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EXPRESSION OF VITAMIN D3 RECEPTOR IN TUMOR TISSUE AND RELATIONSHIP BETWEEN CLINICAL FEATURES, PROGNOSTIC INDICATORS AND EXPRESSION OF VITAMIN D3 RECEPTOR IN HODGKIN LYMPHOMA

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Abstract:
Background and objectives: In our study, we aimed to investigate the expression of vitamin D receptor and the relationship between clinical features, prognostic indicators, and expression of vitamin D receptor in Hodgkin lymphoma. **Materials and Methods:** Pathology records and medical files of patients with Hodgkin lymphoma were evaluated. Forty-two tissue samples were analyzed retrospectively. Vitamin D receptor staining was performed with immunohistochemistry. The patients were divided into low, medium, and intense staining subgroups. The demographic data, clinical and biochemical values of patients were reviewed retrospectively, and the relationship between clinical features, prognostic indicators, and vitamin D receptor expressions were examined. **Results:** VDR staining was positive in Reed-Sternberg cells of all Hodgkin lymphoma patients. The

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cases were divided into three groups according to VDR staining intensity as low, medium and intense staining and compared with known clinical prognostic parameters. Only the presence of symptom B was statistically significantly different. Gender, bone marrow involvement, extralymphatic involvement, mediastinal mass, bulky mass, mean leukocyte count, and treatment response were associated with vitamin D receptor staining intensity, but they were statistically insignificant. **Conclusion:** Our study is the second study showing VDR in tumor Hodgkin lymphoma tumor tissues and is meant to be the first to evaluate its association with clinical and biochemical prognostic laboratory tests. Vitamin D receptor staining in all Hodgkin lymphoma patients led to the conclusion that VDR can be used in the histopathological differential diagnosis of HL. More studies are needed to assess and demonstrate the relationship between prognostic and diagnostic indicators and vitamin D receptor intensity of immunohistochemically detected VDR in tumor tissues of Hodgkin lymphoma. Also, further studies with serum vitamin D levels and other histologic subtypes can provide more reliable results.

Keywords: Hodgkin lymphoma, vitamin D, vitamin D receptor, prognostic indicator

1. Introduction

Vitamin D is associated with various diseases besides bone metabolism diseases. Several studies have shown that vitamin D has protective effects against Schizophrenia, Multiple sclerosis, Type 1 diabetes [1,2,3].

Vitamin D and its analogs have different effects on cancer incidence and mortality. It has been determined that low serum vitamin D levels are associated with increased risk and mortality for some types of cancer (breast, colon, lung, prostate, lymphoma, esophagus, etc.) [4,5,6,7].

There are limited studies in which the vitamin D receptor (VDR), which must be bound in order to show the effect of vitamin D in tissues, was examined in normal and tumor tissues. It was shown in a study that VDR was intensively stained in the Hodgkin's lymphoma tissues relative to the non-Hodgkin's lymphomas [14].

In our study, we aimed to investigate the vitamin D receptor levels in tumor tissue of patients with Hodgkin's lymphoma, as well as vitamin D receptor expression and its relation with the clinical features and prognostic markers.

2. Material and Methods

In our study, tumor tissue biopsy specimens and medical file records of 42 patients diagnosed with Hodgkin's Lymphoma were evaluated. The tissue biopsy specimens of 42 patients who were admitted to the Celal Bayar University Faculty of Medicine, Hafsa Sultan Hospital between January 2012 and August 2015, diagnosed with Hodgkin's lymphoma and whose clinical and laboratory information were able to be obtained were

planned to be evaluated retrospectively. Ethical approval was taken from Celal Bayar University, Faculty of Medicine, Scientific Research Ethics Committee. Vitamin D receptor staining was performed immunohistochemically in the tumor tissues of patients with Hodgkin lymphoma.

Patients' demographic data (age, sex), clinical features (presence of B symptoms, stage, subtype, splenic involvement, bone marrow involvement, extralymphatic field involvement, number of nodal areas, bulky mass, mediastinal mass ratio) and biochemical values (albumin, erythrocyte sedimentation rate, LDH, hemoglobin, leukocyte, lymphocyte, eosinophil) were recorded by retrospective file evaluation. Patients were staged according to the Ann-Arbor staging system and grouped as early-stage (stage 1-2) and advanced stage (stage 3-4). The prognostic features of early-stage patients were obtained from the prognostic scoring system of the NCCN guideline and advanced-stage patients prognostic features were obtained from the IPS scoring system. Also, responses to the first 4-6 cycles of treatment were obtained with retrospective file evaluation. The relationship between patients' clinical and prognostic features, as well as the intensity of vitamin D receptor staining, was investigated.

2.1 Immunohistochemistry

Vitamin D3 receptor antibody (Cell Signaling 12550 S, Danvers, USA) was stored at -20 ° C until tissue sections were done. 3.5 micron-meter sections from formalin-fixed, paraffin-embedded tissues were made ready for use after 4 hours of waiting in 58˚C vacuum furnace for 4 hours, and printing barcodes. In a fully automated immunohistochemistry and fluorescence in situ hybridization device in the pathology laboratory, after boiling with citrate for 60 minutes, vitamin D receptor antibody titration was performed at 37°C for 52 minutes, and hematoxylin was used for the background dye with a waiting time of 8 minutes and the Bluing reagent with a waiting time of 4 minutes. Images obtained from the tissues were evaluated using standard light microscopy. Colonic adenocarcinoma was used as a positive control, and the stained cells were seen as brown and the non-stained cells as blue. Hodgkin's lymphoma preparations were divided into three groups according to the intensity of VDR staining of Reed-Sternberg cells as low, medium, and intense staining. In the same preparation, it was observed that different tumor cells (RS) were stained at different densities. Moreover, the density at which more than 50% of the tumor cells were stained was mainly accepted when classifying the preparations.

The samples were examined and classified by two independent pathologists. An Olympus BX53 microscope was used to acquire images. Photographs were recorded on a computer with the Olympus DP2-BSW program.

2.2 Statistical Analysis

Data recorded in Excel format were analyzed using the SPSS 21.0 statistical program. The clinical parameters were compared with the intensity of the vitamin D receptor staining using the chi-square test. $p < 0.05$ was considered statistically significant.

3. Results

Of the 42 Hodgkin lymphoma patients included in the study, 54.8% (n=23) were male and 45.2% (n=19) were female. The clinical characteristics of our patients included in the study are summarized in Table 1.

Table 1: Clinical characteristics of patients with Hodgkin lymphoma

	Number (n=42)	**Percent (%)**
Mean Age	44,0±16,7 (19-78)	
Gender		
Male	23	54,8
Female	19	45,2
Subtype		
NSHL	19	45,2
MSHL	15	35,7
LZHL	0	0
LFHL	0	0
NLPHL	1	2,4
Unidentified	7	16,7
Ann-Arbor Stage		
Stage I	8	19
Stage II	9	21,4
Stage III	12	28,6
Stage IV	13	31
Extranodal Involvement		
No	27	64,3
Yes	15	35,7
Spleen Involvement		
No	29	69
Yes	13	31
Bone Marrow Involvement		
No	28	66,7
Yes	11	26,2
Not Performed	3	7,1
B symptoms		
No	23	4,8
Yes	19	45,2
Mediastinal Mass		
No	39	92,9
Yes	3	7,1
Bulky Mass		
No	34	81

Yes	8	19
Mean number of nodal areas (CT/PET CT)	4,7±3,2 (1-13)	
LDH (U/L)	226±98,3 (119-610)	
Mean albumin level(g/dl)	4,0±0,4 (2,8-4,8)	
Sedimentation rate (mm/hour)	41,3±31,2 (5-126)	
Mean hemoglobin level (g/dl)	12,9±2,0 (7,8-16,3)	
Mean leukocyte count (10^3/μl)	9,3±4,2 (2,7-21,2)	
Mean lymphocyte count (10^3/μl)	1,8±1,0 (0,3-4,9)	
Mean eosinophil count (10^3/μl)	0,2±0,1 (0-0,7=	
Prognostic Score		
Early stage good prognosis	9	21,4
Early stage poor prognosis	8	19
Advanced stage good prognosis	15	35,8
Advanced stage poor prognosis	10	23,8
PET/CT Treatment response		
Progression	5	11,9
Regression	36	85,7
Untreated	1	2,4

Vitamin D receptor was positive in all examined preparations. When evaluating the preparations, colon adenocarcinoma case preparation was used as a positive control. The stained cells were brown, and the unstained cells were blue (Figure 1-3). Patients were evaluated in 3 groups according to their intensity of staining as low (1), medium (2), and intense (3) staining (Figure 1-3). Different tumor cells showed a different density of staining in the same preparation (Figure 1). The density at which more than 50% of the tumor cells were stained was mainly accepted when classifying the preparations. 23.8% of patients (n = 10) showed low, 47,6% (n = 20) medium, and 28.6%' s (n = 12) showed intense staining (Table 2).

Table 2: VDR staining intensity

VDR staining intensity	Number of patients	Percent (%)	Cumulative Percent (%)
Low	10	23,8	23,8
Medium	20	47,6	71,4
Intense	12	28,6	100,0
Total	42	100,0	

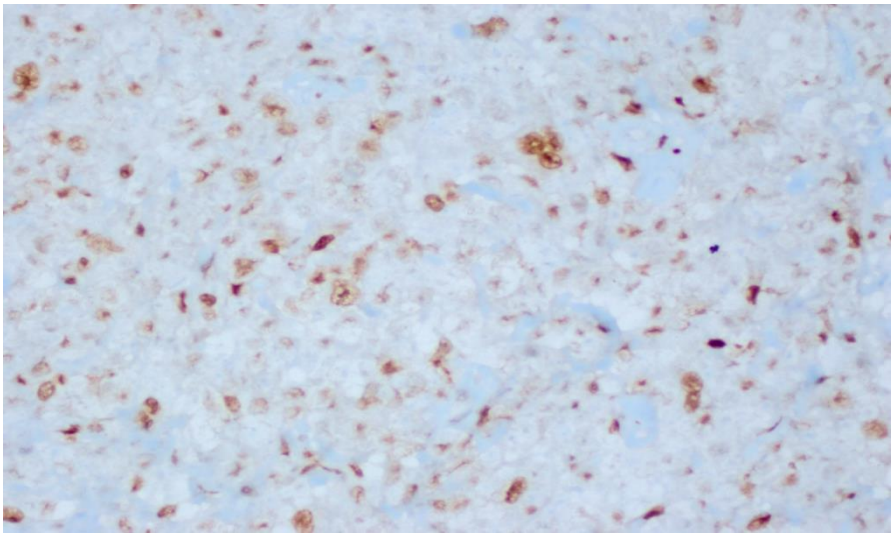

Figure 1: Classical Hodgkin Lymphoma, HRS cells, (VDR X 400), Low staining

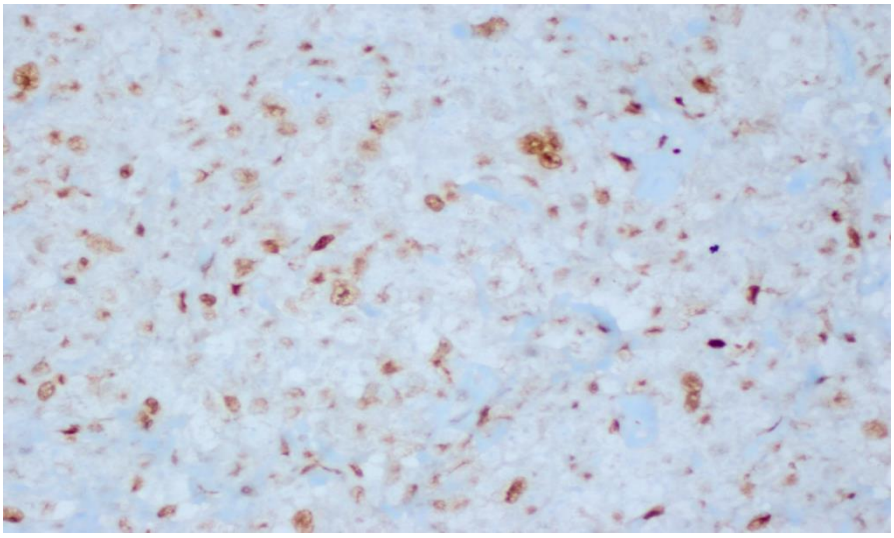

Figure 2: Classical Hodgkin Lymphoma, HRS cells, (VDR X 400), Medium staining

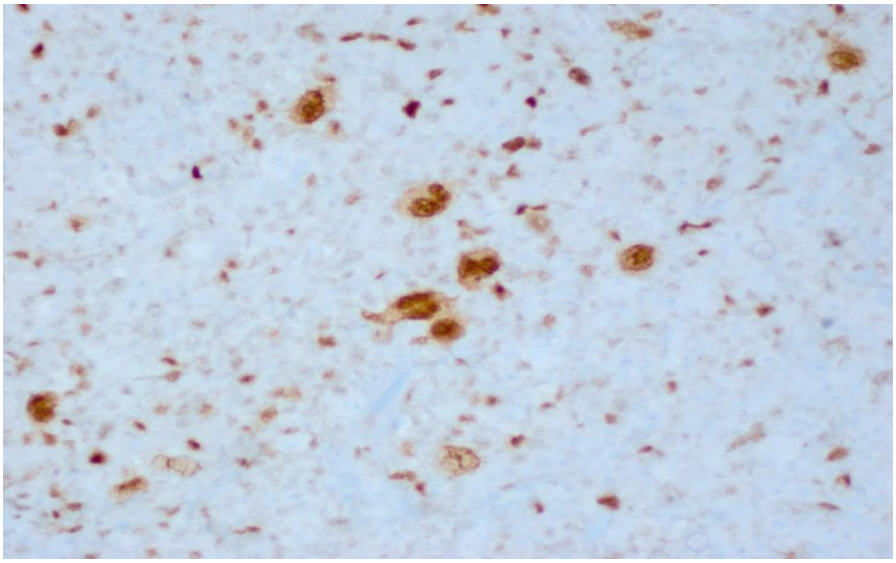

Figure 3: Classical Hodgkin Lymphoma, HRS cells, (VDR x 400), Intense staining

In the comparison with B symptoms (fever, weight loss, night sweats), 10% (n = 1) of the patients who had low staining, 65% (n = 13) of the patients who had medium staining, and 41.7% (n = 5) of the patients who had intensive staining had B symptoms. A statistically significant difference was observed between the presence of B symptoms and vitamin D receptor staining intensity (p=0.016) (Table 3).

Table 3: Relationship between VDR and B symptoms

			VDR staining intensity			Total
			Low	Medium	Intense	
B symptoms	No	Number	9	7	7	23
		% In B symptoms	39,1%	30,4%	30,5%	100,0%
		% In VDR	90,0%	35,0%	58,3%	54,8%
	Yes	Number	1	13	5	19
		% In B symptoms	5,3%	68,4%	26,3%	100,0%
		% In VDR	10,0%	65,0%	41,7%	45,2%
Total		Number	10	20	12	42
		% In B symptoms	23,8%	47,6%	28,6%	100,0%
		% In VDR	100,0%	100,0%	100,0%	100,0%
p value						0,016

In comparison with gender, there was an equal number of men and women in the low staining group. 55% (n=11) male and 45% (n = 9) female patients were medium stained. 58.3% (n=7) of the patients with intense staining were male, and 41.7% (n=5) were female. It was observed that male patients had more medium and intense staining rates. No statistically significant difference was found between the staining characteristics and gender in the statistical evaluation. (p=0,926) (Table 4).

Table 4: Relationship between VDR and gender

			VDR staining intensity			Total
			Low	Medium	Intense	
Gender	Male	Number	5	11	7	23
		% In Gender	21,7%	47,8%	30,4%	100,0%
		% In VDR	50,0%	55,0%	58,3%	54,8%
	Female	Number	5	9	5	19
		% In Gender	26,3%	47,4%	26,3%	100,0%
		% In VDR	50,0%	45,0%	41,7%	45,2%
Total		Number	10	20	12	42
		% In Gender	23,8%	47,6%	28,6%	100,0%
		% In VDR	100,0%	100,0%	100,0%	100,0%
P value						0.926

In comparison with the stages of the patients, there was no linear relationship between the stage and the staining characteristics. There was no statistically significant difference. (p=0,168)

A comparison of pathological or imaging-determined bone marrow involvement and staining characteristics showed a 10% (n=1) involvement in low stained cases, 30.3% (n=6) in medium stained cases, 33.3% (n=4) in intensely stained cases. The presence of bone marrow involvement increased with increasing intensity of staining. However, no statistically significant difference was found between bone marrow involvement and vitamin D receptor staining characteristics. (p=0,734)

No statistically significant difference was found between the subtypes and the vitamin D receptor staining intensity in comparison with the subtypes of patients (p=0,805)

MMR (maximum tumor width/maximum intrathoracic width ratio) specified in the NCCN guideline was calculated for each patient. It was accepted as positive for mediastinal mass in patients with MMR ratio greater than 0.33. No mediastinal mass was detected in any of the low stained cases. Mediastinal mass was observed 5% (n=1) in medium stained cases, 16.7% (n=2) in patients with intensive staining. There was an increase in the percentage of mediastinal mass with the increase in staining intensity, but no statistically significant difference was found in the statistical evaluation. (p=0,280)

It was found that 40% (n=6) of the patients with extralymphatic lesions were intensely stained, 46.7% (n=7) medium stained, and 13.3% (n = 2) were low stained. An increase in the percentage of extralymphatic lesions was observed with the increase in staining intensity, but no statistically significant difference was found in the statistical comparison. (p=0,342)

It was observed that 50% (n=4) of the cases with bulky mass (larger than 10 cm) had medium staining, and 50% (n=4) of the patients had intense staining. Patients who had bulky masses had no low staining. There was a correlation between the increase in staining density and the percentage of bulky mass, but no statistically significant difference was found. (p=0,139)

No statistically significant difference was observed between the patients with regression or progression and the intensity of staining after the first-line treatment. (p=0,835)

Patients were divided into two groups as early stage (stage 1 and 2) and advanced stage (stage 3 and 4). There was no statistically significant difference between stage characteristics and VDR staining intensity. (p=0,809)

The mean leukocyte count of patients was $7,4x10^3/\mu l$ in low stained cases, $9,5x10^3/\mu l$ in medium stained cases, and $10,5x10^3/\mu l$ in patients with intensive staining. The mean leukocyte count increased with an increase in staining intensity. There was no statistically significant difference between leukocyte count and vitamin D receptor staining intensity. (p=0,214)

The nodal areas of the patients were defined according to the Ann-Arbor staging system. The mean number of nodal areas was 4.3 in the low stained cases, 4,7 in the medium stained cases and 5,2 in the intensely stained cases. The number of nodal areas

increased with an increase in staining intensity. No statistically significant difference was found in statistical evaluation. (p=0,667).

4. Discussion

Although the relationship between vitamin D and bone diseases is known, the relationship between different types of cancers has recently been remarkable. Most of the studies are related to serum vitamin D level, some studies have examined the relationship between sun exposure and regional vitamin D and cancer, and it was observed that there were quite different results [4, 5, 6]. However, there are few studies in the literature investigating the relationship between Hodgkin's lymphoma and vitamin D, which are mostly in the form of studies involving different cancer groups [7]. VDR was found in the cytoplasm and nucleus in target cells such as normal intestinal epithelium, renal tubular cells, and bone cells, also in blood cells such as macrophages, dendritic cells, T lymphocytes [8]. The complex combination of vitamin D with VDR activates many genes that may cause cell growth, differentiation, and apoptosis. It has been shown that active vitamin D decreases the growth of cells by regulating the genes responsible for cell proliferation by VDR in laboratory studies. [9]. Among the studies investigating VDR expression, there are limited data on vitamin D receptor expression in lymphoma.

Hickish et al. investigated the presence of vitamin D receptor expression in lymph node biopsy specimens of 13 non-Hodgkin lymphoma patients, and staining was detected in 11/13 patients. Ten of the patients who had staining showed low staining. Intense staining was observed in T cells in macrophages and in paracortex [10]. Wang et al. compared vitamin D receptor expression and prognostic factors in tumor tissues of 61 patients with pancreatic cancer. Vitamin D receptor has been shown to be a potential prognostic factor associated with differentiation and progression in pancreatic cancer [11].

Ditsch et al. investigated the relationship between vitamin D receptor expression and prolonged survival in tumor tissue in 82 breast cancer cases. VDR expression was associated with tumor size and lymph node involvement among clinical prognostic factors. VDR expression showed a significant difference between progression-free survival and overall survival. Better progression-free survival was observed in patients with high immunoreactivity scores for VDR expression, and better overall survival was observed in those with higher scores than those with moderate/negative immunoreactivity scores [12]. In a study conducted in India, serum D vitamin value in patients with breast cancer was a risk factor, and the use of vitamin D receptor expression as a prognostic factor in response to chemotherapy was investigated. Vitamin D deficiency was found in breast cancer patients (66%) and control group (31.2%). VDR expression was significantly decreased in breast cancer tissue compared to benign breast tissue. In patients with VDR positive and high scores, the complete response rate to neoadjuvant chemotherapy was found to be significantly higher. It was thought that

vitamin D deficiency might be a risk factor for breast cancer development, and VDR can be used as a determining factor for response to breast cancer [13].

In a single study by Renné et al. pathological preparations of a total of 193 lymphoma cases (55 Hodgkin lymphoma, 135 B-NHL) were used. If there is a vitamin D receptor staining in more than 50% tumor cell, the case is considered as positive staining. In the patients with Hodgkin lymphoma 80% (n=44/55) and in non-Hodgkin lymphoma patients only 17.4% (n=24/138) had positive staining. A statistically significant difference was found between the Hodgkin and non-Hodgkin patients in terms of staining. In the subgroups of Hodgkin's lymphoma, the most common staining positivity was nodular sclerosis type 88.5% (n=23/26), 75% (n=15/20) mixed cellular subtype and 67.7% (n = 6/9) nodular lymphocyte predominant subtype [14]. In our study, only patients with Hodgkin lymphoma were included because of the significant difference in staining compared to non-Hodgkin lymphoma cases. Our study is the first study to compare the prognostic factors of Hodgkin lymphoma cases with vitamin D receptor expression immunohistochemically. Vitamin D receptor staining of all Reed-Sternberg cells in tumor tissues of all patients with Hodgkin's lymphoma suggests that VDR may be a candidate for use in the differential diagnosis of classical Hodgkin's lymphoma.

In our study, 54.8% (n = 23) of the patients with Hodgkin lymphoma were male and 45.2% (n = 19) were female. In the literature, 62% of patients with Hodgkin's lymphoma were male, 38% of the patients are women in Turkey [15]. In the comparison between gender and VDR expression, it was observed that there was a high percentage of medium and intensive staining in male patients (p=0,926). In male patients, the presence of medium and intense staining suggests that the male gender, which is one of the poor prognostic criteria in IPS scoring, may be associated with VDR [16].

96.7% (n = 41) of the patients included in the study were compatible with the 95% classic

Hodgkin lymphoma rate reported in the literature. 45.2% (n = 19) of the cases had nodular sclerosing, 37.5% (n = 15) of the mixed cellular subtype, which were compatible with rates of 70% nodular sclerosing, and 20-25% mixed cellular in the literature. In the literature, the rare (5%) nodular lymphocyte predominant subtype was found to be compatible with 2.4% (n=1) in our study [17]. Lymphocyte-rich and lymphocyte-depleted type Hodgkin lymphoma cases were not observed.

Bone marrow involvement detected by immunohistochemistry or imaging was seen in 26.2% (n=11) of the patients and was considered to be well above the 5% reported in the literature [18]. When only bone marrow involvement was diagnosed immunohistochemically, the rate was 2.3% (n = 1), which was close to the literature. In a study by Bangerter et al., 38 (86%) of 44 patients with bone marrow involvement on PET CT showed positive biopsy [19]. Young et al. confirmed the presence of infiltration in biopsies from sites with bone marrow involvement on PET CT. Moreover, 59% of 45 patients in the study showed that the stage of the disease changed [20]. It is thought that the rate of detection of bone marrow involvement may increase with the expansion of PET CT in staging and response to treatment. In our study, the comparison between bone

marrow involvement and staining characteristics showed that the presence of bone marrow involvement increased with increasing staining intensity, but no statistically significant difference was observed. It was thought that this result might be due to the small number of patients included in the study.

Extralymphatic lesions were seen in 35.7% (n = 15) of the cases, and bone marrow (26.2%), liver (16%), lung (2.3%), and nasopharynx (2.3%) involvement were detected. More than one extralymphatic lesion was observed in the same patient. The rate of the extralymphatic lesion was higher than the rate of 10-15% found in the literature, and this was attributed to the fact that bone marrow involvement, which constitutes the majority of the cases, was more than expected in the present patients.

B symptoms were observed in 45.2% (n = 19) of our patients, and it was compatible with 35-40% in the literature [17]. In comparison with B symptoms, a significant difference was found between the presence of B symptoms and vitamin D receptor staining intensity. The presence of B symptoms is known as poor prognostic criteria in patients with Hodgkin lymphoma [21]. A significant correlation between VDR expression and the presence of B symptom suggests that the intensity of VDR expression may be a potential prognostic criterion in patients with Hodgkin lymphoma.

40% (n = 17) of the patients with Hodgkin lymphoma and 60% (n = 25) of the patients with advanced stage were included in our study, and a statistically significant relationship was found between VDR and B symptoms, among prognostic clinical findings and laboratory test. Male gender, bone marrow involvement, extralymphatic area involvement, mediastinal mass, bulky mass, mean leukocyte count, number of nodal areas, treatment response rates and VDR staining intensity were not statistically significant. There was no correlation between other clinical and prognostic factors such as age, stage, spleen involvement, hemoglobin, albumin, LDH, sedimentation value, lymphocyte and eosinophil count, subtype data, and prognostic groups and VDR staining intensity. The low number of patients led to a small number of comparable subgroups. This is likely to affect the results. The absence of Hodgkin lymphoma subgroups other than mixed cellular and nodular sclerosis makes it challenging to evaluate the relationship between VDR and histological subtypes.

5. Conclusion

Our study is the second study showing VDR in Hodgkin's lymphoma tumor tissue and its relationship with important prognostic clinical and laboratory features according to the literature data. A statistically significant difference between VDR staining intensity and the presence of B symptoms, which is known as poor prognostic criteria, suggests the use of VDR intensity as a potential prognostic criterion and further studies are needed to support this.

The staining of all Reed-Sternberg cells with vitamin D receptor in tumor tissues of all cases of Hodgkin lymphoma suggests that VDR may be a candidate marker, especially in the histopathological differential diagnosis of classical Hodgkin lymphoma. In order to evaluate the diagnostic and prognostic significance of VDR detected by the immunohistochemical method in tumor tissue in patients with Hodgkin lymphoma, more comprehensive studies, including serum vitamin D level, other histological subtypes and treatment results, are considered to be useful.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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