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ORIGINAL PAPER

Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL)—Clinicopathological Features Based on the Data of Two Hungarian Lymphoma Centres

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Abstract Clinicopathological features of nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) differ from those of the classical Hodgkin lymphoma (cHL). Our aim was to examine clinical presentation, therapeutic and survival results of NLPHL patients in Hungary based on the data of two centres, and incidentally we analyzed the clinicopathological characteristics and differential diagnostic difficulties of this rare entity. We analyzed the clinical features, treatment and survival data of 536 Hodgkin lymphoma patients who had been diagnosed and primarily treated in our institutes between 1995 and 2004. Mean follow-up time was 82.7 (3–144) months of the total 536 HL patients. Sixteen (3%) of the patients were diagnosed with NLPHL, 93% of them presented with early-stage disease. None of the patients showed extranodal or splenic involvement or bulky disease. One patient received chemotherapy alone, six received only involved field radiotherapy while six underwent combined modality treatment. We applied watch and wait strategy in three cases. Overall response rate was 100% (93.75% complete). Two NLPHL cases transformed to non-Hodgkin's lymphoma. In contrast to the classical HL, the 10-year prognosticated overall survival rate was 100 vs. 82%, the event free survival was: 75% vs. 70%. In NLPHL group there were no late or multiple relapses and none of them died. Conclusions: NLPHL is a rare disease, thus these are limited experiences with its diagnosis and treatment. Since the disease has an excellent outcomeit is very important to prefer less toxic or local therapies to reach long term survival similar to that of the normal population.

Keywords Nodular lymphocyte predominant Hodgkin lymphoma · Classical Hodgkin lymphoma · Differential diagnosis · Immunohistochemistry · Treatment · Prognosis

Abbreviations

ABVD	adriamycine, vinblastine, dacarbazine, bleomycine
aHSCT	autologous hemopoetic stem cell transplantation
ALCL	anaplastic large cell lymphoma
BEACOPP	bleomycine, etoposid, adriamycine, cyclophosphamide, vincristin, procarbazine, prednisolone
CEP	etoposid, prednimustin
CCNU	
cHL	classical Hodgkin lymphoma
CMT	combined modality treatment
CRu	undetermined complete remission
COPP/	cyclophosphamide, vincristin, procarbazine/
ABV	adriamycine, bleomycine, vinblastine
CR	complete remission
CVP	cyclophosphamide, vincristin, prednisolone
DHAP	dexamethasone, cytarabin, cisplatine
DLBCL	diffuse large B-cell non-Hodgkin lymphoma
EBV	Epstein-Barr virus
EFRT	extended field radiotherapy
EFS	event-free survival
EMA	epithelial membrane antigen

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EORTC	European Organization for Research and Treating Cancer
ETFL	European Task Force on Lymphoma
FDC	follicular dendritic cell
FDG	18-fluoro deoxyglucose
GSHG	German Study Hodgkin Group
HD	Hodgkin's disease
HDT	high dose therapy
HE	haematoxylin-eosin
HRS	Hodgkin, Reed-Sternberg cells
IFRT	involved field radiotherapy
INRT	involved nodal radiotherapy
IPS	International Prognostic Score
L&H	lymphocyte and histiocyte cell
LD	lymphocyte depletion
LMP	latent membrane protein
LPHD	lymphocyte predominant Hodgkin's disease
LRcHL	lymphocyte rich classical Hodgkin lymphoma
MC	mixed cellularity
NLPHL	nodular lymphocyte predominant Hodgkin lymphoma
NR	non-responder
NS	nodular sclerosing
ORR	overall response rate
OS	overall survival
PET	positron emission tomography
PR	partial remission
PTCG	progressive transformed germinal centre
(R)-CHOP	(rituximab)-cyclophosphamide, adriamycine, vincristin, prednisolone
REAL	Revised European and American Lymphoma classification
T/HrBCL	T-cell/histiocyte rich B-cell lymphoma

Introduction

The principle of Rye classification—used to define the histological subtype of Hodgkin's disease (HD)—was the presence of the malignant Hodgkin and Reed–Sternberg (HRS) cells or its variant forms in a subtype specific background. In 1937 Jackson [1] was the one to described first the LPHD characterized by histiocytes in a lymphocyte rich background and he named this entity "early HD". Because of the long, indolent course usually observed, in 1944 Jackson and Parker [2] named it "paragranuloma" to differ it from Hodgkin "granuloma". In 1966 paragranuloma was renamed lymphocyte and/or histiocyte predominant Hodgkin's disease by Lukes and Butler [3]. They described Hodgkin's disease's nodular and diffuse form and introduced the diagnostically crucial variant HRS cell labelled lymphocyte and histiocyte (L&H) cell [4]. Upon practical considerations, the nodular and diffuse forms were contracted into lymphocyte predominant subtype in a Rye symposium the same year [5]. In the late 1980s, it was shown that unlike the classical HRS cells, the malignant cells of LPHD are characterized by a B-cell specific antigen profile. Based on this and on the observation that the disease has an indolent course LPHD was suggested to be classified among low-grade non-Hodgkin lymphomas. In the early 1990's Küppers et al. proved that atypical L&H cells are B-cells, originating from the germinal centre and thus are characterized by a specific antigen profile. Based on these pathological features and the specific clinical characteristics of the disease the NLPHD was distinguished from other, so called classical subtypes of Hodgkin's disease as a distinct clinicopathological entity in the REAL classification [6]. It was in the late 1990s, that the B-cell origin of HRS cells was clearly proven by immunoglobulin gene rearrangement, and subsequently the term Hodgkin lymphoma in general was introduced in the WHO classification in 1999 [7].

According to the present WHO classification, Hodgkin lymphomas comprise two disease entities: nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and classical Hodgkin lymphoma (cHL). Latter has 4 histological subtypes: mixed cellularity (MC), nodular sclerosis (NS), lymphocyte rich (LR) and lymphocyte depleted (LD) form [7].

NLPHL has characteristic morphological and immunohistochemical features. It shows nodular proliferation of scattered large neoplastic cells, the so called lymphocytic/histiocytic cells (L&H cells) or popcorn cells in a large spherical meshwork of follicular dendritic cells (FDCs) filled with non-neoplastic small lymphocytes. The nodules of NLPHL represent progressively transformed germinal centres. The small lymphocytes in these nodules are a mixture of polyclonal B cells with a mantle zone phenotype (IgM and IgD+), and numerous T cells, many of which are CD57 and MUM1 positive, that surround the tumour cells. Tumour cells of NLPHL are LCA positive, express B-cell markers (CD20, CD79a), immunoglobulin, J chain, and epithelial membrane antigen but lack the expression of CD15 and CD30, the characteristic markers for classic Hodgkin lymphoma (cHL). Popcorn cells also express the nuclear protein encoded by the bcl-6 gene, which is required for normal germinal centre B-cell development [8–11].

NLPHL is a "benign" disease featured by an indolent course, good therapeutic response, even spontaneous remission. Curable relapses are frequent and the disease progresses to non-Hodgkin lymphoma more frequently than classical Hodgkin lymphoma [8, 9].

NLPHL is a disease with low prealence, thus so we have little diagnostic and clinical experience. In our survey we

reviewed the histological and clinical data of HL patients treated in two Hungarian centres and incidentally we analyzed the differential diagnostic difficulties of NLPHL, our therapeutic experiences as well as treatment opportunities.

Patients and Methods

Data of 536 HL patients were collected, who were diagnosed and primary treated in the National Institute of Oncology and in the 3rd Department of Internal Medicine, University of Debrecen between 1995 and 2004, after the introduction of REAL classification. The study was closed in January of 2007; the mean follow-up time was 82.7 (3–144) months.

Histological classification of the cases was given according to the REAL/WHO classification [7]. Biopsy specimens were routinely processed and embedded in paraffin wax. Five-micrometer sections were cut and stained for hematoxylin and eosin (HE). Then 4 μm sections were cut from the same tissue blocks and were stained using the DAKO EnVision™+ System. The antibodies used were specific for the following antigens: CD3, CD5, MUM1, CD20, bcl-6, CD35, CD30, CD15, EMA (Dako)

The staging of the disease was done according to the Ann-Arbor principals and its modification in Cotswolds [12]. Lymphadenomegaly was considered bulky if its greatest diameter was more than one-third of the greatest diameter of the chest, greater than 10 cm in the mediastinum, or more than 7 cm in other localizations. Prognosis was determined according to the EORTC guideline in early stages [13] and according to the International Prognostic Score (IPS) published by Hasenclever and Diehl in the advanced stages [14]. If the cases had been diagnosed before 1998 prognosis was calculated retrospectively, in advanced cases, the prognosis was considered favourable if the IPS was 0–3, and unfavourable if it was at least 4. Patients were treated according to the international and Hungarian guidelines with radio—or chemotherapy alone or with combined modality treatment. [15, 16]. In cases of primary non-responder patients, as well as early or repeated relapses, high dose chemotherapy and autologous hemopoetic stem cell transplantation (HDT and aHSCT) was performed. 1–2 months after the end of the treatment, restaging examinations were done and, if necessary, 18-fluorodeoxyglucose positron emission tomography was also carried out to assess the viability of the residual tumour mass. Treatment response was defined according to the WHO guidelines: complete/partial remission (CR, PR), non-responder (NR) and undetermined complete remission (CRu), as it was recommended in the Cotswold modification [12], in these cases FDG/PET or rebiopsy was made. Survival analysis was performed using the Kaplan-Meier method. The statistical analysis was done by SPSS software. We used log-rank, χ^2 and Fischer-tests depending on the nature of the data. Nominal P values less than 0.05 were considered significant.

Results

Sixteen of the 536 Hodgkin lymphoma cases were classified as NLPHL based on histological and immunohistochemical features. Figure 1 shows the typical nodular pattern of NLPHL. The at least partially nodular proliferation of scattered neoplastic cells, so called L&H cells or popcorn cells (Fig. 1A) in a large spherical meshwork of FDCs (Fig. 1B) is a diagnostic criterion of the disease. The background of the nodules is filled with non-neoplastic small polyclonal B-cells. Figure 1C and D shows the typical immunophenotype of popcorn cells. They are CD20, bcl-6 and EMA positive. The small lymphocytes in the background are also CD20 positive but they are bcl-6 negative. MUM1 and CD3 positive T-cells form rosettes surrounding the tumour cells (Fig. 1E,F).

Table 1 shows the general characteristics of patients, as well as their distribution according to the stage and prognosis, while age distribution is shown in Fig. 2. NLPHL patients, in comparison with patients with cHL, were younger, characterized by an unimodal age distribution and male predominance. More than 90% of NLPHL patients were in an early stage and nearly two-third of patients had favourable prognosis. The peripheral, most often the cervical regions were involved. Accordingly cHL patients were older, had bimodal age distribution, more specifically we observed slight female predominance and significantly more patients had advanced disease in this group. Only one of the NLPHL patients had B symptoms and none of them had bone-marrow, intracavital or spleen involvement, neither was bulky tumour observed.

Three NLPHL and five cHL patients were not treated but were closely observed. Watch and wait strategy seemed sufficient because after complete excision of the pathological lymph node there was no other involved region on control examinations. We did not to treat five cHL patients. Two of the five were young women planning pregnancy and three other patients refused treatment. In stage I/A NLPHL patients received only radiotherapy. If the prognosis was unfavourable we applied combined modality treatment, while advanced stage patients received chemotherapy alone. Nearly two-thirds of cHL patients received CMT and only 2%, whose disease was limited and had favourable prognosis, received radiotherapy alone. One stage III/A patient refused chemotherapy. Treatment data are shown in Table 2. All of the treated NLPHL patients achieved complete remission. The overall response rate was

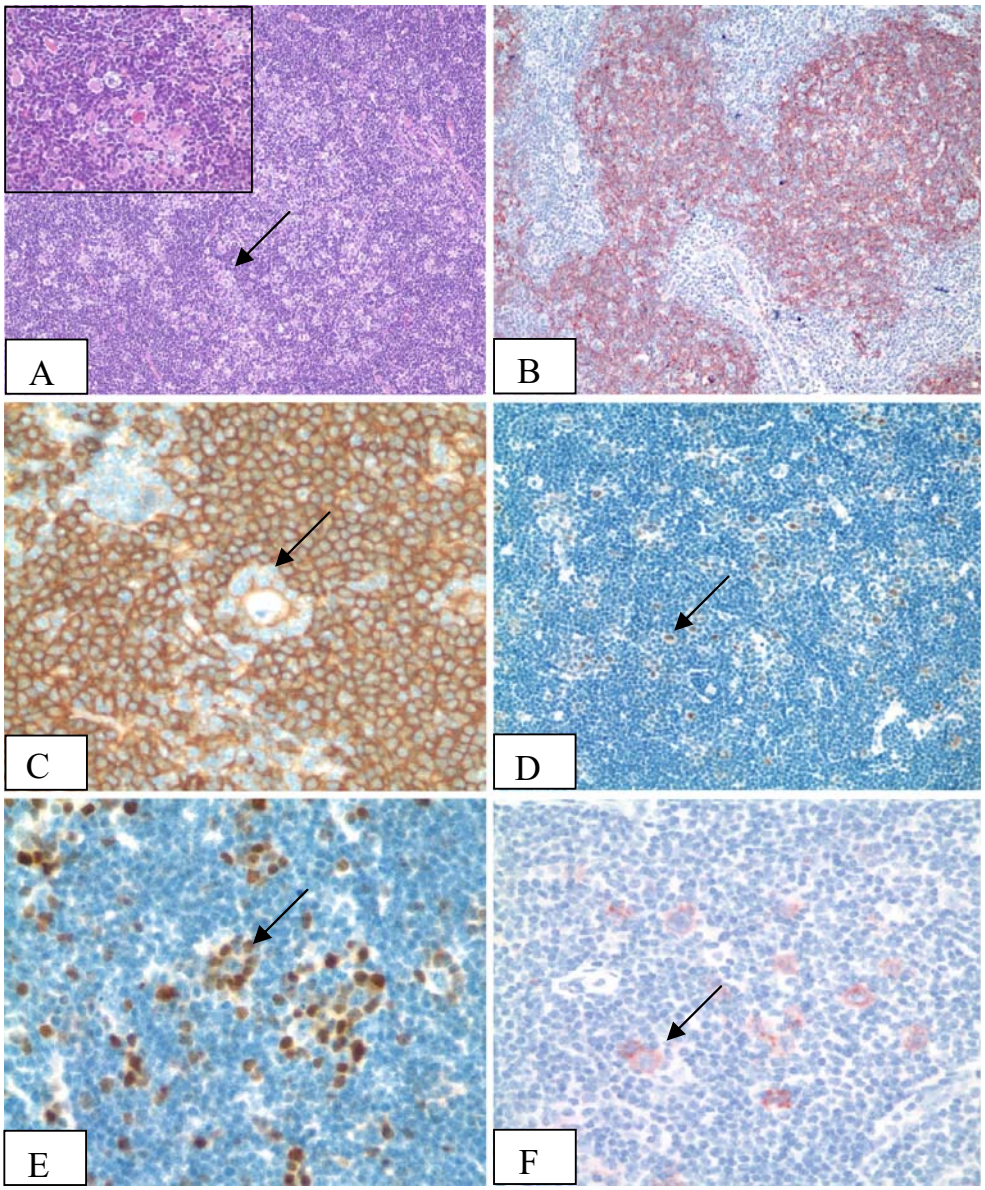

Fig. 1 **A** Typical morphology of NLPHL with hematoxylin and eosin. Scattered L&H cells within a nodular background dominated by small lymphocytes (HE ×100), *insert*: L&H cell with multilobated, folded nuclei. (HE ×400). **B** Dens nodular, partially serpiginous CD21 positive FDC network (CD21 immunohistochemistry ×100). **C** Popcorn cells and the small lymphocytes in the background are CD20 positive. There are CD20 negative small lymphocytic rosettes surrounding the tumour cells (CD20 immunohistochemistry ×400). **D** Nuclear bcl-6 expression in popcorn cells. (bcl-6 immunohistochemistry x100). **E** MUM1 positive T cell rosettes surrounding the L&H cells (×200). **F** Popcorn cells are EMA positive (×200)

more than 90% in the cHL group too. Relapse rates were similar in the two groups, two of the NLPHL patients had a relapse within 24 months, and there was no late or repeated relapse. Data of treatment response and relapse rates are shown in Table 3. Among the 536 patients 58 (10.8%) died in the follow-up period, all of them had cHL. Forty-five died from the progression of the disease, six from secondary malignancy (three lung, one colon, one mesopharynx tumor and one NHL) and six from other causes (four coronary artery disease/acute myocardial infarction, one pneumonia, one stroke). Overall and event free survival rates are shown in Fig. 3. Ten-year prognosticated OS was 100%, EFS was 75% in NLPHL, while OS and EFS were 82 and 70% in cHL cases, respectively. Survival data of LRcHL were similar to cHL.

Non-Hodgkin lymphoma occurred concurrently or subsequently in eight of the 536 Hodgkin lymphoma patients, and in two of the 16 NLPHL patients. One of the NLPHL patients had concurrent diffuse large B-cell lymphoma (Fig. 4), which showed the same immunohistochemical features as NLPHL. Tumour cells were CD20 and bcl-6 positive but CD10 and MUM1 negative. In another patient, the so called micronodular T cell/histiocyte-rich B-cell lymphoma developed subsequently (Fig. 5). Clinically, the relapse presented in the form of liver involvement. As a result of prominent fibrosis the histological pattern was nodular, and no FDC meshwork underlying the nodules could be demonstrated by staining for CD21 or CD35. The nodules contained scattered blasts with the same immunophenotype as L&H cells of the previous NLPHL but the

Table 1 Clinical features of our patients

	NLPHL*	cHL	LRcHL	Significance
Number of patients	16 (3%)	520 (97%)**	30 (5.6%)	–
Male	11 (69%)	252 (48%)	15 (50%)	N.S.
Female	5 (31%)	268 (52%)	15 (50%)	
Gender ratio (M/F)	2.2	0.94	1	N.S.
Average age (years)	32.3 (15–62)	41.6 (14–83)	42.7 (19–74)	N.S.
Stages (number of patients)				
I	8	42		$P<0.001$***
II	7	279		
	15	321		
III	1	110		
IV	–	89		
	1	199		
A/B signs	15/1	299/221	18/12	$P=0.0821$ N.S.
Bulky (%)	–	26.5	6.7	–
Early F/UF	11/4	87/234	4/13	$P<0.001$
IPS 0–3/≥4	1/0	143/56	13/0	–

NLPHL Nodular lymphocyte predominant Hodgkin lymphoma, *LRcHL* lymphocyte rich classical Hodgkin lymphoma, *cHL* classical Hodgkin lymphoma, *F* favourable, *UF* unfavourable, *IPS* International Prognostic Score
*Involved regions in stage I-II: cervical: 11, axillar: 4, clavicular: 1, inguinal: 2
**With LRcHL patients. Significance was calculated to compare the NLPHL and cHL patients
***Early (I and II) and advanced (III and IV) stages were compared.

background contained mainly reactive T-cells and histiocytes. Because of the concurrent high grade lymphoma, the first patient received R-CHOP (rituximab, cyclophosphamide, adriablastin, vincristine, prednisolone) treatment. The other patient received chemotherapy after the diagnosis of NHL. Both of them are still in complete remission. In six patients of the 420 cHL cases NHL developed, more than 2 years after the primary diagnosis of HL. Four DLBCL, one anaplastic large cell lymphoma (ALCL) and one indolent B-cell lymphoma were diagnosed. The latter patient received CVP, the others underwent (R)-CHOP treatment. One DLBCL patient was non-responder and died but all the others are in complete remission.

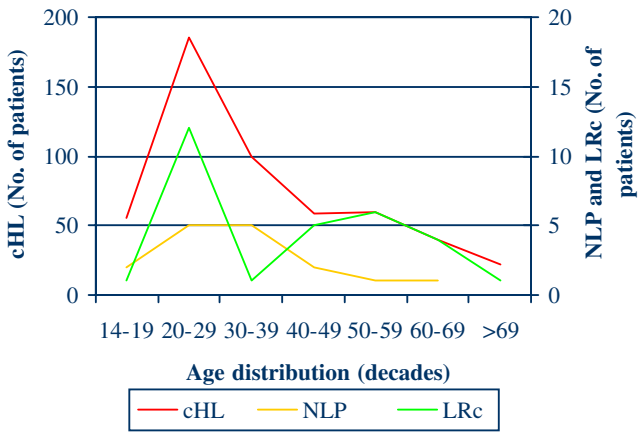

Fig. 2 Age distribution of the nodular lymphocyte predominant Hodgkin lymphoma (*NLPHL*), classical Hodgkin lymphoma (*cHL*) and lymphocyte rich cHL (*LRcHL*) patients

Discussion

According to the international and Hungarian data, the incidence of HL is about 2/100,000 person, which means 140–170 new adult patients per annum in Hungary [9, 17]. In the western countries, occurrence of NLPHL is 5–7% among the total number of HL patients diagnosed according to the REAL/WHO classification [6, 7]. The 3% ratio found in our survey is slightly smaller than this, however the difference is not significant. Our lower incidence could be the result of the method, that we reviewed only the cases which were diagnosed as NLPHL. Hidden cases can remain among reactive or progressively transformed cases as well as in the groups of other differential diagnostic categories.

Detailed morphological and immunohistochemical examination is essential for the precise histological classification of NLPHL [18].

NLPHL needs to be differentiated from reactive lymphoid tissue containing progressively transformed germinal centers (PTGC), classical Hodgkin lymphoma (cHL) and T-cell/histiocyte-rich B-cell lymphoma (THRBCL) [10, 11]. Differentiation from low grade lymphomas showing nodular appearance, such as follicular lymphoma containing polilobated tumour cells is also very important. Table 4 shows a simplified differential diagnostic algorithm of NLPHL.

PTGCs preceding or concurrent with NLPHL have been reported [10] but it is not considered as a premalignant condition. It does not predispose significantly to NLPHL, however close clinical follow-up is important because a

Table 2 Treatment of our 536 Hodgkin lymphoma patients

Treatment	All patients	NLPHL*	cHL**	stages (NLPHL)			
				I.	II.	III.	IV.
Radiotherapy	17	6	11	11 (5)	5 (1)	1	–
Chemotherapy	166	1	165	15	46	60 (1)	45
CMT	343	6	337	24 (2)	227 (4)	50	42

NLPHL Nodular lymphocyte predominant Hodgkin lymphoma, *cHL* classical Hodgkin lymphoma, *CMT* combined modality treatment
*"watch and wait" in case of one I/A and two II/A stage patients
**"watch and wait" in case of five patients, after operation in two cases treatment of two patients is unknown. Numbers in brackets apply to NLPHL patients.

small subset of patients with reactive hyperplasia and PTGC subsequently develops NLPHL. PTGCs do not contain atypical popcorn cells and germinal centres showing follicular hyperplasia besides progressively transformed germinal centres are almost always present.

NLPHL differs in its histological and clinical presentation from classical Hodgkin lymphoma. It does not show expression of CD15 and CD30, the typical markers for cHL. NLPHL is not related to EBV infection, and LMP1 and EBNA are negative, whereas 20–40% of cHLs in the Western world are EBV positive. The cellular background of cHL is more heterogenic, in addition to the CD3 positive T cells, contains a number of plasma cells, eosinophils and histiocytes. In the majority of NLPHL cases CD4+ CD63 double positive T cells constitute a significant number of background cells [19]. Both HRS and L&H cells originate from the germinal centre but HRS cells not express BCR and immunoglobulin specific transcription factors like PU.1, BOB-1 and OCT-2 [20, 21]. Differential diagnostic features are summarized in Table 5.

Another main issue is differentiation of NLPHL from T/HRBCL, a variant of DLBCL in which neoplastic B cells account for less than 10% of the infiltrate. Tumour cells of T/HRBCL can show centroblastic, immunoblastic, HRS like or L&H like morphology. Both the biological behaviour and the treatment are different in this disease, therefore distinguishing the two entities is crucial. The antigen profiles of the tumour cells of NLPHL and T/HRBCL are similar. Both can express CD20, CD79a, CD19, bcl-6, bcl-2, EMA, PU.1 and J chain but CD79a and bcl-2 are more often expressed in T/HRBCL. However transcription factor PU.1 is more commonly expressed in NLPHL. In contrast to the tumour cells' immunophenotype, evaluation of the background composition of these tumours can be much more helpful in the differentiation. A follicular environment, documented by the presence of meshwork of FDCs, is at least partially preserved in NLPHL, but is absent in T/HRBCL. Small B cells are abundant in NLPHL, but rare in T/HRBCL where CD3 positive cytotoxic T cells form the nonneoplastic background. The large spherical CD21, CD35 positive FDC meshwork contains the typical L&H cells surrounding CD3, CD4, CD57, MUM1 positive, TIA-1 and granzyme B negative T cell rosettes. Histiocytes are numerous in T/HRBCL but few in NLPHL [11]. One of our transformed

Table 3 Treatment response and relapse rates of 536 Hodgkin lymphoma patients

Stage	HL-patients		Treatment response			ORR(%)	Relapse	
			CR/CRu	PR	NR		*N*	(%)
Early	NLPHL	12[c]	12	–	–	100	2/12	16.7
	cHL[a]	317[d]	278	10	19	93.8[d]	35/278	11
Advanced	NLPHL	1	1	–	–	100	–	–
	cHL[b]	196[e]	160	14	19	90.1[e]	30/196	18.7
All	NLPHL	13	13	–	–	100	12.5	
	cHL	513	438/87.5%	24/4.9%	38/7.6%	92.4	14.7	

HL Hodgkin lymphoma, *NLPHL* nodular lymphocyte predominant HL, *cHL* classical HL, *CR* complete, *CRu* undetermined complete, *PR* partial remission, *NR* non responder, *ORR* overall response rate
[a] One I/A and 1 II/A stage patients were observed, 2 I/A stage patients were observed after an opus.
[b] Two III/A stage patients' treatment is unknown, 1 IV/B stage patient is observed (PR).
[c] Three patients are observed.
[d] Ten patients are lost of follow-up.
[e] Three patients' treatment responses are unknown. Treatment response rate (%) was calculated as a percentage of the 505 patients whose treatment type and the responses were known.

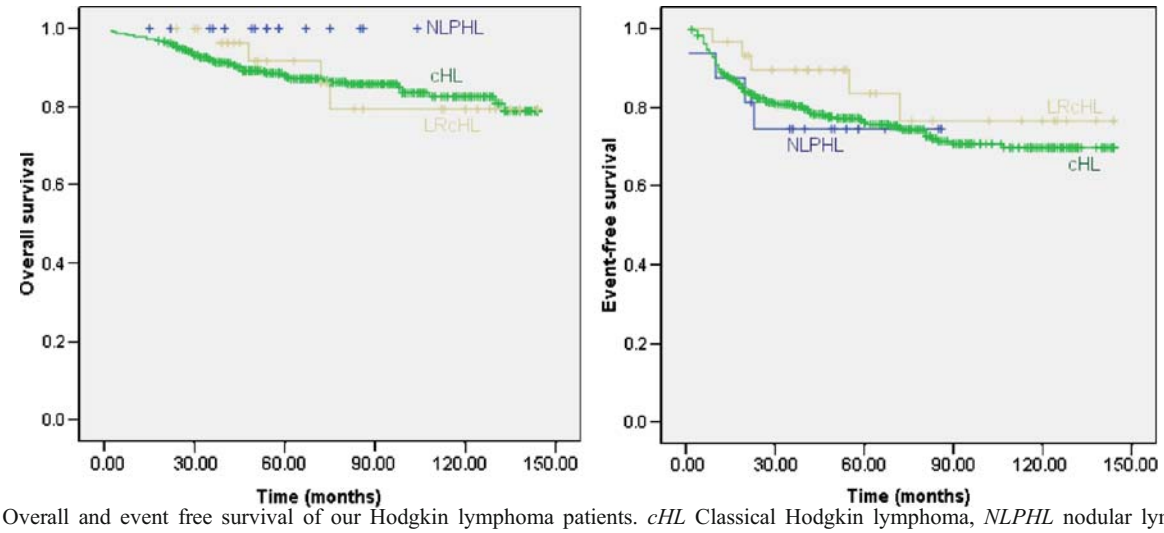

Fig. 3 Overall and event free survival of our Hodgkin lymphoma patients. *cHL* Classical Hodgkin lymphoma, *NLPHL* nodular lymphocyte predominant HL, *LRcHL* lymphocyte rich classical HL

cases showed the peculiar morphology of the micronodular T-cell/histiocyte rich B-cell lymphoma. This entity has been described in the spleen but our case in the liver showed the same pattern as it was published by Dogan and his colleagues [22, 23]. In the majority of the cases the two entities can be distinguished on the basis of the above mentioned features. However, it is known that there are cases showing overlapping traits which may represent a grey zone between these two entities [24].

The characteristic immunohistochemical features of specific type of low grade lymphomas (CD10, CD5, CD23, cyclinD1 expression) help to differentiate NLPHL from low grade lymphomas showing nodular appearance. Follicular lymphomas show bcl-6 and/or CD10 expression while in NLPHL only the scattered tumour cells are bcl-6 positive. It is always necessary to exclude mantle cell or small lymphocytic lymphoma in cases of concurrent positivity of CD20 and CD5. In nodal marginal zone lymphomas L&H cells can not be detected and B cells show monoclonal light chain expression while the small B lymphocytes in the background of NLPHL are polyclonal.

Fan and his colleagues identified six distinct immunoarchitectural patterns of NLPHL: classical (B-cell-rich) nodular, serpiginous/interconnected nodular, nodular with prominent extranodular L&H cells, T-cell-rich nodular, diffuse with a T-cell-rich background [T-cell-rich B-cell lymphoma (TCRBCL)-like], and a diffuse B-cell-rich pattern [25].

Beside the pathological alterations NLPHL also has proper clinical appearance. Characteristically this is the disease of young and middle-aged men. Based on data of large studies (ETFL: European Task Force on Lymphoma, GSHG: German Hodgkin Study Group) the average age of patients is between 30 and 40 years, age-distribution is unimodal, and usually nearly two-thirds of the patients are male, similar to our findings [9, 26]. Usually the disease is diagnosed in an early stage, and mostly the peripheral lymph nodes (cervical and inguinal, occasionally axillary, supra-, and infraclavicular nodes) are involved. In the ETFL study 53% of patients, in the GHSG study 63% of patients were in early stage, while in our survey only one patient had advanced stage lymphoma. B signs are rarely

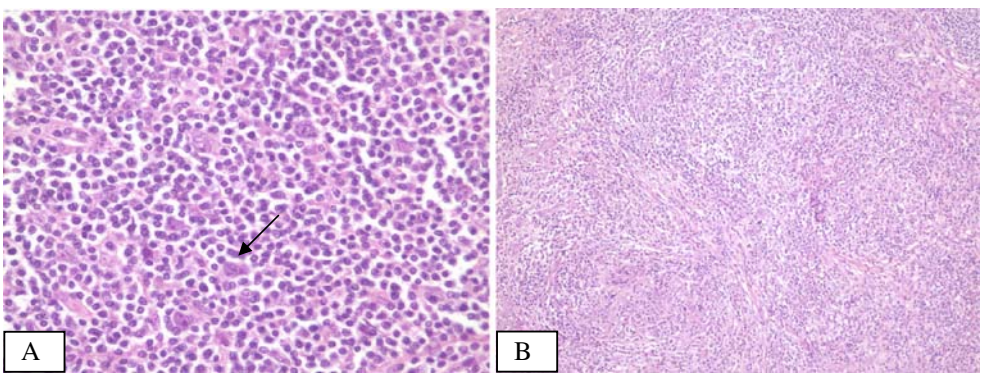

Fig. 4 Coincidence of typical NLPHL and diffuse large B-cell lymphoma. **A** In the axillary block a few lymph node showed typical morphology of NLPHL (*arrow*). Popcorn cells in a lymphohistiocytic background (HE ×400). **B** Other lymph nodes showed diffuse proliferation of centroblasts (HE ×200)

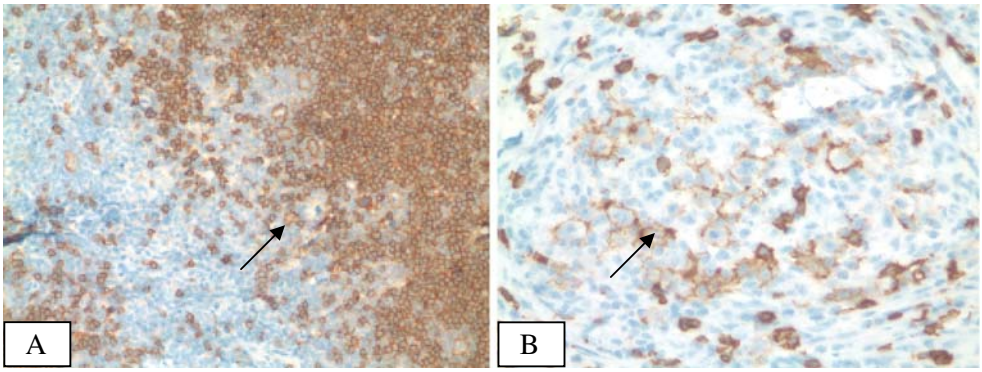

Fig. 5 Subsequent NLPHL and micronodular T cell/histiocyte rich B cell lymphoma. **A** First lymph node biopsy showed NLPHL. Scattered L&H cells can be seen in a small lymphocytic background (*arrow*) (CD20 immonohistochemistry ×200). **B** Five-years later hepatic involvement showed micronodular pattern with scattered large atypical cells (*arrow*) (CD20 immonohistochemistry ×400)

presented same as intracavital occurrence, spleen, bone-marrow or extranodal involvement and bulky tumor, our findings were similar to this [8, 9]. Although LRcHL shows great morphological similarity to NLPHL, its clinical course is more like that of classical form [9], patients are in an advanced stage even more frequently and their prognosis is often unfavourable. More than one-third of our LRcHL patients had advanced disease although their prognosis was favourable in every case. Similar to this, 40% of cHL patients had advanced stage disease, however, nearly one-third of this group had unfavourable prognosis and this also applies for international data [9, 26]. T/HrBCL is typically the disease of middle-age males, diagnosed in advanced clinical stage often with B signs and bone-marrow involvement and has unfavourable prognosis (Table 6.).

In the last decades, successful treatment of HL allowed mending survival, the 10-year prognosticated overall survival (OS) is more than 90% in case of NLPHL, and hits 80% in cHL [8, 9, 26]. Our data support this, the prognosticated 10-year OS was 100% in NLPHL and 82% in cHL in our cohort of patients. Subsequently we have to face late treatment complications. Mortality among the cured lymphoma patients is higher than that of the general population, which is explained by second malignancies and cardiovascular complications [27, 28]. Although there is no solid evidence, pediatric data suggest the importance of the watch and wait strategy in early, favourable NLPHL cases and our data shows the same, of course close observation is necessary. FDG-PET can be helpful to select these patients, although some authors found that in NLPHL the avidity of FDG-PET is not as high as it is in cHL [29], we don't agree with it.

In early, limited, favourable NLPHL cases (I, perhaps II stage) use of radiotherapy alone as primary treatment is evidence and it is also clear that application of involved field is just as good as the extended field was [30–32]. The suggested cumulative dose is 30–36 Gy [9]. Based on the data of MD Anderson Cancer Centre task force, in I-II stage NLPHL cases, additional full dose chemotherapy (CMT) has no benefit on either the overall or on the event free survival, although this is rsult of a relatively small study (N=48). As opposed to these results, Canadian colleagues found that both the OS and the EFS were improved by application of two cycles of ABVD (two ABVD+IFRT; N=92) [33]. Lately, surveys (e.g.: GSHG H17 study [34]) are investigating if the use if involved nodal (IN-RT) irradiation does not adversely affect the survival of NLPHL (and after chemotherapy also of cHL) patients. In three of our NLPHL patients, we followed the watch and wait

Table 4 Differential diagnosis of nodular lymphocyte predominant Hodgkin lymphoma

	Tumour cells immunophenotype	Cellular background	Histological pattern
NLPHL	Bcl-6, EMA, CD20	Mantle zone type small B-cells, T-cell rosettes surrounding tumour cells	Nodular Meshwork of FDC
PTGC	Atypical cells not present	Residual germinal centre cells, mantle zone type small B-cells	Nodular Meshwork of FDC
cHL	CD30, CD15	T-cells, histiocytes, eosinophils	Nodular/ diffuse
T/HRBCL	CD20	T-cells, histiocytes	Diffuse No FDC meshwork
Low grade B-cell non-Hodgkin lymphomas	CD20, CD10, CD5, CD23, cyclinD1	Not diagnostic	Diffuse/nodular If nodular meshwork of FDC

NLPHL Nodular lymphocyte predominant Hodgkin lymphoma, *PTGC* progressively transformed germinal centers, *cHL* classical Hodgkin lymphoma, *T/HRBCL* T-cell/histiocyte rich large B-cell lymphoma, *FDC* follicular dendritic cell

Table 5 Morphological and immunohistochemical characteristics of NLPHL and cHL

	NLPHL	cHL (LR)
Histological pattern	(at least partially) nodular	Diffuse, interfollicular, nodular
Tumour cells	L&H, popcorn	HRS, lacunar
CD30	−	+
CD15	−	+
CD20	+	−/+(≈25%)
CD45	+	−
J-chain	+	−
EMA	+	−
EBV	−	+ (≈ 50%)
Oct-2	+	−
BOB.1	+	−
Bcl-6	+	−
Ig genes (“one cell” PCR)	Rearranged, clonal, mutated-functional	Rearranged, clonal, mutated, crippled- non functional
Cellular background	Lymphocyte, histiocyte	Lymphocyte, histiocyte, plasma cell, eosinophil and neutrophil
Fibrosis	Rare	Common
Background nonneoplastic lymphocytes	T<B (CD20+polyclonal	T(CD3)+>B
CD57+ T cells rosette	+	−
TIA 1+ cells	Few	Numerous

NLPHL Nodular lymphocyte predominant, *cHL* classical Hodgkin lymphoma

strategy after the in toto excision of involved lymph node and we did not find involvement in any other region. All three patients have stable disease. In six cases with early stage and favourable prognosis, we used radiotherapy alone and CMT in six patients with unfavourable disease. Our patient with advanced stage disease received chemotherapy alone, according to the international and Hungarian guidelines that the treatment of advanced stage disease does not differ from the treatment of cHL [8, 9, 15, 16].

Given the CD20 positivity of L&H cells, application of rituximab in NLPHL can be logical theraputic decision to moderate late treatment toxicities. Ekstrand et al [35] used rituximab as primary treatment, and also in relapse, and found a therapeutic response of 100%, although the average EFS was only 10.2 months as opposed to a GHSG study [36], where it was more than 33 months ORR 94%. Using non-mutagenic rituximab would be beneficial as it may help to reduce both early and late treatment toxicity. In addition, Younes et al. (MD. Anderson Cancer Centre) found that rituximab also influence the microenvironment of the malignant cells (polyclonal B-cell depletion) which can be favourable in CD20 negative cHL cases too. There

Table 6 Comparison of the clinical features of nodular lymphocyte predominant (NLPHL) lymphocyte rich (LRcHL) and classical Hodgkin lymphoma (cHL) and T-cell/histiocyte rich B-cell lymphoma (T/HrBCL)

	NLPHL	LRcHL	cHL	T/HrBCL
Age distribution	Unimodal 20–40 years	Often >50 years	Bimodal: 30 and 60 years	≈years
Gender	Male>>female	Male>female	Male = female	Male>>female
Localisation	Peripherial regions, slow progression	Subdiaphr. often spleen	Mediastinum, (bulky), peripherial, abdomen, spleen	Disseminated, mesenterial, spleen
Bone-marrow	Occasionly	Rarely	10–15%	50–70%
B-symptoms	Rarely	Rarely	40–50%	50–70%
Stage	Usually I/II	I-II/ also III	I-IV	often IV
Treatment	ww,RT, ABVD±RT, Rituximab	ABVD±RT	ABVD±RT	R-CHOP
Course	indolent, late, multiplex relapses, great survival	Favorable, early relapse	Aggressive, curable, early relapses (30%)	Aggressive, partially curable
Survival (10 years)	90–100%	85–95%	65–80%	40–60%

ABVD Adriablastine, vinblastine, dacarbazine, bleomycin, *R-CHOP* rituximab, cyclophosphamide, adriablastine, vincristine, prednisolone, *RT* radiotherapy, *ww* watch and wait

are promising phase-II studies in advanced stage cHL with R-ABVD [38, 37]. According to these studies—as well as others at John Hopkins University—the HRS cells may have malignant precursor cells which are CD20 positive, hence they could be a new target of monoclonal antiCD20 antibodies [39].

It is well known that NHLs occur more often in NLPHL (3–7%) than in cHL. In most cases, DLBCL or T/HrBCL, a variant histological type, develops. The two diseases (NLPHL and NHL) can appear at the same time or subsequently therefore differentiating can sometimes be difficult. The clinical course of DLBCL developed in NLPHL is not well described. By molecular analysis of L&H cells and malignant DLBCL cells, clonal relationship was found between the two [40, 41]. There were two hypotheses to explain the simultaneous occurrence of HL and NHL; the first one suggested that the two lymphoma originate from one common cell, the other supposed that there is a NHL-HL or HL-NHL transformation. Single-cell analyses confirmed the former. Mouse-model studies indicated that the loss of different transcription factors (Pax5, E2A, EBF) leads to variable B-cell differentiation, as demonstrated by B-cell plasticity [42] which could explain the occurrence of variant B-lymphomas in a single patient. According to case reports and small studies the composite DLBCL has an indolent disease course and excellent prognosis (similar to the observation in our patient) [43, 44]. However, an American workgroup found that DLBCL after NLPHL has an aggressive course and unfavourable prognosis [45]. From the two of the 16 NLPHL patients that developed NHL, in one case it was composite DLBCL this patient received R-CHOP therapy while in the other case sequential T/HrBCL developed 20 months after CMT (ABVD+IFRT) and also R-CHOP was used as a treatment. Both patients were well-curable and they are in complete remission, although the follow-up time is as yet only 17 months in the first and 36 months in the second case.

We concluded -based on the international and our own experiences—that NLPHL is a rare disease with excellent clinical course, and because of this its precise diagnosis is of outstanding importance. For differential diagnosis, the use of immunohistochemistry is indispensable and special hematopathological knowledge is necessary as well. Diagnostic and treatment experiences are limited; especially large comparative studies are missing. In Hungary, there are six to eight new cases annually, thus it is very important to analyze cumulative data of the centres. The early stage patients with favourable prognoses need special attention because we have to strive to therapeutic modesty, to avoid late treatment complications that can unfavourably influence long-term life expectancy of patients with an otherwise good prognosis. This is why the precise pathological diagnosis is so important. In this subgroup of patients, similar survival to that of the general population can be a realistic aim, but in order to achieve it precise diagnosis and well-designed treatment are required. Frontline use of rituximab can be less toxic treatment alternative, as well as reduced cycle or less toxic protocols e.g.: A(B)V chemotherapy or IF/IN-RT, maybe the combination of them as mini-CMT.

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