Nodular Lymphocyte Predominant Hodgkin Lymphoma

ALFRED IAN LEE, a ANN S. LACASCE b

aDepartment of Medicine, Brigham and Women’s Hospital, Boston, Massachusetts, USA; bCenter for Hematologic Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA

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ABSTRACT

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) is a rare subtype of HL with unique clinicopathologic features. The hallmark histologic feature is the presence of malignant LP cells, unusual CD20+/CD15−/CD30+ variants of Reed-Sternberg cells, embedded within a nodular pattern of infiltrating lymphocytes. Compared with classical HL, NLPHL shows a slightly older median age at presentation (30–40 years), greater male predominance (3:1), less mediastinal involvement (<15%), and lower occurrence of classical HL risk factors. The differential diagnosis includes progressive transformation of germinal centers, lymphocyte-rich classical HL, and T-cell/histiocyte-rich large B-cell lymphoma, the latter of which may share a common biologic relationship. The vast majority of patients present with limited stage disease (70%–80%), the standard treatment for which is involved field radiotherapy at 30–36 Gy. Response rates to primary therapy exceed 90%, although relapses are common and may occur years after the initial diagnosis. Secondary malignancies, particularly non-Hodgkin lymphoma, may also occur at a frequency similar to that of relapsed NLPHL. Patients with advanced stage disease may have lower response rates and overall survival times than those with limited stage disease. For relapsed disease, treatment options include the salvage therapies used in classical HL, and rituximab. The Oncologist 2009;14:739–751

INTRODUCTION

Approximately 8,000 Americans are diagnosed each year with Hodgkin lymphoma (HL) [1]. The vast majority have classical HL, while 5%–10% belong to the histologic subtype known as nodular lymphocyte predominant HL (NLPHL). The earliest depiction of NLPHL appeared in 1936, with Rosenthal’s observation that the overall survival (OS) of HL patients correlated directly with the extent of lymphocyte proliferation within involved lymph nodes [2]. This was substantiated in 1944, when Jackson and Parker described three histologic variants of HL—paragranuloma, granuloma, and sarcoma—and noted a particularly favorable prognosis for the lymphocyte-rich paragranuloma variant [3, 4], an observation echoed in several ensuing studies [5–10]. Subsequent classification systems alternately referred to the paragranuloma subtype as “lymphocytic and/or histiocytic (L&H)” [11] or “lymphocytic predominance” [12]. In 1994, the revised European-Amer-
Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) has a number of distinctive histopathologic characteristics. Representative histologies are displayed in Figure 1. Of note, in studies of NLPHL incorporating central pathologic review, up to half the cases were ultimately assigned a different diagnosis, illustrating the difficulty in pathologic interpretation of this disease [19, 23, 27, 30, 33, 34, 41].

**Definition**
The WHO 2008 defines NLPHL as a “monoclonal B-cell neoplasm characterized by a nodular, or a nodular and diffuse, proliferation of scattered large neoplastic cells known as popcorn or popcorn like characterized lymphocytes (LP cells)—formerly called L&H cells for lymphocytic and/or histiocytic Reed-Sternberg cell variants. These cells reside in large spherical meshworks of follicular dendritic cell processes that are filled with non-neoplastic lymphocytes and histiocytes” [20].
L&H or LP Cells

The malignant neoplastic cell in NLPHL is the L&H cell, renamed in the WHO 2008 classification as the LP cell, a monoclonal B cell of germinal center (GC) origin.

Histology

Whereas classical RS cells have either bilobed nuclei or two nuclei, each containing distinct nucleoli, LP cells have a single, large, folded or multilobated nucleus. They are often referred to by the more descriptive name of “popcorn cells” [38]. LP cell nuclei typically contain multiple small basophilic nucleoli that are smaller than those of classical RS cells. Curiously, the ETFL study reported the coexistence of RS cells in addition to LP cells in a substantial percentage of NLPHL cases [19]. The current consensus, however, is that although cells that appear to be RS cells by morphologic criteria can occasionally be seen in NLPHL, such cells are negative for CD15 and CD30 and therefore are not classical RS cells [20].

Immunophenotype

Whereas RS cells are typically positive for CD15 and/or CD30 and negative for surface B-cell markers, LP cells are negative for CD15 and CD30 and positive for CD19, CD20, CD22, CD45, and CD79a. The REAL and WHO 2008 classifications reported rare CD30 positivity in NLPHL [13, 20], but in most of these cases the CD30+ cells were non-neoplastic extrafollicular immunoblasts [19]. Like RS cells, LP cells express Pax-5/B cell–specific activator protein. In contrast to RS cells, which typically do not express Oct-2 or B cell Oct-binding protein 1, LP cells are positive for both transcription factors. LP cells are also positive for Bcl-6, supporting a GC origin [42].

Genetics

Single-cell polymerase chain reaction assays demonstrate that LP cells typically contain rearranged immunoglobulin (Ig) genes and variably express Ig mRNA [13, 43–49].

Table 2. Clinical presentation of NLPHL in major retrospective studies after REAL classification

<table>
<thead>
<tr>
<th>Country</th>
<th>USA</th>
<th>UK</th>
<th>Italy</th>
<th>Multiple European and U.S. centers (ETFL)</th>
<th>USA</th>
<th>Australia</th>
<th>France (GOELAMS)</th>
<th>Germany (GHSG)</th>
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<th>Europe (EORTC and GELA)</th>
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<tbody>
<tr>
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<td>73</td>
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<td>68</td>
<td>219</td>
<td>75</td>
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<td>44</td>
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<td>Median, 29</td>
<td>Median, 25</td>
<td>&lt;40, 71%; ≥40, 29%</td>
<td>Median, 37</td>
<td>&lt;45, 72%; ≥45, 28%</td>
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<td>NC</td>
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a Study by Regula et al. (1988) [23] included for historical reasons, despite its publication prior to the REAL classification.
b Studies by Creman et al. (1995) [26] and Wirth et al. (2005) [36] contain overlapping patients.
c Stage distribution and extranodal sites are from Shimabukuro-Vornhagen et al. (2005) [35]. n of patients, median age, gender distribution, and B symptoms are from Nogova et al. (2008) [37].
d Study by Wirth et al. (2005) [36] restricted to limited-stage disease.

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; ETFL, European Task Force on Lymphoma; GELA, Groupe d’Etude des Lymphomes de l’Adulte; GHSG, German Hodgkin Study Group; GOELAMS: Groupe Ouest-Est d’Etude des Leucemies et Autres Maladies du Sang; NA, not applicable; NC, not commented upon in original article; NLPHL, nodular lymphocyte predominant Hodgkin lymphoma; REAL, revised European–American lymphoid.
Ig heavy chains show evidence of somatic hypermutation consistent with the cells’ GC derivation [43]. Most LP cells express J chain [19, 50], the absence of which may be associated with a poorer prognosis [33]. Comparative genomic hybridization assays show greater genomic instability in LP cells, with multiple different chromosomal abnormalities (+1, +2q, +3, +4q, +5q, +6, +8q, +11q, +12q, +x, −17) in up to two thirds of cases [47, 51]. Others have observed rearrangements of bcl-6, including t(3;22) (q27;q11), t(3;7) (q27;p12), t(3;9) (q27;q11), and t(3;14) (q27;q32), the latter involving the Ig heavy chain locus [52, 53].

Figure 1. Nodular lymphocyte predominant Hodgkin lymphoma, hematoxylin and eosin stains. (A): Low-power view, showing nodular organization of cellular infiltrates. (B): High-power view, showing lymphocyte predominant cells with single, large, folded, multilobated nuclei and cellular infiltrates comprised mostly of lymphocytes. Images provided by, and reproduced with permission from, Scott Rodig, M.D., Ph.D., Brigham & Women’s Hospital, Harvard Medical School.
Molecular Biology
LP cells express multiple signaling molecules (Fyn, Syk, B-cell link protein, phospholipase C-γ2) that are not expressed in RS cells [54]. Many of these are activated via signaling through the B cell/Ig receptor. Their role in the pathophysiology of NLPHL is unknown.

Epstein-Barr Virus
LP cells are typically negative for all markers of Epstein-Barr virus (EBV) including EBV-encoded RNA [19].

Reactive Background
The lymph node architecture in NLPHL is replaced by a nodular, or mixed nodular and diffuse, infiltrate comprised of polyclonal lymphocytes, follicular dendritic cells (FDCs), and epithelioid histiocytes, with intermingled LP cells. Unlike classical HL infiltrates, plasma cells, eosinophils, and neutrophils are rarely seen in NLPHL. The infiltrating lymphocytes in NLPHL are usually small B cells, although CD4+CD8+ T cells and even T cell–rich infiltrates can be seen [55, 56]. Surrounding the LP cells are CD4+ T-cell rosettes [19]; these are typically CD57+, indicative of a GC derivation [57]. CD21+ FDCs form an extensive meshwork within the nodules. Epithelioid histiocytes may form large aggregates resembling granulomas.

Nodular or Diffuse Architecture
Some cases of NLPHL show nodules interspersed with areas of diffuse lymphocyte infiltration; such cases with diffuse effacement of nodal architecture and <10%–30% nodularity have sometimes been referred to as diffuse NLPHL [19, 30]. A few studies have observed higher rates of recurrent disease with nodular than with diffuse histology [23, 29, 30], whereas others have found no clinical distinction [24, 26, 32, 33, 41].

Cytokines
The relative paucity of B symptoms and other markers of inflammation in NLPHL suggests that systemic cytokine release is not prominent, in contrast to classical HL [58]. One group has shown lower interleukin (IL)-2, IL-4, and IL-13 expression levels than in classical HL, and greater production of IL-10, transforming growth factor β, and interferon γ than in normal GC counterparts, similar to that of regulatory Tr1 cells [59].

Differential Diagnosis of NLPHL and Associated Disorders
Progressive Transformation of GCs
Progressive transformation of germinal centers (PTGC) was first described by Lennert and Müller-Hermelink as “germinat centers that are lost in a mass of lymphocytes” [60]. This disorder is seen in 5%–10% of patients with non-specific lymphadenitis (reactive hyperplasia), with 20% of patients having a relapsing course [61]. It typically affects focal areas within reactive lymph nodes, although a “florid” form involving multiple sites within individual lymph nodes and/or multiple lymph nodes has been described affecting young men [62]. Histologically PTGC is characterized by lymph nodes with large, well-defined nodules containing an excess of B cells [63, 64]. Some studies have reported 10%–30% of PTGC patients with antecedent, concurrent, or subsequent HL, particularly NLPHL [65, 66], while others have not demonstrated such a correlation [62]. PTGC itself is thought not to be a premalignant condition, despite a possible clinical association with HL/NLPHL. Histologically, the critical distinction between PTGC and NLPHL is the absence or presence, respectively, of LP cells.

T-Cell/Histiocyte-Rich Large B-Cell Lymphoma
T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) is a morphologic variant of diffuse large B-cell lymphoma (DLBCL), comprising <5% of all DLBCL cases [67]. Early studies noted striking histologic similarities between THRLBCL and NLPHL, but entirely distinct clinical courses [68–72]. In the literature, many cases previously diagnosed as purely diffuse NLPHL were likely THRLBCL, owing to a probable morphologic and biologic overlap between the two diseases [20]. Numerous cases of patients with both THRLBCL and NLPHL presenting synchronously or metachronously have been reported [47]. Pathologically, the WHO 2008 classification describes THRLBCL as “characterized by a limited number of scattered, large, atypical B cells embedded in a background of abundant T cells and frequently histiocytes” [20]. The median age at presentation is in the 40s, with a male predominance. The majority of THRLBCL patients present with advanced stage disease, with frequent involvement of the spleen, liver, and bone marrow. OS of THRLBCL patients is similar to that of DLBCL patients when treated with DLBCL therapies [73], but inferior to that of HL patients when treated with HL therapies [47].

LRCHL
Like NLPHL, LRCHL is characterized by nodular, or rarely diffuse, cellular infiltrates lacking in neutrophils and eosinophils [20]. Up to one third of cases previously diagnosed as NLPHL were likely LRCHL [20]. Both diseases have a similar presentation and clinical course, as discussed above. Pathologically, absence of LP cells distinguishes LRCHL from NLPHL.
Association of NLPHL with Non-Hodgkin Lymphoma

Beyond the biologic relationship between NLPHL and THRLBCL, a higher risk for non-Hodgkin lymphoma (NHL) has been observed in long-term studies of NLPHL patients, with about 1%–5% of NLPHL patients eventually developing or dying from NHL. The risk for secondary NHL in NLPHL patients may exceed that in nodular sclerosis classical HL [35, 74]. Molecular analyses of Ig heavy chain gene rearrangements indicate that some cases of secondary NHL may share a common clonal origin with primary NLPHL [75, 76].

**MANAGEMENT OF NLPHL**

The National Comprehensive Cancer Network (NCCN) recommends involved field radiotherapy (IFRT) or regional radiotherapy for NLPHL patients with limited stage disease, and combined modality therapy (CMT) or chemotherapy (CM) for those with advanced stage disease (Fig. 2) [77]. Of note, the NCCN guidelines are based primarily on evidence compiled from retrospective studies, as there are very few prospective clinical trials of NLPHL.

**Clinical Course**

Table 3 summarizes treatment and outcomes presented in major studies of NLPHL [23, 26–28, 30, 31, 33, 37, 41, 78]. In all studies, radiotherapy (RT) as a single-modality therapy was used primarily in limited stage disease, whereas CMT was reserved mostly for advanced stage disease; few patients were treated with CM alone. Response rates to first-line treatment in these studies were universally high, with 90%–100% of patients achieving a complete remission (CR) with primary therapy. Relapses following primary therapy were common, occurring in 10%–35% of patients, with a median time to first relapse of 3–6 years and a pattern of continuous relapses in many studies. Nonetheless, OS was excellent, with 10-year survival rates in the range of 80%–90%, although in the ETFL study this was lower for patients with stage IV disease [33].

Long-term therapy-related toxicities from secondary malignancies and cardiopulmonary disease [79] are of particular concern with NLPHL given the generally long survival time of these patients and the possibly increased representation of pediatric cases. In a retrospective review from the Harvard cancer centers of 71 NLPHL patients, 86% of whom received RT as single-modality treatment, only one of nine deaths occurred as a result of NLPHL, compared with five from secondary malignancies [30]. Similar observations have been reported in other series [23, 27], most notably a multicenter Australian study of 202 patients with limited stage NLPHL, in which five of 41 deaths were attributable to HL and 11 to secondary malignancies, including eight solid tumors arising from within a prior RT field [36]. Other studies, however, have reported HL-specific death rates equal to or greater than those for secondary cancers or cardiovascular complications [31, 41]. In the ETFL study, among 31 deaths, eight were from HL, four from cardiac causes, and 10 from secondary malignancies (two NHLs, five leukemias, and three solid tumors) [33].

Three studies have demonstrated similar outcomes for NLPHL and LRCHL patients. The ETFL analysis examined 219 NLPHL and 115 LRCHL patients treated with RT, CM, or CMT [33]; CM was mechlorethamine, vincristine, procarbazine, and prednisone (MOPP)-like, doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD)-like, or hybrid MOPP–ABVD-like, with CR rates of 96% for both diseases. Eight-year freedom from treatment failure (FFTF) and OS varied inversely with disease stage, with similar outcomes for the two diseases when stratified by stage. Relapses occurred in 21% of NLPHL and 17% of LRCHL patients. Twenty-seven percent of patients with first relapse were similar for NLPHL and LRCHL, the survival time of NLPHL patients after relapse was significantly longer than that of LRCHL patients, ex-

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**Stage I to II NLPHL**

Involved field radiotherapy (IFRT) 30–36 Gy or regional radiotherapy (RT) is recommended for all patients with stage IA to IIA disease. Chemotherapy followed by IFRT is recommended for patients with stage IB to IIB disease. For the rare patient with stage I to II who has B symptoms, combined modality therapy with chemotherapy and IFRT is recommended.

**Stage III to IV NLPHL**

Chemotherapy with or without RT is an appropriate treatment option for stage III to IV disease. Alternatively, asymptomatic patients with stage IIIA–IIB disease can undergo either observation (category 2B) or treatment with local RT for palliation.

**End of Treatment Restaging**

Restaging occurs after completion of initial therapy, and then observation is recommended for asymptomatic patients with unconfirmed complete response and at patients experiencing complete response.

**Figure 2.** National Comprehensive Cancer Network (NCCN) recommendations for the treatment of nodular lymphocyte predominant Hodgkin lymphoma (NLPHL).

NCCN categories of evidence and consensus: category 1, recommendation based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus; category 2A, recommendation based on lower-level evidence and there is uniform NCCN consensus; category 2B, recommendation is based on lower-level evidence and there is non-uniform NCCN consensus (but no major disagreement); category 3, recommendation is based on any level of evidence but reflects major disagreement. All recommendations in NCCN Practice Guidelines are category 2A unless otherwise noted.

cept for patients aged >45, who fared poorly in both diseases. The EORTC analyzed 73 patients with NLPHL, 21 with LRCHL, and 2,649 with non-LRCHL classical HL treated with RT, CM, or CMT, with CM consisting of epi- rubicin, bleomycin, vinblastine, and prednisone or hybrid MOPP–ABV [28]. No statistically significant differences in 8-year relapse-free survival (RFS) or OS were found among the diseases. The GHSG examined 394 NLPHL and 7,904 classical HL patients treated with RT, CM, or CMT, with CM consisting of hybrid cyclophosphamide, vincristine, procarbazine, and prednisone (COPP)–ABVD, COPP–ABV–ifosfamide, methotrexate, etoposide, and prednisone (IMEP), baseline or escalated bleomycin, etoposide, and doxorubicin plus COPP (BEACOPP), or ABVD [35, 37]. Compared to classical HL, NLPHL patients had a small but statistically significant increase in 50-month FFTF and OS. Relapse rates for NLPHL and classical HL patients were similar, but NLPHL patients had fewer early and more late relapses.

### Limited Stage Disease

Several retrospective studies exclusively of patients with limited stage NLPHL have established limited field RT as the standard of care for stage IA or IIA NLPHL (Table 4) [34, 36, 80–82].

One study from MD Anderson Cancer Center evaluated patients with stage I or II NLPHL treated with RT or CMT [81]; 27% of patients relapsed, with no significant differences in the distribution of in-field versus out-of-field relapse patterns or the 10-year RFS or OS between the

| Table 3. Treatment and responses to therapy in studies of NLPHL, all disease stages |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Primary treatment modality/RT | RT | CM | CMT | RT | CM | CMT | RT | CM | CMT |
| a NLPHL patients | 73; nodular, 31; diffuse, 42 | 64; nodular, 31; diffuse, 33 | 50 | 71; nodular, 51; diffuse, 14; unclassified, 6 | 219 | 70; nodular, 58; diffuse, 12 | 68 | 73 | 34 |
| In the EORTC study, for treatment modality as stratified by stage, percentages included LRCHL patients. For clinical outcomes, percentages were for NLPHL patients only. |
| a The EORTC study included NLPHL patients enrolled in the H7 and H8 trials of HL treated with RT versus CMT, and the H34 trial of HL treated with CM versus CMT. For the H34 trial, 10% had CM but were subsequently not randomized to further treatment, while 40% had a PR after initial therapy and were considered trial failures. |
| Abbreviations: CM, chemotherapy; CMT, combined modality therapy (chemoradiotherapy); CR, complete remission; EORTC, European Organization for Research and Treatment of Cancer; ETFL, European Task Force on Lymphoma; FFP, freedom from progression; FFR, freedom from relapse; FFTF, freedom from treatment failure; GHSG, German Hodgkin’s Study Group; HL, Hodgkin lymphoma; LRCHL, lymphocyte-rich classical Hodgkin lymphoma; NC, not commented upon in original article; NLPHL, nodular lymphocyte predominant Hodgkin lymphoma; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial remission; RFS, relapse-free survival; RT, radiotherapy; SD, stable disease. |

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In contrast, an earlier retrospective analysis from MD Anderson Cancer Center of NLPHL patients treated with RT, CM, or CMT, 96% of whom had stage I or II disease, found a significantly greater RFS in patients treated with RT alone than in those treated with CMT (Table 3) [41]; the interpretation, however, was com-

| Table 4. Treatment and responses to therapy in studies of NLPHL, limited stage disease only |
|---------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Wirth et al. (2005) [36] (Australia) |
| n of patients | 36 | 48 | 42 | 131 | 202 |
| Stage | IA, 75%; IIA, 25% | I, 63%; II, 38% | IA, 57%; IIA, 43% | IA, 100% | I, 80%; II, 20% |
| Primary treatment | | | | | |
| RT | Limited field (IFRT, regional, mantle), 78%; EFRT (STNI, TNI), 22% | 77% | None | EFRT, 34%; IFRT, 34% | None |
| CM | None | None | 2%<sup>b</sup> | None | None |
| CMT | None | 23%<sup>a</sup> | 98%<sup>b</sup> | 31%<sup>c</sup> | None |
| Response to primary treatment | | | | | |
| CR | NC | NC | 98% | Total, 99%; EFRT, 98%; IFRT, 100%; CMT, 98% | NC |
| PD/SD | | | | | |
| FFS | 5-yr RFS: stage IA IFRT or regional RT, 95%; stage IIA EFRT, 100% | 10-yr RFS<sup>a</sup>; RT, 77%; CMT, 68% | 15-yr FFP, 80% | 43-mo FFTF for total population, 95%. 24-mo FFTF, EFRT, 100%; IFRT, 92%; CMT, 97% | 10-yr, 88%; 15-yr, 82%;<sup>e</sup> 20-yr, 82% |
| OS | 5-yr: stage IA IFRT or regional RT, 100%; stage IIA EFRT, 100% | 10-yr<sup>f</sup>; RT, 90%; CMT, 100% | 15-yr, 86%<sup>e</sup> | 43-mo for total population, 99%; 78-mo EFRT, 94%; 17-mo IFRT, 100%; 40-mo CMT, 96% | 10-yr, 88%; 15-yr, 83%; 20-yr, 74% |

<sup>a</sup> Chemotherapy regimens: MOPP or NOVP.
<sup>b</sup> In the GOELAMS trial, all patients were initially treated with chemotherapy. Patients who responded proceeded to radiation. Patients who did not respond to initial chemotherapy proceeded to salvage therapy. Chemotherapy regimens: ABVD, EBVM, or a seven-drug regimen of epirubicin, bleomycin, vinblastine, vincristine, cyclophosphamide, etoposide, and methotrexate.
<sup>c</sup> Chemotherapy regimen: ABVD.
<sup>d</sup> p not significant for 10-year RFS rate for RT versus CMT.
<sup>e</sup> p not significant for 10-year OS rate for RT versus CMT.
<sup>f</sup> p not significant for 24-month FFTF rate for EFRT versus IFRT versus CMT.

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; CM, chemotherapy; CMT, combined modality therapy (chemoradiotherapy); CR, complete remission; EBVM, epirubicin, bleomycin, vinblastine, and methotrexate; EFRT, extended field radiotherapy; FFP, freedom from progression; FFTF, freedom from treatment failure; GHSG, German Hodgkin’s Study Group; GOELAMS: Groupe Ouest-Est d’Etude des Leucemies et Autres Maladies du Sang; IFRT, involved field radiotherapy; MOPP, mechlorethamine, vincristine, procarbazine, and prednisone; NC, not commented upon in original article; NLPHL, nodular lymphocyte predominant Hodgkin lymphoma; NOVP, mitoxantrone, vincristine, vinblastine, and prednisone; OS, overall survival; PD, progressive disease; PF5, progression-free survival; RFS, relapse-free survival; RT, radiotherapy; SD, stable disease; STNI, subtotal nodal irradiation; TNI, total nodal irradiation.
complicated by the fact that patients who received RT tended to have earlier stage disease than those who received CMT. A follow-up study from MD Anderson Cancer Center analyzed patients with stage IA or IIA NLPHL treated with limited field RT or extended field RT (EFRT), the latter including subtotal nodal irradiation or total nodal irradiation [80]; 5-year RFS and OS for all patients were 95%–100% regardless of the RT field.

The GHSG studied patients with stage I A NLPHL treated with RT (EFRT or IFRT) or CMT [82]. CR rates with first-line therapy were 98%–100%. FFTF and OS did not differ significantly among patients treated with the different modalities.

A multicenter retrospective Australian study examined patients with stage I or II NLPHL treated with RT [36]. The prognosis was excellent, with 20-year progression-free survival and OS of 82% and 74%, respectively. Failure-free progression (FFP) was inversely associated with the number of involved disease sites. Following first recurrence, 10-year freedom from relapse was 52%. No patient who received RT at a dose of 30–35 Gy experienced an in-field relapse.

In summary, for limited stage NLPHL, because nodal involvement is typically peripheral, mediastinal involvement rare, and outcomes similar for limited field RT compared to more extensive RT fields or to more intensive treatments, IFRT at a dose of 30–36 Gy has become the standard of care [83]. Alternately, the French GOELAMS group has advocated for CMT in limited stage NLPHL patients using anthracycline-based CM, although this is experimental [34].

Advanced Stage Disease

There are limited data to guide the management of advanced stage NLPHL patients. In single-institution series, most patients with stage III or IV NLPHL were treated with CM or CMT using MOPP-like, ABVD-like, or hybrid CM regimens (Table 3) [26, 27, 33]. One study from the U.K. showed a clear decrement in CR rate as a function of stage, with no impact of stage on remission duration or OS [27], whereas the ETFL study reported a negative impact of stage on both FFTF and OS [33]. In general, our understanding of advanced stage NLPHL is poor, and better treatment options are needed for such patients.

Relapsed Disease

Management of relapsed NLPHL is a significant problem, owing to the high frequency of late and multiple relapses. The prognosis of most relapsed patients is favorable, with roughly 50%–70% of patients maintaining a durable remission after first relapse [33, 36]. In most series, relapses are managed with the same salvage therapies as those used for classical HL, although the monoclonal anti-CD20 antibody rituximab has recently been introduced as an option for the treatment of relapsed disease, as discussed below [84–88].

Observation Versus Upfront Therapy

Early studies of adult patients with NLPHL published before the REAL classification found prolonged remissions in some patients treated with surgery alone [21, 22]. More recently, in the pediatric literature, at least three small retrospective series of pediatric patients, mostly with limited stage disease, have shown that observation following lymphadenectomy is feasible, particularly if CR is attained after surgery [89–91]. In these studies, partial remission (PR) after lymphadenectomy was associated with higher relapse rates and a lower event-free survival (EFS), but in all cases OS was 100%.

CM Alone

Among the retrospective studies in Table 3, only a small percentage of advanced stage NLPHL patients were treated with CM alone (Table 3). One Italian single-institution review [31] and two retrospective pediatric series [92, 93] found no difference in response rates among patients treated with RT, CM, or CMT. A Dutch single-institution review of seven pediatric patients treated with CM alone found a high relapse rate [94], whereas a multicenter retrospective study from the U.K. found no difference in the RFS for pediatric patients treated with CM compared with RT [95]. Differences in outcomes between these pediatric studies were potentially attributable to the use of alkylator-based CM in the latter, as discussed below.

Alkylator- Versus Nonalkylator-Based CM Regimens

Whether or not alkylator-based CM regimens may have more activity than nonalkylator-based regimens in NLPHL has not been clearly defined. Among studies in adult patients, a Harvard hospital series found that eight of 12 patients treated with MOPP or MOPP-like CM (either unimodality treatment or CMT) as primary or salvage therapy sustained a durable CR, compared with two of six patients treated with ABVD or etoposide, vinblastine, and doxorubicin [30]. Some pediatric studies have also suggested a lower relapse rate in children treated with alkylator-based therapy [89, 98, 94, 96]. By contrast, the French GOELAMS group has advocated for anthracycline-based CM in combination with RT, based on their data showing high 15-year FFP and OS among limited stage NLPHL patients treated with CMT using ABVD, epirubicin, bleomycin, vinblastine, and methotrexate, or a seven-drug
epirubicin-containing regimen [34]. The GHSG has used both alkylator-based (COPP–ABVD, COPP–ABV–IMEP, or baseline or escalated BEACOPP) and nonalkylator-based (ABVD) regimens for NLPHL patients treated in their clinical trials.

For investigators favoring the use of alkylator-based CM regimens in NLPHL patients, some have advocated the use of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or cyclophosphamide, vincristine, and prednisone (CVP) with or without rituximab (as discussed below), particularly given the proposed biologic relationship between NLPHL and THRLBCL [97]. CVP is presently under investigation in the pediatric setting; preliminary results of 18 patients with limited stage disease, of whom 15 received CVP upfront and three received CVP following first relapse, showed 12-month EFS and OS rates of 94% and 100%, respectively [98].

Role of Rituximab
Rituximab, a monoclonal anti-CD20 antibody, has shown promise in the treatment of relapsed NLPHL, and may have a role for initial therapy as well. The use of rituximab has been reported in classical HL, where it has been postulated to deplete inflammatory CD20^+ B cells [99]. This is in contrast to its function in NLPHL, where it is thought to act directly upon malignant LP cells via surface CD20, with encouraging findings in two case reports and two phase II studies [84–88].

A phase II study from the GHSG enrolled 14 NLPHL patients with relapsed disease, of whom central review confirmed relapsed NLPHL in 10 and either THRLBCL or CD20^+ classical HL in four [87]; after treatment with 4 weekly doses of rituximab (375 mg/m^2), the overall response rate (ORR) was 86% (CR rate, 57%), with 75% of responding patients in continuous remission at a median follow-up of 12 months. A follow-up GHSG report of 21 patients, 15 of whom had relapsed NLPHL and the remainder of whom had relapsed THRLBCL or CD20^+ HL, reported an ORR of 100% among patients with stage I–II disease, with a median time to progression of 33 months [88]. The median OS had not been reached at the time of reporting.

Conflicting results were observed in a phase II study from Stanford/Washington University, which enrolled 22 patients with NLPHL, 12 previously untreated and 10 with relapsed disease [84]. The ORR was 100% (CR rate, 45%); however, at 13 months of follow-up, nine patients had a clinical relapse, with a median time to relapse (TTR) of 9 months. The likelihood of relapse was higher in patients who achieved a PR and did not differ significantly for previously treated versus treatment-naïve patients. Five relapsed patients underwent tissue biopsy, demonstrating recurrent NLPHL in three cases and DLBCL in two (one of which was THRLBCL). The frequency of DLBCL following rituximab treatment was higher than that in previous series without rituximab [35, 74]. However, pathologic review of initial NLPHL tissue from the two patients who developed DLBCL showed extranodal LP cells on initial presentation, thought to correlate with a biologic predisposition toward transformation [100], rather than a rituximab effect.

The encouraging results for rituximab in relapsed NLPHL, coupled with its low toxicity, have prompted the GHSG to initiate a trial of rituximab in upfront treatment of stage IA NLPHL patients without risk factors. The role for rituximab in concert with combination CM is also being explored, with case reports of two adult first-degree relatives with familial NLPHL being successfully treated with upfront rituximab plus CHOP, with remissions lasting 34–40 months [97].

**SUMMARY**

NLPHL is a unique clinicopathologic entity, distinct from other histologic subtypes of classical HL except for LRCHL, with which there are some shared features. Compared with classical HL, NLPHL shows a slightly older median age at presentation (30–40 years), greater male predominance (3:1), less mediastinal involvement (<15%), greater representation of limited stage disease (70%–80%), and lower occurrence of classical HL risk factors. The malignant neoplastic cell in NLPHL is the LP cell, which is immunophenotypically distinguished from classical RS cells by virtue of being positive for CD20 and negative for CD15 and CD30.

The histopathologic diagnosis of NLPHL is problematic, with a high rate (up to 50%) of rediagnosis in studies incorporating central pathologic review, underscoring the need for experienced pathology in conferring a diagnosis of this disease. The differential diagnosis includes PTGC, LRCHL, and THRLBCL, the latter of which may share a common biologic origin with NLPHL. Standard treatment for limited stage disease is IFRT at 30–36 Gy. There is no standard treatment for advanced stage disease, although CM or CMT are typically used.

Response to primary therapy is excellent, particularly in limited stage disease, where CR rates exceed 90%. The OS rate is high in limited stage disease (8-year OS rate >90%), but significantly lower in advanced stage disease, particularly in stage IV disease (8-year OS rate <50%). Relapses are common in NLPHL, occurring in 10%–20% of patients. The median TTR is a few to several years after the initial diagnosis, with late relapses be-
ing prevalent. Multiple relapses can also occur in up to one third of relapsing patients. Treatment options for relapsed disease include salvage therapies used in classical HL, and rituximab.

Areas presently under investigation include the role of observation following lymphadenectomy in limited stage disease, particularly in pediatric patients; the potential benefit of alkylator-based CM versus nonalkylator-based regimens; and the use of rituximab in upfront therapy.

**AUTHOR CONTRIBUTIONS**

Conception/design: Alfred Lee, Ann LaCasce  
Collection/assembly of data: Alfred Lee  
Data analysis: Alfred Lee  
Manuscript writing: Alfred Lee, Ann LaCasce  
Final approval of manuscript: Alfred Lee, Ann LaCasce

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**REFERENCES**


94 almost or non-advanced nodular lymphocyte predominant Hodgkin’s lymphoma (NLPHL or nodular paragranuloma) treated with chemotherapy only. Leuk Lymphoma 2006;47:1504–1510.


