Lymphocyte predominant Hodgkin's disease: Pathology and clinical implication*

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Summary

The special nature and course of lymphocyte rich variants of Hodgkin's disease (HD) has been the subject of pathological and clinical studies since the 1930s. Patients with lymphocyte predominant (LP) HD, predominantly male and 25-45 years old, usually present with early clinical stage, cervical or inguinal involvement and few if any adverse prognostic factors. The disease progresses slowly, with fairly frequent relapses which are rarely fatal. Nonetheless, cases with advanced stage and deaths from Hodgkin's disease have been observed in LP HD. Recently, immunological studies have lead to a clear distinction between LP HD and classical HD including a lymphocyte rich classical version (LRCHD). Secondary low-grade NHLs occur more frequently after LP HD than after classical HD. They seem to be disease-related rather than treatment-induced. LP HD patients in earlier studies have tended to have a better prognosis than classical HD patients. When cohorts of the same clinical stage are compared, under modern protocol treatment this advantage seems to be minimal or absent. LP HD patients tend to relapse frequently but they survive these relapses better than classical HD patients.

The resemblance to non-neoplastic disorders, capability for ongoing mutation, favorable clinical presentation and good survival rates after relapse all suggest that the optimal primary treatment strategy might be less intensive for LP HD than for classical HD. Late toxicities, which contribute considerably to the death rate, could thus be reduced. The long survival of several early stage LP HD patients without any treatment beyond lymph node excision could favour a 'watch-and-wait' strategy, albeit only after rigorous staging. New experimental therapy techniques such as immunotherapy might also be suitable. These possibilities must first be tested in a large-scale prospective study.

Key words: histopathology, Hodgkin's disease, lymphocyte predominance, prognosis, treatment strategy

Introduction

The early stage characteristics, indolent course and relatively good prognosis of lymphocyte rich variants of Hodgkin's disease have been recognised since 1937. Nomenclature and classification schemes have evolved from Jackson and Parker's distinction [1] between para-granuloma (lymphocyte rich), granuloma ('mainstream' HD) and sarcoma (lymphocyte depleted) in 1944, through the more detailed subclassification of Lukes and Butler [2] into nodular and diffuse lymphohistiocytic HD in 1966 to the simplification of the Rye Classification [3], based on the need for a clinically useful scheme, in which just one lymphocyte predominance category was recognised (Table 1). Later, the advent of new staining techniques including immunological methods enabled pathologists to reveal the nature and antibody marker profile of the malignant HRS cells [4]. In 1994 the International Lymphoma Study Group, in a complete review of the lymphoma classification structure (Revised European–American Lymphoma = R.E.A.L. Classification), distinguished between classical HD, including a lymphocyte rich variant (LRCHD) as a provisional entity, and LP HD, on the basis of tumour cell morphology and the antibody markers CD15, CD30, CD20, CD45, EMA and EBV [5]. The R.E.A.L. Classification was consolidated by the World Health Organisation (WHO) working group in 1997.

Earlier studies consistently demonstrated that patients with a lymphocyte rich variant of HD enjoyed a better prognosis than those with other forms [6–10]. However, the introduction of clinical staging [11] showed that the extent of disease was a more important prognostic factor than histology and that the localised nature of LP HD could well account for the good prognosis of this subtype. In addition, modern therapeutic strategies were able to improve survival and cure rates for all types of patients, and prognostic differences due to histology were often no longer evident [12–14]. The clinical relevance of the recent R.E.A.L. and WHO Classifications, particularly the distinction between LP HD and LRCHD, has been clarified by the international retrospective study by the European Task Force on Lymphoma (ETFL) described in the next section.

* Participants are listed in the Acknowledgements.
Table 1. Historical development of the classification and nomenclature of lymphocyte predominance HD

<table>
<thead>
<tr>
<th>Year of publication</th>
<th>Authors</th>
<th>Lymphocyte predominance</th>
<th>Other HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1944</td>
<td>Jackson and Parker</td>
<td>Paragranuloma</td>
<td>Granuloma, sarcoma</td>
</tr>
<tr>
<td>1966</td>
<td>Lukes and Butler</td>
<td>Lymphohistiocyte nodular</td>
<td>Nodular sclerosis</td>
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<tr>
<td></td>
<td></td>
<td>Lymphohistiocyte diffuse</td>
<td>Mixed cellularity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diffuse fibrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reticular</td>
</tr>
<tr>
<td>1966</td>
<td>Rye conference</td>
<td>Lymphocyte predominance</td>
<td>Nodular sclerosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mixed cellularity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lymphocyte depletion</td>
</tr>
<tr>
<td>1974</td>
<td>Lennert and Mohri</td>
<td>Nodular paragranuloma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diffuse paragranuloma LP (others)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Partial involvement</td>
<td></td>
</tr>
<tr>
<td>1994</td>
<td>R E A L (HLSG)</td>
<td>Lymphocyte predominance</td>
<td>Nodular sclerosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mixed cellularity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lymphocyte rich classical</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lymphocyte depletion</td>
</tr>
</tbody>
</table>

Clinical results

This section summarises recent results on clinical aspects of lymphocyte predominance Hodgkin’s disease. All major studies (at least 50 cases) since 1980, including preliminary results of the ETFL project mentioned above, have been included [15–24]. The studies are listed in Table 2. In all reports before or shortly after the announcement of the REAL classification in 1994, the cases included were selected according to the definition 'lymphohistiocytic nodular' of Lukes and Butler or 'lymphocyte predominance' of the Rye conference. Only in two studies (Bodis, von Wasielewski), apart from the ETFL project, were the selected cases representative of the R.E.A.L. category ‘LPHD’.

The ETFL project on LPHD was initiated as an international, multicentre, retrospective study in 1994, in order to investigate the clinical characteristics and course of patients diagnosed with LPHD classified by morphological and immunophenotypical criteria. The Revised European–American classification of lymphoma neoplasms (R.E.A.L.) [5] formed the basis for the histopathological classification. Clinical data and biopsy material (paraffin blocks) of all available cases diagnosed initially as lymphocyte predominance HD (LPHD–Rye) were collected from 17 European and American centres (listed in the Appendix). Untreated patients and those younger than 16 years were excluded from the analysis. Cases were newly classified, without prior knowledge of any corresponding clinical data, by a team of expert pathologists according to a modified REAL-classification using morphological and immuno-histochemical criteria. The following categories were used: LPHD (51%), LRCHD (27%), NHL (3%), classical HD (5%), reactive lesions (3%) and technically inadequate sample (11%). Originally, LPHD was subdivided according to lymph node architecture into nodular, diffuse and nodular-and-diffuse cases, but since no significant differences in clinical characteristics or prognosis between these categories were seen they were pooled for subsequent analysis. Data from the 1984–1993 trials of the German Hodgkin’s Lymphoma Study Group (GHSG), reviewed NS and MC cases, are presented here as a comparison to the project LPHD cases.

Patient characteristics and initial presentation

The median age of LPHD patients at first diagnosis ranged in the various reports between 29 and 42 years. For the ETFL data the median was 35 years, comparable with MC (GHSG: 35 years, Table 3) and somewhat older than NS (GHSG: 30 years). This statistic clearly depends on age inclusion criteria, especially on whether or not pediatric patients were included. All studies report a strong male predominance, and in the ETFL data about 70% of LPHD patients were male.

Stage I accounted for between 34% and 59% and stage IV for between 1% and 12% in all studies. In the ETFL data, 53% of LPHD patients had stage I and only 6% had stage IV. Thus, the proportion of early stages is consistently high in comparison with classical HD, and stage IV is consistently rare, although not negligible (Table 3). B symptoms were present in only 6% to 15% of cases in all reports, far less than in classical HD.

For a reliable comparison of the frequencies of in-
There are some reports on the course of disease in untreated LPHD patients, but no prospective study has been performed. Among the 51 nodular LP cases reported by Miettinen, 31 were given no treatment except possibly surgical removal of the tumor, since malignant disease was not suspected. After seven years median follow-up only seven of the untreated patients died; 27% of all patients relapsed. These results suggest that the survival of LPHD cases is good, even without treatment, but since the majority (42 of 51) were not originally diagnosed as malignant lymphoma, it seems likely that especially mild examples would predominate in this sample. Other publications [16, 26] also describe small numbers of cases receiving surgical treatment only, with acceptable survival rates despite the fact that many of these patients suffered a relapse. In summary, there is some evidence to support the hypothesis that certain LPHD patients do well without any therapy beyond excision.

Most LPHD patients received first-line therapy similar to that prescribed for classical HD patients. In the major studies surveyed here, survival varied between 98% at 4 years and 71% at 10 years. Failure free survival (FFS) or a similar measure, usually the HD-specific measure 'relapse free survival' (RFS), varied between 88% (5 years) and 74% (10 years). These results were in most studies achieved using radiotherapy. Borg-Grech found no significant difference in either relapse-free or overall survival between LPHD and classical subtypes treated at the same institution. Von Wasielewski observed a significantly better survival for immunophenotypically confirmed LPHD compared with cases showing a classical immunophenotype.

The Hodgkin-specific survival and FFS results for ETFL project LPHD cases are compared with those of GHSG classical HD cases in Figures 1 and 2. In these results pooling all stages, LPHD appears to fare somewhat better. However, when the very different patterns of clinical stage between LPHD, NS and MC are taken into consideration, using a stage-stratified analysis, no significant differences to classical HD are found, neither in SV nor in FFS (the only exception is stage 1 FFS, where LP does significantly better than MC). The results

<table>
<thead>
<tr>
<th>Involved site</th>
<th>LP (n = 63)</th>
<th>NS (n = 433)</th>
<th>MC/LD (n = 223)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper neck</td>
<td>14</td>
<td>4</td>
<td>4</td>
<td>0.006</td>
</tr>
<tr>
<td>Side of neck (L, R)</td>
<td>41</td>
<td>46</td>
<td>62</td>
<td>0.002</td>
</tr>
<tr>
<td>Mediastinum</td>
<td>8</td>
<td>73</td>
<td>46</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lung hilum (L, R)</td>
<td>5</td>
<td>15</td>
<td>14</td>
<td>0.006</td>
</tr>
<tr>
<td>Upper abdomen</td>
<td>5</td>
<td>13</td>
<td>18</td>
<td>0.01</td>
</tr>
<tr>
<td>Lower abdomen</td>
<td>8</td>
<td>8</td>
<td>17</td>
<td>0.002</td>
</tr>
<tr>
<td>Inguinal (L, R)</td>
<td>10</td>
<td>10</td>
<td>3</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Seven hundred nineteen laparotomy-staged patients reported by Mauch et al. [Ref. 25: modified from Tables 6 and 7]. Table entries are percentages of patients.

**Table 4.** Prevalence of involvement in nodal sites and spleen according to histological subtype.

**Table 3.** Patient characteristics of LP cases (ETFL project) compared with classical HD (GHSG).

- **Median age**
  - LPHD (n = 219): 35
  - NSHD (n = 599): 30
  - MCHD (n = 174): 35
- **Male sex**
  - LPHD: 74%
  - NSHD: 49%
  - MCHD: 73%
- **Stage**
  - LPHD: 53%
  - NSHD: 10%
  - MCHD: 21%
  - LPHD: 28%
  - NSHD: 47%
  - MCHD: 32%
  - LPHD: 14%
  - NSHD: 29%
  - MCHD: 35%
  - LPHD: 6%
  - NSHD: 14%
  - MCHD: 13%
- **B symptoms**
  - LPHD: 10%
  - NSHD: 42%
  - MCHD: 35%

a The GHSG enrolled patients up to 75 years of age. The median age for LPHD remained at 35, whether patients over 75 were excluded or not.
show a tendency (not statistically significant) to more frequent late relapses and better long-term survival in LPHD compared with classical HD. Survival after relapse was significantly better for the LPHD patients. This suggests that LPHD cases tend to relapse just as frequently as other subtypes, but the relapse is less aggressive, resulting in frequent multiple relapses and good survival rates.

**Transformation to NHL**

The possibility of occurrence of a NHL after primary LPHD is clinically important because of the following considerations: (1) choice of monitoring strategy after primary treatment and of diagnostic measures in the event of a malignancy, (2) choice of primary treatment to destroy the seed of a potential concomitant NHL, and (3) choice of primary treatment to avoid treatment-related NHL.

Seven of the major studies give information on secondary NHL, although in one of these only the fatal cases are given. Median follow-up ranged from 7 to 11 years. In total, 15 NHL cases among 367 LP patients (2.6%) were reported. In the ETFL project secondary neoplasia data were not systematically collected, but six cases (2.9%) were reported after LPHD. These rates can be compared with those for HD as a whole from the International Database on Hodgkin's Disease (IDHD) [27], where the cumulative incidence rate for secondary NHL was estimated as 1.0% after 10 years. A significantly higher risk for secondary NHL, increased by a factor 1.8, was found for LP patients compared with NS and MC (P < 0.01).

Regarding the causal role of treatment for secondary NHL, in the report of Miettinen four of the five secondary NHLs occurred in untreated patients. In the above-mentioned IDHD analysis, combined modality therapy was associated with increased risk in univariate analysis but not in multivariate analysis. Regarding the possible clonal relationship between LPHD and subsequent NHL, adequate histological and molecular data are still lacking.

In summary, there is evidence that NHLs are more likely following LPHD than following other subtypes of HD. Treatment would seem to play at most a minor role in causing secondary NHL.

**Consequences for future treatment**

LPHD is generally considered to have the best prognosis of all histological subtypes of HD. However, clinical data from trials employing state-of-the-art radiotherapy, chemotherapy or combined modality suggest that this prognostic difference is small or negligible under modern treatment. A reduction of treatment intensity for LPHD compared with classical HD is not indicated by these data alone.

A possible advantage from treatment reduction is suggested by the observed causes of death of LPHD patients. Only 4% of patients in the ETFL series, as well as in the report by Regula, died of HD, while just as many died of fatal secondary leukemias and solid tumours (ETFL: 4%, Regula: 7%), which are recognised as treatment related. These numbers suggest that current treatment strategies might be too intensive, particularly when other late effects such as cardiac and pulmonary complications are taken into account. Disadvantages of treatment reduction could include the greater risk of disease progression or of transformation to NHL. Secondary NHLs following LPHD are relatively frequent and are usually seen as a development of the primary disease rather than treatment induced. They were responsible for 1% of deaths in both the ETFL and Regula series.

A 'watch-and-wait' treatment strategy, in which patients are monitored without treatment until the disease shows signs of progression, has been advocated for LPHD and for other indolent lymphomas [28]. However, most authors report only anecdotal cases and prospective randomised trials do not exist. Miettinen [23] described 31 of 51 cases with LPHD who remained untreated because the original histological diagnosis was not malignant. The survival for these 31 patients, mostly in stage IA, was 93% at 5 years and 80% at 10 years. Five of the 51 untreated patients developed a diffuse large-cell non-Hodgkin's lymphoma 4–11 years after the onset of the primary nodular LPHD. In the series of Hansmann [16] 9 of 24 patients with nodular LPHD in stage IA who were not treated after lymph node biopsy remained free of disease even after 7–14 years. A prospective trial with explicit inclusion criteria is required in order to assess the feasibility, risks and benefits of a watch-and-wait strategy.

It is important to notice that about 20%-25% of the patients with LPHD are diagnosed in stage III or IV. Patients with advanced stage LPHD had an overall survival and tumor free survival substantially worse than...
patients with early stage LPHD and similar to advanced stage classical HD patients. This implies that thorough staging and, in the case of advanced stage, aggressive treatment is needed irrespective of histological subtype.

A potential new avenue for clinical research in LPHD is the use of immunotherapy, for instance immunotoxins, bispecific antibodies or the monoclonal antibody ‘Rituximab’. The latter antibody is directed against the B-cell restricted CD20 antigen; this antigen is expressed by the L&H cells of LPHD but rarely by the HRS cells of classical HD. First experiences with indolent follicular B-cell lymphomas have shown unexpectedly good results, with about 55% overall responses even in heavily pretreated patients [29, 30]. Relapses occur up to 20 years after primary diagnosis of LPHD, in the ETFL study in about 50% of cases. Twenty-seven percent of patients relapsing after LPHD suffered multiple recurrences, mostly again nodular LPHD lesions which are rarely fatal. Survival after LPHD relapses is more than 70% after 10 years in the ETFL study. This favourable course implies that immunotherapy could turn out to be a realistic strategy for relapsing LPHD patients, and perhaps also for the newly diagnosed.

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