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Original Article

Nodular Lymphocyte Predominant Hodgkin Lymphoma: A Single Center Experience

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ABSTRACT

Aim: Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare subtype of lymphoma classified within Hodgkin lymphomas. Often the diagnosis is made at an early stage. Treatment varies according to the stage of the disease and the underlying prognostic factors. Because of cluster of differentiation 20 expression, rituximab-based agents can be used for treatment. In this study, we aimed to present the demographic, treatment, and survival data of patients with NLPHL in the context of the existing literature.

Methods: In our study, demographic characteristics, laboratory findings, disease stage, and treatments administered to patients diagnosed with NLPHL between 2012 and 2024 were evaluated.

Results: Of the 13 patients enrolled in the study, seven were male, and the median age was 44 years. Of the patients, eight were in the early stage and five were in the advanced stage. One patient had liver involvement, three had splenic involvement, seven had subdiaphragmatic involvement, and four had a bulky mass. Rituximab was added to the treatment regimens of six patients. Progression was observed in two patients. One patient died from Coronavirus disease 2019-related pneumonia. While the 2-year and 5-year overall survival of our patients were both 92%, progression-free survival was 100% at 2 years and 45.5% at 5 years.

Conclusion: NLPHL is a rare condition that, despite its generally favorable prognosis, requires effective treatment because of the risk of recurrence and transformation into diffuse large B-cell lymphoma (DLBCL). Although data on the transformation of subdiaphragmatic involvement into DLBCL exist in the literature, information on disease progression is lacking.

Keywords: Nodular lymphocyte-predominant hodgkin lymphoma, overall survival, progression free survival

Introduction

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare subtype, accounting for 5%-13% of all patients with Hodgkin lymphoma (HL) [1]. NLPHL occurs predominantly in males, accounting for 75% of patients. NLPHL usually occurs between the ages of 30 and 40 [2,3].

In NLPHL, the malignant cells are called lymphocyte-predominant (LP) cells. Although Reed-Sternberg cells and LP cells seen in classical HL originate from germinal centre cells, they show morphological differences [4]. Unlike Reed Sternberg cells, LP cells express cluster of differentiation 20 (CD20) from B cell markers, while they do not express CD15 and CD30 [5].

Most patients have localized disease with a slowly progressive course. It usually involves peripheral lymph nodes. Central lymph node involvement and extranodal involvement are rarely observed. Bone marrow involvement is observed in 1-2%, liver involvement in 2-3%, and spleen involvement in 5% [1].

Because the pathological and clinical features of the disease differ from classical HL, the treatment approach also differs. The ideal treatment for NLPHL has not yet been determined. Depending on disease stage and patient risk factors, treatment options include monotherapy, anti-CD20 antibody therapy, radiotherapy (RT) alone, or combination therapy involving anti-CD20 antibody with or without RT plus chemotherapy regimens such as doxorubicin, bleomycin, vinblastine, and dacarbazine

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(ABVD) or cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Treatment selection should primarily take into account effectiveness and toxicity, since the disease progresses slowly and has a good prognosis [6]. Although this disease is associated with longer survival than lymphoma, it also has higher rates of secondary malignancies and treatment-related deaths; therefore, patient-specific treatment selection is important [7].

In this study, we aimed to contribute survival data to the literature by evaluating treatments given, demographic characteristics, clinical and laboratory values, stage, and prognostic risk factors of patients we followed with an NLPHL diagnosis.

Methods

The study included 13 patients diagnosed with NLPHL who were followed at the Fırat University Faculty of Medicine Adult Hematology Clinic between December 2012 and December 2024. Ethics committee approval, was obtained from the Fırat University Rectorate Non-Interventional Scientific Research Ethics Committee (approval no: 2025/06-48, date: 24/04/2025). Since the data were collected from medical records without revealing the identities of the participants and the study was retrospective, consent was not obtained from the patients.

The patients' data were obtained from the patient files and the hospital information system. The following variables were evaluated: Age; gender; survival status; mean follow-up time; recurrence status; stage; international prognostic index (IPI) score in advanced-stage (stage III-IV) disease; presence of adverse risk factors in early-stage (stage I-II) disease; subdiaphragmatic involvement; liver and spleen involvement; presence of bulky disease; treatment response; haemogram and biochemical parameters; overall survival (OS); and progression-free survival (PFS) were evaluated.

For early-stage patients, mediastinal mass, extranodal disease, involvement of ≥ three nodes, and elevated sedimentation rate (>30 mm/h in the presence of B symptom, >50 mm/h in the absence of B symptom) were considered adverse risk factors, and lymphocyte counts below 1,000/mm³ were considered indicative of lymphopenia.

Patients in the early stage received only RT, and patients in both early and advanced stages received chemotherapy ± Rituximab ± RT, according to the follow-up physician's decision. The time from diagnosis to death or last follow-up was defined as OS, and the time from remission after treatment to relapse or death was defined as PFS. Complete response (CR) was defined as the absence of disease symptoms, a positive positron emission tomography (PET) at baseline or a negative PET in those with any residual mass, or absence of involvement on subsequent biopsies when initial bone marrow involvement was present.

Patients' responses were evaluated according to the Lugano response criteria [8]. Recurrences occurring within 12 months after treatment were considered early recurrences.

Statistical Analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) for Windows, version 25.0 (SPSS, IBM Corp., Armonk, NY, USA). Descriptive statistics are presented as n and % for categorical variables and median (minimum-maximum) for continuous variables. The Kaplan-Meier method was used to determine survival times; $p<0.05$ was considered statistically significant.

Results

The median age of patients is 44 years (range 18-73 years); 53% are male and 46% are female. Of the patients, five were diagnosed at stage I and three at stage II; in total, eight were diagnosed at an early stage. Among patients with early-stage disease, two had a negative risk factor, whereas six had none. At diagnosis, five patients had advanced disease. According to IPI scores for patients with advanced-stage disease, two patients were classified as low risk and three were classified as intermediate risk. Liver involvement was present in only one patient, splenic involvement in three, subdiaphragmatic involvement in seven, and bulky disease in four (Table 1).

Table 2 shows the patients' laboratory results at the time of diagnosis; three patients had anemia and one patient had lymphopenia.

As first-line treatment, three patients received RT only, two received ABVD, two received ABVD+RT, three received R-ABVD, one received R-ABVD+RT, and two received R-CHOP therapy. Progressive disease was present in two patients. In one of these patients, an early relapse occurred after first-line treatment despite an initial CR; autologous Hematopoietic stem cell transplantation was performed after Rituximab, cisplatin, cytarabine, dexamethasone, and the patient is still being followed in remission. The other patient was treated with rituximab-bendamustine; rituximab, gemcitabine, dexamethasone, cisplatin; and R2 (rituximab, lenalidomide), due to refractory disease. Eleven patients achieved CR after first-line treatment, while two patients experienced progression. One of the two patients with progression was stage II with a bulky lesion, and the other was stage IV without a bulky lesion; subdiaphragmatic involvement was detected in both patients. Table 3 presents information on the clinical course of the patients.

During a median follow-up of 60 months (range, 8-144 months), median OS was not reached, and the 2- and 5-year OS rates were both 92.5%. Median PFS was 54.0 months (95% confidence interval: 0.0-112.26), and 100% 5-year PFS with 2- and 5-year PFS being 45.5%. Twelve of the patients are still alive, while one patient is deceased. An ex-patient died of Coronavirus disease (COVID)-related pneumonia while in CR after first-line treatment.

Discussion

NLPHL is a rare subtype of HL with a slow course, with a good prognosis. Patients diagnosed with NLPHL have been shown

Table 1. Characteristic features of patients

Variables	n=13	%
Age		
Median (min-max)	44.0 (18-73)	
Gender		
Male	7	53.8
Female	6	46.2
Stage		
Stage-1	5	38.5
Stage-2	3	23.1
Stage-3	2	15.4
Stage-4	3	23.1
Advanced stage IPI score		
1	1	20.0
2	1	20,0
3	3	60.0
Early stage negative risk factor		
No	6	75.0
Yes	2	25.0
L involvement		
No	12	92.3
Yes	1	7.7
Spleen involvement		
No	10	76.9
Yes	3	23.1
Subdiaphic involvement		
No	6	46.2
Yes	7	53.8
Bulky disease		
No	9	69.2
Yes	4	30.8
1st line treatment		
RT only	3	23.1
ABVD	2	15.4
ABVD+RT	2	15.4
R-ABVD	3	23.1
R-ABVD+RT	1	7.7
R-CHOP	2	15.4
Relapse		
No	11	84.6
Yes	2	15.4
Mortality		
Alive	12	92.3
Ex	1	7.7

RT: Radiotherapy, ABVD: Doxorubicin, bleomycin, vinblastine, dacarbazine, R-CHOP: Rituximab, cyclophosphamide, adriamycin, vincristine, prednisone, Li: Liver, IPI: International prognostic index

to account for 5-13% of HL cases [9,10]. Among our patients, those diagnosed with NLPHL constitute 9% of all patients with HL. From this perspective, it appears consistent with the literature. In this subtype of lymphoma, which is more common in males aged 30-40 years, 53% of our patients were male, and the median age in our study was 44 years [2]. Although our study is compatible with the literature in terms of sex distribution, with a higher prevalence in males, the patients' mean age was slightly higher than that reported in the literature.

The clinical course of NLPHL is indolent, and patients are usually in an early stage at initial diagnosis. In our study, 61% of our patients were early-stage, which is consistent with the literature [11]. Despite a slow course and good prognosis, transformation to diffuse large B-cell lymphoma (DLBCL) is observed during patient follow-up. The risk of transformation to DLBCL is higher in patients with a bulky mass, subdiaphragmatic disease, and splenic involvement [12]. In our study, a bulky mass was observed in 30% (n=4) of patients, subdiaphragmatic involvement in 53% (n=7) of patients, and spleen involvement in 23% (n=3) of patients; no transformation to DLBCL was observed in any of our patients. Although no transformation was observed in our

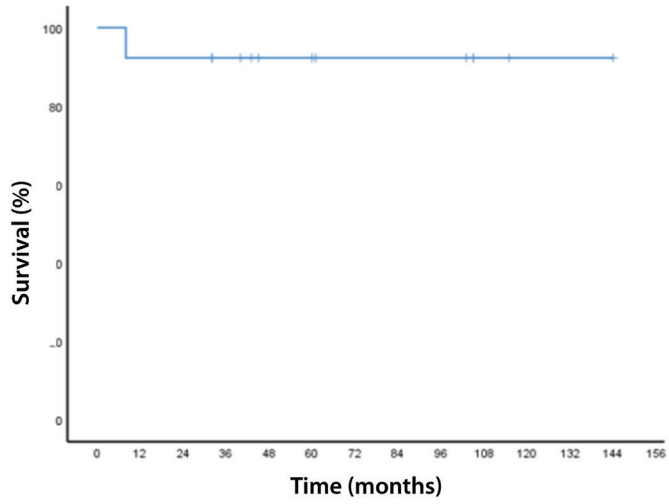

Figure 1. Overall Survival Curve

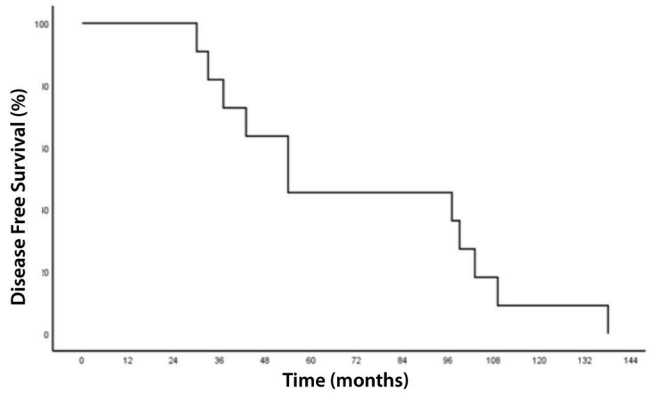

Figure 2. Progression-free Survival Curve

Table 2. Laboratory results at the time of diagnosis of patients

Patient	WBC	HB	PLT	LYM	NEU	ALB	ALT	CR	LDH	SEDIM	CRP
1	4050	13.1	283000	1440	1660	4.3	42	1.2	220	11	11
2	6680	10.1	406000	1460	4430	4.8	11	0.54	167	11	3
3	4230	14.3	199000	1020	2270	4.2	50	0.6	234	7	3
4	8920	15.4	339000	1190	6990	4.8	38	0.82	283	20	3
5	5180	15.9	254000	1210	3110	3.9	28	0.78	226	7	3
6	5990	15.4	230000	1330	3920	4.4	26	0.49	287	7	3
7	8950	11.6	210000	1100	6930	4.3	19	0.5	204	35	3
8	8240	12.6	219000	1690	5530	3.8	13	0.65	254	66	32
9	5370	13.8	210000	990	3370	4.6	15	0.84	276	18	8
10	6990	14	189000	1240	3490	4	19	0.61	218	11	3
11	8260	12.6	330000	2930	4700	4.6	18	0.44	245	21	4
12	6740	13.9	256000	1370	4660	4.5	28	0.7	159	11	3
13	4160	10.5	329000	1380	2500	4.4	17	0.47	192	8	3

WBC: White blood cell, HB: Haemoglobin, PLT: Platelet, LYM: Lymphocyte, NEU: Neutrophil, ALB: Albumin, ALT: Alanine aminotransferase, CR: Creatinine, LDH: Lactate dehydrogenase, SEDIM: Sedimentation rate, CRP: C-reactive protein

Table 3. Clinical course of patients

Patient	Age	Gender	Stage	Liver	Spleen	Subdiaphragmatic invol	Bulky disease	1. Line treatment	Mortality
1	45	Male	3	No	No	Yes	No	R-ABVD	alive
2	29	Female	3	No	No	Yes	No	R-ABVD+RT	alive
3	51	Male	2	No	No	Yes	Yes	ABVD	alive
4	38	Male	2	No	No	No	Yes	R-ABVD	alive
5	29	Male	4	Yes	Yes	Yes	Yes	R-ABVD	Ex
6	32	Male	1	No	No	No	No	RT only	alive
7	18	Female	2	No	No	No	No	ABVD	alive
8	68	Female	4	No	Yes	Yes	No	R-CHOP	alive
9	73	Male	4	No	Yes	Yes	Yes	R-CHOP	alive
10	56	Female	1	No	No	No	No	ABVD+RT	alive
11	37	Female	1	No	No	No	No	RT only	alive
12	66	Male	1	No	No	Yes	No	RT only	alive
13	44	Female	1	No	No	No	No	ABVD+RT	alive

RT: Radiotherapy, ABVD: Doxorubicin, bleomycin, vinblastine, dacarbazine, R-CHOP: Rituximab, cyclophosphamide, adriamycin, vincristine, prednisone

patients, subdiaphragmatic involvement in two patients who progressed drew our attention.

In the literature, splenic involvement is observed in 5% of patients, whereas hepatic involvement is observed in 2-3% [1]. In our patient group, splenic involvement was observed in 23% (n=3) of patients, and hepatic involvement in 7% (n=1). We attribute the discordance between our data and the literature to the small number of patients.

In this rare subtype of lymphoma, the prognosis is usually good and survival rates are high. Eichenauer et al. [13] evaluated 85 early-stage NLPHL patients and found 5-year PFS and OS to be 90% and 100%, respectively. According to the study conducted by Xing et al. [14] involving 42 patients with advanced-stage NLPHL, 5-year OS and 10-year OS were 89% and 86%, respectively; 5-year PFS and 10-year PFS were 72% and 63%, respectively. In the study by Lazarovici et al. [15] involving 314 patients, 10-year PFS was 44% and 10-year OS was 94%. Although results for survival in studies of NLPHL differ in the literature, we believe these discrepancies are attributable to differences in disease stage (some studies included early-stage patients, others late-stage), sample size, and adverse risk factors. In our study, the median 5-year OS was 92% during the 60-month follow-up period, while 2-year PFS was 100% and 5-year PFS was 45%.

Due to the rarity of NLPHL, there is no standardized method of treatment, as studies to guide treatment selection are retrospective. Defining the optimal treatment method remains a significant challenge given that studies are generally small and single-center. When we examine studies in the literature on early-stage disease, Chen et al. [16], in a study of 113 patients, found that the addition of chemotherapy to RT did not improve PFS or OS compared with RT alone. Eichenauer et al. [17] compared combined modality therapy (CMT), extended field radiotherapy (EF-RT), involved field (IF)-RT, four-week standard-dose rituximab treatment, and found that rituximab treatment alone increased the risk of relapse, whereas CMT was equivalent to EF-RT and IF-RT in disease control. They emphasized that IF-RT would be the appropriate treatment for Stage IA patients because of concerns regarding toxicity [17]. Among other studies of treatment for early-stage NLPHL, Savage et al. [18] conducted a study of 88 patients, comparing 32 who received RT alone with 56 who received ABVD, found that both OS (93% vs. 85%) and PFS (93% vs. 66%) rates were higher in the ABVD arm during the 10-year follow-up period. Despite these data, it is difficult to interpret differences among treatment methods and regimens because adverse risk factors were not assessed in these early-stage patient populations treated with each approach. In our study, three patients with Stage I disease received only RT. In Stage I, two patients also received ABVD+RT. In stage 2, two patients were given ABVD and one patient was given R-ABVD. Only two of our early-stage patients had adverse risk factors, and no transformation to DLBC, relapse, or death occurred during follow-up.

Data on the optimal treatment of advanced-stage NLPHL are also limited, as this rare subtype of lymphoma accounts for only 20% of advanced-stage cases. Xing et al. [14] compared advanced-stage NLPHL with classical HL; both groups received ABVD-like chemotherapy and reported that, although OS was similar in both groups, NLPHL patients had a higher recurrence rate than patients with classical HL. Similarly, in their study evaluating treatment outcomes of classical HL and NLPHL treated with ABVD, Ames et al. [19] reported that, among eight patients with stage III-IV NLPHL treated with ABVD, the 5-year recurrence rate was over 50%, and they had the highest recurrence rate compared with all groups (early-advanced-stage HL, early-stage NLPHL). The PFS of patients with advanced NLPHL was lower than that of patients with early-stage NLPHL and of patients with classical HL at early and advanced stages (47% vs. 97%, 85%, and 74%) [19]. According to the results of R-CHOP treatment in NLPHL conducted by Fanale et al. [20] with 59 patients in both early and advanced stages, 27 patients received R-CHOP and the estimated 5 and 10-year PFS during a median follow-up period of 6.7 years was found to be 88.5% and 59.3%, respectively, and among the patients who received systemic treatment, the PFS of those who received R-CHOP was shown to be better compared to all other regimens. Consistent with these studies, R-CHOP therapy is more effective than ABVD-based therapies for patients with advanced-stage disease. In our study, two of the patients with advanced disease received R-ABVD, two received R-CHOP, and one received R-ABVD+RT. While our patient who received R-ABVD achieved CR after treatment, another of our patients died from COVID pneumonia, and one of our patients who received R-CHOP therapy was switched because of refractoriness to treatment.

Study Limitations

The limitations of our study are that it is based on a single center; that data on the regions in which patients received RT were not available; and that survival data by stage could not be calculated because of the small number of patients.

Conclusion

As a result, demographic information, treatment methods, and survival data of this extremely rare group of patients were reported in the literature. Although data on the transformation of subdiaphragmatic involvement into DLBCL exist in the literature, we believe that it will lead to further studies in this regard, since information on disease progression is lacking.

Ethics

Ethics Committee Approval: Ethics committee approval, was obtained from the Fırat University Rectorate Non-Interventional Scientific Research Ethics Committee (approval no: 2025/06-48, date: 24/04/2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: K.O., A.U., Concept: K.O., Design: K.O., Data Collection or Processing: K.O., A.U., Analysis or Interpretation: K.O., Literature Search: K.O., A.U., Writing: K.O., A.U.

Conflict of Interest: No conflict of interest was declared by the authors.

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