

**RESEARCH ARTICLE**

The time to relapse correlates with the histopathological growth pattern in nodular lymphocyte predominant Hodgkin lymphoma

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Abstract

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) can present with different histopathological growth patterns. The impact of these histopathological growth patterns on relapse characteristics is unknown. We therefore analyzed paired biopsies obtained at initial diagnosis and relapse from 33 NLPHL patients who had received first-line treatment within German Hodgkin Study Group (GHSg) trial protocols, and from a second cohort of 41 relapsed NLPHL patients who had been treated outside GHSg studies. Among the 33 GHSg patients, 21 patients presented with a typical growth pattern at initial diagnosis, whereas 12 patients had a variant histology. The histopathological growth patterns at initial diagnosis and at relapse were consistent in 67% of cases. A variant histology at initial diagnosis was associated with a shorter median time to lymphoma recurrence (2.8 vs 5.2 years; $P = .0219$). A similar

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tendency towards a shorter median time to lymphoma recurrence was observed for patients presenting with a variant histology at relapse, irrespective of the growth pattern at initial diagnosis. Results obtained from the 41 NLPHL patients who had been treated outside GHSG studies were comparable (median time to lymphoma recurrence for variant histology vs typical growth pattern at initial diagnosis: 1.5 vs 7.0 years). In conclusion, the histopathological growth pattern remains consistent at relapse in the majority of NLPHL cases, and has major impact on the time of relapse.

1 | INTRODUCTION

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) is a rare lymphoma entity that accounts for approximately 5% of all Hodgkin lymphoma cases. The malignant lymphocyte predominant (LP) cells are consistently positive for CD20 but usually lack CD30.¹ The clinical course of NLPHL is mostly indolent, and the majority of patients are diagnosed with early-stage disease. However, a tendency towards late relapses and histological transformation into aggressive B-cell non-Hodgkin lymphoma (B-NHL) has been described.²

A histopathological classification for NLPHL has been proposed by Fan and colleagues, based on the localization of the LP cells within the tumor infiltrate, and the composition of the microenvironment; six distinct growth patterns have been defined. Growth patterns A and B (typical growth patterns) are characterized by the localization of LP cells within nodules composed of reactive B cells. Growth patterns C to F (variant histology) are associated with an increased proportion of LP cells located outside of the nodules, T-cell-rich nodules, or a diffuse background resembling T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL).³

Cases presenting with LP cells localized within the nodules appear to have a favorable prognosis due to a non-invasive growth pattern. In contrast, a previous analysis from the German Hodgkin Study Group (GHSG) has revealed that a variant histology correlates with more advanced disease at initial diagnosis, and poorer clinical outcomes after stage-adapted first-line treatment.^{4,5}

Studies addressing the question whether the characteristics of relapse differ between patients with a typical growth pattern, and those with a variant histology, are currently lacking. We therefore performed an analysis investigating the pathological and clinical parameters of patients who experienced NLPHL recurrence, after stage-adapted first-line treatment.

2 | MATERIALS AND METHODS

Patients who had been included in a previous retrospective GHSG study, evaluating the prognostic impact of variant histology in newly diagnosed NLPHL, were screened with respect to disease progression during follow-up.⁵ Those with available biopsies from both the initial NLPHL diagnosis (expert review was mandatory for enrollment into GHSG studies), and lymphoma recurrence, were considered eligible

for the present analysis. Biopsies were reviewed by a panel of 13 expert hematopathologists at a multi-head microscope, and the patients were grouped according to their histopathological growth pattern at initial NLPHL diagnosis (typical growth pattern vs variant histology). Descriptive analyses were performed to compare demographic and baseline characteristics between the groups. The Kaplan-Meier method was used for survival analyses.

The panel of expert hematopathologists also reviewed paired biopsies that were obtained at the time of the initial diagnosis, and at lymphoma recurrence from NLPHL patients who were treated outside GHSG studies. No statistical analyses were performed for these patients due to a lack of systematic follow-up. The investigation of these biopsies was approved by the ethics committee of the University Hospital Frankfurt (No 157/17). The study was conducted in accordance with the Declaration of Helsinki.

Immunohistochemical IgD-staining was performed for a subset of patients using anti-IgD antibody (IR517, DAKO, Glostrup, Denmark) and the Envision-FLEX detection system (DAKO) as previously described.⁶

3 | RESULTS

Biopsies from both the initial NLPHL diagnosis and lymphoma recurrence were available for 74 patients (33 GHSG patients and 41 patients treated outside GHSG studies).

Among the GHSG patients, a total of 21 patients (64%) initially presented with a typical growth pattern, whereas 12 patients (36%) presented with a variant histology. The median age at the initial NLPHL diagnosis (39 years vs 39.5 years), and the median observation time from the initial diagnosis (10.2 years vs 9.4 years), were comparable between patients with a typical growth pattern and those with a variant histology (Table 1). Patients with a variant histology more often presented with advanced disease than those presenting with a typical growth pattern (5/12 patients; 41.7% vs 3/21; 14.3%). Thus, the baseline characteristics of patients included in this study were consistent with previous reports.^{7,8}

Patients treated outside GHSG studies initially presented with a typical growth pattern in 18/41 cases (44%) and with a variant histology in 23/41 cases (56%). The median age was 32.5 years for individuals with typical growth patterns, and 33 years for patients with a variant histology (Table 2).

TABLE 1 Patient characteristics and treatment at initial NLPHL diagnosis and lymphoma recurrence (patient group treated within GHSG studies)

	Typical growth pattern	Variant histology
Histopathological growth pattern at initial NLPHL diagnosis	21 patients	12 patients
Median age at initial NLPHL diagnosis	39 years	39.5 years
Median observation from initial NLPHL diagnosis	10.2 years	9.4 years
Median time to lymphoma recurrence	5.2 years	2.8 years
Histopathological growth pattern at lymphoma recurrence	19 patients	12 patients (+2 patients with transformation into aggressive B-NHL)
First-line treatment		
RT alone	5/21 patients (23.8%)	1/12 patients (8.3%)
Anti-CD20 antibody alone	1/21 patients (4.8%)	3/12 patients (25.0%)
Ctx +/- RT	15/21 patients (71.4%)	8/12 patients (66.7%)
Second-line treatment		
Anti-CD20 antibody alone or RT alone	10/19 patients (52.6%)	2/14 patients (14.3%)
Ctx +/- anti-CD20 Ab +/- RT	6/19 patients (31.6%)	1/14 patients (7.1%)
HDCT + ASCT	3/19 patients (15.8%)	4/14 patients (28.6%)
No therapy	0/19 patients (0.0%)	1/14 patients (7.1%)
Unknown	0/19 patients (0.0%)	6/14 patients (42.9%)

Abbreviations: NLPHL, nodular lymphocyte predominant Hodgkin lymphoma; B-NHL, B-cell non-Hodgkin lymphoma; RT, radiotherapy; Ctx, chemotherapy; HDCT, high-dose chemotherapy; ASCT, autologous stem cell transplantation.

TABLE 2 Patient characteristics at initial NLPHL diagnosis and lymphoma recurrence (patient group treated outside GHSG studies)

	Typical growth pattern	Variant histology
Histopathological growth pattern at initial NLPHL diagnosis	18 patients	23 patients
Median age at initial NLPHL diagnosis	32.5 years	33 years
Median time to lymphoma recurrence	7.0 years	1.5 years
Histopathological growth pattern at lymphoma recurrence	17 patients	19 patients (+5 patients with transformation into aggressive B-NHL)

Abbreviations: NLPHL, nodular lymphocyte predominant Hodgkin lymphoma; B-NHL, B-cell non-Hodgkin lymphoma.

Among the patients treated within GHSG studies, a variant histology at initial NLPHL diagnosis was associated with a significantly shorter median time to lymphoma recurrence, than a typical growth pattern (2.8 years vs 5.2 years; $P = .0219$) (Table 1 and Figure 1). At relapse, 19/33 patients (58%) had NLPHL with a typical growth pattern, and 12/33 patients (36%) had NLPHL with a variant histology; 2/33 patients (6%) had histological transformation into aggressive B-NHL (Table 1). The histopathological growth patterns at initial diagnosis and at relapse were consistent in 22/33 cases (67%). A switch from a typical growth pattern to a variant histology or vice versa was

documented for 9/33 patients (27%) (five cases with a variant histology at relapse after a typical growth pattern at initial diagnosis and four cases with a typical growth pattern at relapse after a variant histology at initial diagnosis) (Tables S1 and S2). The median time to lymphoma recurrence tended to be shorter for the 14 patients relapsing with a variant histology or aggressive B-NHL than for the 19 patients with typical growth patterns at relapse (2.5 years vs 5.2 years; $P = .133$), irrespective of their histopathological growth patterns at initial NLPHL diagnosis. After exclusion of the two patients with aggressive B-NHL at recurrence, and restriction of the analysis to patients with NLPHL histology only at relapse, this effect became significant (2.5 years vs 5.2 years to NLPHL recurrence; $P = .004$).

Patients treated outside GHSG studies had a median time to lymphoma recurrence of 1.5 years in case of a variant histology, and 7.0 years in case of a typical growth pattern at initial NLPHL diagnosis. In this patient group, the histopathological growth patterns at initial NLPHL diagnosis and at relapse were consistent in 25/41 cases (61%). Disease recurrence with a different growth pattern occurred in 11/41 cases (27%), and 5/41 patients (12%) experienced histological transformation into aggressive B-NHL (Table 2).

The IgD-immunostaining was performed in biopsies from nine patients who had switched from a typical growth pattern at initial NLPHL diagnosis, to a variant histology at relapse or vice versa. None of the cases presented with IgD-positive LP cells at initial diagnosis or relapse.

At relapse, patients initially treated within GHSG studies received different salvage therapies, ranging from single-agent anti-CD20 antibody treatment to high-dose chemotherapy followed by autologous stem cell transplantation (ASCT). Patients who presented with a

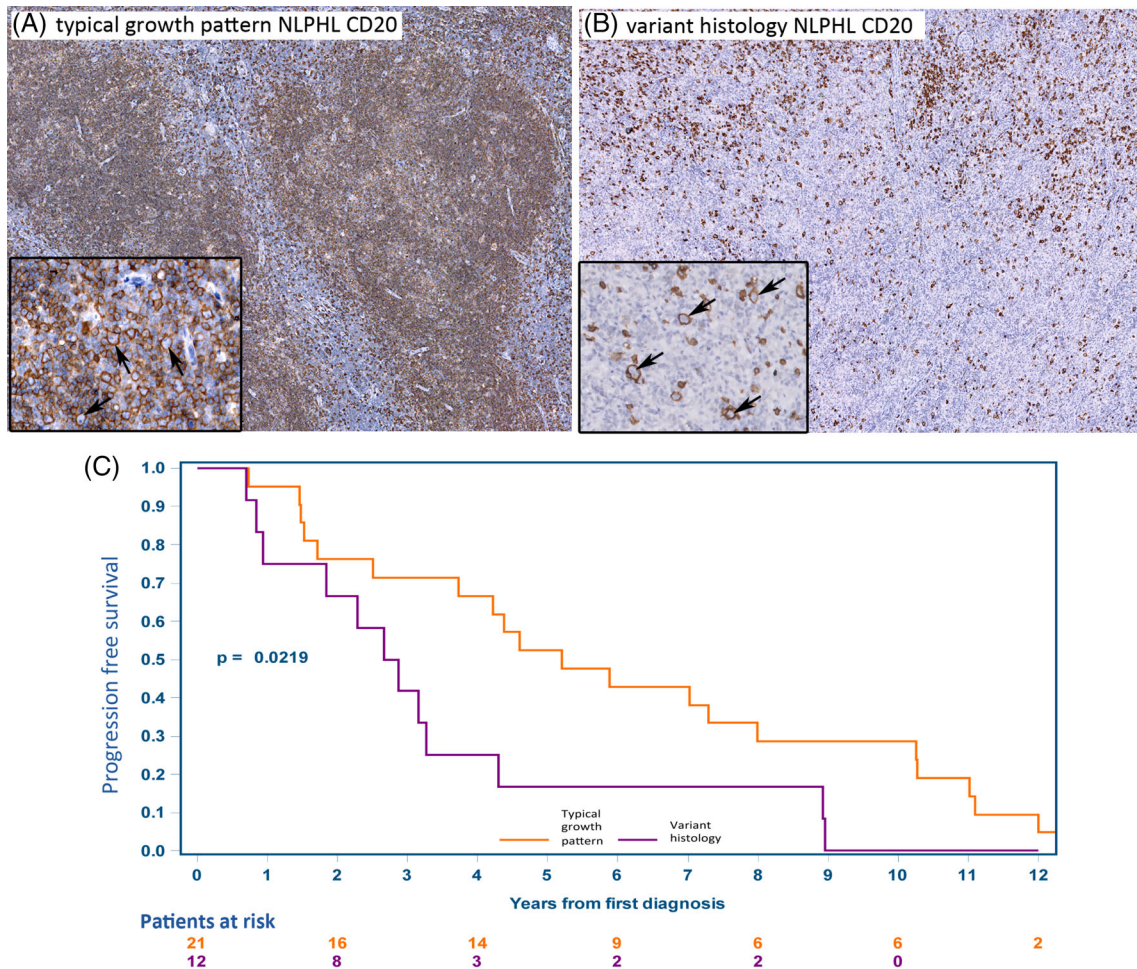


FIGURE 1 A, An example of an NLPHL case with a typical growth pattern (CD20-immunostaining, 40 \times); insert displays CD20-positive LP cells (arrows, 400 \times). B, An example of an NLPHL case with a variant histology (CD20-immunostaining, 40 \times); insert displays CD20-positive LP cells (arrows, 400 \times). C, Time to lymphoma recurrence, according to the histopathological growth pattern at initial NLPHL diagnosis

typical growth pattern at relapse mostly had non-aggressive second-line approaches, such as single-agent anti-CD20 antibody therapy or radiotherapy (RT) alone. In contrast, patients with a variant histology or histological transformation into aggressive B-NHL, more often received salvage treatment with conventional chemotherapy optionally combined with an anti-CD20 antibody and/or RT and high-dose chemotherapy followed by ASCT, respectively (Table 1). The five-year overall survival estimate after lymphoma recurrence was 95.8% (95%-CI: 87.8%-100%).

4 | DISCUSSION

Lymphoma recurrence during follow-up was documented for 73 of the 413 patients included in the previous GHSG study analyzing the prognostic impact of the histopathological growth pattern in newly diagnosed NLPHL cases.⁵ Relapses thus represent a relevant problem in NLPHL. Among the patients who had received first-line treatment within GHSG studies, those who presented with a variant histology at the initial NLPHL diagnosis had a shorter median time to lymphoma recurrence than those with typical growth patterns at initial diagnosis.

This is in agreement with the results from previous studies indicating an association between a variant histology and a more aggressive clinical course.^{5,9,10} The higher proportion of cases with a variant histology in the patient group treated outside GHSG studies may be related to the fact that these cases are more difficult to diagnose and were therefore more frequently sent for expert review.

The occurrence of aggressive B-NHL at relapse underscores that NLPHL patients are at a relevant risk for histological transformation.¹¹⁻¹³ Thus, a biopsy to confirm the NLPHL diagnosis should be obtained from all patients with a history of NLPHL, if disease recurrence is suspected. One aim of the present study was to characterize the histological presentation of NLPHL relapses, and to determine whether histopathological growth patterns occur at random or follow a regular system. The relative consistency of histopathological growth patterns between initial diagnosis and relapse is in line with the usually observed indolent behavior and slow progression of NLPHL. However, a switch from a typical growth pattern to a variant histology at relapse, may represent a stepwise progression of disease in a subset of patients. Likewise, an even smaller number of patients presented with histological transformation into aggressive B-NHL. In

patients that presented with a variant histology at initial NPLHL diagnosis, and with a typical growth pattern at disease recurrence, relapses frequently occurred late. This matches with the usually indolent presentation of NPLHL with typical growth pattern, regardless of the pattern at initial diagnosis. However, the question whether these late relapses of typical NPLHL are clonally related to the initial biopsy, or if both derive from a common lymphoma stem cell, should be addressed in future studies.

The outcome of the 33 patients who were treated within GHSG studies was favorable. This is in line with several previous studies reporting very good outcomes for patients with relapsed NPLHL.^{14,15} The observation that salvage treatment at relapse differed between patients with typical growth patterns and a variant histology, is in agreement with a previous GHSG analysis that included 99 patients with relapsed and refractory NPLHL. According to this study, various factors, such as the time between the initial NPLHL diagnosis and disease recurrence, the stage at initial diagnosis, and the first-line treatment, influenced the choice of salvage therapy.¹⁴ These factors also correlate with the histopathological growth pattern.

In summary, the present analysis for the first time provides information regarding the consistency of histopathological growth patterns between the initial NPLHL diagnosis and lymphoma recurrence. The relative stability of histopathological growth patterns may reflect a stable microenvironment and tumor clone within the individual patient. Crucial additional oncogenic events may be necessary to cause a change in the histopathological growth pattern. The results of the present study highlight the prognostic impact of the histopathological growth pattern, as a variant histology at initial NPLHL diagnosis was associated with a shorter time to lymphoma recurrence indicating differences in terms of growth dynamics and aggressiveness between cases with typical growth patterns and a variant histology. However, data should be interpreted with caution because of the limited number of patients and further confirmation is necessary before final conclusions can be drawn.

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CONFLICT OF INTEREST

The authors report no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

S.H. and D.A.E. designed the study, performed data interpretation, and wrote the manuscript; AP performed data analysis and interpretation; A.M., H.W.B., A.C.F., G.O., S.C., F.F., L.Q.M., H.S., W.K., P.M., A.E., and M.L.H. were involved in data acquisition and the contribution of essential materials. All authors drafted and approved this manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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