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Histopathological and clinical features of nodular lymphocyte-predominant Hodgkin lymphoma and their impact on prognosis: first report from Iran

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Abstract

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare subtype of Hodgkin lymphoma (HL). It shows different histoarchitectural patterns which are reported to be of prognostic significance. This study aimed to investigate the clinicopathological features of NLPHL cases in Shiraz, Iran, and their possible impact on prognosis. Between March 2014 and November 2019, all records for lymphoma were extracted from the electronic files of hospitals affiliated with Shiraz University of Medical Sciences. The slides of all NLPHL cases were extracted and reviewed. Other necessary data was retrieved from hospital records and through direct contact with patients. Among 1168 lymphoma cases, 382 were HLs and 19.1% (73) of them were of the NLPHL type. The median age of NLPHL patients was 34 years. Of the patients, 51.5% showed variant patterns, and 11% of them had BM involvement. The variant morphology was significantly associated with BM involvement ($p = 0.02$). Patients with higher stage tumors had lower OS and PFS rates. Stage, BM involvement, and infra-diaphragmatic involvement were significantly associated with outcomes. The rate of NLPHL and variant morphology seems to be high in our center in Iran. The variant morphology was associated with a higher BM involvement rate but not with OS or PFS. Higher stage, BM, and subdiaphragmatic disease involvement were associated with worse outcomes.

Keywords Nodular lymphocyte-predominant Hodgkin lymphoma · NLPHL · Hodgkin lymphoma · Architectural pattern · Prognosis

Introduction

Hodgkin lymphoma (HL) accounts for 15–25% of malignant lymphomas [1, 2]. About 5% of HL cases are reportedly of the nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) type [2–4]. Unlike the classic subtypes of HL, NLPHL lacks the classical Hodgkin Reed-Sternberg cells (HRS). Instead of HRS, NLPHL is characterized by a characteristic kind of neoplastic cell called lymphocyte-predominant (LP) cells. These cells do not express CD15 or CD 30, but they do express B cell markers, including CD20 [3]. Epidemiologic, morphologic, and immunophenotypic features of NLPHL are summarized in Table 1.

NLPHL affects mostly males in their 4th decade of life and follows a favorable prognosis in most cases. It is generally a localized disease with an indolent clinical course; however, some cases present with advanced disease characterized by marrow and spleen involvement as well as B symptoms [3]. NLPHL shows variable histoarchitectural growth patterns. Fan et al. in 2003 reported six morphologic patterns in NLPHL patients (Table 2) [6]. It has been reported that there are correlations between growth patterns and the clinical course of the disease [7–10].

To the best of our knowledge, there is no report from Iran addressing the histoarchitectural or other clinicopathological

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Table 1 Common epidemiologic, morphologic, and immunophenotypic features of nodular lymphocyte-predominant Hodgkin lymphoma [3, 5]

Epidemiology	Accounts for about 5–10% of Hodgkin lymphomas
	Predominantly affects males
	Most patients are aged between 30 and 50 years
Morphology	Neoplastic cells are called lymphocyte-predominant (LP) cells which have popcorn-like folded nuclei. LP cells are mostly located in the center of reactive B cell nodules and are rimmed by a rosette of T follicular helper cells.
Immunophenotype	LP cells: CD20+, OCT2+, CD75+, CD79a+, BOB1+, PAX5+, CD45+, BCL6+, CD10-, EMA+(50%), CD15-, CD30-
	T follicular helper cells rosette: PD1(CD279)+, CD57+, BCL6+

aspects of NLPHL or their prognostic effects. The current study aimed to find the relative prevalence of NLPHL, the frequency of its different morphologic growth patterns, and the effects of its clinicopathological features on survival and prognosis at hospitals affiliated with Shiraz University of Medical Sciences, Shiraz, Iran. Shiraz University of Medical Sciences is regarded as a referral center in southern Iran.

Materials and methods

Patients and clinical data

The current study was conducted at the Hematopathology Center of Shiraz University of Medical Sciences, Shiraz, Iran. Between March 2014 and March 2019, all records for lymphoma were extracted from the electronic files of hospitals affiliated with Shiraz University of Medical Sciences. The relative prevalence of NLPHL between Hodgkin lymphomas and other types of lymphomas was calculated. Other data including age, gender, primary location of the tumor, stage, BM involvement, treatment information, recurrence, and survival were retrieved from hospital records and through direct contact with patients when needed. The study protocol was approved by the Research Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1398.466).

Morphology and immunohistochemistry review

The immunohistochemistry (IHC) and hematoxylin and eosin (H&E) slides of all NLPHL cases were extracted from the pathology archives. To confirm the diagnosis of NLPHL CD20, CD30, CD15, CD3, and PD1 slides were reviewed. In some cases, CD57, PAX5, OCT2, BOB1, CD23, and LMP1 stains were also available. LP cells were positive for CD20 and negative for CD15, and CD30. PAX5, OCT2, and BOB1 were helpful in some difficult cases. Rosetting T cells were positive for CD3 and PD1. In challenging cases, CD57,

Table 2 Immunoarchitectural patterns of nodular lymphocyte-predominant Hodgkin lymphoma according to Fan et al. [3, 6]

Pattern		Description
Typical	A	Classic nodular pattern, B cell-rich: LP cells are mostly located inside the nodules of small non-neoplastic B cells. LP cells are surrounded by a rim of reactive CD57/PD1-positive T cells
	B	Serpiginous/interconnected nodular pattern: similar to pattern A. The only difference is that B cell nodules are interconnected
Variant	C	Nodular with prominent extra-nodular L&H (LP) Cells: LP cells are frequently located outside the nodules. The background is predominantly composed of reactive T cells as well as small nodules of reactive B cells. LP cells outside the nodules may be surrounded by CD57/PD1(+/-) T cells
	D	Nodular with T cell-rich background: The nodules are mostly composed of reactive T cells with few reactive B cells. LP cells are surrounded by a rim of reactive CD57/PD1-positive T cells
	E	Diffuse pattern (T cell-rich B cell lymphoma-like): LP cells are in a diffuse background of reactive T cells and may be surrounded by CD57/PD1(+/-) T cells. Presence of at least one B cell nodule containing LP cells is necessary to rule out T cell/histiocyte-rich large B cell lymphoma
	F	(Diffuse), "moth-eaten" with B cell-rich background: The background is predominantly composed of reactive B cells. There are small areas of reactive T cells giving a moth-eaten appearance to the background. LP cells are surrounded by a rim of reactive CD57/PD1-positive T cells

CD4, and CD8 staining were also available [3, 5].The cases were subtyped morphologically based on CD20 and/or PAX5, CD3, PD1, and/or CD57stained slides into six patterns (A to F), according to Fan's categorization (Table 2) [5, 6]. In cases exhibiting a minor pattern, if the minor and major patterns were in the same category (both were in typical or variant categories), the case was subtyped according to the major pattern. If there was a minor or major component of variant pattern while the other pattern was typical, according to Hartmann et al. [7], these cases were classified based on their variant pattern. Then they were reclassified as classic (patterns A and B) and variant (patterns C to F) types. To differentiate NLPHL from T cell/histiocyte-rich large B cell lymphoma, immunostaining for PD1, CD20, CD3, CD4, and CD8 was used. If there was at least one small B cell nodule containing LP cells, the case was diagnosed as NLPHL. This criterion was present in all cases with D or E patterns. In addition, the presence of PD1-positive T cell rosettes surrounding LP cells was regarded in favor of NLPHL. Dominance of CD8-positive T cells at the stroma was also considered in favor of T cell/histiocyte-rich large B cell lymphoma [5].

Statistical analysis

Fisher's exact and chi-square tests were used to check the relationship between category variables. The Mann-Whitney U test was used to examine the differences in mean ages with variables in the two groups. The Shapiro-Wilk test was employed to assess normality, and Levene's test was used for homogeneity of variances. Univariate analysis was conducted by univariate Cox regression for the influence of age, gender, stage, BM involvement, pattern, and subdiaphragmatic involvement on overall survival (OS) and progression-free survival (PFS) times. Variables with significant or borderline significant values ($p \le .10$) in the univariate analysis were entered the Cox model for multiple analyses. All analyses were performed using the SPSS statistical software, version 22. p values less than 0.05 were considered statistically significant.

Results

Between March 2014 and November 2019, 1168 cases of lymphoma were diagnosed in hospitals affiliated with Shiraz University of Medical Sciences, Shiraz, Iran. Among these cases, 382 (32.7%) were Hodgkin lymphomas. NLPHL accounted for 19.1% ($n = 73$) of the Hodgkin lymphomas. The median age of 73 NLPHL patients was 34 years (ranging between 3 and 74) with a mean of 36.33 ± 14.59 years. There was no significant difference in age between male and female subjects (35.35 ± 13.19 vs. 38.59 ± 16.15, respectively, $p = 0.39$). The majority of patients were male (69.9%). Eight cases (11%) showed BM involvement, and in 3 of these cases, BM was the primary site of disease presentation (Fig. 1). The median follow-up time was 25 (ranging between 1 and 62) months. At 5 years, the estimation of overall survival was 85%. All cases displayed morphologic and immunophenotypic features characteristic of NLPHL, confirming the original diagnosis. After slide review, 7 cases were excluded from further analysis because of incomplete data, most notably due to small sample size which was not enough to be classified in a morphological pattern subtype. In the remaining cases, 3 (4.7%) of non-BM samples were core needle biopsies and the other non-BM samples ($n = 61$, 95.3%) were excisional biopsies.

Clinical and demographic characteristics of patients are summarized in Table 3. Sixty percent of tumors were located primarily in the cervical and axillary lymph nodes. There were 5 cases with extranodal primary sites. Two of them were located in the bone marrow, and the others were located in the thigh, submandibular, and retroperitoneal soft tissues. Most patients (66.7%) received chemotherapy plus radiotherapy as primary treatment (Table 3). Different chemotherapy regimens (ABVD, CHOP, or CVP) were used, generally including rituximab. Three patients needed salvage therapy who received chemotherapy based (ICE or DHAP) regimens. Pattern A of Fan et al.'s classification was the most frequent pattern (40.9%). Variant morphology was identified in 51.5% of patients. Seventeen cases

Fig. 1 Bone marrow involvement by NLPHL in one of the cases. **a** and **b** The H&E slide shows lymphocytic aggregates in BM containing LP cells ($\times 40$ and $\times 400$, respectively). **c** Large CD20-positive LP cells are seen ($\times 200$). **d**, **e**, and **f** Background lymphocytes are mostly CD4-positive T cells ($\times 40$, $\times 40$, and $\times 200$, respectively). This feature is in favor of NLPHL rather than T cell/histiocyte-rich large B cell lymphoma
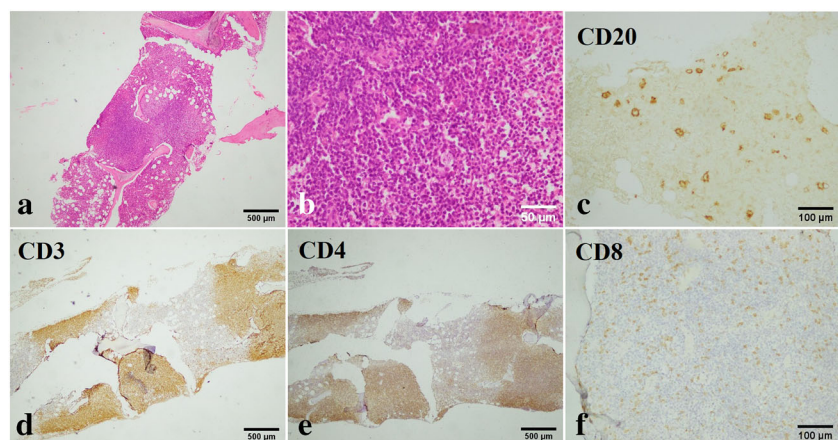
Table 3 Clinical, histological, and demographic characteristics of patients

Variable	Categories	Mean ± SD, or n (%)
Age (years)	–	36.56 ± 15.22
Gender	Female	20 (30.3)
	Male	46 (69.7)
Immunoarchitectural Pattern	A	27 (40.9)
	B	5 (7.6)
	C	19 (28.8)
	D	3 (4.5)
	E	12 (18.2)
	F	0 (0)
Histoarchitectural Pattern	Typical	32 (48.5)
	Variant	34 (51.5)
Primary Site	Neck LN	18 (27.3)
	Axillary LN	24 (36.4)
	BM	2 (3)
	Submandibular LN	3 (4.5)
	Inguinal LN	6 (9.1)
	Others	13 (19.7)
Subdiaphragmatic involvement	Supra-diaphragmatic	50 (75.8)
	Infra-diaphragmatic	16 (24.2)
BM involvement	Not involved	60 (90.9)
	BM involved	6 (9.1)
Ann Arbor Stage	I	43 (65.2)
	II	12 (18.2)
	III	6 (9.1)
	IV	5 (7.6)
Outcome	Dead	4 (8.8)
	Alive with recurrence or progression	7 (15.5)
	Alive with no recurrence or progression	34 (75.5)
Treatment	Not treated	4 (8.9)
	Radiotherapy	2 (4.4)
	Chemotherapy and radiotherapy	30 (66.7)
	Chemotherapy	9 (20)
Survival time (months)	–	26.92 ± 17.43

showed a minor pattern as well. In 13 of them, the minor and major patterns were in the same category (both were in typical or variant categories). These cases were subtyped according to the major pattern. In 4 of them, there was a minor or major component of variant pattern, while the other pattern was typical. These cases were classified based on their variant pattern. Pattern A was the most common pattern identified in cervical lymph nodes, while in axillary lymph nodes pattern C was more common (Table 4). Sequential biopsies were available in 3 patients. One of them showed diffuse large B cell lymphoma (DLBCL) in the relapsed sample.

Table 4 Primary site of the disease in relation to morphological patterns

Primary site	Morphological pattern					
	A	B	C	D	E	F
Neck LN	9	2	4	1	2	0
Axillary LN	7	3	10	2	2	0
BM	0	0	1	0	1	0
Submandibular LN	1	0	0	0	2	0
Inguinal LN	3	0	0	0	3	0
Others	7	0	4	0	2	0

Fig. 2 Pattern A immunoarchitecture in one of the cases. **a** and **b** The H&E slide shows LP cells within nodular aggregates (× 100 and × 400, respectively). **c** PAX5 staining reveals the background is mostly composed of small B cells in a nodular fashion (× 40). **d** and **e** CD20 staining highlights large LP cells located in reactive B cell nodules (× 100 and × 400, respectively). **f** LP cells are surrounded by CD57-positive T follicular helper cells (× 400)
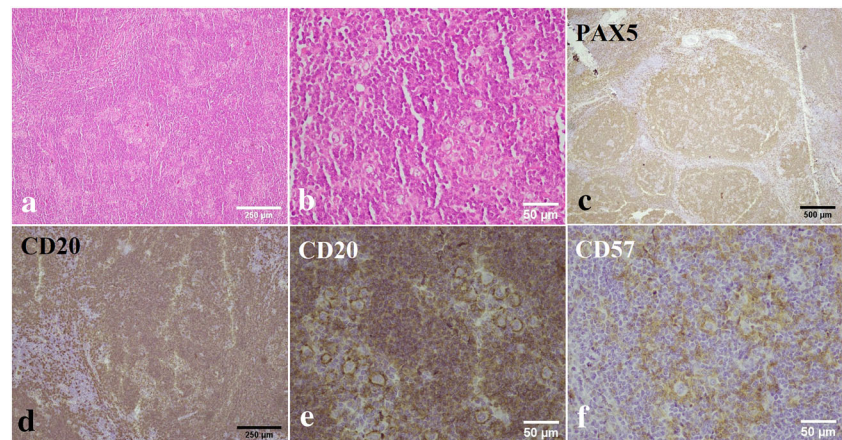
Figures 2 and 3 demonstrate findings in NLPHL with "typical (Pattern A)" and "variant (Pattern C)" morphologies.

The relationship between histoarchitectural patterns (typical versus variant) and other demographic and clinical characteristics of patients are shown in Table 5. There was a significant association between BM involvement and histoarchitectural pattern ($p = 0.025$). All patients with BM involvement exhibited variant morphology. Two (33%) of them showed pattern C and 4 (66.6%) exhibited pattern E. Patients with BM involvement had a younger age than those who did not (26.33 ± 20.94 vs. 37.58 ± 14.37, respectively, $p = 0.05$).

The univariate and multiple Cox regression analyses for the influence of age, gender, BM involvement, histoarchitectural pattern, stage, treatment, and subdiaphragmatic involvement on overall survival (OS) and progression-free survivals (PFS) are presented in Tables 6 and 7. The univariate analysis for overall survival time revealed that age, gender, BM involvement, histoarchitectural pattern, treatment, and subdiaphragmatic involvement are not significant risk factors for death at the level of 0.1 (all $p > 0.1$). Tumors with higher stages (III and IV) had lower survival rates than others (HR = 11.17, $p = 0.038$ for univariate and HR = 9.79, $p = 0.05$ for multiple Cox regression analysis) (Table 6, Fig. 4). After entering multiple Cox regression for adjustments histoarchitectural pattern showed no significant correlation with overall survival (Table 6, Fig. 5).

After adjustment for other variables, age (HR = 0.95, $p = 0.04$) and stage (HR = 14.08, $p = 0.03$) showed a significant correlation with PFS (Table 7). No significant correlation was found between histoarchitectural pattern and PFS (Table 7, Fig. 5).

The relationship between stage, subdiaphragmatic, and BM involvement with outcome is shown in Table 8. There are significant associations between disease stage, subdiaphragmatic, and BM involvement with outcome variables.

Discussion

Among the 1168 lymphoma cases involved in the current study, 32.7% ($n = 382$) of them were Hodgkin lymphomas. NLPHL accounted for 19.1% of the Hodgkin lymphomas. NLPHL is reported to account for 3–8% of HLs in Western

Fig. 3 Pattern C immunoarchitecture in one of the cases. **a** and **b** The H&E slide shows LP cells located mostly outside of the nodular structures (× 100 and × 400, respectively). **c** The background contains a large number of CD3-positive T cells (× 400). **d** and **e** There are small nodules of reactive B cells, but LP cells are frequently located outside of the nodules (× 40 and × 400, respectively). **f** Some LP cells are rimmed by PD1-positive follicular T helper cells (× 400)
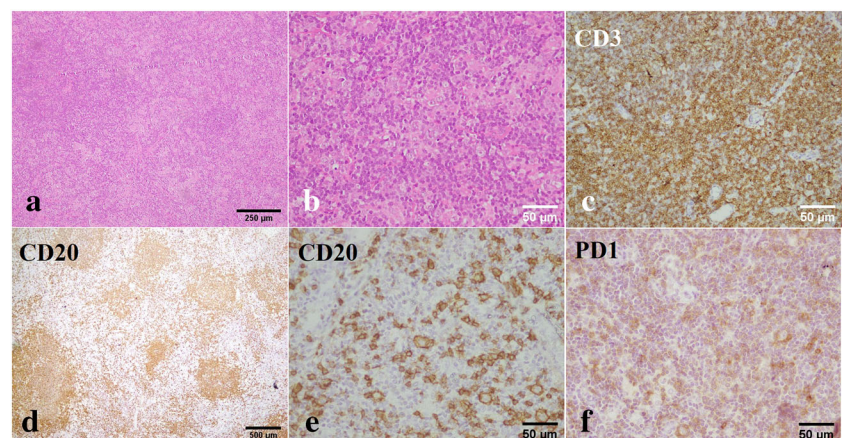
Table 5 Baseline characteristics of patients between two groups of histoarchitectural pattern

		Typical (n = 32)	Variant (n = 34)	p value
Age (years)		38.31 ± 13.39	34.91 ± 16.8	0.6[a]
Gender	Female	12 (37.5)	8 (23.5)	0.22[b]
	Male	20 (62.5)	26 (76.5)	
Primary site	Neck LN	11 (34.4)	7 (20.6)	0.64[c]
	Axillary LN	10 (31.3)	14 (41.2)	
	BM	0 (0)	2 (5.9)	
	Submandibular LN	1 (3.1)	2 (5.9)	
	Inguinal LN	3 (9.4)	3 (8.8)	
	Others	7 (21.9)	6 (17.6)	
Subdiaphragmatic involvement	Supra-diaphragmatic	26 (81.3)	24 (70.6)	0.31[b]
	Infra-diaphragmatic	6 (18.8)	10 (29.4)	
Stage	Low stage (I and II)	29 (90.6)	26 (76.5)	0.12[b]
	High stage (III and IV)	3 (9.4)	8 (23.5)	
Outcome	Dead	1 (4.5)	3 (13)	0.26[c]
	Alive with recurrence or progression	2 (9.1)	5 (21.7)	
	Alive with no recurrence or progression	19 (86.4)	15 (65.2)	
BM involvement	Not involved	32 (100)	28 (82.4)	0.025[c]
	BM involved	0 (0)	6 (17.6)	

[a] Mann-Whitney U test

[b] Chi-square test

[c] Fisher's exact test

countries [1–3, 11]. Its incidence is even lower in Asian countries [12, 13]. In a study reported in 2014 from our center, 9% of HLs were of NLPHL type [14]. Mozaheb et al. studied 391 lymphoma cases in Mashhad, Iran, and reported that 6.3% of their HLs were NLPHL [15]. In another study from Iran conducted by Shamloo et al. on 513 head and neck lymphoma cases, 200 HLs were identified, 24 (12%) of which were of the NLPHL type [16]. The higher incidence of NLPHL in the current study compared with studies from other countries as well as previous reports from Iran can be explained by various

Table 6 Univariate and multiple Cox regression analysis (overall survival)

Variable		Univariate			Multiple		
		Hazard ratio (HR)	95% CI for HR	p value	Hazard ratio (HR)	95% CI for HR	p value
Age	–	0.98	(0.91–1.06)	0.67			
Gender	Female	0.03	(0–1032)	0.52			
	Male	1					
BM involvement	Not involved	0.38	(0.04–3.67)	0.4			
	BM involved	1					
Histoarchitectural pattern	Typical	0.33	(0.03–3.17)	0.34	0.49	(0.05–4.89)	0.54
	Variant	1			1		
Stage	Low stage (I and II)	1			1		
	High stage (III and IV)	11.17	(1.15–108.99)	0.038	9.79	(0.98–98.1)	0.05
Treatment	Not treated	0.04	(0–6108.9)	0.66			
	Received treatment	1					
Subdiaphragmatic involvement	Supra-diaphragmatic	0.35	(0.05–2.5)	0.29			
	Infra-diaphragmatic	1					

Table 7 Univariate and multiple Cox regression analysis (progression-free survival)

Variable		Univariate			Multiple		
		Hazard ratio (HR)	95% CI for HR	p value	Hazard ratio (HR)	95% CI for HR	p value
Age	–	0.95	(0.9–0.99)	0.025	0.95	(0.91–0.99)	0.038
Gender	Female	1.55	(0.41–5.91)	0.52			
	Male	1					
BM involvement	Not involved	1			1		
	BM involved	5.05	(1.43–17.89)	0.012	7.65	(0.6–97.75)	0.12
Histoarchitectural pattern	Typical	0.39	(0.1–1.47)	0.16	1.42	(0.24–8.29)	0.69
	Variant	1			1		
Stage	Low stage (I and II)	1			1		
	High stage (III and IV)	10.26	(2.65–39.73)	0.001	14.08	(1.32–149.81)	0.028
Treatment	Not treated	0.04	(0–227.16)	0.47			
	Received treatment	1					
Subdiaphragmatic involvement	Supra-diaphragmatic	1			1		
	Infra-diaphragmatic	9.86	(2.61–37.27)	0.001	0.54	(0.03–11.06)	0.69

reasons. Recent publication of more precise diagnostic criteria for this entity may have led to better identification of this subtype, which may have caused its relative increased frequency. All the previously mentioned studies from Iran were published at least 3 to 4 years ago, and at that time NLPHL may have been under-diagnosed. It should be noted that in the most recent studies, NLPHL accounted for 12% of HLs which is similar to the current study [16]. Nevertheless, a recent increase in this lymphoma type cannot be excluded. Further studies are needed to confirm these results.

NLPHL mostly affects men in their 4th decade of life [3]. About 69.9% of patients in the current study were males, which is in line with other studies. In a study on 471 NLPHL cases, 75.8% of patients were males [17]. Similar results were reported by Molin et al. [18]. In another study reported by Eladl et al. from Japan, 64% of their NLPHL cases were males [12]. The median age of patients in the present study was 34 years (mean: 36.33 ± 14.5). Similar results have been reported by other researchers, and the reported median ages range between 32 and 56 years [12, 17, 19–22]. One study reported a significantly older age in affected females compared with males (59 vs. 44, $p = 0.39$), but others (including the current one) did not find such differences [18].

Fig. 4 Kaplan-Meier curve for the relative OS of the high-stage (III and IV) and low-stage (I and II) groups of the NLPHL cases ($p = 0.05$)
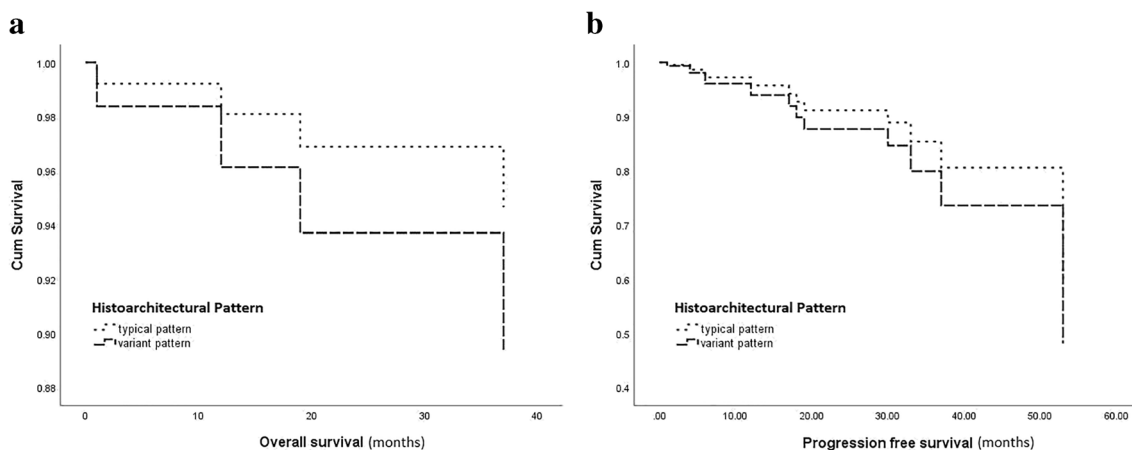
a

b
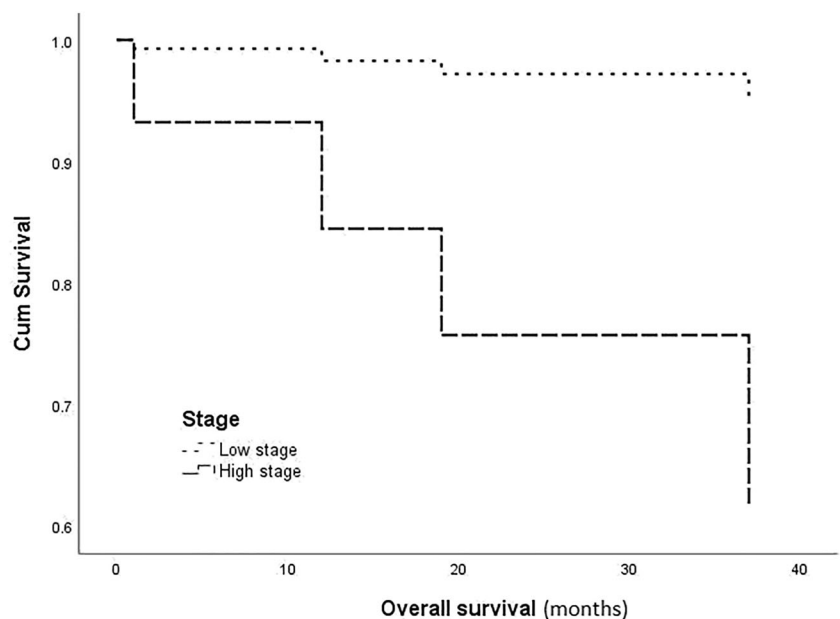
Fig. 5 **a** and **b** Kaplan-Meier curves for the relative PFS ($p = 0.69$) and OS ($p = 0.54$) of the cases with typical and variant NLPHL histoarchitectures

Regarding the histoarchitectural patterns, 48.5% of patients in this study showed a typical growth pattern, and the others were included in the variant group. Types A, C, and E of Fan's classification were the most prevalent types, respectively. The rate of typical morphology varies in different studies ranging between 47 and 78% [7, 8, 10, 23]. Some studies have reported a higher rate of typical morphology than the current results [8, 23]. Hartmann et al. studied 423 NLPHL cases and reported that 72% of their patients showed a typical morphological pattern [7]. Another study by Agbay et al. reported that 47% of their NLPHL cases showed the classic pattern, and the others had a variant morphology or a mixture of typical and variant morphology [10]. In a study by Hartmann et al., which considered 33 cases treated within the German Hodgkin Study Group (GHSG) and 41 cases treated outside the GHSG, the typical morphology was identified in 64% of cases inside the GHSG and 44% of those out of it [19]. The authors declared that because of the more complicated diagnosis, these patients had not been involved in the GHSG study [19]. To determine

the exact rate of typical and variant morphologies in NLPHL, more studies on larger sample sizes are needed. In addition, as the patients with more difficulties in diagnosis do not usually enter clinical trials, studies that include all diagnosed cases are preferred rather than ones including a selected number of cases.

The current study found a significant association between variant morphology and BM involvement. All patients with BM involvement showed the variant morphology. No significant association was found between histoarchitectural patterns and OS, PFS, or patient outcome. Similarly, in a study by Panjwani et al., all cases with BM involvement showed variant morphology [9]. In line with the current study, Hartmann et al. found a significant association between variant morphology and advanced disease. They also reported a significant association between variant morphology and a higher relapse rate and introduced variant morphology as an independent prognostic factor [7]. Another study by Agbay et al. found that BM involvement by lymphoma in NLPHL patients is more common in variant morphology ($p = 0.02$), which is similar to the current results [10]. Hartmann et al.

Table 8 Fisher's exact test for the relationship between stage, subdiaphragmatic, and BM involvements with outcome of patients

Variable		Outcome			
		Dead	Alive with recurrence or progression	Alive without recurrence or progression	p value
Subdiaphragmatic involvement	Supra	2 (50)	1 (14.3)	31 (91.2)	< 0.001
	Infra	2 (50)	6 (85.7)	3 (8.8)	
BM involvement	Not involved	3 (75)	4 (57.1)	33 (97.1)	0.012
	BM involved	1 (25)	3 (42.9)	1 (2.9)	
Stage	I	0 (0)	2 (28.6)	26 (76.5)	
	II	1 (25)	1 (14.3)	6 (17.6)	< 0.001
	III	2 (50)	3 (42.9)	0 (0)	
	IV	1 (25)	1 (14.3)	2 (5.9)	

found that presentation in an advanced stage is more common in patients with variant morphology [19]. In addition, they found that time to relapse correlates with histoarchitectural growth patterns (5.2 vs. 2.8 for typical and variant morphologies, respectively) [19]. Other studies on childhood NLPHL have also reported lower rates of complete response, higher rates of relapse, higher rates of unfavorable presentation, and lower EFS in variant morphology compared with typical morphology [23, 24]. The absence of a significant association between survival and histoarchitectural patterns in the current study may be related to the limited sample size as well as the short follow-up period (median follow-up time = 25 months). Furthermore, a limitation of the current study is that the patients did not receive uniform treatment and this may have influenced the results.

Several factors have been reported to affect the prognosis in NLPHL patients. In the current study, it was found that adverse outcome was associated with higher stages, BM involvement, and subdiaphragmatic disease involvement. In addition, patients with higher stage tumor (III and IV) showed lower OS and PFS rates. Eichenauer et al. studied 471 NLPHL cases and reported that PFS and OS were significantly related to BM and liver involvement. They also showed that OS was lower in advanced stage patients [17]. In line with the current results, Agbay et al. also found that disease progression and relapse were more frequent in patients with BM involvement [10]. Furthermore, the rate of BM involvement in the current study was 11% which is somewhat higher than reported elsewhere [9, 10]. It may be explained by the influence of a higher proportion of variant morphology in this study. In addition, in 3 (4.1%) cases in this study, the primary site of disease presentation was BM. To the best of our knowledge, such presentation has not been reported by others.

In conclusion, to the best of our knowledge, this is the first report from Iran on the histoarchitectural and clinical aspects of NLPHL. Higher frequencies of variant morphology as well as BM involvement were found compared with most other studies. The histoarchitectural patterns were associated with BM involvement but not with OS or PFS. Stage, BM involvement, and subdiaphragmatic involvement were significantly associated with outcome. Patients with higher stage tumors had lower OS and PFS rates.

Compliance with ethical standards

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