathologic subtypes			
Nodular sclerosis	13/29	-	-
Mixed cellularity	15/29	-	-
Lymphocyte rich	1/29	-	-
Bulky disease positive	7/29	-	-
Stages			
1/2	8/29	-	-
3/4	21/29	-	-

HL: Hodgkin's lymphoma, RL: Reactive lymphadenopathy

The characteristics of the patients are given in Table 1 and 2.

Immunohistochemistry

MC and MVD expressions were studied immunohistochemically using sections prepared from formalin-fixed, paraffin-embedded blocks. All immunohistochemical stains were performed on the Ventana Benchmark automated staining system (Ventana Benchmark GX, Tucson, AZ, USA) using 4 µm-thick paraffin tissue sections. The primary antibodies used in this study were: CD34 (Mouse Monoclonal Antibody, Clone: QBEnd/10, Leica, Newcastle, United Kingdom) and MC Tryptase (AA1, 1:100, Thermo Scientific, USA). Diaminobenzidine was used as chromogen. We used appendices as positive controls. For negative controls, primary antibodies were omitted. A pathologist evaluated immunohistochemical staining of CD34 and MC Tryptase blinded. MCs were counted per high-power field (original magnification x 400; objective x 40, and eye piece x 10) and mean numbers per 10 high-power fields were calculated (Figure 1) [11].

When CD34 staining was used, MVD expressions were calculated according to the method described by Weidner et al. [10]. In brief, each section was observed under low-powered fields at ×100 magnification to find its high points of MVD (in three such hot spots in each case). After the most intense area of neovascularization in the tumor (hot spot) was identified, MVDs were evaluated on a 200× field (20× objective and 10× ocular; 0.785 mm^2) (Figure 2). MCs and MVDs were counted in the same area of malignant tumor tissue in HL and interfollicular areas in RL tissues. All counting was performed by one of the authors.

Table 2. Laboratory features of patients with Hodgkin's lymphoma

	Mean ± SD	Minimum-maximum
WBC/mm^3 (mean ± SD)	11 214±4419	(5000-21000)
Lymphocyte/mm^3 (mean ± SD)	2 400±947	(800-3800)
Hemoglobin/gr/dL (mean ± SD)	11±2.5	(5.2-14)
ESR/h (mean ± SD)	59±34	(16-125)
LDH/IU/dL (mean ± SD)	491±206	(178-1430)
Albumin (gr/dL)	4±0.8	(2.6-5)

WBC: White blood cell count, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase, SD: Standard deviation, IU: International unit

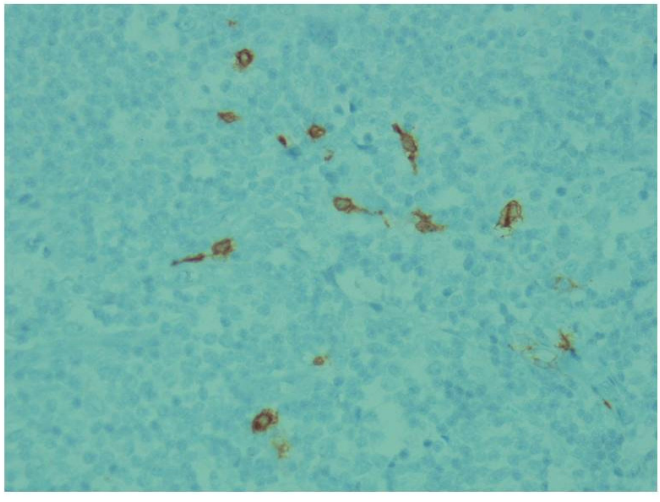

Figure 1. Distrubution of mast cells in patients with Hodgkin lymphoma visualized by immunohistochemical staining for mast cell tryptase (original magnification, ×400)

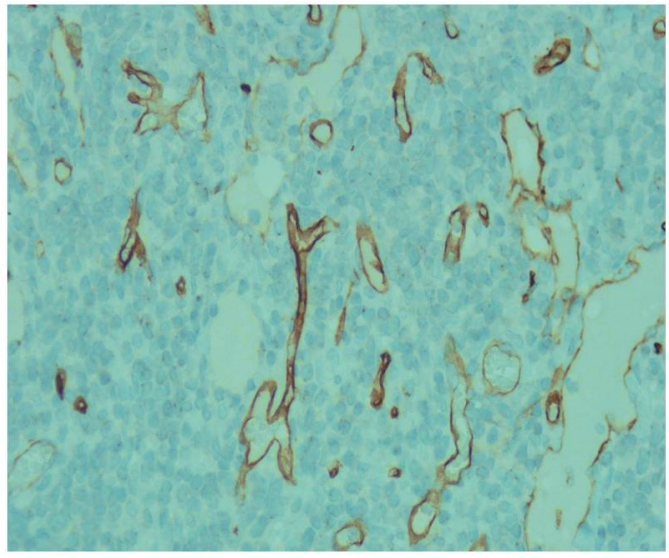

Figure 2. Expression of CD34 in tumour vasculature (original magnification, ×400)

Statistical Analysis

Statistical analyses were performed using the SPSS software version 17. The Kolmogorov-Simirnov test was used to determine if variables were normally distributed. To compare groups, Student's t-test and Mann-Whitney U tests were used, where appropriate and the Pearson corelation test was used to investigate the association between variables.

RESULTS

The MC and MVD values of HL and RL groups are summarized in Table 3. The MC counts and MVD expressions in the HL group ranged from 10 to 138 (mean ± SD: 70±31) and 21 to 38 (mean ± SD: 27±3.8), respectively. In the RL group, the MC values ranged from 10 to 125 (mean ± SD: 56±27) and MVD 20 to 49 (mean ± SD: 33±7.5), respectively. In comparison of MC between both groups Student's t-test revealed a significantly revealed significantly different ($p<0.001$) and higher MC values in HL. In comparison of mean MVD expressions between both groups Student's t-test revealed significantly different ($p<0.001$) and higher MVD expressions in RL as compared to HL. No correlation was found between levels of MC and MVD in HL ($r=-0.055$; $p>0.05$). On the other hand in RL, correlation analysis revealed a significant and positive correlation between MC values and MVD expressions ($r=0.405$; $p<0.05$).

Comparison between MC values and MVD expressions in terms of histopathologic subgroups (nodular sclerosis vs mixed cellularity), bulky involvement (positive vs negative), B-symptoms (positive vs negative), disease stages (early vs advanced) in HL are summarized in Table 4. MC values ranged from 10 to 138 (mean ± SD: 82±34.5) in nodular sclerosis and from 23 to 117 (mean ± SD: 61±26) in mixed cellularity subgroup. In comparison of MC values between two groups, statistical tests revealed significantly different ($p<0.05$) and higher MC counts in nodular sclerosis subgroup as compared to mixed cellularity subgroup (Figure 3). Similarly, mean MC counts were significantly different according to presence or absence of a bulky disease (mean ± SD: 89.5±24, range 70-138 vs mean ± SD: 63±31, range 10-117, respectively) ($p<0.05$). Although MC values of B symptom- positive patients were higher (75±31, range: 10-111) compared to B-symptom- negative patients (65±31, range: 24-138), the difference was not statistically significant ($p>0.05$). Also, MC values in advanced stages (stages 3 and 4) of HL (68±35, range: 10-138) were lower compared to early stages (stages 1 and 2) (75±19, range: 41-101), but the difference were not statistically significant ($p>0.05$). The mean MVD values were not statistically different between histopathologic subgroups contrary to MC counts (Figure 4). In addition, no difference was observed in MVD values with respect to bulky involvement or presence of B-symptoms. While mean MVD values were statistically significantly different, and higher in advanced stages ($p<0.05$) (Figure 5). According to Pearson correlation test, MC counts were positively correlated with patients' ages ($r=0.470$) ($p=0.01$), and histologic subgroups ($r=0.404$; $p=0.03$), while negatively correlated with serum lactate

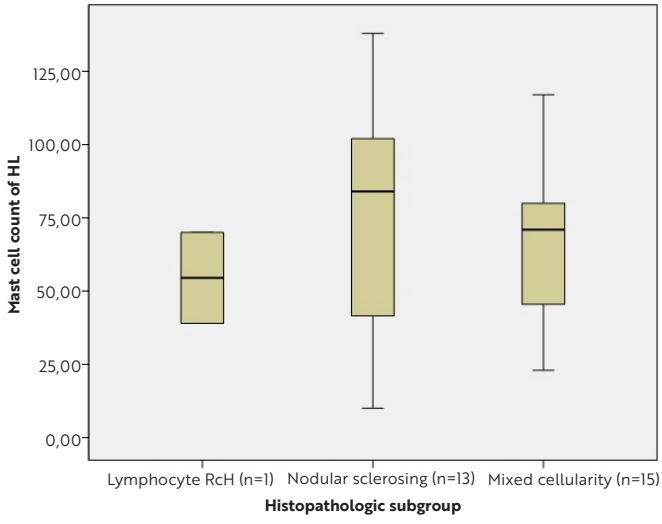

Figure 3. The comparison of mast cell count according to histopathologic subgroups

ML: Modgkin's lymphoma

Table 3. The comparison of mast cell count and microvessel density in Hodgkin lymphoma and reactive lymphadenopathy tissues

	Hodgkin lymphoma (n=29)	Reactive lymphadenopathy (n=30)	p
	Mean ± SD (min.-max.)	Mean ± SD (min.-max.)	
Mast cell count	70±31 (10-138)	27±3.8 (21-38)	p<0.001
MVD expression	27±3.8 (21-38)	33±7.5 (20-49)	p<0.001

MVD: Microvessel density, SD: Standard deviation, min.: Minimum, max.: Maximum

dehydrogenase enzyme levels (r=-0.404; p=0.04) at initial diagnosis. Any correlation was not found between MC and MVD, in terms of the presence of B-symptoms, and advanced stages of the disease (r=-0.055, p=0.778; r=0.134, p=0.497; r=-0.105, p=0.589, respectively). The MVD expression was only positively correlated with advanced stages (r=0.474; p=0.009), but not with age, histologic subgroups, presence of a bulky disease or B-symptoms (r=0.338, p=0.07; r=-0.079, p=0.685; r=-0.200, p=0.317; r=0.033, p=0.867, respectively).

DISCUSSION

Angiogenesis is a hallmark of tumor growth and progression in both solid tumors and hematological malignancies. Currently, antiangiogenic therapy is a promising tool for preventing tumorogenesis as well as initiating cancer treatment. MCs secrete proangiogenic and angiogenic factors and contribute to the formation of new blood vessels by increasing migration, proliferation of endothelial cells that facilitates growth of the tumor.

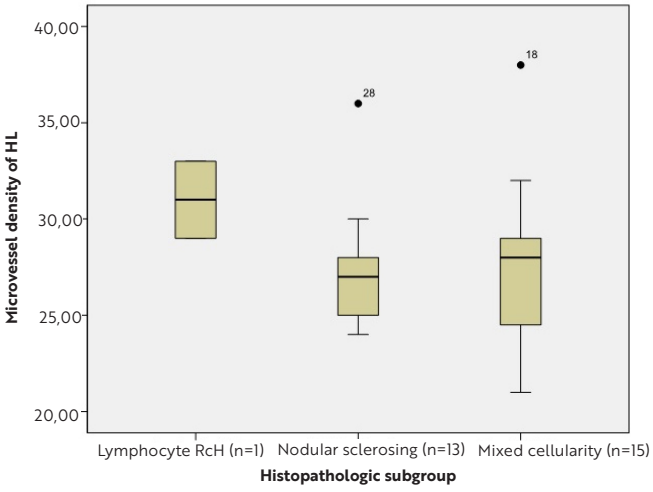

Figure 4. The comparison of microvessel density expression according to histopathologic subgroups

ML: Modgkin's lymphoma

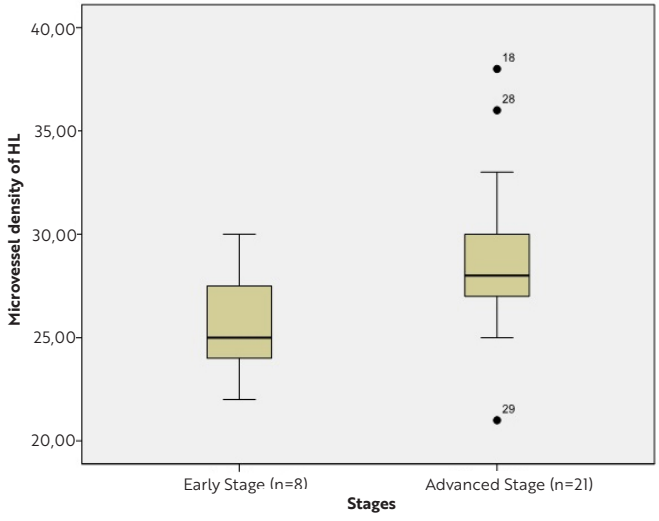

Figure 5. The comparison microvessel density according to stages

ML: Modgkin's lymphoma

Table 4. The Comparison of mast cell count with microvessel density between histopathologic subgroups, Bulky disease (positive vs negative), B-symptom (positive vs negative), stages (early vs advanced) in Hodgkin lymphoma

	Mast cell count Mean ± SD (min.-max.)	p	MVD expression Mean ± SD (min.-max.)	p
Histologic subtype				
Nodular sclerosis	82±34.5 (10-138)	p<0.05*	28±4.2 (24-38)	p>0.05
Mixed cellularity	61±26 (23-117)		26±3 (21-32)	
Bulky disease				
Positive	89.5±24 (70-138)	p<0.05*	25±2 (21-29)	p>0.05
Negative	63±31 (10-117)		28±3 (22-38)	
B-symptom				
Positive	75±31 (10-111)	p>0.05	28±3 (22-38)	p>0.05
Negative	65±31 (24-138		27±3 (21-36)	
Englund				
Early stage (1/2)	75±19 (41-101)	p>0.05	24±2 (22-29)	p<0.05*
Advanced stage (3/4)	68±35 (10-138)		28±3 (21-38)	

MVD: Microvessel density, SD: Standard deviation, min.: Minimum, max.: Maximum

Several studies have shown the effect of MC through their strong angiogenic potential in occurence and progression of solid and hematological tumors. Also, it was reported that angiogenesis and tumorogenesis were decreased in MC- deficient mice [12-14]. In the present study, we aimed to determine the relationship between MVD and MC in HL and RL tissues of children. It was noticed that MC in HL tissue was increased compared to RL. Also, MVD was found to be lower in the HL group than in the RL group. On the other hand, MVD in HL, which is an indicator of angiogenesis, was found to be high in patients in advanced stage rather than early-stage disease.

Previously, MC was found to be highly correlated with angiogenesis in chronic inflammatory diseases, and benign lymphadenopaties as well as tumors. Ribatti et al. [4] reported that angiogenesis and MC density together with tryptase activity increased simultaneously with pathological progression in B-cell non-HLs. In the present study a positive correlation was determined between MC and angiogenesis in the RL group. However; any correlation could not be found between MC and MVD in HL. We supposed that MC contributes to the formation of angiogenesis in RL, but angiogenesis is more complicated process in HL.

HL differs from other malignant lymphomas in that it displays distinct histopathological features. It is characterized by the presence of a few tumour cells, Hodgkin and Reed-Sternberg (HRS) cells, surrounded by various inflammatory cells including B and t-cells, eosinophils, basophils, macrophages, plasma cells and MCs. HRS cells interact with the cells in the surrounding microenvironment by production of both cytokines and chemokines and through direct cell contact. Several studies regarding the association between increased MC counts and nodular sclerosis histology in HL have been reported in the literature [10-14]. Andersen et al. [11] reported that a high number of tumor MCs were associated with nodular sclerosis subtype histology in adult HL. They have determined that degree of MC infiltration was not a prognostic factor in HL of nodular sclerosis subtype. In contrast, mixed cellularity HL with a high number of intratumoral MCs correlated significantly with poorer outcome both in terms of overall and event-free survival [11]. Molin et al. [15] reported that patients with increased MC infiltration had poor prognosis in HL with a proposed mechanism involving the stimulation of HRS by CD30L produced by MCs. In the present study, the number of MCs was found to be higher in the nodular sclerosis subgroup and bulky disease than in the mixed cellularity subgroup which made us think that MCs play an important role in the formation of the tumorogenesis and fibrosis which is distinctive feature of nodular sclerosis histology. Similarly, a significantly positive correlation was reported between the rate of fibrosis and the number of MCs in nodular sclerosis histology [16]. Therefore, according to our data the presence of higher MC counts in the nodular sclerosis subtype can be considered as evidence of its involvement in the histopathological structure and the formation of fibrotic bands. Keresztes et al. [17] retrospectively studied histological samples from 104 patients with HL, and correlated MC positivity with better overall survival. However inconsistent with previous studies, in their study this difference had only a borderline statistical significance. In the present study, because of the limited number of patients and high survival rates (93%), we could not statistically evaluate this correlation.

So far, studies regarding the contribution of MC to tumor angiogenesis are still contradictory and limited in number especially in pediatric HL. Korkolopoulou et al. [18] investigated angiogenesis in 286 HL patients using a morphometric approach. They reported that parameters of the vessels such as their calibers showed a gradual increase through Ann Arbor stages 1-4. Conversely, in their study MVD expressions declined in advanced stages of the disease. MVD expressions in HL were lower compared to the RL group, but higher in patients in the advanced stage rather than early stage of the disease. In addition, MVD expressions were correlated with advanced stage. On the other hand, although statistically insignificant, the number of MCs were lower in patients in the advanced stage of the disease despite higher MVD expressions. This result supports the fact that MCs are more active in the early stages and MC migration is reduced by various cytokines in the advanced stages Similarly, Glimelius et al. [8] studied the relationship between the extent of angiogenesis and MC, but any significant correlation could not be found between increased MVD expressions and higher MC counts. Also, they reported that increased MVD expressions are important for the prognosis of HL.

Englund et al. [19] studied MC infiltration in tissues of pediatric patients with HL. They determined increased MC counts in cases with advanced stages and in the presence of B-symptoms. In cases with high MC counts (≥62 per 10 HPF), hemoglobin and albumin levels were lower, but ESR was elevated. In cases with MC counts over median values (≥24 per 10 HPF), ESR and CRP were elevated. In the present study, MC counts were negatively correlated with LDH which is an indicator of advanced disease, and positively correlated with age and nodular

sclerosis subtype. There weren't any correlation with other prognostic factors such as increased white blood cell counts, albumin levels, ESR, and advanced stage of the disease.

Study Limitations

There are some limitations to the present analysis. Firstly, we could not analyse MC and MVD in patients with relapsed or primary refractory disease, because of the limited number of patients. Secondly, we could not determine whether increased MCs have an impact on poor prognosis of pediatric patients with HL.

CONCLUSION

The mean MC counts were higher especially in nodular sclerosis subtype of HL. On the other hand, MC in HL was not found to be correlated with MVD contrary to RL. Our data suggest that MC may have limited contribution to angiogenesis in childhood HL.

Ethics

Ethics Committee Approval: This study was approved by the Research Ethics Committee of the Ankara Children Hematology and Oncology Training and Research Hospital (approval number: 2015-059).

Informed Consent: Since our study had a retrospective design, informed consent was not obtained from the patients.

Peer-review: Internally peer-reviewed.

Author Contributions

Surgical and Medical Practices: D.Ö., E.K., S.E., A.Y.E., M.I., Concept: D.Ö., E.K., Design: D.Ö., S.E., Data Collection and/or Processing: D.Ö., E.K., Analysis and/or Interpretation: D.Ö., Literature Search: D.Ö., Writing: D.Ö.

Conflict of Interest: The authors have no conflict of interest to declare.

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