Histopathological growth patterns in patients with advanced nodular lymphocyte-predominant Hodgkin lymphoma treated within the randomized HD18 study: a report from the German Hodgkin Study Group

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Summary

We retrospectively investigated histopathological growth patterns in individuals with advanced nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) treated within the randomized HD18 study. In all, 35/60 patients (58%) presented with atypical growth patterns. Patients with atypical growth patterns more often had stage IV disease ($P = 0{\cdot}0354$) and splenic involvement ($P = 0{\cdot}0048$) than patients with typical growth patterns; a positive positron emission tomography after two cycles of chemotherapy (PET-2) tended to be more common ($P = 0{\cdot}1078$). Five-year progression-free survival [hazard ratio (HR) = 0·86; 95% confidence interval (CI) = 0·49–1·47] and overall survival (HR = 0·85; 95% CI = 0·49–1·51) did not differ between the groups after study treatment with PET-2-guided escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone). Thus, advanced NLPHL is often associated with atypical growth patterns but their prognostic impact is compensated by PET-2-guided escalated BEACOPP.

Keywords: nodular lymphocyte-predominant Hodgkin lymphoma, histopathological growth pattern, BEACOPP, interim positron emission tomography.

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Introduction

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare lymphoma entity accounting for approximately 5% of all Hodgkin lymphoma (HL) cases. The disease has distinct pathological and clinical characteristics.[1] A total of six histopathological growth patterns have been described based on the localization of the malignant lymphocyte predominant cells within the affected tissue and the composition of the tumour microenvironment.[2] The histopathological growth patterns are divided into typical growth patterns (pattern A and B according to Fan *et al.*) and atypical growth patterns (pattern C to F according to Fan *et al.*). Atypical growth patterns are associated with more advanced disease at initial diagnosis, a worse progression-free survival (PFS) and earlier disease recurrence in comparison with typical growth patterns.[3,4]

Only a minority of NLPHL patients initially present with advanced stages. No standard treatment has been defined for this patient group until now.[5] Activity has been demonstrated for both HL-directed protocols and regimens commonly used in B-cell non-Hodgkin lymphoma (B-NHL).[6–10] The outcome of 84 patients with newly diagnosed advanced NLPHL treated within the randomized German Hodgkin Study Group (GHSG) HD18 study for advanced HL has been reported recently. Treatment consisted of escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) guided by interim positron emission tomography after two cycles of chemotherapy (PET-2). At five years, PFS and overall survival (OS) rates were 82·4% and 94·8% respectively.[11]

The impact of the histopathological growth pattern in patients with advanced NLPHL is largely undefined. We thus conducted a retrospective analysis addressing this issue. Individuals that had PET-2-guided escalated BEACOPP within the HD18 study were taken into account.

Patients and methods

Patients with biopsy-proven NLPHL (as confirmed by expert review) treated within the randomized GHSG HD18 study for newly diagnosed advanced HL were eligible for the present analysis. Lymphoma tissue was requested and the histopathological growth pattern was determined by an expert haematopathologist (A.R., W.K., M.-L.H., P.M., H.-W.B., A.C.F., S.H.) for the patients from whom sufficient material was obtained. Design, inclusion criteria and treatment of the HD18 study were reported elsewhere.[12] The study was approved by the review boards of the participating sites and conducted in accordance with the Declaration of Helsinki.

Data were analyzed descriptively. Fisher's exact tests were used to explore and quantify differences between patients with typical growth patterns and atypical growth patterns, respectively. PFS and OS according to the histopathological growth pattern were analyzed using the Kaplan–Meier method including hazard ratios (HR) and 95% confidence intervals (95% CI) obtained from Cox regression models. PFS was defined as time from completion of initial staging until disease progression, relapse or death from any cause and was censored at the date of last information on the disease status. OS was defined as time from completion of initial staging until death from any cause and was censored at the date of last information for surviving patients. SAS version 9·4 for Microsoft Windows (SAS Institute, Cary, NC, USA) was used for all analyses.

Results

Lymphoma tissue to determine the histopathological growth pattern was available for 60/84 patients (71%; Figure S1). Among the 60 patients with a defined histopathological growth pattern, 35 (58%) presented with atypical growth patterns and 25 (42%) with typical growth patterns. Patients with atypical growth patterns more often had stage IV disease (9/35 patients; 26%) than patients with typical growth patterns (1/25 patients; 4%; $P = 0{\cdot}0354$). Splenic involvement was also more common in patients with atypical growth patterns (17/35 patients; 49% vs. 3/25 patients; 12%; $P = 0{\cdot}0048$). Liver and/or bone marrow involvement were documented for 4/35 patients (11%) with atypical growth patterns and none of the patients with typical growth patterns ($P = 0{\cdot}2585$). The PET-2 was positive for 16/35 patients (46%) presenting with atypical growth patterns and 6/25 patients (24%) presenting with typical growth patterns ($P = 0{\cdot}1078$; Table I).

During follow-up, there were five cases of NLPHL recurrence among the 60 patients with a defined histopathological growth pattern. Four cases occurred in patients with atypical growth patterns. One patient with disease recurrence had a typical growth pattern. The times to NLPHL recurrence for patients with atypical growth patterns were 18·2, 31·3, 48·1 and 55·3 months, respectively. In contrast, the time to NLPHL recurrence was 55·9 months for the patient that had initially presented with a typical growth pattern (Table I).

Patients with atypical growth patterns had five-year PFS and OS rates of 79·7% (95% CI: 64·9–94·5%) and 93·4% (95% CI: 84·5–100%), respectively. The five-year PFS and OS rates for patients with typical growth patterns were 85·1% (95% CI: 69·0–100%) and 92·0% (95% CI: 81·4–100%), respectively. Thus, there was no evidence for PFS (HR: 0·86; 95% CI: 0·49–1·47) and OS (HR: 0·85; 95% CI: 0·49–1·51) differences between both groups (Table I, Fig 1).

Discussion

In the present analysis including 60 patients with advanced NLPHL, individuals with atypical growth patterns accounted for 58% of cases. Hence, the rate was higher than in previous reports such as a large analysis from the GHSG including

Table I. Characteristics and outcome of patients according to the histopathological growth pattern.

Parameter	All NLPHL patients	Patients without documented HGP	All patients with documented HGP	Typical HGP	Atypical HGP	*P* value or HR (95% CI)
All patients	84	24	60	25	35	
Male	67 (80%)	20 (83%)	47 (78%)	18 (72%)	29 (83%)	0·3546
Female	17 (20%)	4 (17%)	13 (22%)	7 (28%)	6 (17%)	
Median age (range)	43 (18–60)	42 (19–58)	43 (18–60)	40 (18–60)	43 (18–60)	0·3294
Stage III	69 (82%)	19 (79%)	50 (83%)	24 (96%)	26 (74%)	0·0354
Stage IV	15 (18%)	5 (21%)	10 (17%)	1 (4%)	9 (26%)	
Splenic involvement	32 (38%)	11 (46%)	20 (34%)	3 (12%)	17 (49%)	0·0048
Liver and/or bone marrow involvement	8 (10%)	3 (13%)	4 (7%)	0 (0%)	4 (11%)	0·2585
PET-2-positive	31 (37%)	9 (37%)	22 (37%)	6 (24%)	16 (46%)	0·1078
PET-2-negative	53 (63%)	15 (63%)	38 (63%)	19 (76%)	19 (54%)	
4 × eBEACOPP	27 (32%)	9 (38%)	18 (30%)	11 (44%)	7 (20%)	0·1456
6 × eBEACOPP	24 (29%)	7 (29%)	17 (28%)	6 (24%)	11 (31%)	
8 × eBEACOPP	33 (39%)	8 (33%)	25 (42%)	8 (32%)	17 (49%)	
Radiotherapy	10 (12%)	5 (21%)	5 (8%)	0 (0%)	5 (14%)	0·0692
5-year PFS (95% CI)	82·4% (73·2–91·7)	83·3% (65·7–100)	82·1% (71·3–92·9)	85·1% (69–100)	79·7% (64·9–94·5)	HR = 0·86 (0·49–1·47)
5-year OS (95% CI)	94·8% (89·9–99·8)	100% (100%)	92·7% (85·8–99·6)	92% (81·4–100)	93·4% (84·5–100)	HR = 0·85 (0·49–1·51)
Disease progression or relapse	10 (12%)	5 (21%)	5 (8%)	1 (4%)	4 (11%)	0·3899
Median time to relapse (months)	53·6 (15·3–109·7)	57·9 (15·3–109·7)	48·1 (18·2–55·9)			

CI, confidence interval; eBEACOPP, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; HGP, histopathological growth pattern; HR, hazard ratio; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival.

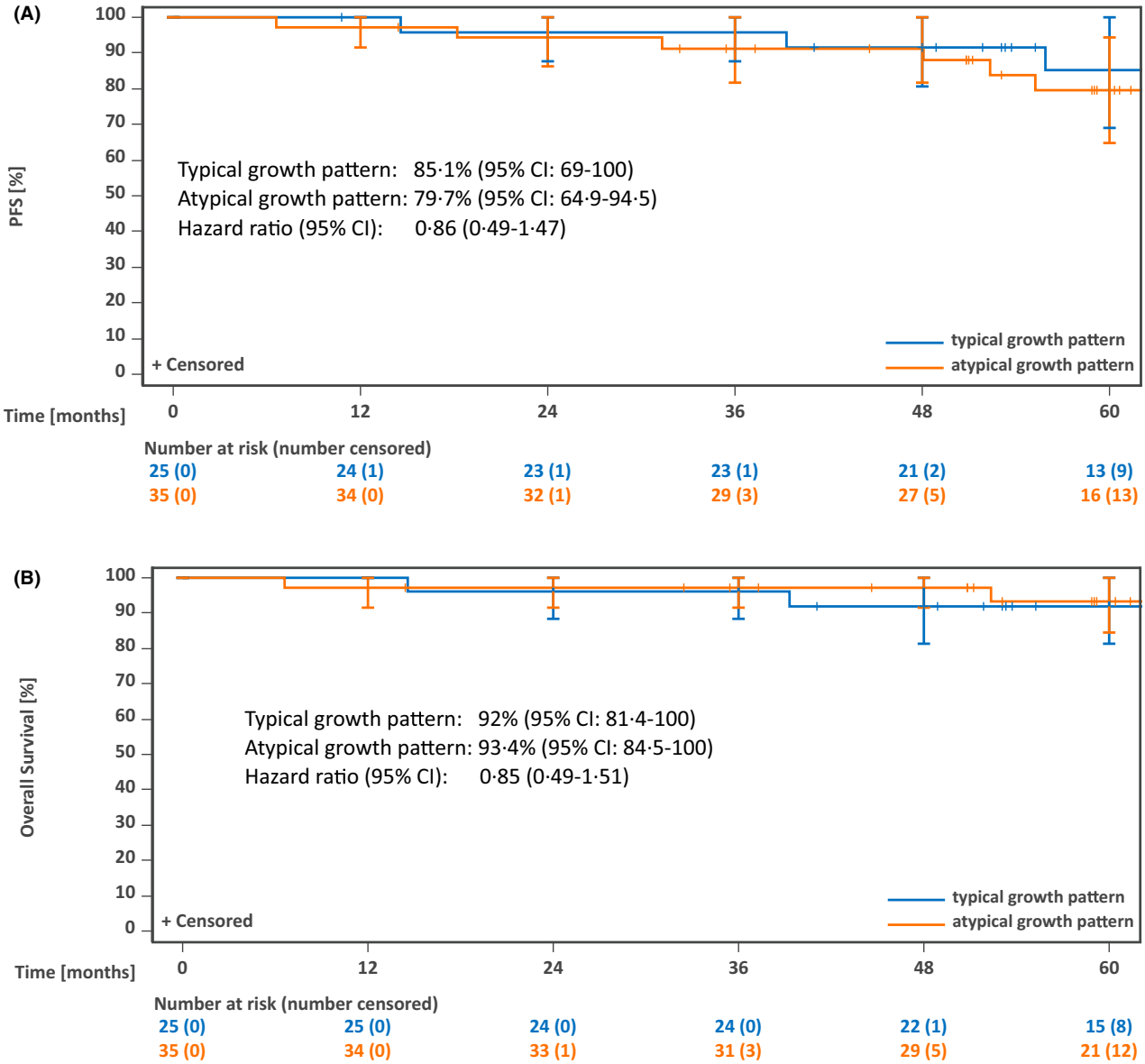

Fig 1. Progression-free survival (A) and overall survival (B) according to the histopathological growth pattern. CI, confidence interval. [Colour figure can be viewed at wileyonlinelibrary.com]

423 NLPHL patients of all stages in which the proportion of individuals with atypical growth patterns was 25%. Despite this difference, results from both analyses are consistent since the previous study indicated a higher rate of atypical growth patterns in patients with advanced stages than in patients with early stages.[3]

Patients with atypical growth patterns included in the present analysis more often presented with stage IV disease and splenic involvement at initial NLPHL diagnosis than patients with typical growth patterns. Liver and/or bone marrow involvement were seen in 11% of patients with atypical growth patterns but no patient with a typical growth pattern presented with involvement of these localizations. A previous analysis comprising 471 NLPHL patients of all stages who had stage-adapted first-line treatment within the randomized GHSG HD7 to HD15 studies had demonstrated that involvement of liver and/or bone marrow is associated with an impaired survival outcome.[6] Different earlier studies had identified splenic involvement as a risk factor for the development of histological transformation into aggressive B-NHL.[13,14] Thus, poor-risk factors were more common in patients with atypical growth patterns than in patients with typical growth patterns. This impression is supported by the tendency towards a higher rate of positive PET-2 results among patients with atypical growth patterns observed in the present analysis.

Although patients with atypical growth patterns more often presented with poor-risk factors, the present analysis indicated no evidence for differences in terms of five-year PFS and OS between individuals with atypical growth patterns and patients with typical growth patterns. Hence, adverse factors appear to be diminished by treatment with PET-2-guided escalated BEACOPP.

The present analysis has limitations. Though it is one of the largest studies on histopathological growth patterns in NLPHL, the results have to be interpreted with caution since the overall number of individuals taken into account is still low. This limitation is mainly due to the rarity of NLPHL.

In summary, the present analysis demonstrated that patients with advanced NLPHL often present with atypical growth patterns. Poor-risk factors are more frequently observed in patients with atypical growth patterns than in patients with typical growth patterns. However, first-line treatment with PET-2-guided escalated BEACOPP appears to compensate the previously described adverse prognostic impact of atypical growth patterns. Analyses evaluating the prognostic impact of the histopathological growth pattern in patients with advanced NLPHL treated with other common protocols such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, prednisone) and (R)-ABVD (rituximab, doxorubicin, bleomycin, vinblastine, dacarbazine) are pending until now.

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Author contributions

DAE, IB, SK, HG, MF, BvT, AR, WK, MLH, PM, HWB, ACF, AE, PB and SH provided study material or patients. DAE, IB, HG and SH analyzed data. DAE, IB, HG and SH wrote the paper. All authors approved the final manuscript.

Conflicts of interest

BvT reports grants, personal fees and non-financial support from MSD, Takeda and Novartis; personal fees and non-financial support from BMS; personal fees from Amgen, Pfizer, Gilead Sciences, and Roche. All other authors declare no potential conflicts of interest.

Supporting Information

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

Fig S1. Chart displaying the patients from the HD18 study that were excluded and ultimately included in the present analysis respectively. HL, Hodgkin lymphoma; ITT, intention-to-treat; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma.

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