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Relationship of Histological Subtypes to Prognosis in Early Stage Hodgkin's Disease: A Review of 312 Cases in a Controlled Clinical Trial

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Abstract—*To assess the prognostic significance of a newer histologic classification of Hodgkin's disease (HD), microscope slides from the time of diagnosis of* 312 *clinical stage IA or B, IIA or B and IIIA patients were reviewed in* 1987, 6–10 *years after their participation in a radiochemotherapeutic trial* (1976–1982).

Overall, the diagnostic reproducibility of the Rye classification by the same pathologist was confirmed. However, a new analysis showed an improvement in the differential diagnosis between HD and non-Hodgkin's lymphomas (NHL) by the identification of 24 *NHL* (8%) *amongst the patients originally diagnosed as HD. Most of the NHL identified on review had been classified originally as mixed cellularity.*

On review, none of the new histological subtypes of HD was significant for prognosis of relapse-free survival or overall survival. Only identification of NHL was shown to have an independent prognostic value on relapse rate (P = 0.012) *and on overall survival* (P = 0.10). *It is concluded that diagnosis of HD by itself remains, in* 1988, *the sole histologic factor influencing the prognosis of these patients.*

INTRODUCTION

THE HISTOLOGICAL DIAGNOSIS of Hodgkin's disease (HD) has been emphasized over the last 10 years. The separation of new subtypes, such as nodular paragranuloma [1], the 'syncitial variant' of nodular sclerosing HD [2] and the interfollicular form [3] and the improvement of the differential diagnosis between HD and non-Hodgkin's lymphomas (NHL), particularly peripheral T-cell lymphomas [4] and large cell anaplastic lymphomas [5], have all received much attention.

To assess the input of these new entities, and their prognostic value on relapse and survival, the histologic material of patients participating in a clinical trial between 1976 and 1982 was systematically reviewed.

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PATIENTS AND METHODS

Patients

From 1976 to 1982, 335 patients with previously untreated clinical stage IA or B, IIA or B and IIIA HD were enrolled in a clinical trial conducted by the Pierre et Marie Curie Group [6]. After clinical and radiological staging, the patients were given three cycles of MOPP (mechlorethamine hydrochloride, vincristine, procarbazine and prednisone). Subsequent treatment was then randomized

between limited or extended field radiation therapy. Individuals with poor prognostic features (age >40 years, or mixed cellularity or lymphocytic depletion histologic types, or stage II without mediastinal involvement, or presence of B symptoms) [7] or stage III were given three additional cycles of MOPP following radiation therapy.

The initial histological material could not be located for 23 patients, and therefore the study population consisted of 312 patients. Their initial characteristics are given in Table 1.

Pathological review

Originally, diagnoses were first determined by each participating centre and then reviewed independently by three haematopathologists (GC, JD and PPSM) on morphological grounds (haematoxylin–eosin and Giemsa stains), according to the Rye modification of the Lukes and Butler classification [8]. By consensus of the three reviewing pathologists, a diagnosis was established. The 1987 review diagnoses were performed by one pathologist (JD) according to a nomenclature [9] based on the Lukes–Rye classification and his own criteria of subclassification. The latter primarily recognizes the following subtypes within the nodular sclerosing type: cellular phase; lymphocytic predominance in the intra-nodular population without eosinophils (subtype 1); intra-nodular mixed cellularity (subtype 3); intra-nodular lymphocyte depletion with either heavy fibrosis (subtype 4F) or a high number of tumour cells (subtype 4S). The latter subtype has recently been called the 'syncitial variant' by Strickler *et al.* [2]. JD's subclassification also integrates the nodular paragranuloma, according to the definition given by Poppema *et al.* [1], into the lymphocytic predominance type, which are included in the mixed cellularity type an interfollicular form according to Doggett *et al.* [3], and a subtype with a high number of lymphocytes according to Lennert and Mohri [10].

Table 1. *Initial characteristics of the* 312 *patients included in the study*

Age in years, mean (S.D.)	32.9 (12.3)
15–19	11%
20–29	36%
30–39	29%
40–49	13%
50–70	11%
Sex M/F	188/124
B symptoms	22%
Sedimentation rate mm	
1st hour, mean (S.D.)	38.7 (34.3)
Clinical stage I	31%
II	61%
III	8%
Mediastinal involvement	54%
Stage E+	6%
Histological type:	
Lymphocytic predominance	5%
Nodular sclerosis	52%
Mixed cellularity	40
Lymphocytic depletion	—
Unclassified	3%
Treatment modalities:	
3 MOPP—IF RT	13%
3 MOPP—STNI	14%
3 MOPP—IF RT—3 MOPP	38%
3 MOPP—STNI—3 MOPP	36%
Mean follow-up in	
months (S.D.)	74 (25)
range	6–120

IF RT: involved fields radiotherapy; STNI: subtotal nodal irradiation (w/o spleen RT).

The NHL were classified according to the expanded form of the Kiel classification based on the results of Suchi *et al.* [4]. No immunochemistry was performed.

Statistical methods

The kappa statistic [11] was used in comparisons of diagnoses.

The patients' initial characteristics, treatment and follow-up data were prospectively recorded. Time at risk was defined as time elapsed between date of first cycle of chemotherapy and date of first relapse or date of last known vital status or 1 July 1987, whichever came first.

Disease-free survival and overall survival were computed using the Kaplan–Meier method.

The Cox proportional hazards model [12] was used to assess the independent prognostic value of the factors tested on both relapse-free and overall survival, with adjustment for age, sex, number of involved lymph nodes areas, mediastinal involvement, presence of B symptoms, sedimentation rate and stratification of treatment type. Data were stored and analysed at the Medical Statistics Department of the Institut Gustave-Roussy. Analysis was performed using a specific database management system [13] and the BMDP statistical software [14].

RESULTS

A concurrence of 97% had been observed for the histology between JD's and the original consensus diagnosis using the Rye classification; therefore, the original diagnosis was used in the analysis. In the present study, a concurrence of 88% was observed between the original and review diagnosis (Table 2). Here, 24 patients originally diagnosed as HD [19 mixed cellularity (MC) type] were on review rediagnosed as NHL. No cases of lymphocyte-depleted (LD) type were observed in this series, either originally or upon review.

Discrepancies observed between original and

Table 2. Agreement between original and review diagnosis according to Rye classification

	Original diagnosis HD (consensus)				Total
	LP	NS	MC	Unclassified	
Review diagnosis HD					
Lymphocytic predominance (LP)	13	2	—	—	15
Nodular sclerosis (NS)	4	158	6	—	168
Mixed cellularity (MC)	—	—	99	—	99
Unclassified	—	—	1	5	6
Non-Hodgkin lymphoma	—	2	19	3	24
Total	17	162	125	8	312

Accuracy = (13 + 158 + 99 + 5)/312 = 88%.
Weighted kappa: 0.82, $P < 0.001$.

review diagnosis are given in Table 3. These 37 cases included two nodular paragranulomas initially classified in the nodular sclerosis (NS) type; four and six cases of NS respectively originally listed in the lymphocytic predominance (LP) and the MC groups; one case in the newly described unclassified HD and 24 NHL. Moreover, 20 cases displayed concomitant aspects of NS and interfollicular forms. Among the NHL, 12 peripheral T-cell lymphomas (two of angioimmunoblastic type; 10 of pleomorphic, medium and large cell type); 10 large cell anaplastic lymphomas; one case with concomitant aspects of NS and large cell anaplastic lymphoma; and one mediastinal clear cell lymphoma were recognized (Table 4).

The initial characteristics of the 24 patients diagnosed with NHL were not statistically different from those of the remaining 288 HD patients on review (i.e. age, sex, B symptoms, sedimentation rate, mediastinal involvement) except for clinical stage (NHL patients being more often stage III) and Rye classification of MC (P values: 0.001 and <0.001, respectively). Twelve of the 14 patients whose disease progressed during treatment (one patient) or who relapsed (13 patients) underwent a second biopsy, upon which the diagnosis of NHL was made.

Overall, NHL patients had a poor prognosis with a 5-year disease-free survival equal to 50% (S.D. 10%) and an 8-year survival equal to 71% (S.D. 9%) compared to 89% (S.D. 2%) and 90% (S.D.

Table 3. Distribution of histological subtypes (1987 review) according to original Rye classification

	Original diagnosis (consensus)			
	LP	NS	MC	Unclassified
Review diagnosis HD				
Lymphocytic predominance type (LP)				
common type	7			
nodular paragranuloma	6	2		
Nodular sclerosis type (NS)				
cellular phase	4			
subtype 1		1		
subtype 3		82	3	
subtype 4S		64	3	
NS subtype 3 *and* MC interfollicular		11	9	
Mixed cellularity type (MC)				
common type			52	
with a large proportion of lymphocytes			8	
interfollicular			29	
with a large proportion of epithelioid cells			1	
Unclassified			1	5
Non-Hodgkin lymphoma		2	19	3

Table 4. Characteristics of the 24 patients diagnosed as non-Hodgkin lymphoma on review

Case No.	Sex/Age	Stage	Med. involv.	Review diag.	Initial treatment	Clinical outcome
1	M/18	IIIA,E+	+	T-c	6M-IF	Relapse (33 mo), alive (113 mo)
2	M/30	IIA	−	T-c	6M-STNI	Relapse (40 mo), alive (88 mo)
3	M/31	IIIA	+	T-c	6M-IF	Relapse (36 mo), alive (59 mo)
4	M/46	IIA	−	T-c	6M-IF	Relapse (5 mo), deceased
5	M/29	IA	−	T-c	6M-STNI	CR alive (73 mo)
6	M/42	IIB	+	T-c	6M-IF	Relapse (18 mo), deceased from NHL (46 mo)
7	M/31	IA	−	T-c	6M-STNI	CR alive (70 mo)
8	F/30	IIA	−	T-c	6M-IF	Relapse (9 mo), alive (70 mo)
9	F/53	IIIA	−	T-c	6M-IF	Relapse (14 mo), alive (110 mo)
10	M/46	IIIA	−	T-c	6M-IF	Relapse (38 mo), alive (110 mo)
11	M/25	IIIA	−	T-c	6M-STNI	Relapse (56 mo), deceased
12	F/57	IIA	−	T-c	6M-IF	Relapse (46 mo), deccreased
13	F/39	IIA	+	LCA	3M-IF	CR alive (100 mo)
14	M/33	IIA	+	LCA	6M-STNI	CR alive (87 mo)
15	M/19	IIA	−	LCA	6M-STNI	CR alive (69 mo)
16	M/27	IIB,E+	+	LCA	6M-IF	Relapse (9 mo), deceased
17	M/31	IIA	+	LCA	6M-IF	Relapse (16 mo), alive (89 mo)
18	F/34	IIA,E+	+	LCA	6M-STNI	Relapse (9 mo), deceased
19	F/22	IIIA	−	LCA	6M-STNI	CR alive (85 mo)
20	F/37	IIA	−	LCA	6M-IF	CR alive (84 mo)
21	M/36	IIB	+	LCA	6M-IF	CR alive (76 mo)
22	M/43	IIIA	−	LCA	6M-IF	CR alive (62 mo)
23	M/24	IIB	+	LCA	6M-IF	CR alive (78 mo)
24	F/22	IA	+	B-c	6M-STNI	Progression, deceased

T-c: T-cell lymphoma (cases 6 and 8: angioimmunoblastic type lymphoma); LCA: large cell anaplastic lymphoma (case 13: with concomitant NS aspect); B-c: mediastinal clear cell lymphoma of B cell type; 3M or 6M: three or six cycles of MOPP; IF: involved field RT; STNI: subtotal nodal RT (without spleen RT); CR: complete remission; in parentheses: time in months from therapy to relapse or last known vital status.

2%) for HD patients, respectively.

In the multivariate analysis the following pathological subgroups were considered (Table 3): LP type (15 patients), NS cellular phase + subtype 1 + subtype 3 (90 patients), NS subtype 4S (67 patients), mixed NS subtype 3 and MC interfollicular (20 patients), MC common type + high proportion of lymphocytes + high proportion of epithelioid cells (61 patients), MC interfollicular (29 patients), and NHL (24 patients).

After adjustment of initial clinical and biological features and treatment, none of the pathological subgroups displayed an independent prognostic value either on relapse-free survival or overall survival. Besides age and mediastinal involvement, only the 'NHL' parameter was demonstrated to significantly influence relapse-free survival ($P = 0.012$) (Table 5). For overall survival, age over 60 years [relative risk (RR) = 6.23, $P < 0.01$] and, to a lesser extent, NHL (RR = 4.52, $P = 0.10$) were found to be of prognostic value.

Histological material from relapse biopsy was available for 25 of the 46 relapse patients. In addition to the 12 patients diagnosed as having NHL on review (see above and Table 4), six patients were diagnosed as having NHL as a second neoplasm, one of peripheral T-cell lymphoma type and five of large cell anaplastic lymphoma type. Their characteristics and clinical outcome are given in Table 6. NHL occurred during initial treatment or at the end of initial treatment in two patients (cases 1 and 3), during the first year post therapy in three patients, and in one patient (case 6), 51 months after initial treatment was completed.

DISCUSSION

Since the introduction of the Rye classification [8], there has been much enthusiasm for its usefulness, and agreement rates among pathologists for the four main types have greatly improved [15]. The present study confirms the diagnostic reliability of the Rye classification even when reviewed 20 years later. The discrepancies in Table 3 are clear in 12 cases. Two cases, initially listed in the NS type, are now recognized as nodular paragranulomas thanks to a better understanding of the histological features of this new entity [1]. In another 10 cases, initially included in the LP or MC types, the presence of lacunar cells allowed for the diagnosis of NS, despite the lack of typical collagen bands. Twenty cases displayed concomitant aspects of NS and interfollicular patterns. Such cases reinforce the hypothesis that interfollicular HD may be closely related to the NS type—as a continuous spectrum of the disease—despite its inclusion into the MC group [3].

Table 5. *Cox regression: Results for a model allowing all the variables simultaneously (overall* P *value* <0.0001)

Variable	Relative risk of relapse	*P* value
Age		
15–29 years	1*	
30–39 years	1.98	
40–49 years	2.60	
50–70 years	3.74	<0.01†
Mediastinal involvement		
No	1	
Yes	2.64	0.04
NHL‡		
No	1	
Yes	6.25	0.01

*Reference category.
†Test for trend.
‡Non-Hodgkin lymphoma on review.
Other variables included in the model were sex, B symptoms, number of initial lymph node areas involved, erythrocyte sedimentation rate, and review pathological subgroups, with stratification on treatment modalities (see Table 1).

Eight per cent of the patients originally diagnosed as having HD were found to have NHL on review. This finding is consistent with Miller *et al.*'s study [16] which identified 14 NHL (8%) amongst 180. patients treated for advanced HD. In the present study, mixed cellularity HD was the most frequent subtype of HD confused with NHL. This is in contrast with Bennett *et al.* [17] who reported 9% (eight cases out of 85) of NHL after review of all the cases originally diagnosed as LP that were included in the trials conducted by the British National Lymphoma Investigation. In the same series, no cases of NHL were reported where histological material was originally classified as NS, MC or LD types [18]. Peripheral T-cell lymphoma, large cell anaplastic lymphoma, and mediastinal clear cell lymphoma of B-cell type have recently been described [4, 5, 19] and are known to exhibit pleomorphic features with heterogeneous cellular infiltrates and Reed–Sternberg-like cells. Their identification confirms the improvement of the differential diagnosis between 'true' HD and NHL.

Contrary to what has generally been published, five of the six NHL diagnosed on relapse biopsy material in patients for whom the original diagnosis of HD was confirmed were large cell anaplastic lymphomas and occurred a short time after HD diagnosis or completion of treatment. These cases are therefore probably not secondary to treatment. Our findings are also consistent with the existence of mixed forms, i.e. coexisting HD and NHL, or transitional forms, since one case (case 13, Table 4) displayed concomitant NS subtype 3 and large cell anaplastic lymphoma. It is therefore strongly recommended that systematic lymph node biopsy be performed for every patient who relapses. Moreover, three cases with synchronous HD and NHL were recently reported, demonstrating coexisting HD and NHL even apparently localized to various initial sites [20]. On the other hand, a sixth case of NHL which occurred 5 years after HD diagnosis in a 49-year-old male patient is more likely to be treatment related [21]. Therefore the 5-year incidence of NHL in the population study can be estimated to be at least 0.4% (S.D. 0.4%).

In the multivariate analysis of initial patient characteristics, review diagnoses and treatment, none of the histological NH subgroups had any prognostic influence either on relapse-free survival or overall survival. The basic [22] prognostic value of the Rye classification has been abolished by therapeutic improvements in early stages of HD. By contrast to a report of Hansmann *et al.* [23], neither relapse nor histologic progression were observed amongst the eight nodular paragranulomas, but our follow-up period is still too short to draw firm conclusions. The subclassification of the NS type has been questioned, particularly the prognostic influence of the numbers of tumour cells. Cases with large numbers of tumour cells have recently been reported as having a poor prognostic value [24]. We have not found this to be the case.

NHL histological diagnosis was associated with the worst outcome of any factor of HD. The high rate of relapses observed in that group of patients

Table 6. *Characteristics of the six patients who developed a non-Hodgkin lymphoma secondary to Hodgkin's disease*

Case No.	Sex/Age	Stage	Mediastinal involvement	Review diagnosis	Initial treatment	Clinical outcome
1	F/45	IIB	−	MC common type	6M-STNI	LCA (4 mo), alive with disease
2	F/38	IA,E+	+	NS subtype 3	3M-STNI	LCA (8 mo), deceased
3	F/19	IB	+	NS subtype 3	6M-IF	LCA (9 mo), deceased
4	F/22	IIIA	+	NS subtype 4S	6M-STNI	LCA (13 mo), deceased
5	M/47	IIB	−	MC common type	6M-IF	LCA (19 mo), deceased
6	M/49	IA	−	MC common type	6M-STNI	T-c (60 mo), alive in CR

T-c: T-cell lymphoma; LCA: large cell anaplastic lymphoma; 3M or 6M: three or six cycles of MOPP; IF: involved fields RT; STNI: subtotal nodal RT without spleen RT; CR: complete remission; in parentheses: time in months from therapy to NHL occurrence.

(14 out of 24) is understandable since a combination of MOPP and radiation therapy is not the appropriate treatment for high grade lymphomas. Despite this, the NHL survival rate was reasonable and possibly due to more effective salvage therapy, usually ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) and radiotherapy.

The present study highlights the main problems of early stage HD in 1988, i.e. the difficulties that the pathologist may experience in differentiating HD from the NHL, particularly large cell lymphomas containing heterogeneous cellular infiltrates and atypical Reed–Stenberg cells. This problem may be alleviated by immunohistologic methods.

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