Workshop on the relationship between nodular lymphocyte predominant Hodgkin’s lymphoma and T cell/histiocyte-rich B cell lymphoma


1University of Würzburg, Würzburg, Germany; 2British Columbia Cancer Agency, Vancouver, Canada; 3Department of Health & Human Services, NIH-NCI, Bethesda, USA; 4The Netherlands Cancer Institute, Amsterdam, The Netherlands; 5The Norwegian Radium Hospital and Institute for Cancer Research, Oslo, Norway; 6Universitaire Ziekenhuizen Leuven, Leuven, Belgium; 7University Hospital Groningen, The Netherlands; 8Institut Paoli-Calmettes, Marseille; 9Hôpital Saint-Louis, Paris, France; 10Clinic of Internal Medicine I, University of Cologne, Cologne, Germany

Introduction

The workshop on ‘grey zone lymphoma’ during the Fifth International Congress on Hodgkin’s Lymphoma covered the relationship between nodular lymphocyte predominant Hodgkin’s lymphoma (NLPHL) and T cell/histiocyte-rich B cell lymphoma (T/HRBCL) [1–3], which is regarded as a variant of diffuse large B cell lymphoma (DLBCL) in the WHO classification [4].

NLPHL has been distinguished from lymphocyte rich classical Hodgkin’s lymphoma (CHL) [5, 6] and identified as a lymphoma derived from follicular center B cells [7]. Because of its close morphological relationship to B cell non-Hodgkin lymphomas (B-NHLs), problems of distinction may occur [8]. However, patients with NLPHL usually show a distinct clinical presentation, and are treated differently from patients with B-NHLs. The molecular genetic basis of this difference between Hodgkin’s lymphoma (HL) and NHL has been addressed by Poppema, presenting preliminary results obtained from serial analysis of gene expression (SAGE) of HL cell lines. A member of the family of non-coding RNA-like molecules, Bic, was expressed in tumor cells in 46 of 52 CHL and six of six NLPHL, but in none of the NHLs investigated.

NLPHL and T/HRBCL may occur concurrently or subsequently in the same patient. Several authors reported on a total series of 34 patients who developed both NLPHL and T/HRBCL (either synchronously or metachronously) in the course of their disease (de Jong, 13; Delabie, 10; and Jaffe, 9). In de Jong’s series T/HRBCL, affecting 13 of 27 patients, was the most frequent secondary NHL in patients successfully treated for NLPHL. Jaffe’s report included one patient relapsing with NLPHL after T/HRBCL and three family pairs manifesting both NLPHL and T/HRBCL.

Applying comparative genomic hybridization after single cell microdissection, de Wolf-Peeters found a significantly higher number of genomic imbalances in NLPHL (11.6 per tumor) than in T/HRBCL (5.6 per tumor). Gains in the short arm of chromosome 6 were unique in NLPHL and did not occur in T/HRBCL. These findings provide evidence for a distinct clonal progression of NLPHL and T/HRBCL, although it cannot be excluded that both entities arise from a common germinal center (CG) precursor. Additional studies are required to clarify the pathogenesis of those cases of T/HRBCL that develop in association with NLPHL.

It may be difficult to draw a border between NLPHL and T/HRBCL for the diagnostic pathologist in every case. This distinction is rarely aided by the immunophenotype of the tumor cells, as these do not differ significantly with an extended panel applied to both entities by Rüdiger. However, the different expression of transcription factors might in the future help to define differences in the tumor cells that might explain the clinical course of the diseases. PU.1, when evaluated semi-quantitatively, might be one good candidate, because it is apparently down-regulated in T/HRBCL compared with NLPHL (Delabie). With regard to B cell development, data on PU1 expression, together with the frequent expression of BCL2 protein in T/HRBCL but not NLPHL, might suggest that T/HRBCL corresponds to a later stage of B cell development than NLPHL. However, single-cell studies revealed ongoing mutations in T/HRBCL, very similar to events known from NLPHL [9].

The immunomorphology of the inflammatory background infiltrate greatly aids the differential diagnosis. The paucity of small reactive B cells is part of the definition of T/HRBCL. However, none of the speakers had a precise cut-off for how many small B cells are allowed in T/HRBCL. Criteria included ‘rare to infrequent’, ‘a virtual absence’ and ‘almost none’. Specific criteria are needed to compare results of different studies and to define progression of NLPHL to T/HRBCL. A further aspect comes from the studies by Rüdiger, who described cases in the grey zone between NLPHL and T/HRBCL.
exhibited a nodular growth pattern of CD20+ tumor cells, which were accompanied by very few small reactive B cells. He suggested classifying these as a nodular form of T/HRBCL. Although these tumors frequently presented with stage IV and B symptoms, their prognosis was excellent after aggressive chemotherapy. Therefore, they could also represent a risk type of NLPHL. Cases with T/HRLBL exhibiting nodular areas morphologically were clinically more comparable to T/HRLBL than to NLPHL (Xerri).

The clinical relevance of the differential diagnosis between HL and NHL was underscored by data from the GELA group: Gisselbrecht showed that 77 patients reclassified as HL, who were treated with regimens for aggressive NHL, showed a worse survival (54 and 77% for 5-year event-free and overall survival, respectively) than a historical control in the HL studies. From the same multicentric study, Xerri presented evidence that 42 patients with T/HRBCL showed a similar clinical presentation and outcome as a matched control group of 122 patients with ‘classic’ DLBCL, selected for International Prognostic Index (IPI) parameters statistically identical to those of T/HRBCL patients. Distinct from these data, Gascoyne presented results from a collaborative study involving three centers with 53 patients. They identified a specific subset of cases referred to as ‘paragranuloma-type’ of T/HRBCL, and demonstrated an inferior survival. The overall 5-year survival was only 20%. Interestingly, the only long-term survivors were those patients who had undergone a bone marrow transplant. It is likely that similar cases are included in the previously described studies from GELA and Rüdiger, but the lack of consistent diagnostic criteria precludes the meaningful analysis of heterogeneous patient groups.

Much has still to be done to satisfactorily define the diseases and guide treatment appropriately. A database developed as a joint effort from the German Hodgkin’s Lymphoma Study Group (Wiedenmann) and the German High Grade Lymphoma Study Group might provide sufficient well characterized and uniformly treated patients to achieve results in the near future.

1. The relationship between NLPHL and T/HRLBL

E. S. Jaffe & T. Barry, NCI/NIH, Bethesda, MD, USA: NLPHL and T/HRLBL: evidence for a biological overlap

Background

NLPHL can histologically and immunophenotypically resemble T/HRBCL [2, 3]. However, a true biological relationship between these diseases remains unproven. We provide epidemiological and clinical data linking NLPHL and T/HRBCL, by reporting both sequential and familial occurrences.

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<tr>
<th>Table 1. NLPHL and T/HRBCL in the same patient and in family pairs</th>
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<tr>
<td><strong>NLPHL and T/HRBCL</strong></td>
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<td>Sequential biopsies in the same patient</td>
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<td>NLPHL→T/HRBCL</td>
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<td>T/HRBCL→NLPHL</td>
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<td>Concurrent NLPHL and T/HRBCL in multiple sites at a single time point</td>
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<td>Progression within a single site</td>
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<td>Familial pairs manifesting both NLPHL and T/HRBCL</td>
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Patients and methods

The files of the NCI Hematopathology Section were searched for patients or families in which the diagnosis of both NLPHL and T/HRBCL had been made. Nine patients and three families were identified, as shown in Table 1.

Case records and morphology were reviewed, and immunohistochemistry using the avidin–biotin–peroxidase technique was performed to confirm the diagnosis in each case.

Results

**Sequential biopsies.** Two patients (aged 34 and 65 years) initially presented with NLPHL and subsequently developed T/HRBCL after 21 months and 16 years, respectively. At the time of T/HRBCL, both patients had an advanced-stage disease [bone marrow (BM) or spleen/liver involvement]. One patient (age 36 years) initially presented with T/HRBCL and following treatment, subsequently developed NLPHL 8 years later.

**Concurrent.** In three patients (median age 39 years), NLPHL and T/HRBCL were identified in biopsies from different anatomic sites. BM involvement was present in two of three cases.

**Progression.** Three patients (median age of 57 years) presented with lymph nodes that showed features of both NLPHL and T/HRBCL. Two of these patients were noted to have generalized lymphadenopathy at presentation.

**Familial.** Three families were identified manifesting both NLPHL and T/HRBCL. A nephew and uncle from one family had a diagnosis of autoimmune lymphoproliferative syndrome (ALPS) [10, 11]. Sibling pairs with both NLPHL and T/HRBCL were identified in two additional families without known ALPS. Clinically, in each family the family member with NLPHL had localized disease in contrast to the family member with T/HRBCL, who presented with advanced-stage disease.

**Conclusions.** NLPHL and T/HRBCL can occur in sequential biopsies from the same patient, in biopsies from different sites in the same patient and in siblings/kinship members from the same family. In many of these cases, histological features of T/HRBCL were associated with clinical progression. These unusual cases support a close biological relationship between these usually distinct clinicopathological entities. Occasional
cases manifest overlapping features of both NLPHL and T/HRBCL in a single site, and may represent a true biological interface, i.e. ‘grey zone’ between these two related lymphomas.

D. de Jong¹, B. M. P. Aleman², F. E. van Leeuwen³, Departments of ¹Pathology, ²Radiotherapy and ³Epidemiology, The Netherlands Cancer Institute, Amsterdam, The Netherlands: The relationship of NLPHL and T/HRLBL: an epidemiological study

Introduction

Long-term survivors after treatment of HL are at risk for late complications, including the development of secondary malignancies [12], especially breast cancer, gastro-intestinal carcinomas and leukemia. Secondary NHL is less frequently reported, but conceptually takes a different position because a direct clonal relationship between the two malignancies cannot be excluded beforehand [13, 14].

The incidence of NHL after CHL is significantly lower than after NLPHL, in which an incidence of 5–10% of NHL has been reported. To gain insight in differences in biological behavior in terms of the development of NHL, we investigated the distribution of the subtypes of NHL that develop after CHL and NLPHL.

Patients and methods

Cohort 1. Thirty-five patients who developed NHL after treatment of HL, who were identified in a cohort of 1253 patients treated for HL between 1966 and 1986 in two Dutch cancer centers [15]. Additionally, 13 patients treated after 1986 in one of these centers were included (The Netherlands Cancer Institute) [16]. For these patients, data on initial treatment, follow-up and salvage therapy were collected.

Cohort 2. Thirty-four patients with a diagnosis of NLPHL and NHL derived from the PALGA, Dutch Network and National Database for Pathology.

For all patients, diagnostic biopsies of the HL and NHL were reviewed and immunohistochemistry was updated when possible. The diagnostic criteria for NLPHL and T/HRBCL were very strict as to include only unequivocal cases, excluding all possible ‘grey zone’ or composite cases.

Our study population was compared to a population-based cohort of patients registered at the Dutch Comprehensive Cancer Center West (CCCW) between 1981 and 1989 [17]. The χ² test with a significance level of 0.05 was used for testing differences in characteristics between the cohorts and the reference population.

Results

Review resulted in exclusion of four of 48 patients from cohort 1 because diagnostic material could not be obtained or a diagnosis of NHL could not be confirmed. Twelve of 34 patients from cohort 2 were excluded because a diagnosis of NHL or NLPHL could not be confirmed, four cases were considered as ‘grey zone’ lymphomas and excluded on this basis. A total of 66 patients were evaluable, 39 cases of CHL and 27 cases of NLPHL.

The age at diagnosis of HL, age at diagnosis of NHL and the interval between HL and NHL were not significantly different between the CHL and the NLPHL groups. CHL patients developed extranodal disease significantly more frequently (41% versus 13.6%), especially in the digestive tract (28% versus 9.1%). The distribution of NHL subtypes is listed in Table 2. Significantly, both CHL and NLPHL patients developed preferentially DLBCL, CHL patients also developed other types of small B cell lymphoma, including follicular lymphoma (FL), marginal zone lymphoma, MALT-type and mantle cell lymphoma (MCL). Most strikingly, half of the DLBCL after NLPHL were of T/HRBCL type.

Conclusions and discussion

In this study, we demonstrate that compared with a population-based cohort, secondary NHL after treatment of CHL are more frequent in the digestive tract and are more frequently of DLBCL type, but other types of NHL do occur. Secondary NHL after NLPHL, however, are preferentially nodal and very strikingly of T/HRBCL type. Precluding data on the clonal relation between the NHL and NLPHL in this series, but with the knowledge from the literature that a clonal relation has been demonstrated in several cases, it can be hypothesized that the production of cytokines resulting in a dominant background pattern is an intrinsic property of the malignant B cell in NLPHL and the subsequent NHL. However, upon transformation, a shift in the cytokine pattern results in a different composition of the background

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<th>CHL (n = 39)</th>
<th>NLPHL (n = 27)</th>
<th>CCCW database (n = 1168) (%)</th>
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<tr>
<td>DLBCL</td>
<td>28 (71.8%)</td>
<td>12 (44.4%)</td>
<td>40.2</td>
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<tr>
<td>T/HRBCL</td>
<td>2 (5.1%)</td>
<td>13 (48.1%)</td>
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<td>FL</td>
<td>2</td>
<td>-</td>
<td>20</td>
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<tr>
<td>MCL</td>
<td>1</td>
<td>-</td>
<td>3.5</td>
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<tr>
<td>Marginal zone lymphoma, MALT-type</td>
<td>4</td>
<td>-</td>
<td>2.8</td>
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<tr>
<td>B-NHL, unclassifiable</td>
<td>1</td>
<td>-</td>
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<tr>
<td>PTCL, NOS</td>
<td>1 (2.6%)</td>
<td>2 (7.4%)</td>
<td>4.4</td>
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pattern. Alternatively, cytokines may be produced by bystander/accessory cells with a similar shift in the spectrum during evolution. Therefore, the development of T/HRBCL after NLPHL may be placed in the same continuum of disappearance of B cells from the background infiltrate and influx of T cells as is seen in diffuse areas of NLPHL and areas with fragmentation of the dendritic meshworks. However, the tumor cells in T/HRBCL represent full transition to a transformed/aggressive phase of disease on the basis of transforming genomic alterations.

The development of NHL after CHL may in many cases follow a fully different mechanism, resulting in various types of NHL.

J. Delabie, P. Krajci & E. Torlakovic, The Norwegian Radium Hospital and Institute for Cancer Research, Oslo, Norway: Histological transformation of NLPHL to T/HRBCL: study of 10 cases and role of transcription factor PU.1

T/HRBCL is a variant of diffuse large cell lymphoma. This variant of lymphoma has some distinctive clinical features such as male predominance and advanced-stage at presentation [1]. Histologically, the lymphoma cells resemble the lymphocytic and histiocytic (L&H) Hodgkin’s cells of NLPHL and share also the abundance of reactive cells, but T/HRBCL lacks the typical background of small B cells and epithelioid cells observed in NLPHL. The histological similarities between NLPHL and T/HRBCL suggest a possible relationship between the two entities [3, 16, 18]. To find further evidence of such a relationship, we reviewed our database of cases of composite HL and NHL. We identified 10 cases of composite NLPHL and T/HRBCL and studied the expression of the B cell transcription factor PU.1 in both components.

Seven of the patients presented with NLPHL and subsequently developed T/HRBCL with a mean interval of 10 years (intervals between 2 and 24 years), whereas three patients presented with the composite lymphoma at diagnosis. In the first group of patients, the stage at diagnosis was I, II or III, whereas it was stage IV at relapse. In the second group of three patients, the stage at diagnosis was I, II and III, respectively. The identification of composite NLPHL and T/HRBCL confirms a relationship between both entities. Since we have previously observed that the B cell transcription factor PU.1 is expressed in NLPHL but not in T/HRBCL, we studied the expression of this transcription factor in the current 10 cases [19]. We found that PU.1 was expressed in NLPHL in all cases but was absent (six cases) or showed reduced expression (four cases) in the T/HRBCL.

Our study indicates that T/HRBCL may occur as a progressed form of NLPHL and that reduced expression of the transcription factor PU.1 may be a marker of progression. Whether the down-regulation of PU.1 contributes to the progression is not known and needs to be investigated further.

2. The molecular approach

C. de Wolf-Peeters, S. Franke, I. Wlodarska & R. Achten, Department of Haematology and the Centre of Human Genetics of the K.U. Leuven, Belgium: Results of a collaborative study of the Department of Pathology, the Department of Haematology and the Centre of Human Genetics of the K.U. Leuven, Belgium

A series comprising 19 cases of NLPHL and 17 cases of T/HRBCL was analyzed by comparative genomic hybridization [20]. Comparative genetic hybridization was applied on DNA collected from four to five malignant cells per case. These cells were obtained by microdissection from frozen tissue sections and the extracted DNA was amplified by means of degenerate oligonucleotide primed PCR before performing the analysis. Using this approach, distinct profiles of chromosomal gains and losses were detected in both lymphomas. The most striking difference concerned the number of genomic imbalances: whereas overall 221 imbalances (on average 11.6 per tumor) were found in NLPHL, T/HRBCL featured only 91 imbalances in total (5.6 per tumor).

These results are in line with cytogenetic reports and indicate the presence of very complex chromosomal changes in paragranuloma. The high number of chromosomal imbalances observed in NLPHL contrasts with the significantly less complex karyotype of T/HRBCL. In addition, several recurrent aberrations were found in NLPHL and in T/HRBCL, with only a few overlapping in both disorders. Based on these findings a common origin for paragranuloma and T/HRBCL cannot be excluded, but it is very unlikely that T/HRBCL evolves directly from paragranuloma. These findings underscore the intrinsic differences between NLPHL and T/HRBCL, two entities that are also characterized by substantial immunomorphological dissimilarities [21] and a distinct clinical behavior [22]. Therefore, as a rule, a correct differential diagnosis is feasible and essential to determine the optimal therapeutic approach.

S. Poppema, R. Rust, A. van den Berg, Department of Pathology & Laboratory Medicine University and University Hospital, Groningen, The Netherlands: Gene activities in NLPHL

The L&H-type Reed–Sternberg (RS) cells from NLPHL express several surface and cytoplasmic molecules (CD19, CD20, CD22, CD75, CD79a, etc.) that are also expressed in normal GC B cells. In addition, L&H cells frequently contain Ig mRNA and express Ig molecules, including Ig light chain, Ig heavy chain and J chain. Surprisingly, in a proportion of cases the L&H cells only produce IgD immunoglobulin. The demonstration of J chain expression constituted the first evidence that the L&H cells produce immunoglobulin and establishes another similarity to a subset of GC B cells that also are
J chain positive. In accordance with the expression of immunoglobulin, Ig transcription and co-activator factors like Oct2 and BOB.1 can be demonstrated in L&H cells. In addition to these B cell markers and immunoglobulin-associated genes, L&H cells also express genes like human leukocyte antigen (HLA) class I and II, CD45, EMA, bcl-6, CD40, CD80 and CD86. Several of these genes are expressed in L&H cells but not in classical RS cells. These include the various B cell markers and the genes associated with Ig production. CD20 is an exception, as this gene is expressed in up to 40% of CHL. Other genes that are largely restricted to L&H-type RS cells are CD45, EMA and bcl-6. However, there are also a number of genes that are generally expressed in classical RS cells but not in L&H cells. These include CD15, CD30 and CD138, and also Bcl-2, Fascin, Restin, IL13 and TARC (CCL17).

Gene expression studies in HL-derived cell lines employing the SAGE technique may result in the identification of genes involved in the malignant transformation of RS precursor cells and genes responsible for the characteristic phenotype of HL. In addition, in this way a complete expression profile of classical and L&H-type RS cells can be constructed. We use the following HL-derived cell lines: L428, which is derived from CHL [nodular sclerosis (NS) Epstein–Barr virus (EBV) negative], DEV, which is derived from NLPHL, and for comparison RAY, which is an EBV-transformed lymphoblastoid B cell line. This allows the identification of genes expressed in DEV and L428, but not RAYDEV and RAY, but not L428, DEV, but not L428 and RAY, L428, but not DEV and RAY, etc.

Preliminary results reported at the meeting indicate a number of differentially expressed genes. These include ‘known tags’ highly expressed in HL, such as TARC, Fascin, Restin, CD30 and nuclear factor (NF)-κB, and several ‘unknown tags’ highly expressed in HL. One tag occurred at a frequency of 0.1%. This tag, named Bic, was expressed in the nuclei of RS cells in 46 of 52 HL cases (88.5%), including 40 of 46 CHL cases and six of six NLPHL cases. No expression was found in the tumor cells of NHL cases.

Bic most likely belongs to the family of non-coding mRNA-like molecules, and expression of Bic is associated with demethylation of the Bic gene region. High expression of Bic may be associated with escape of apoptosis from the RS cell precursors. Interestingly, expression of the Bic gene is thus found in the RS cells of CHL as well as NLPHL, and this may point to a common pathogenetic mechanism.

The clinical relevance of the differential diagnosis was highlighted by three contributions. These show that it is indeed very important to differentiate NLPHL from T/HRBCL, and that T/HRBCL (from a clinical point of view) belongs to the group of DLBCL.

3. Histological cut-off points and consequences for treatment

T. Rüdiger1, L. Bourdova2 & H. K. Müller-Hermelink1,
1Department of Pathology, University of Würzburg, Germany; 2Department of Pathology, Plzeň, Czech Republic: Nodular growth pattern in T/HRLBL: a problem in the differential diagnosis to NLPHL.

We investigated 106 cases (24 NLPHL, 17 T/HRBCL and 65 cases with overlapping features). Immunophenotyping included CD20, CD79a, J chain, EMA, CD30, bcl-2 and various transcription factors for the tumor cells, and CD3, CD4, CD8, CD57, TIA1 and CD68 to assess background composition. Pathological findings were correlated to clinical presentation and outcome.

Results

All cases could be classified as either NLPHL (n = 53) or T/HRBCL (n = 53). Tumor cells in NLPHL and T/HRBCL showed a remarkably similar antigen expression profile, only bcl2 protein was expressed more frequently in T/HRBCL than in NLPHL. Background composition, in contrast, was significantly different: small B cells and rosettes of CD3+, CD4+ and CD57+ cells were typical in NLPHL, while CD8+ cells and histiocytes dominated in T/HRBCL. Clinically, none of the NLPHL presented with stage IV disease.

In addition, we identified 17 cases with exclusively nodular growth pattern that exhibited immunomorphological features of T/HRBCL within the nodules. In most cases, this pattern co-existed with typical nodules of NLPHL. In contrast to NLPHL, these tumors presented at high clinical stages, similar to T/HRBCL. However, outcome after stage-adjusted therapy was very favorable.

Conclusions

Contrary to previous descriptions, T/HRBCL might exhibit a nodular growth pattern. Presence of small reactive B lymphocytes rather than degree of nodularity might be the major criterion to distinguish NLPHL from T/HRBCL. The identification of cases described here may be important to avoid under-treatment of patients.

R. D. Gascoyne1, J. Delabie2, J. M. Connors3, B. F. Skinnider1, C. de Wolf-Peeters4 & G. Delsol4,

TCRBCL is a heterogeneous disorder lacking precise diagnostic criteria, as is HRBCL. Both may be related to each other and to NLPHL. We sought to determine the clinical significance of this lymphoma subtype within the rubric of DLBCL.
Fifty-three cases were compiled from the files of three centers (Vancouver, Leuven and Toulouse) based on the recognition of a common histological appearance. All authors reviewed the cases after criteria for uniform diagnosis were established. Paraffin-section immunostains were performed and the clinical data collected. A total of 53 cases were studied, all with similar histological features. Biopsies revealed a diffuse architecture with nodularity. Histological structures assessed by both hematoxylin–eosin (H&E) review and stains for follicular dendritic cells. The vast majority of background reactive cells consisted of small T cells and histiocytes distributed throughout the sections. Virtually no small B cells were detected. The neoplastic cells were large with polyploid nuclei in many cases. In the majority of cases these cells resembled ‘popcorn’ cells of NLPHL. In some cases these cells tended to cluster, but without obviously nodularity. Importantly, stains for CD21 were negative. The large neoplastic B cells stained positively for CD20, CD45, CD75 and CD79a. EMA and Bcl-6 were studied in a subset of cases and revealed positive staining of the large cells in 91 and 100%, respectively. The background small T cells expressed CD3, but lacked co-expression of CD57. Paraffin stains for CD4 and CD8 were not performed, but flow cytometric immunophenotyping on a subset showed marked CD4 excess in 11 of 13 cases.

The median age of the patients at diagnosis was 43 years (range 19–77 years). The majority of the patients were male (81%) and 91% had either stage III or IV disease. The BM was involved in 53% of the patients. Splenomegaly was recorded in 53% of patients and hepatic involvement in 21%. An elevated lactate dehydrogenase (LDH) concentration was seen in 53% of T/HRBCL cases, respectively. T/HRBCL patients did not observe any difference in terms of survival and clinical prognosis parameters among T/HRBCL cases displaying either nodular or diffuse pattern.

In summary, paragranuloma-type T/HRBCL appears to be a unique disease entity within the group of lymphomas currently classified as T/HRBCL. We believe that HRBCl and paragranuloma-type T/HRBCL are identical, and both related to NLPHL. Despite a high frequency of BM involvement, CNS disease was not detected. The poor clinical outcome of these patients is probably related to the frequent BM involvement and advanced-stage of disease.

4. Treatment and outcome


In order to evaluate the clinical and prognostic relevance of T/HRBCL as a putative entity, we performed a matched control analysis. Sixty-three cases out of 3500 patients included in the LNH-93 study for aggressive lymphoma were initially considered as probable T/HRBCL. After second reviewing by a panel of four pathologists and exclusion of cases in which there was a suspicion of NLPHL, DLCL or CHL, 42 cases were identified as ‘true’ T/HRBCL. We selected a control group of 122 patients with ‘classical’ DLCL by matching with patients treated in the LNH-93 study regarding several parameters: age, stage, LDH, performance status (PS) and IPI.

Histological characteristics of the 42 T/HRBCL cases showed diffuse architecture in 21 cases, and areas of nodularity (NLPHL-like) in 11 cases, whereas 10 cases could not be classified due to the size of the biopsy. The nodularity did not involve more than 30% (~10% in most cases: rare isolated nodules). BM involvement in nodular cases showed a typical T/HRBCL pattern. Phenotypical analysis showed CD20 positivity on large atypical cells in all cases, EMA positivity in 26 of 30 cases (86%), CD30 positivity in two of 30 cases and CD15 positivity in none of 30 cases. In the diffuse areas, small reactive lymphocytes were CD3+ in all cases, whereas in the nodular areas small lymphocytes were CD20+, IgD+, CD57+. BM involvement and/or splenomegaly was present in 35 and 60% of T/HRBCL cases, respectively. T/HRBCL patients were more frequently stage III–IV than stage I–II. However, although T/HRBCL had a particular histopathological and clinical presentation, its prognosis was not worse than classical DLCL after statistical mismatch analysis. Moreover, we did not observe any difference in terms of survival and clinical prognosis parameters among T/HRBCL cases displaying either nodular or diffuse pattern.

We conclude that there is no obvious reason to separate T/HRBCL from classical DLCL in terms of therapeutic strategy and management of patients. Since there is no clear-cut histophenotypical border between nodular (NLPHL-like) and diffuse T/HRBCL variants and their clinical presentation is very similar, NLPHL-like T/HRBCL should be considered as a T/HRBCL rather than diffuse NLPHL. This has important therapeutic consequences, since the prognosis of HD patients treated like NHL is significantly worse than classically treated HL patients [23].


Distinction between HL and some subtypes of lymphoma might constitute for pathologist, as well as for clinician, a grey zone. These patients can be treated inappropriately either as HL or NHL. Among 2855 lymphomas included in the LNH-87 protocol, 77 had a diagnosis of HL after histological review by a panel of pathologists [1]. Diagnosis was misinterpreted as NHL in 46 cases, in 20 as anaplastic large-cell lymphoma (ALCL) or ALCL-HL, in 12 as peripheral T-cell lymphoma (PTCL), in six as B cell and in eight as unclassifiable. The
other 31 cases had at first been considered by the panel as ALCL-HL or PTCL, and were subsequently changed to HL. The 5-year event-free survival and overall survival were 54 and 77%, respectively, after completion of a lymphoma-designed treatment. A result lower than expected was obtained with CHL treated with Hodgkin’s protocol. T/HRBCL represents another type of lymphoma reported frequently as HL or PTCL. Among the 3500 patients included in the LNH-93 protocol and after review of 80% of the slides, 42 patients were identified as T/HRBCL. They were matched (one for three) for age, stage, LDH, PS, number of extranodal sites with 122 large B cell lymphoma patients (BCL) included in the same study. Patients characteristics were as follows: age <60 years, 76%; localized stage, 22%; disseminated stage, 77%; PS >2, 13%; LDH higher than normal, 60%; and international prognostic index >2, 51%. When adjusted with the factors of the international prognostic index, they presented with more BM involvement (35% versus 26%), hepatomegaly (30% versus 12%) and splenomegaly (60% versus 17%). The complete remission rate after treatment was 58% for T/HRBCL patients versus 73% for the BCL (P = 0.09). The T/HRBCL 5-year event-free survival (58%) and overall survival (63%) were similar to BCL (52% and 66%, respectively). T/HRBCL patients should be treated like BCL patients according to their prognostic factors with chemotherapy. On the opposite LPHL and lymphocyte-rich CHL (LRCHL) patients have a good prognosis with a complete response rate of 96% and should be managed in a conservative manner. The percentage of HL-specific survival is related to the stage of disease, and ranges from 99 to 40% for NLPHL and 91 to 67% in LRCHL [2]. NLPHL should not be over-treated; localized radiotherapy should be used and sometimes chemotherapy in bulky or disseminated stages. New approaches with anti-CD20 antibodies are under investigations. In conclusion, distinction between the different subtypes have implication in the management of these diseases.

S. Wiedenmann, V. Diehl & J. Wolf, Clinic of Internal Medicine I, University of Cologne, Germany, for the GHSG: Grey zone lymphoma

The pathological discrimination between the so-called grey-zone lymphoma, the T/HRBCL, the NLPHL and the LRCHL, has been a long-standing problem and created a difficult task for pathologists. Therefore, the question arose whether the pathological differentiation of these entities is of clinical relevance and not merely of academic interest. Would the differentiation influence treatment choice? Does the outcome differ in these three entities?

Since little has been reported in the literature on these so-called grey zone lymphoma, the workshop on this topic at the Fifth International Symposium on Hodgkin’s Lymphoma aimed to answer these questions. Owing to the relatively low incidence of these cases, clinical data are difficult to obtain and large-scale clinical studies are lacking. Therefore, the database of the German Hodgkin’s Lymphoma study group and the German Study Group on High Grade NHL were evaluated. From a cohort of 6677 HL patients in the GHSG, that were enrolled into the HD-7 to HD-12 study and the LP study, all patients with a reference histology by the GHSG pathologists panel were selected (85% of cases) and screened for the diagnosis T/HRBCL, NLPHL and LRCHL. Patients between the age of 16 and 75 years had to have biopsy-proven HL at diagnosis to be eligible. Additionally, 1271 cases in the NHL-B study of the German High-grade Lymphoma Study Group (DSHNHL) were screened for the diagnosis T/HRBCL and were included in the analysis. The T/HRBCL data of the GHSG and the DSHNHL were pooled for the final analysis. In summary 344 grey zone lymphomas being reviewed by reference pathologists were identified out of 7948 cases in total: 43 patients were diagnosed as T/HRBCL, 190 NLPHL and 111 LRCHL.

Through the combined effort of the GHSG and the DSHNHL the largest datapool on grey zone lymphoma has been established, which will be a basis for the first retrospective clinical study comparing T/HRBCL, NLPHL and LRCHL with respect to treatment, outcome and prognosis.

Conclusions

The workshop clearly highlighted the fact that consistent and uniform criteria for the diagnosis of T/HRBCL are lacking. Currently, cases described as T/HRBCL probably encompass at least three entities with overlapping clinical and pathological features. In particular, the existence of a specific histological subtype of T/HRBCL, sharing a close relationship to NLPHL, appeared to be a common theme throughout the workshop discussions. However, well-defined criteria to allow reproducible diagnosis have not yet been formulated. None the less, the workshop has created the nidus on which further discussion and collaboration can take place, with a large collection of cases having complete clinical records that can now be used to answer many of the unresolved questions.

A further area of controversy was identified concerning the distinction between ‘progressed’ NLPHL and T/HRBCL. This distinction has significant clinical implications and thus will be a major focus of research in planned clinicopathological studies. Importantly, the workshop has brought together interested parties and experts in the field whose combined efforts will almost certainly produce meaningful insights into the biology and clinical correlates of this ‘grey zone’.

References


