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Special Article

Lymphocyte-Predominant Hodgkin's Disease

An Immunohistochemical Analysis of 208 Reviewed Hodgkin's Disease Cases from the German Hodgkin Study Group

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There is wide consensus that lymphocyte predominance Hodgkin's disease (LPHD) represents a distinct clinicopathological entity of B-cell origin. However, inconsistent results of immunophenotyping studies and low confirmation rates among multi-center trials pose the question of whether LPHD really expresses heterogeneous marker profiles or whether it represents a mixture of morphologically similar entities. Among 2,836 cases reviewed by the German Hodgkin Study Group, immunophenotyping was performed on 1) cases classified or confirmed as LPHD by the reference panel (n = 104) or 2) cases not confirmed as LPHD but classified as classical HD (cHD) within the reference study trial (n = 104). In most cases, immunohistochemistry revealed a phenotype either LPHD-like (CD20$^+$, CD15$^-$, CD30$^-$, CD45$^+$) or cHD-like (CD15$^+$, CD30$^+$, CD20$^-$, CD45$^-$). In 27 cases, the immunophenotype was not fully conclusive. Additional markers for Epstein-Barr virus and CD57 and in situ hybridization for mRNA light chains allowed for a more clear-cut distinction between LPHD and cHD. However, in 25 of 104 cases, immunohistochemistry disproved the morphological diagnosis of LPHD of the panel experts, whereas 13 cases originally not confirmed as LPHD showed a LPHD-like immunopattern. Immunohistochemically confirmed LPHD cases showed a significantly better freedom from treatment failure (P = 0.033) than cHD; this was not observed in the original study classification based only on morphology (P > 0.05). Significantly better survival for LPHD cases improved from P = 0.047 (original study classification) to P = 0.0071 when classified by immunohistochemistry. Our results show that LPHD is a more immunohistochemical rather than a purely morphological diagnosis. Immunophenotyping of HD biopsies suspected of being LPHD is mandatory when a modified therapy protocol, that is, one different from those used in cHD, is discussed. (Am J Pathol 1997, 150:793–803)

Lymphocyte predominant Hodgkin's disease (LPHD) is generally recognized as a distinct clinicopathological entity of B-cell origin[1–4] that should be separated from the classical Hodgkin's disease (cHD) ie, nod-

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Figure 1. *LPHD: strong positivity for the B-cell marker CD20 in the neoplastic giant cells in a case of paragranuloma. Note that the diagnostic cells are surrounded by small, CD20⁻ lymphocytes.*

ular sclerosis, mixed celluarity, and lymphocytic depletion. It has been stated that a reliable separation of LPHD from cHD by histopathology and immunophenotyping is not difficult.[3] However, this opinion is challenged by two observations. First, the results of large multi-center studies show a strikingly low confirmation rate of 23 to 52% of the cases contributed as LPHD when reclassified by a panel of experts.[5–8, 20] Second, although it is believed that LPHD has a distinct immunophenotype ($CD15^-$, $CD20^+$, $CD30^-$, $CD45^+$; Figure 1 for CD20), a review of the literature shows a puzzling diversity, suggesting that at least one-quarter of the cases differ from the typical immunophenotype with CD15 positivity in up to 37% (for review see Refs. 9–11).

The revised European American Classification of lymphoid neoplasms[12] has revitalized the subtype of lymphocyte-rich classical HD as a provisional entity. Originally described by Lukes et al[13] and Lennert and Mohri,[14] its morphological similarity to LPHD is already reflected by the name. As the immunophenotype of lymphocyte-rich-cHD is also classic ($CD15^+$, $CD20^-$, $CD30^+$, $CD45^-$), it may be speculated that some of the above mentioned differences in the immunophenotype of LPHD are caused by a mixture of entities in several studies.

In this study we immunophenotyped those cases of the German Hodgkin Study Group (GHSG) that have been contributed with the diagnosis of LPHD by the primary pathologist and all cases classified or at least suspected of being LPHD by the panel of pathologists of the GHSG.

In addition to the antibodies mentioned above and anti-Epstein-Barr virus (anti-EBV), we included CD57 as a helpful marker for LPHD.[15–17] Based on recent observations that Ig light chain mRNA can frequently be detected in LPHD but not MCHD[18,19], *in situ* hybridization (ISH) was performed with randomly selected cases.

Both the original classification by the GHSG and the classification after immunophenotyping with a panel of antibodies and ISH were correlated with clinical data in all patients. Furthermore, follow-up data for 124 patients were available for up to 120 months. The question to answer was whether the diagnosis of LPHD should be strictly reserved for only those cases fulfilling both morphological and immunophenotypical criteria.

Materials and Methods

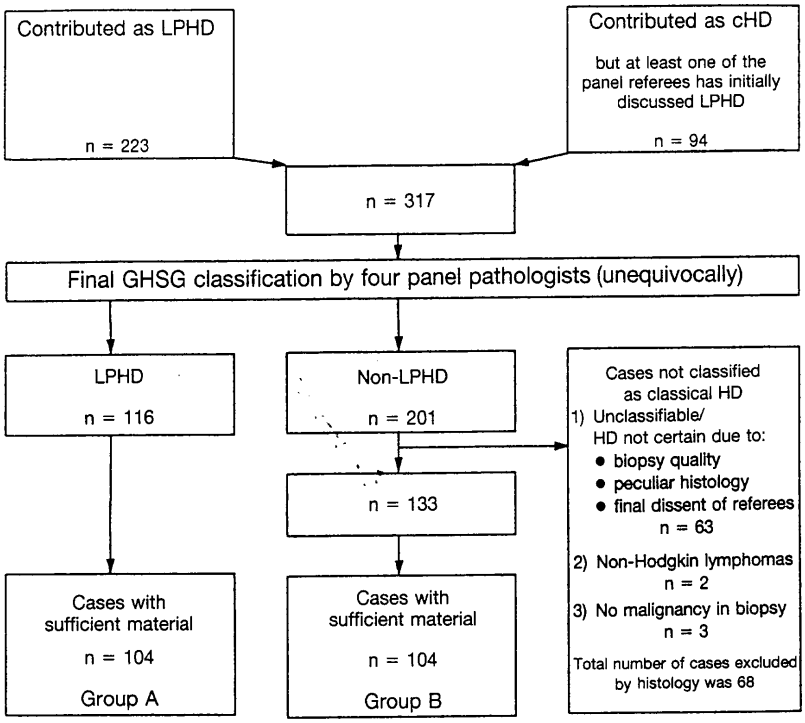
A total of 2,836 diagnostic biopsies submitted as HD to the GHSG were reconsidered by a panel of four referee histopathologists (R. Fischer, A. Georgii, M.-L. Hansmann, and K. Hübner) as previously described.[20] Diagnosis was done on a set of sections from each biopsy stained with hematoxylin and eosin, Giemsa, periodic acid Schiff, and silver impregnation.

Among the 317 cases either contributed as LPHD or initially suspected as being LPHD by at least one of the panel members, 116 of 2,836 (4.1%) cases were in the end unequivocally classified as LPHD by the panel. Another 133 cases were classified as cHD by morphology, and 68 cases could not be confirmed as HD as is shown in detail in Scheme 1.

In 208 of the 249 cases confirmed as being HD, sufficient material was available and cases were divided into two groups according to their final panel diagnosis: group A (LPHD) and group B (cHD).

Antigen Retrieval and Immunohistochemistry

Cases with at least several unstained slides or paraffin blocks available were included. Sections (2 μm) were mounted on poly-L-lysine-coated slides and air



Scheme 1. *Flow chart of case recruitment for this study.*

dried overnight (54°C). Specimens were dewaxed in xylene, rehydrated, and transferred to Tris-buffered saline.

Antigen retrieval techniques were applied as described previously.[21] Heating was performed in a microwave oven (900 W) using citrate buffer (0.01 mol/L, pH 6.0). Continuous irradiation lasted 30 minutes (22 minutes at 100°C). Afterwards, specimens were cooled to room temperature and transferred to Tris-buffered saline. Antibodies applied are summarized in Table 1. Detection was done by the alkaline phosphatase anti-alkaline phosphatase APAAP method, followed by a counterstain with hemalaun.

mRNA ISH for Ig Light Chains

For some of the cases the results of Ig light chain mRNA ISH have been reported recently.[19] Another 43 cases have been investigated within this study using the microwave-enhanced ISH technique. In brief, after microwave pretreatment, mRNA ISH was performed using standard DAKO Kits (K045 and K046) according to the supplier's instructions but with prolonged incubation times (hybridization, detection antibody, and substrate incubation for 12 hours each). mRNA ISH was possible only when sufficient paraffin blocks were available. Therefore, not all cases could be analyzed for Ig light chain mRNA.

Table 1. *Antibodies Used in this Study*

Antibody	Clone/name
CD45	LCA*
CD20	L26*
CD30	BerH2*
CD15	LeuM1†
CD57	HNK-1†
CD3	Polyclonal*
EBV-LMP	CS 1–4*

*Dako, Hamburg, Germany.
†Becton Dickinson, Deisenhofen, Germany.

Evaluation

For each case, the whole slide was evaluated independently by two of the authors (R. von Wasielewski and M. Werner) without knowledge of the respective diagnosis. Histological preservation of the slides was almost unaffected by microwave pretreatment and allowed a reliable distinction of L&H/RS cells.

For all antibodies, cases showing a majority of diagnostic cells specifically stained were scored positively. Within questionable cases, cells were counted (at least 40 cells per slide when detectable), and a positivity threshold was defined as 20% or more stained diagnostic cells.

For CD57, the area with the highest number of positive cells on the slide was determined under low magnification, and all positive cells within one high-power field (×400) were counted. This score was termed CD57-HPF_{max}.

Table 2. *Definition of Immunophenotyping Groups*

Immunophenotyping groups	CD3	CD15	CD20	CD30	CD45	CD57
1) LPHD-like, $CD57^+$	−	−	+	−	+/−	+
2) LPHD-like, $CD57^-$	−	−	+	−	+/−	−
3) cHD-like, $CD57^+$	−	+	−	+	−	+
4) cHD-like, $CD57^-$	−	+	−	+	−	−
5) Inconsistent	−	−/+	−/+	−/+	−/+	−/+

Only cases exceeding the 20% threshold limit were scored positively. CD45 was frequently difficult to score because of the close proximity of non-neoplastic bystander lymphocytes ($CD45^+$). A reliable evaluation could be performed only when neoplastic giant cells bordered on one another. Therefore, this marker was often of limited use in our hands.

Appropriate positive and negative controls were performed with each staining series. All clinical and follow-up data from the cases were obtained from the files of the GHSG study center in Cologne, Germany (J. Franklin).

Results

Immunohistochemical analysis and ISH revealed three categories: cases with a typical LPHD-like immunophenotype pattern, cases with a cHD-like immunophenotype pattern, and cases with phenotypes that were not fully conclusive. The first two categories were further subdivided according to the number of $CD57^+$ lymphocytes present. When the CD57-HPF_{max} score was higher than 120, it was regarded as high/+, otherwise as low/−. None of the cases showed T-cell-specific membrane staining of CD3 in the diagnostic cells. Thus, the marker CD3 is not mentioned further (Table 2).

Group A

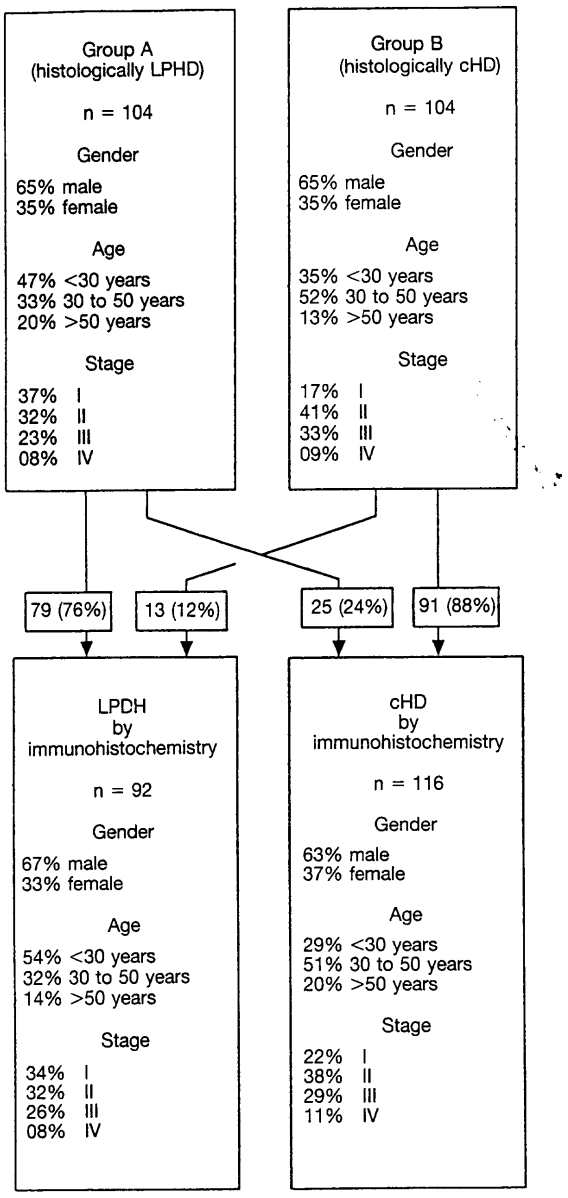
Overall, immunohistochemistry confirmed the GHSG classification of LPHD in 79 of 104 cases (76%). In 62 cases, the results were fully conclusive, another 5 cases showed a low CD57 score, and 12 cases showed inconsistent immunophenotypes. In 25 of 104 cases (24%), the immunophenotype was cHD-like. The detailed results including the numbers of positive/investigated cases with mRNA light chain ISH and basic clinical data are shown in Table 3 and Scheme 2.

Group B

In 91 of 104 cases, the final classification as cHD of the GHSG was confirmed by the retrospective immunohistochemical analysis from this study. In 13 cases, which had not been confirmed by the panel pathologists as LPHD, immunohistochemistry showed a LPHD-like phenotype, which favors the

Table 3. *Results of Immunophenotyping According to the Two Histological Groups*

Immunophenotyping categories		Total number	GHSG classification	
			LPHD, group A	cHD, group B
LPHD-like				
1)	High CD57	73	62	11
	Ig light chain mRNA	25/28	16/19	9/9
	EBV	0/45	0/33	0/11
2)	Low CD57	6	5	1
	Ig light chain mRNA	3/5	2/4	1/1
	EBV	0/5	0/4	0/1
cHD-like				
3)	High CD57	2	2	0
	Ig light chain mRNA	0/1	0/1	−/−
	EBV	0/2	0/2	−/−
4)	Low CD57	100	22	78
	Ig light chain mRNA	0/25	0/10	0/15
	EBV	21/46	5/19	16/27
Not fully consistent				
5)	See Table 4	27	13	14
	Ig light chain mRNA	7/16	7/8	0/8
	EBV	8/25	1/12	7/13
Total number		208	104	104



Scheme 2. *Comparison of clinical data of study patients. Groups A and B are defined by GHSG classification (on morphology, upper half) or by retrospective immunohistochemical analysis (lower half).*

classification of the contributing pathologists (Table 3 and Scheme 2).

In groups A and B, no difference in the gender distribution was detectable, but in Group A there was a higher percentage of younger patients (<30 years) and of patients with a limited stage of disease (I and II constituted 69% in group A *versus* 58% in group B; Scheme 2).

When classification was done based on immunohistochemical categories (Table 2), none of the cases with a LPHD-like marker pattern showed EBV positivity, but 28 of 33 (85%) were positive for light chain mRNA (Table 3; Figure 2). Moreover, positivity for both Ig light chain mRNA and EBV was never observed in any case. No case showing a high CD57 score was EBV positive either. In contrast, no light

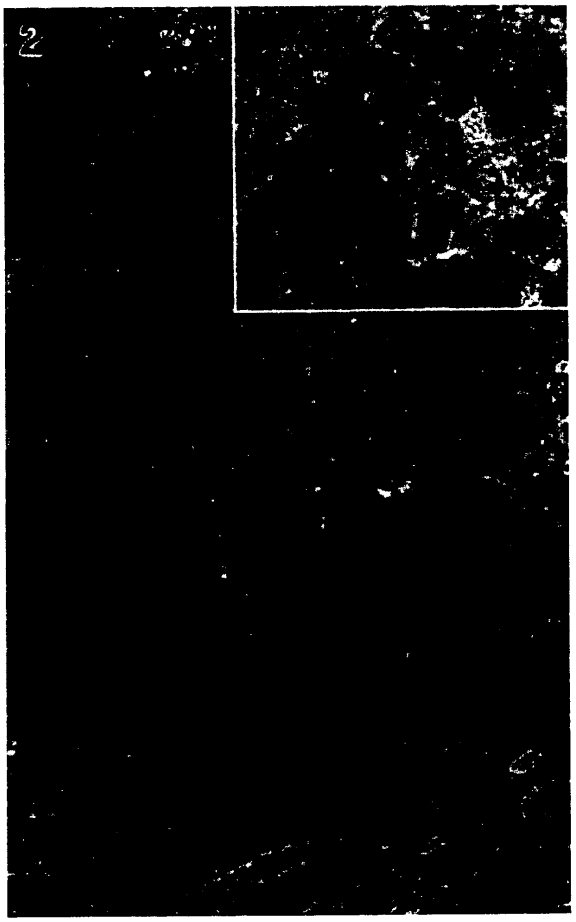


Figure 2. *LPHD: κ-light chain* in situ *hybridization. Multiple giant cells show positive hybridization signals.* Inset: *Higher magnification of a positive Sternberg-Reed cell (same case). λ mRNA was not detectable.*

chain mRNA positivity was observed among the cHD-like cases (Table 3), but a high percentage of EBV-positive cases among those cHD that had been classified as mixed cellularity HD was noted (72%; data not shown).

Among the six biopsies with LPHD-like immunopattern but low number of CD57-positive cells (Table 3), three cases had rather small biopsies and another two scored 100 and 110, respectively, in CD57-HPF_{max}, thus exhibiting a borderline value. One case was classified as TCR.BCL as mentioned later. Two cases showed a cHD-like marker pattern but with a high CD57-HPF_{max}.

In 27 of 208 cases, immunohistochemical results were not fully consistent with a LPHD-like or cHD-like marker profile (Table 3). The detailed results of these cases are shown in Table 4. Among these, five cases showed CD20 and CD15 positivity in the same case, whereas a coincidence of CD20 and CD30 was more frequently detected (n = 14). Only two of the latter group were positive for EBV, both with a low CD57 score.

The last column in Table 4 displays the most likely classification according to immunophenotyping and

Table 4. *Detailed Results of Cases Showing Inconsistent Immunophenotypes*

Number	CD				mRNA	EBV	FD	PC	Most likely classification by immunophenotype
	15	20	30	57					
1	+	+	−	+	Kappa	−	LP	LP	LP
2	+	+	−	+	Kappa	−	MC	LP	LP
3	+	+	+	+	NA	−	MC	LP	(LP)
4	+	+	+	−	−	+	LP	MC	cHD
5	+	+	+	−	NA	−	LP	MC	(cHD)
6	−	+	+	+	Kappa	−	LP	LP	LP
7	−	+	+	+	Kappa	−	LP	LP	LP
8	−	+	+	+	NA	−	LP	LP	(LP)
9	−	+	+	+	NA	−	LP	LP	(LP)
10	−	+	+	+	NA	−	LP	LP	(LP)
11	−	+	+	+	NA	−	LP	LP	(LP)
12	−	+	+	+	NA	−	NS	MC	(LP)
13	−	+	+	−	−	+	LP	LP	cHD
14	−	+	+	−	NA	−	LP	NS	(cHD)
15	−	+	+	−	−	−	MC	NS	(cHD)
16	−	+	+	−	−	−	MC	MC	(cHD)
17	−	−	+	−	Kappa	−	LP	LP	LP
18	−	−	+	−	Kappa	−	LP	LP	LP
19	−	−	+	−	Kappa	−	LP	LP	LP
20	−	−	+	−	NA	NA	LP	NS	(cHD)
21	−	−	+	−	−	+	LP	MC	cHD
22	−	−	+	−	−	+	LP	NS	cHD
23	−	−	+	−	−	+	LP	MC	cHD
24	−	−	+	−	NA	+	LP	MC	cHD
25	−	−	+	−	−	+	MC	MC	cHD
26	−	−	+	−	−	−	NS	NS	cHD
27	−	−	−	−	−	+	LP	MC	cHD

FD, first diagnosis by contributing pathologist; PC, panel classification; +, positive; −, negative; NA, not available. Speculative classifications are shown in parentheses.

ISH. Within the histologically confirmed LPHD cases, the panel of markers supported the diagnosis of LPHD in 7 of 13 cases (54%) clearly, but in 5 of 13 cases (38%) only speculatively, whereas one case was regarded as cHD (7%; case 13). Among the histologically unconfirmed LPHD cases, all but one case (12) showed an immunophenotype more in accordance with cHD. Overall, immunophenotyping supported the histological GHSG classification in 92.6% of these cases, although the marker profiles were not fully LPHD- or cHD-like.

Among the cases showing an LPHD-like immunophenotype, only 4 of 92 showed a pure diffuse architecture. However, the majority exhibited at least in part a nodular growth pattern, which was seen best in the silver impregnation staining. Immunohistochemical analysis revealed no differences between the two groups with the exception of one case with a diffuse architecture. This biopsy showed an interspersed population of atypical large $CD20^+$ cells and a very low CD57 score (Figure 3, a and b) but with a very high background of small T lymphocytes ($CD3^+$). This case was negative for mRNA and EBV, taken together, an immunophenotype and the histology of a T-cell-rich B-cell lymphoma.

None of the cHD-like cases scored positive for CD45 (LCA), whereas 53 of 92 (57.6%) of the LPHD-like cases clearly showed LCA positivity (Table 2). A reliable evaluation of CD45 proved to be difficult unless two or more diagnostic cells attached to each other, a phenomenon not often seen in LPHD.

The percentages of confirmed and unconfirmed cases based on immunohistochemistry in both groups A and B is shown in Scheme 2. The distribution in terms of gender and stage of disease changed very little, but in the LPHD-like group there was a shift to younger patients (54% < 30 years) when compared with group A.

A comparison of freedom from treatment failure and overall survival between the groups, either defined by the GHSG or by immunohistochemistry is shown in Table 5. Freedom from treatment failure became significantly better for LPHD only after immunohistochemical but not after GHSG classification. The significance of a better survival in LPHD cases improved from $P = 0.047$ to $P = 0.0071$ when classified according to immunohistochemical results.

Among the immunohistochemically confirmed LPHD cases, only one patient died according to the

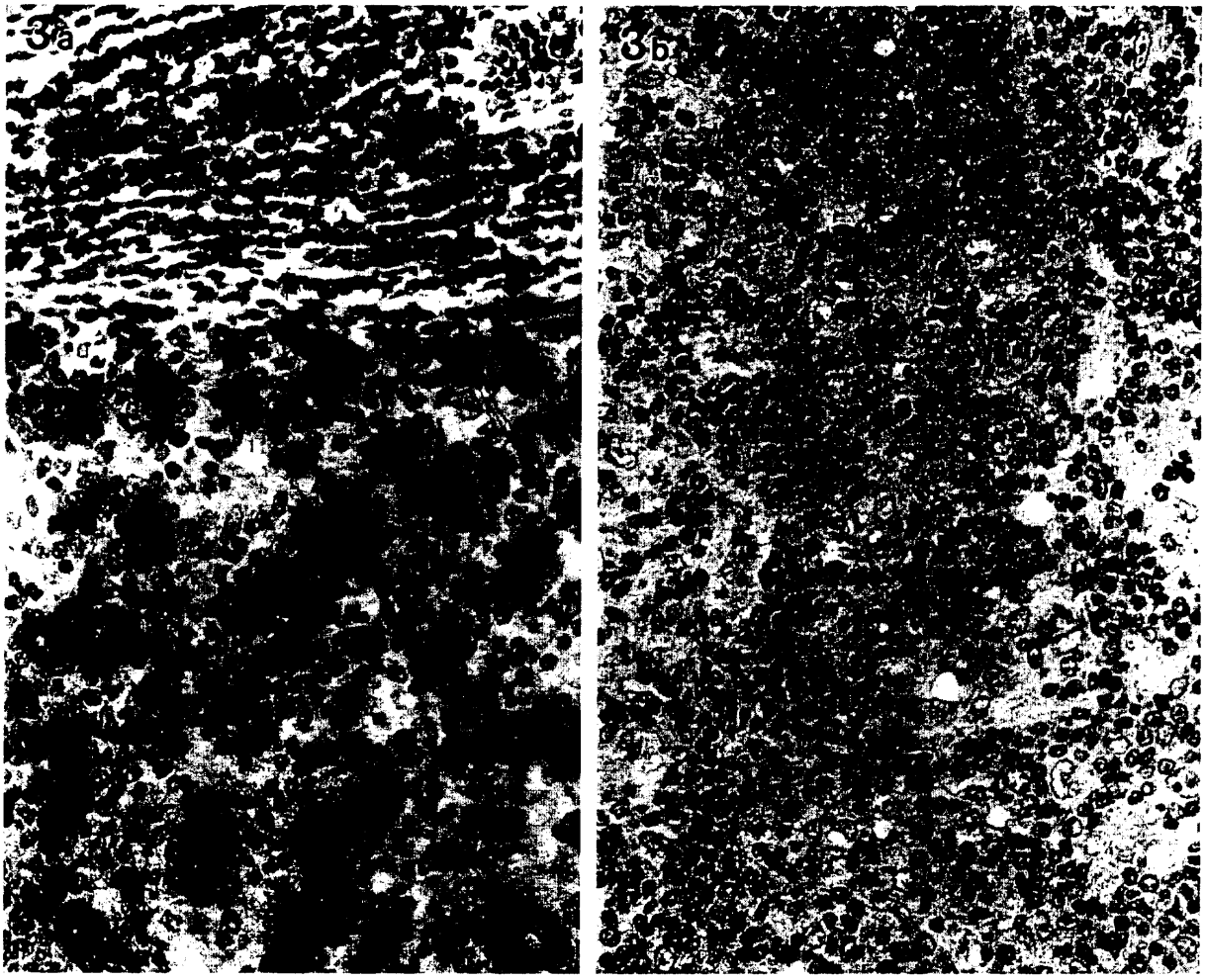


Figure 3. *TCR.BCL.* a: *Strong positivity for the B-cell marker CD20 in the atypical blasts.* b: *Only single non-neoplastic cells show CD57 expression.*

follow-up data so far available. The cause of death is recorded as not HD related.

Discussion

Among the histologically confirmed cases of LPHD from the GHSG, approximately two-thirds showed a LPHD-like immunophenotype. However, in addition to cases with an immunophenotype that was not fully conclusive, there was nearly one-quarter of cases showing a cHD-like immunophenotype (Scheme 2). This is supported by low numbers of CD57-positive cells, by the lack of detectable Ig light chain mRNA in the diagnostic cells, and a frequent positivity for EBV. The overlap between morphological classification (some of these cases were independently classified as LPHD by five pathologists, ie, the primary pathologist and four panel experts) and the results of immunohistochemistry can be explained in two ways. First, LPHD is an entity with a nonuniform phenotype showing approximately 20% of cases with aberrant phenotypes. This explanation fits well with a considerable number of published results.[9,10,22] In consequence, this would definitely refute the common belief that only rare cases of LPHD show a cHD-like immunophenotype.

However, the results of this study hint at a second possible explanation; ie, separation of LPHD from cHD by histology is frequently difficult, either because the rarity of cases (less than 5% of all HD) limits the level of diagnostic proficiency of many pathologists or because morphology is an imprecise discriminant in LPHD classification *per se*. Whatever holds true, the result is an impure mixture of entities.

Whereas nearly all studies discussed their immunohistochemical results from the viewpoint of morphology, Nicholas et al[23] published an approach in which most LPHD with aberrant phenotypes were reclassified as cHD. Our results demonstrate that the gap between LPHD and cHD broadens as more

Table 5. *Comparison of Freedom from Treatment Failure and Survival of Patients Classified According to Morphology (GHSG Classification) or to Immunohistochemistry and ISH Results*

A

GHSG classification	LPHD	cHD (unconfirmed LPHD)	*P* value
FFTF	12/69	15/55	0.052
SV	3/69	8/55	0.047

B

Immunohistochemical classification	LPHD-like	cHD-like	*P* value
FFTF	10/60	17/64	0.0325
SV	1/60	10/64	0.0071

Only when classification was based on immunohistochemistry did LPHD cases show significantly better freedom from treatment failure (FFTF) ($P < 0.05$) and a very significant better survival (SV; $P < 0.01$) than classical HD (see Figure 6). Events counting for freedom from treatment failure were all failures of treatment, not achieving a complete remission after primary therapy, relapse, and death. Maximal observation period was 140 months.

suitable markers and/or refined techniques are applied (CD57, EBV, and Ig light chain ISH).

High numbers of CD57-positive cells are known to be characteristic of LPHD, but evaluation was difficult or complicated by image-analyzing systems.[15–17,24,25] Our scoring method of CD57-HPF-$_{max}$ was easy to apply and reliably helped to distinguish LPHD from cHD in many cases. In general, LPHD exhibited greater than 200 cells per HPF_{max} (Figure 4), contrasted with the aggregated cases showing cHD-like immunophenotypes, which scored 45 cells per HPF_{max} on average. One case of the confirmed LPHD cases attracted attention because of a very low CD57 count and the diffuse pattern of CD20-positive neoplastic cells. It was rereclassified by morphology and immunohistochemistry as a typical T-cell-rich B-cell lymphoma, an observation in concordance with Kamel et al.[17]

None of the cases with a LPHD-like immunophenotype showed EBV positivity. This supports previous studies that this entity is not associated with EBV[26–28] but contrasts those reports showing some EBV-positive cases (8 to 14%).[29–32] However, our results favor the possibility that classification itself is the reason for these published differences.

Within the histologically unconfirmed LPHD cases, immunohistochemistry clearly affirmed the GHSG classification in the majority of cases (78 of 104). None of these specimens showed either Ig light chain mRNA or a high CD57 count, but EBV positivity could be demonstrated in the majority of cases classified as mixed cellularity by the panel (Figure 5).

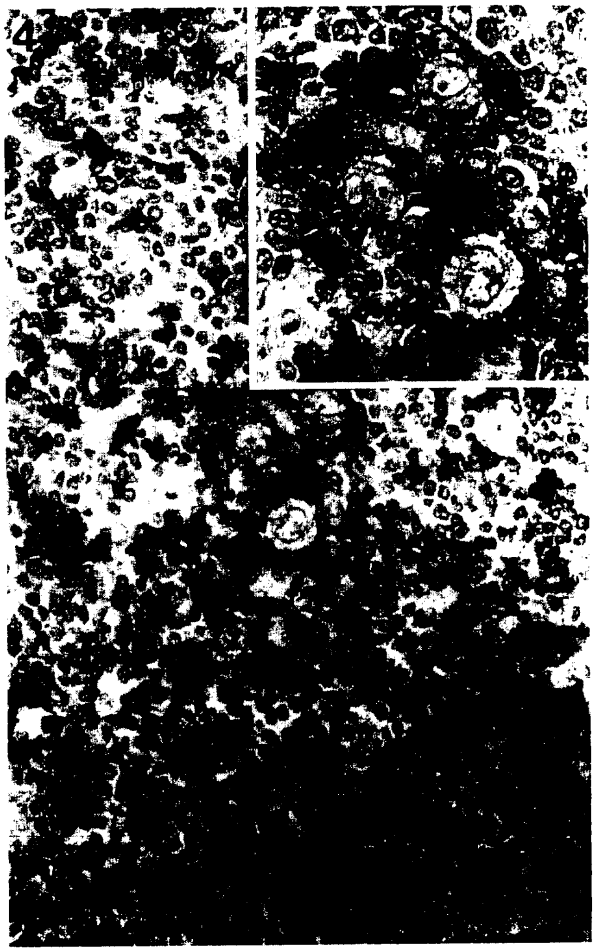


Figure 4. *LPHD: high content of small lymphocytes showing strong CD57 expression.* Inset: *High magnification showing three neoplastic popcorn cells surrounded by CD57 non-neoplastic bystanders.*

Nevertheless, 12 cases showed a typical LPHD-like immunopattern (Tables 2 and 3).

The results of the Ig light chain mRNA analysis showed a strong correlation with immunohistochemical stainings of antibodies (Table 3). The reason for this positive correlation, which was not observed in our recently published results,[19] is explained by the way positivity for the markers was evaluated. Introducing a 20% threshold for calling a case positive for immunohistochemical staining yielded a more distinctive separation of immunophenotypical groups and prevented cases from being positively scored due to single cells. There is no widely accepted rule in the literature defining the percentage of diagnostic HD cells necessary for a respective marker to be considered positive. However, besides the presence of typical popcorn or Hodgkin/Sternberg-Reed cells and uniform staining patterns that are easy to evaluate, there are cases with histologically uncertain giant cells and partial positivities that cannot be denied. It may be assumed that methodical variations of immunohistochemical evaluation also account for mixed immunophenotypes in the literature. There-

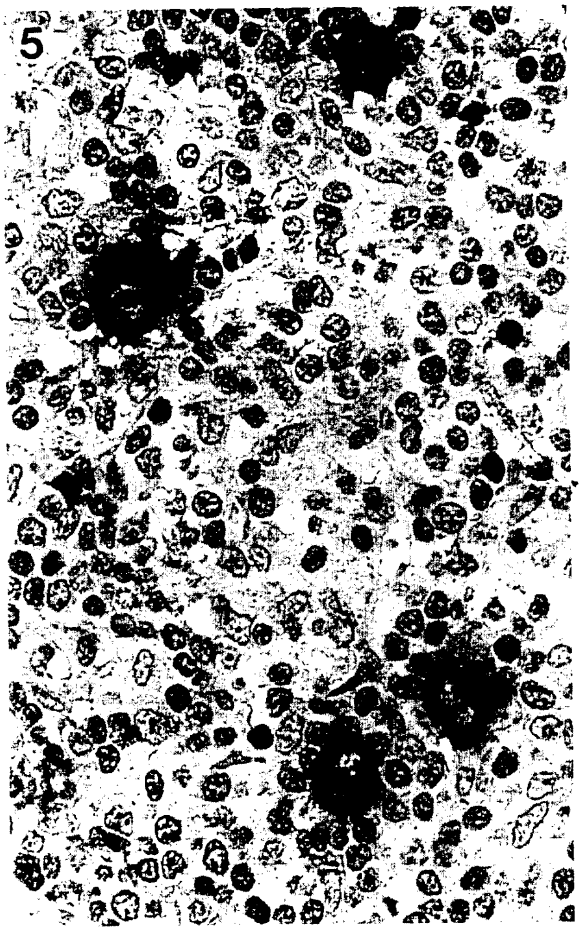


Figure 5. *MCHD: strong signal for EBV-LMP in Hodgkin cells. Whereas a high percentage of MCHD cases scored positive for EBV, this was never observed in any of the immunohistochemically confirmed LPHD cases.*

fore, it was helpful to use the 20% threshold, which accelerated evaluation and optimized inter-observer agreement between the two investigators.

Overall, twenty-seven cases were summarized in the group showing aberrant immunophenotypes (Table 4). Because tissue processing or fixation may also alter immunohistochemical reactions, it is unwarranted to discuss every single case. However, one group of cHD cases lacked CD15 positivity and others exhibited a co-expression of CD15 and CD20 (and CD30), phenomena that have been reported for small subgroups of HD before.[33–35] Seven cases showed a LPHD-like immunophenotype with a high CD57 count, EBV negativity (and light chain mRNA positivity when ISH could be done: 2/2), but additionally CD30 positivity. Thus, CD30 positivity may occur within LPHD, but using the threshold limit, these cases are rare (<8% of LPHD) and should not be confused with cHD lacking CD15 (by histology, CD57, LCA, EBV, and Ig light chain restriction). We have accumulated all data on these cases and have listed the most likely classification in our opinion in Table 4.

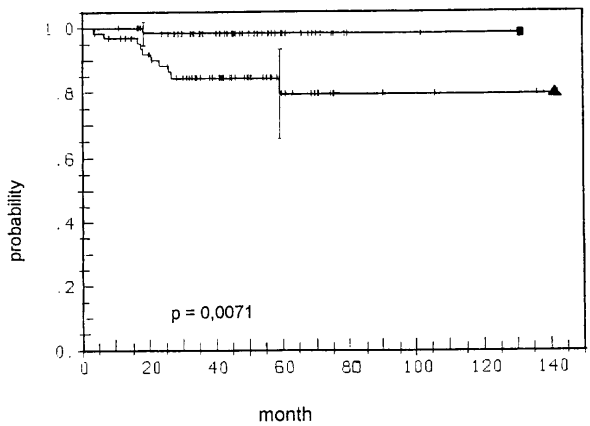


Figure 6. *Comparison of clinical outcome (survival) between immunohistochemically either confirmed LPHD cases (■) or classical HD (▲) cases, P = 0.0071. Detailed numerical data are shown in Table 5.*

LPHD has shown a better clinical outcome than the other subtypes of HD.[6,7,36–38] In general, the clinical data of the GHSG support these observations. To date, the clinical outcome is available for only 124 cases from this immunohistochemical study. Data from patients belonging to the latest study generation had to be omitted because of short observation periods. Nevertheless, our data presented here indicate that the clinical differences between LPHD and cHD have been underestimated so far.

It has been questioned whether the better clinical outcome could justify a modification of therapy for patients with LPHD.[3] However, such deliberations require a reliable separation from the other subtypes of HD, especially the lymphocyte-rich cHD. The panel review system of the GHSG improved the classification of LPHD considerably, as shown here, but even then, cases were not classified according to the immunophenotypic characteristics of this entity.[12] Therefore, our results demonstrate that the diagnosis of LPHD inevitably necessitates a reliable immunohistochemical confirmation, a statement in concordance with the suggestions of two previous studies.[10,23]

Otherwise, a modification (reduction) in treatment could turn out to be ambivalent: an improvement for true LPHD patients but a dangerous step backwards for those erroneously classified as paragranuloma.

Acknowledgments

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