Nodular Lymphocyte Predominant Hodgkin Lymphoma With Nodules Resembling T-Cell/Histiocyte Rich B-Cell Lymphoma

Differential diagnosis between nodular lymphocyte predominant Hodgkin lymphoma and T-cell/ histiocyte rich B-cell lymphoma

Short title: nodular lymphocyte predominant Hodgkin lymphoma

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Abstract

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and T-cell/histiocyte rich B-cell lymphoma (T/HRBCL) are distinct tumors treated differently. They are linked by a morphological and probably a biological continuum, which renders the differential diagnosis difficult. To develop criteria to distinguish the entities along the morphological continuum we correlated the lymph node architecture and immunophenotype of both tumor cells and reactive components of 235 neoplasms in the spectrum of NLPHL and T/HRBCL to clinical data. Two hundred and eighteen cases fitted the WHO criteria of NLPHL (139) or T/HRBCL (79). While tumor cells in both entities were immunophenotypically similar, background composition differed: in NLPHL small B-cells and CD3+CD4+CD57+ T-cells were common, while in T/HRBCL CD8+ cytotoxic T-cells and histiocytes dominated. Follicular dendritic cells (FDC) formed expanded meshworks in NLPHL while absent in T/HRBCL. Seventeen cases represented a “grey zone”: within FDC meshworks neoplastic B-cells resided in a background depleted of small B-cells but rich in T-cells and histiocytes. Tumor cells were either loosely scattered or formed clusters, thus resembling areas of either T/HRBCL or inflammatory DLBCL within the nodules. Patients with these NLPHL with T-cell/histiocyte rich nodules presented at a high stage and with B-symptoms, like T/HRBCL, but had an excellent survival, like NLPHL. This morphological pattern suggests a biological continuum between NLPHL and T/HRBCL.

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Introduction

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) accounts for 6.5% of cases in the German Hodgkin lymphoma study. It is characterized by a nodular, or a nodular and diffuse proliferation of scattered large neoplastic cells (lymphocytic and/or histiocytic (L&H) cells or “popcorn” cells) in large spherical meshworks of follicular dendritic cells (FDC) filled with non-neoplastic small lymphocytes, mainly of B-cell type \(^1\). There have been doubts whether a purely diffuse lymphocyte predominant Hodgkin lymphoma (LPHL) really exists \(^2,3\).

NLPHL has recently been distinguished from the nodular lymphocyte-rich variant of classical Hodgkin lymphoma, based on immunophenotype. In contrast to cHL, tumor cells of NLPHL do not express CD30 and CD15, but they are positive for B-cell markers (CD20, CD79a), immunoglobulins (Ig), J-chain, and epithelial membrane antigen\(^1\). The B-cell phenotype and genetic features of NLPHL, exhibiting clonally rearranged immunoglobulin genes with ongoing mutations\(^4,5\), indicate its close relationship to B-cell non-Hodgkin lymphomas \(^2,6\).

Among B-cell non-Hodgkin lymphomas, T-cell/histiocyte rich B-cell lymphoma (T/HRBCL) represents a variant of diffuse large B-cell lymphoma (DLBCL) in which neoplastic CD20\(^+\) B-cells, accounting for less than 10% of the infiltrate, are scattered among the majority of non-neoplastic T-cells with or without histiocytes\(^2\). Nevertheless, T/HRBCL seems heterogeneous, comprising several subgroups. The tumor cells may resemble centroblasts, immunoblasts, Reed-Sternberg (RS) or L&H cells \(^2,7-11\).

The clinical presentation and treatment strategies of NLPHL and T/HRBCL are different \(^12,13\). NLPHL presents at a localized clinical stage, and pursues an indolent course \(^2\), while T/HRBCL presents typically at a high stage, and its outcome is worse
According to morphological, immunophenotypic, molecular-genetic, and clinical data gathered over several past years, there exists a substantial overlap - a grey zone - between NLPHL and T/HRBCL. Both diseases may occur as composite lymphomas in the same lymph node or in subsequent biopsies, as well as in members of the same family. In addition, a diffuse pattern in NLPHL may represent a morphological tumor progression and transition to T/HRBCL. The tumor cells of NLPHL and T/HRBCL are alike not only morphologically, but also immunophenotypically. Only PU.1, a transcription factor essential for B-cell development, has been described to be more often expressed in NLPHL than in T/HRBCL, albeit in a low number of cases. However, differences in the background composition and growth pattern do exist. To decide treatment and to include patients in clinical studies, it is essential to distinguish NLPHL from T/HRBCL.

The differential diagnosis is not settled for cases sharing architectural and immunomorphologic features of both NLPHL and T/HRBCL. We compared pathological and clinical properties of a large series of cases from the grey zone, as well as of unequivocally diagnosed, typical NLPHL and T/HRBCL, to define criteria to distinguish these entities. After a thorough analysis, 17 cases still could not be readily diagnosed as NLPHL or T/HRBCL and we determined their pathological and clinical characteristics.
Materials and methods

Case selection and immunophenotypic studies

From the files of the Institute of Pathology in Würzburg we retrieved all 235 primary diagnostic lymph node biopsies diagnosed as either T/HRBCL or NLPHL between 1996 – 2001 and reviewed them with immunostains for CD20, CD30, EMA, CD21, CD3. If necessary, additional stains were performed. Among these we identified 64 lymph node specimens with peculiar features: NLPHL displaying abundant tumor cells or a predominantly diffuse growth pattern and T/HRBCL showing some degree of nodularity. These 64 specimens were compared in detail to 41 randomly selected typical control cases of NLPHL (25) and T/HRBCL (16). Altogether, 105 tumors were stained with an extended immunohistochemistry panel on an automated immunostainer (Tecan, Crailsheim, Germany), while 130 cases (86 typical NLPHL and 44 typical T/HRBCL) were not further investigated. In tumor cells, we assessed the reactivity for CD20, CD79a, epithelial membrane antigen (EMA), CD30, bcl-2 (all obtained from Dako, Hamburg, Germany), transcription factor PU.1 (clone G148-74, Pharmingen San Diego, CA; United States), and Ki-67 antigen (Novocastra, New Castle upon Tyne, Great Britain); interferon consensus sequence binding protein for activated T-cells (ICSAT) (Santa Cruz, CA, USA), J-chain (Biogenex, San Ramon, CA, USA). Results were scored positive if more than occasional (>30%) of the tumor cells were positive.

In the reactive background, T-cell subsets were evaluated using CD3, CD4 (Novocastra), CD8 (Dako), CD57, TIA-1 (Immunotech, Marseille, France), granzyme B (Monosan, Uden, Netherlands). To achieve a higher reproducibility of the data, in CD3, CD4, CD8, and CD57 stains, the rosettes around the neoplastic cells were
Macrophages were studied using the antibodies KiM1P (a kind gift from Prof. Dr. R. M. Parwaresch, Kiel) and PU.1. All these were graded semiquantitatively on an interval scale (none< occasional< moderate< many). For comparisons, cases with more than occasional stained background cells/rosettes were considered. The presence and density of FDC meshworks was evaluated using anti-CD21 staining (Dako).

In 47 selected cases (33 T/HRBCL, 2 NLPHL, the 2 diffuse LPHL, and 10 cases not meeting the criteria for either NLPHL or T/HRBCL) numbers of both small non-neoplastic and large neoplastic B-cells were counted separately in CD20 stains in 5 HPF with a 40x objective, using an eyepiece grid in a microscope Olympus BX 50 (Olympus, Japan) and a manual cell counter.

Diagnostic criteria

The diagnoses were established in consensus by LB, TR, and HKMH without knowing the clinical features. The WHO criteria were applied to assign cases to NLPHL or T/HRBCL. Briefly, in NLPHL tumor cells were scattered within preserved FDC meshworks filled with numerous small B-cells (often with a small B-cell mantle), T-cell rosettes, and sometimes with histiocytic granulomas. In diffuse areas of LPHL, tumor cells were also accompanied by small non-neoplastic B-cells, but FDC meshworks were lacking. Such areas were associated with typical NLPHL nodules in all but 2 cases that we considered as diffuse LPHL.

In T/HRBCL the tumor B-cells made up fewer than 10% of the diffuse infiltrate that was mainly composed of T-cells and histiocytes, usually not forming granulomas. No FDC meshworks were detected, and small B-cells were rare to absent.
Seventeen cases that did not meet the diagnostic criteria for either NLPHL or T/HRBCL were considered as a third group and analyzed separately.

**Clinical data**

Data (including age, sex, stage at presentation, B-symptoms, tumor diameter, hemoglobin, serum lactate dehydrogenase, therapy regimen, follow-up) on the 105 cases studied in detail were provided by the German Hodgkin Lymphoma Study Group (on 46 patients) or by referring clinics and physicians (on 59 patients).

**Statistics**

Immunophenotypes were compared by $\chi^2$ tests using Statistica for Windows® (Statsoft GmbH, Hamburg, Germany) to adopt the comparison to the scales used. Clinical data were also compared with Student’s t-test (e.g. age), Spearman’s rank correlation (e.g. stage) or log-rank test (e.g. survival) depending on the nature of data. Nominal p-values below 0.05 were regarded as significant.
Results

Morphology and immunophenotype

The distribution of the diagnoses of all 235 cases is given in Table 1. The remaining 17 cases were in a “grey zone” will be detailed below. The antigen profile of tumor cells of NLPHL and T/HRBCL (Table 2) was remarkably similar. Significant differences were restricted to the expression of PU.1, CD79a, and bcl-2. PU.1 was more commonly expressed in NLPHL. On the other hand, CD79a and bcl-2 were more often positive in T/HRBCL.

In contrast to the tumor cell immunophenotype, the background composition of NLPHL and T/HRBCL differed greatly (Table 2): small CD20+ cells dominated in NLPHL, yet CD3+ cytotoxic T-lymphocytes formed the majority of non-neoplastic background in T/HRBCL. However, rosettes of CD3+ lymphocytes around tumor cells were still significantly more frequent in NLPHL than in T/HRBCL. These rosetting lymphocytes in NLPHL were CD4+ CD57+ follicular T-cells that were negative for TIA-1 and granzyme B. Histiocytes were numerous in T/HRBCL, but few to moderate in number in NLPHL. The meshworks of FDC, while at least partially preserved in NLPHL (with the exception of two cases of diffuse NLPHL), were absent in T/HRBCL. Within NLPHL, the immunophenotype of the tumor cells and background composition correlated with their relationship to FDC meshworks: while tumor cells inside FDC networks showed a higher expression of J-chain and PU.1, those outside expressed significantly more frequently CD79a and bcl-2. In nodular areas many CD4+CD57+ rosettes were detected, but in diffuse areas histiocytes and cytotoxic T-cells were more numerous, but nonetheless significantly fewer than in T/HRBCL.
In 14 cases of otherwise typical T/HRBCL, vaguely nodular areas were detected morphologically and/or immunohistochemically. In only 2 of them (representing less than 1% of the cases reviewed) the nodular areas met the criteria of NLPHL also as to the background composition and the occurrence of FDC meshworks. These latter were regarded as T/HRBCL for the comparison of clinical data.

Such lymphomas exhibiting areas of both NLPHL and T/HRBCL need to be distinguished from 17 cases designated “grey zone” cases, which did not fulfil criteria for either of the entities.

**NLPHL with T-cell/histiocyte rich nodules**

17 cases (7% of all 235 cases) did not fully meet the diagnostic criteria of either NLPHL or T/HRBCL (Table 1) and therefore could not be readily classified. These tumors consisted of nodules with their FDC meshworks at least partially preserved and of a similar size as in NLPHL. The tumor cells appeared mostly like L&H cells or large multilobated centroblasts; Reed-Sternberg-like tumor cells were rarely seen. However, variable portions of the respective lymph nodes, from single nodules in a background of typical NLPHL up to the whole of the specimen, contained peculiar nodules: These attracted attention because, in addition to the tumor cells, they contained abundant T-cells and histiocytes, but conspicuously few small B-cells.

Numerically, on average 0.7 to 4.2 small B-cells were counted per one tumor cell (mean: 2.7 : 1) in T-cell/histiocyte rich nodules, similar to T/HRBCL where, by definition, few small B-cells were seen (small B-cells : tumor cells = 0.3 to 1.5 : 1 (mean: 0.7 : 1). In contrast, small B-cells outnumbered the tumor cells by 20 to 50 : 1 in NLPHL and by 6 : 1 in diffuse LPHL.
In 10 of the 17 cases the cellular composition within these nodules resembled T/HRBCL: within vaguely defined nodules neoplastic cells were loosely scattered in a background of small and activated T-cells and histiocytes (pattern A, Fig 1 left). Unlike typical NLPHL, T-cells within the nodules were mostly cytotoxic expressing TIA-1, and rosettes of CD4+ CD57+ follicular T-cells were observed in only one case. FDC meshworks were preserved throughout the follicle.

In 7 other cases the tumor cells formed clusters of 5 or more cells within the nodules (pattern B, Fig 1 right), thus rather suggesting DLBCL with a prominent inflammatory background of T-cells and histiocytes. However, sheets of blasts reminiscent of follicular lymphoma grade 3b24 were not observed. The nodules were well demarcated and often surrounded by a rim of small B-cells, occasionally with histiocytic granulomas. Importantly, no small B-cells were seen within the nodules. In 4/7 cases, rosettes of CD57+ T-cells could be seen within the nodules, and cytotoxic T-cells were considerably less frequent than in the cases described above. FDCs were retained mostly at the periphery of the follicle but were hardly seen within the sheets of the tumor cells.

Clinical data

The clinical data are summarized in Table 3. Males were predominantly affected. Patients with NLPHL were significantly younger than those with T/HRBCL (39 vs. 49 years). Most patients with NLPHL (80%) presented at stages I and II, but in contrast, 48% with T/HRBCL presented at advanced stages III or IV. Likewise, B-symptoms occurred frequently in patients with T/HRBCL (46%), but only exceptionally in NLPHL (5%). Among NLPHL, cases with diffuse areas did not differ in their clinical presentation and outcome from typical NLPHL. The two patients with purely diffuse LPHL presented in stages I and II, respectively.
Patients with NLPHL with T-cell/histiocyte rich nodules presented at a similar age (median 41 years) as typical NLPHL. However, their stages and the frequency of B-symptoms were more similar to patients with T/HRBCL; namely, 60% of them presented at advanced stages III or IV and 38% had B-symptoms. The two patterns did not correlate with sex or with the presence of B-symptoms, but the stage was significantly different: patients with the T/HRBCL-like pattern accounted for most of the higher stages (5 of the 10 patients at stage IV, 2 at stage III), while all but one patient (stage III) with the DLBCL-like pattern presented at stages I and II.

Treatment differed significantly with diagnosis and with stage. Among the NLPHL patients, 30% (all stage I) were treated only surgically or by local radiotherapy, while most others were treated with COPP/ABVD or BEACOPP, regimens included in the trials of the German Hodgkin lymphoma study. In contrast, 60% of the patients with T/HRBCL were treated with CHOP-based regimen, as is usual in the German high grade lymphoma study.

Patients with NLPHL with T-cell/histiocyte rich nodules were not treated differently from those with NLPHL if stage is taken into account. Due to their higher stages they received intensified regimens more often and 73% of patients received regimen like BEACOPP, CHOP or primary high-dose chemotherapy with autologous stem cell transplantation. In contrast, only 32% of patients with NLPHL received a similar therapy because they presented at stage III.

Patients with NLPHL had a very good prognosis, only one patient of the series died after 20 months of myocardial infarction while his lymphoma was in complete remission. Patients with NLPHL with T-cell/histiocyte rich nodules had a similarly good outcome as those with typical NLPHL (Fig. 2): only one patient died during
treatment. In contrast, patients with T/HRBCL frequently relapsed and 30% of the patients died within the first year (Figure 2).
Discussion

NLPHL and T/HRBCL need to be distinguished for treatment purposes, however, criteria are not completely clear in the WHO classification, neither regarding the numbers of tumor cells and of reactive B-cells and the degree of nodularity required for the diagnosis of NLPHL, nor concerning the count of small B-cells or nodular areas compatible with T/HRBCL. Our immunomorphological study therefore addressed the clinical significance of architectural patterns and the antigen profile of both tumor cells and of non-neoplastic background constituents in a large series of cases.

In NLPHL most tumor cells had an L&H appearance, RS cells were rarely identified. In T/HRBCL the neoplastic cells mostly resembled centroblasts, L&H cells, or immunoblasts, but RS cells were scarce. Unlike other authors, we could not identify strikingly predominating tumor cell variants to subcategorize T/HRBCL according to their morphology.

The immunophenotypic properties of the tumor cells are principally in keeping with previous results. Both CD79a and bcl-2 were more frequently expressed in T/HRBCL than in NLPHL. In contrast, PU.1, a transcription factor necessary in early B-cell differentiation, was expressed in NLPHL but reduced or absent from T/HRBCL. Interestingly, the subtle disparity between the phenotypes of tumor cells seems to reflect their relationship to FDC meshworks. In NLPHL, neoplastic cells inside FDC networks showed a higher expression of J-chain and PU.1 than cells in the same tumors that grew diffusely outside, the latter, in contrast, expressed more frequently CD79a, and bcl-2. Still, immunophenotypic differences between the tumor cells currently cannot be used for diagnostic purposes.
On the other hand, the reactive background greatly aided the diagnosis. A follicular environment was retained in NLPHL, documented by the presence of meshworks of FDC, but was absent from T/HRBCL. By definition, small B-cells are abundant in NLPHL, but rare in T/HRBCL. The nature of the T-cell background was diverse: in NLPHL, T-cells were mainly CD4+ CD57+ follicular T-cells that commonly formed the rosettes, while in T/HRBCL CD8+ cytotoxic T-cells and histiocytes predominated and T-cell rosettes were rarely seen.

The clinical characteristics of such defined groups (Table 3) are in accordance with published data. LPHL with diffuse areas did not present or behave clinically different from conventional NLPHL. It has been doubted whether diffuse LPHL exists, however, in our series of 235 lymphomas, we identified 2 such cases: diffusely scattered tumor cells in a background lacking FDC in the CD21 stain were accompanied by abundant small B-cells which distinguished them from T/HRBCL.

Seventeen cases were clearly in the range between NLPHL and T/HRBCL but differed from both: the tumor cells grew within nodules defined by FDC meshworks in a T-cell and histiocyte-rich background either singly (T/HRBCL-like pattern A) or in clusters (DLBCL-like pattern B). Small B-cells with or without histiocytic granulomas sometimes formed a rim around the follicular structures, but were strikingly absent inside FDC meshworks. Instead, the tumor cells were accompanied by T-cells and histiocytes. Such nodules with features indistinguishable from histiocyte rich B-cell lymphoma occurring in NLPHL have been mentioned previously, yet neither their frequency, nor their clinical significance have been investigated.

Within these T-cell/histiocyte rich nodules the growth patterns resembled either T/HRBCL (Pattern A) or DLBCL (Pattern B) at high magnification (Fig. 1, 3). Pattern A with neoplastic cells scattered loosely in a background of abundant histiocytes and
cytotoxic T-cells, but with only scarce small B-cells, resembled T/HRBCL at high
magnification and may be interpreted as an intrafollicular progression towards
T/HRBCL. In pattern B, cohesive clusters of large blasts in an inflammatory
background could be seen suggesting a morphological transformation towards the
pattern of DLBCL within the follicles. Especially patients with NLPHL with T/HRBCL-
like nodules often presented at a high stage (83% at stage III or IV), while no patient
with pattern B showed stage IV, the usual stage being I or II. Conceptionally, these
patterns may represent different pathways of progression towards DLBCL which
develops in up to 5% of patients with NLPHL 33,34. Interestingly, one half of the
DLBCL occurring in the course of NLPHL are of T/HRBCL variant 13. This further
supports that at least a part of the T/HRBCL may derive from NLPHL and have a
follicular origin 10,35.

We do not believe that these cases represent an independent disease, rather the two
patterns should be regarded as a morphological variants: to refer to the remarkably
composed nodules we propose the descriptive term NLPHL with T-cell rich nodules.
The two patterns of these nodules can also be referred to as “T/HRBCL-like” and
“DLBCL-like nodules”, respectively, because they appear to have different clinical
presentation. Given the excellent prognosis, it will be difficult to decide whether
treatment regimen for Hodgkin lymphoma or for NHL are better suited. Outcome was
also excellent when these patients with limited stages were treated with radiotherapy
or COPP/ABVD, stage adapted regimen for Hodgkin lymphoma. Therefore its
designation as a variant of NLPHL seems appropriate at this time. The recognition of
these patterns helps to make decisions in the differential diagnosis, and given their
remarkable morphology, they should be reproducible among pathologists. These
lymphomas should be recognized and treated in clinical studies to learn more about
their biological behavior and treatment requirements, however, they should probably
not be included in studies reducing treatment intensity for NLPHL patients until more evidence regarding their biological behavior has accumulated.

In conclusion, in the differential diagnosis between NLPHL and T/HRBCL, all cases exhibiting tumor cells in a meshwork of FDC should be regarded as NLPHL, regardless of the nature of accompanying small lymphocytes. In diffuse areas abundant accompanying small B-cells characterize a diffuse growth of NLPHL. Only when tumor cells are diffusely scattered in a T-cell and histiocyte-rich background devoid of small B-cells, T/HRBCL should be diagnosed. In some cases, areas of both NLPHL and T/HRBCL coincide, these we regard as secondary T/HRBCL progressed from NLPHL.
## Tables

Table 1. Distribution of 235 diagnoses in the study. Vertically, counts of the diagnoses entering the study are listed. Horizontally, numbers of the definitive diagnoses are given.

<table>
<thead>
<tr>
<th>New Diagnoses</th>
<th>Original Diagnoses</th>
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<tbody>
<tr>
<td></td>
<td>NLPHL</td>
<td>NLPHL and T/HRBCL with unusual features</td>
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<tr>
<td></td>
<td>(111 cases)</td>
<td>(64 cases)</td>
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<tr>
<td>NLPHL</td>
<td>108</td>
<td>31</td>
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<tr>
<td>(139 cases)</td>
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<tr>
<td>T/HRBCL</td>
<td></td>
<td>22</td>
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<tr>
<td>(79 cases)</td>
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<tr>
<td>NLPHL with T-cell/histiocyte rich nodules</td>
<td>3</td>
<td>11</td>
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</table>
Table 2. Comparison of the immunohistochemical properties of the tumor cells and of the background between NLPHL, NLPHL with T-cell/histiocyte rich-like nodules, and T/HRBCL.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of cases</th>
<th>NLPHL</th>
<th>p (NLPHL vs. T/HRBCL)</th>
<th>T/HRBCL</th>
<th>p (NLPHL vs. T/HRBCL)</th>
<th>CD20</th>
<th>CD79a</th>
<th>J-chain</th>
<th>CD30</th>
<th>EMA</th>
<th>BCL-2</th>
<th>ICSAT</th>
<th>PU.1</th>
<th>CD20</th>
<th>CD3</th>
<th>CD4</th>
<th>CD8</th>
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<td>Tumor cells</td>
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<td>CD20</td>
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<td>J-chain</td>
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<td>PU.1</td>
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<td>1:2,7</td>
<td>&gt;1:1,5</td>
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<tr>
<td>CD3 rosettes</td>
<td>89%</td>
<td>88%</td>
<td>0,02</td>
<td>57%</td>
<td>&lt;0,001</td>
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<tr>
<td>CD4 rosettes</td>
<td>48%</td>
<td>29%</td>
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<tr>
<td>CD8 rosettes</td>
<td>0%</td>
<td>0%</td>
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<td>Marker</td>
<td>CD57 rosettes</td>
<td>CD68</td>
<td>TIA-1</td>
<td>Granzyme B</td>
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<tr>
<td></td>
<td>37%</td>
<td>66%</td>
<td>47%</td>
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<td></td>
<td>31%</td>
<td>94%</td>
<td>76%</td>
<td>35%</td>
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<td>0.018</td>
<td>0.0029</td>
<td>0.032</td>
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<tr>
<td></td>
<td>6%</td>
<td>97%</td>
<td>86%</td>
<td>85%</td>
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<tr>
<td></td>
<td>&lt;0.001</td>
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<td>&lt;0.001</td>
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</table>

Markers for tumor cells are given as percentage of cases, expressing the respective antigen in more than a few cells. Likewise, in the background section the percentage of more than occasional cells/rosettes staining with the respective antibody is given. The CD20 ratio gives the count of tumor cells to reactive small B-cells. For CD3, CD4, CD8, and CD57, rosettes were evaluated to achieve a higher reliability of the data. Nominal p values are given only when the difference is statistically significant.
Table 3. Clinical characteristics of patients with NLPHL, NLPHL with T-cell/ histioyte rich nodules, and T/HRBCL. p values are given only when the difference is statistically significant (<0,05).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>NLPHL</th>
<th>p</th>
<th>NLPHL with T-cell/ histioyte rich nodules</th>
<th>p</th>
<th>T/HRBCL</th>
<th>p (NLPHL vs T/HRBCL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>53</td>
<td>17</td>
<td>35</td>
<td>0,006</td>
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<tr>
<td>Age (years)</td>
<td>39</td>
<td>41</td>
<td>49</td>
<td>&lt;0,01</td>
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<tr>
<td>Hemoglobin (g/l)</td>
<td>142</td>
<td>137</td>
<td>136</td>
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<tr>
<td>Tumor diameter (cm)</td>
<td>5</td>
<td>7</td>
<td>7</td>
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<tr>
<td>LDH (U/l)</td>
<td>205</td>
<td>190</td>
<td>284</td>
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<tr>
<td>Sex (% male)</td>
<td>68</td>
<td>&lt;0,05</td>
<td>94</td>
<td>74</td>
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<tr>
<td>Stage (%)</td>
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<tr>
<td>I</td>
<td>43</td>
<td>20</td>
<td>23</td>
<td>&lt;0,005</td>
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<tr>
<td>II</td>
<td>37</td>
<td>20</td>
<td>29</td>
<td>&lt;0,005</td>
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<tr>
<td>III</td>
<td>20</td>
<td>27</td>
<td>26</td>
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<td>IV</td>
<td>0</td>
<td>33</td>
<td>22</td>
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<tr>
<td>B-symptoms (%)</td>
<td>5</td>
<td>38</td>
<td>46</td>
<td>&lt;0,001</td>
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<tr>
<td>Treatment</td>
<td>Surgery only</td>
<td>6%</td>
<td>0%</td>
<td>0,05</td>
<td>0%</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td></td>
<td>RTx</td>
<td>22%</td>
<td>15%</td>
<td>8%</td>
<td></td>
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</tr>
<tr>
<td>Treatment</td>
<td>LDH</td>
<td>RTx</td>
<td>High dose</td>
<td></td>
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</tr>
<tr>
<td>COPP/ABVD</td>
<td>34%</td>
<td>15%</td>
<td>24%</td>
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<tr>
<td>BEACOPP</td>
<td>30%</td>
<td>39%</td>
<td>8%</td>
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<tr>
<td>CHOP-based</td>
<td>4%</td>
<td>23%</td>
<td>60%</td>
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<tr>
<td>High dose</td>
<td>0%</td>
<td>8%</td>
<td>0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>4%</td>
<td>0%</td>
<td>0%</td>
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</tbody>
</table>

LDH – lactate dehydrogenase

RTx: Radiotherapy only (all patients presenting with stage I disease)

High dose: High dose therapy with autologous stem cell transplantation
Figure legends

Figure 1. Patterns of NLPHL with T-cell/ histiocyte rich nodules (see text): Pattern A (left) and Pattern B (right). H&E (top), CD20 (middle) and CD21 (bottom)
Figure 2. Kaplan-Meier plot of the overall survival (OAS) of NLPHL, NLPHL with T-cell/ histiocyte rich nodules (Tcr-NLPHL) and T/HRBCL.
Figure 3. Schematic depiction of the two patterns of NLPHL with T-cell/histiocyte rich nodules as possible pathways of morphological progression of NLPHL.
Literature


related to lymphocyte predominant Hodgkin's disease, paragranuloma subtype.


Nodular lymphocyte predominant Hodgkin lymphoma with nodules resembling T-cell/histiocyte rich B-cell lymphoma: differential diagnosis between nodular lymphocyte predominant Hodgkin lymphoma and T-cell/histiocyte rich B-cell lymphoma

Ludmila Boudova, Emina Torlakovic, Jan Delabie, Peter Reimer, Beate Pfistner, Sabine Wiedenmann, Volker Diehl, Hans-Konrad Muller-Hermelink and Thomas Rudiger