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Application of quantifiable criteria in the Lukes and Collins classification of non-Hodgkin's lymphomas

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Summary. Measurements of nuclear size and differential counts among six lymphoma cell types were performed on H & E stained sections. In differential counting, the definition of cell types was based on nuclear shape, chromatin pattern, and nucleoli. In a pilot study comprising 93 patients we found actual nuclear size inadequate for use in lymphoma classification. This was due to: 1. great overlap among cytological types; 2. no independent prognostic value of mean nuclear area; 3. contradictory terminology; the large cleaved type belonging to the small cell category (mean nuclear area below 40 μm^2), and the small non-cleaved type belonging to the large cell category (mean nuclear area above 40 μm^2). Differential counting – requiring about 10 min – was an easy way to meet the need for a more objective evaluation of the cellular composition in non-Hodgkin's lymphomas. Quantifiable criteria based on differential counts were applicable in subclassification of three T-cell and seven B-cell types with an intra-observer reproducibility of 80%. More than 25% "large" cell types in a differential count implied an unfavourable prognosis. In test material, using a semi-morphometric classification, a correct prognostic category was obtained in 92% of 461 lymphomas and correct sub-classification obtained in 68%.

Key words: Differential counting – Lukes and Collins classification – Morphometry – Non-Hodgkin's lymphoma – Nuclear size

Introduction

The most widely used histological classifications of non-Hodgkin's lymphomas are those of Rappaport (Rappaport 1966), Kiel (Gerard-Marchant et al. 1974; Lennert 1978), Lukes and Collins (Lukes and Collins 1974), and the Working Formulation (The Non-Hodgkin's Lymphoma Pathologic Classification Project 1982). Changing nomenclature, variable diagnostic criteria, and problems in defining histological subgroups make recommendations for management of the patients on basis of histological type difficult (Rosenberg 1979). Futhermore, problems regarding inter-pathologist agreement and intra-pathologist reproducibility have made comparisons of different studies difficult, if not impossible (NCI Non-Hodgkin's Classification Project Writing Committee 1985).

The purpose of the present investigation was to propose simple quantifiable criteria for the definition of cytological types in the Lukes and Collins classification.

Material and methods

Histological slides were reviewed from 658 consecutively treated patients at the Department of Internal Medicine, The Finsen Institute, from 1970 to 1980. The clinical data and histological classification of the material has previously been described in detail (Ersbøll et al. 1985a). Excluded from the present study were 104 cases (16% of the total): Twenty-six cases were unclassifiable lymphomas (4%), lymphomas with morphology too poorly preserved for evaluation by quantifiable methods comprised 18 cases (3%), and miscellaneous histological types outside the scope of the present study made up a further 60 cases (9%). Pilot material comprising 93 patients was selected in order to establish quantifiable criteria for the different histological types. The 461 remaining patients constituted the test material for the comparison of the conventional and the semi-morphometric classification system.

Histological classification. Formalin fixed, paraffin embedded, haematoxylin and eosin stained lymphoma biopsies were classified according to the Lukes and Collins classification, see Table 1. In cases where further material was available, additional stains were carried out (Giemsa, methyl green pyronin, reticulin, PAS, PAP stains for kappa and lambda light chains, and

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Table 1. U-cell, T-cell, and B-cell types according to the Lukes and Collins classification. Related cytological terms in the Working Formulation and the Kiel classification

Lukes and Collins classification	Working formulation	Kiel classification
Undefined cell type	(No translation provided)	Lymphoblastic, unclassified[c]
T-cell types:		
Small lymphocytic	Small lymphocytic[a]	Lymphocytic, CLL type[a]
Convoluted lymphocytic	Lymphoblastic[c]	Lymphoblastic, convoluted type[c]
Immunoblastic sarcoma	Immunoblastic[c]	Immunoblastic[c]
B-cell types:		
Small lymphocytic	Small lymphocytic[a]	Lymphocytic, CLL type[a]
Plasmacytoid lymphocytic	Small lymphocytic, plasmacytoid[a]	Lymphoplasmacytoid[a]
Follicular center cell:		
small cleaved	Predominantly small cleaved cell[a]	Centroblastic/Centrocytic[a] or Centrocytic[a]
large cleaved	Mixed small and large cell,[a] or Large cell[b]	Centroblastic/Centrocytic[a] or Centrocytic[a]
small non-cleaved	Small non-cleaved[c]	Lymphoblastic, Burkitt type[c]
large non-cleaved	Large cell[b]	Centroblastic/Centrocytic (large),[a] or Centroblastic[c]
Immunoblastic sarcoma	Immunoblastic[c]	Immunoblastic[c]

[a] Low grade malignant
[b] Intermediate grade malignant
[c] High grade malignant

for lysozyme). Because of the retrospective nature of the study, immunological marker analysis of unfixed tissue was not possible. The classification of lymphomas into the U-cell, T-cell and B-cell categories was based on the cyto-morphological features decribed by Lukes and Collins (1974; Lukes et al. 1978).

In the pilot material differential counts and measurements of nuclear size were performed on microphotographs. A single area in each lymphoma was selected according to criteria described earlier (Schultz 1982); these comprised uniform lymphoma proliferations in diffuse lymphomas and central part of nodules in follicular lymphomas. The selected area of the lymphoma was photographed in a Zeiss Photomicroscope II with a 40/1.0 Plan apo Oil objective on Kodachrome 64 diapositive film. Each photographed area measured $140 \times 210\ \mu m^2$ and contained on average 293 cells. The Kodachrome slides were magnified to 14×21 cm corresponding to a final magnification of $1000\times$.

In the reproducibility test of the pilot material and in the test material only 100 cells were counted. In the test material differential counts were performed directly during microscopy. A differential count took less than 10 min.

Classification of cells by differential counting. In conventional histological classifications, cellular morphology is evaluated in order to gain a general view. In differential counts all cells are classified in the histological section regardless of whether the nuclear profiles are "typical" or not and regardless of possible tangentially cut nuclei. It was therefore necessary to introduce the round medium-sized cell and more practical to classify both the smallest and the largest "cleaved cells" as belonging to one medium-sized type. In lymphoma classification, there has been a strong tradition to designate cells according to their size. The cellular size was included in the differential counting terminology, but the definition of cell types was based on nuclear shape, chromatin pattern, and nucleolar features.

One small cell type was recognized; the small lymphocyte which had the following characterstics. The nucleus is round or oval. The largest diameter is less than $1\ ^1/_2$ times the narrowest diameter. The chromatin is pyknotic without visible nucleoli. The cytoplasm is sparse and faintly stained.

Two "medium-sized" cell types were recognized; they were the round medium-sized lymphocyte which has a round or oval nucleus without indentations. The chromatin is coarse and lighter than that of the small lymphocyte. Small basophilic or amphophilic nucleoli may be present. The cytoplasm is sparse and faintly stained; and the cleaved medium-sized lymphocyte. Here, the nucleus is indented or the largest diameter is at least $1\ ^1/_2$ times the narrowest. The chromatin is pycnotic or coarse. The cytoplasm is sparse and faintly stained.

Three "large" cell types were recognized: the lymphoblast with a nucleus which is round or convoluted. The chromatin is fine. One or several small, but distinct nucleoli may be seen. The cytoplasm is usually sparse. The group includes the round triple-nucleolated cell which has a nucleus without indentations, with three or more nucleoli the largest of which has a diameter of at least 2 μm. The cytoplasm is usually deeply basophilic. Finally the pleomorphic large cell has a nucleus which is variable in shape. A large eosinophilic nucleolus with a minimal diameter of 2 μm is present. The cytoplasm is variable in amount and staining.

The number of plasmacytoid cells, cerebriform cells, and histiocytes were also noted in differential counts, but the percentages of these cell types were not used in the semimorphometric classification. We have earlier described the method of differential counting, the intra-observer reproducibility, and the intra-lymphoma variation in detail (Schultz 1982).

All cells in the microphotographs were classified in classes with 1 μm intervals of their diameter. We used a simple visual method with circular and ellipsoid targets similar to an ocular grid. The transparent targets were placed over the cells to be classified. The classification of 100 cells took less than 2 min. A correction for tangentially cut spherical objects was carried out as described by Ito and Abe (1976), and the mean nuclear area calculated. The intra-observer reproducibility of the meth-

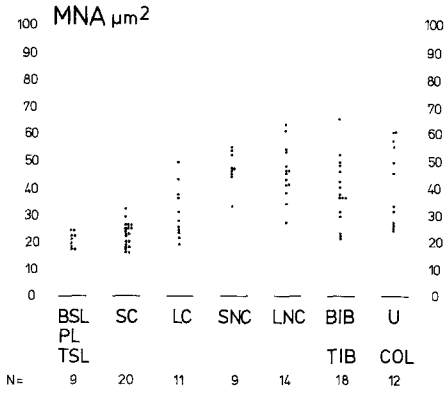

Fig. 1. Mean nuclear area (MNA) in 93 lymphomas classified according to the Lukes and Collins classification. BSL = B small lymphocytic; PL = Plasmacytoid lymphocytic; TSL = T small lymphocytic; SC = Small cleaved cell; LC = Large cleaved cell; SNC = Small non-cleaved cell; LNC = Large non-cleaved cell; BIB = B immunoblastic sarcoma; TIB = T immunoblastic sarcoma; U = Undefined cell type; COL = Convoluted lymphocytic

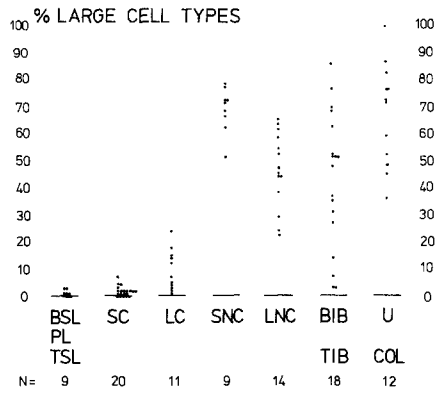

Fig. 2. Percentages of large cell types in 93 lymphomas classified according to the Lukes and Collins classification. BSL = B small lymphocytic; PL = Plasmacytoid lymphocytic; TSL = T small lymphocytic; SC = Small cleaved cell; LC = Large cleaved cell; SNC = Small non-cleaved cell; LNC = Large non-cleaved cell; BIB = B immunoblastic sarcoma; TIB = T immunoblastic sarcoma; U = Undefined cell type; COL = Convoluted lymphocytic

od was high with a correlation coefficient of 0.99 for ten cases examined twice.

The prognostic significance of differential counts and measurements of nuclear areas was studied in the pilot material. Patients with the prognostically favourable intrafollicular pattern (lymphoma cells confined to follicles) and infiltrative follicular pattern (lymphoma cells present in interfollicular tissue, but follicularity preserved throughout the lymphoma) were considered separately (Schultz et al. 1985). The survival was measured in days from diagnosis to death or to the last follow-up before March 1, 1983. Life tables were made according to the method of Kaplan and Meier (1958). Differences in survival were evaluated by log rank tests (Peto et al. 1977).

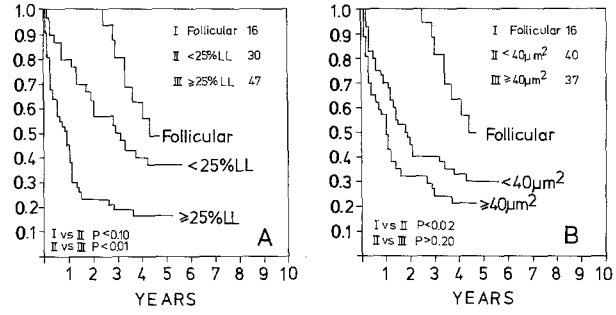

Fig. 3. Survival in 93 patients with non-Hodgkin's lymphomas classified according to **A** Percentages of "large" cell types in differential counts (%*LL*), and **B** Mean nuclear area (μm^2). The group of patients designated "Follicular" had the prognostically favourable intra-follicular and infiltrative follicular patterns. All these lymphomas had less than 25% "large" cell types in differential counts, and mean nuclear areas below 40 μm^2

Results

The nuclear size plays an important role in the nomenclature of the Lukes and Collins classification. A large cellular size generally indicates an aggressive behaviour. In the pilot material, comprising 93 lymphomas, we found a correlation between mean nuclear area (MNA) and different histologic sub-types (Fig. 1). Two broad categories could be distinguished: 1) TSL, BSL, PL, SC, and LC lymphomas with a MNA below 40 μm^2, and 2) SNC and LNC lymphomas with a MNA above 40 μm^2. A large range of sizes, from 20 μm^2 to above 60 μm^2, was found in BIB, TIB, U and COL lymphomas.

The percentages of "large" cell types in differential counts also correlated to the different subtypes (Fig. 2). Less than 25% was found in TSL, BSL, PL, SC, and LC lymphomas. All U, COL, and SNC; and most LNC and BIB lymphomas contained more than 25% large cell types. The deffinition of the "small", "medium-sized", and "large" cell type was not based on nuclear size, but on chromatin pattern, nuclear shape, and nucleolar features (see Material and methods). However, in most lymphomas small lymphocytes had a MNA below 20 μm^2, medium-sized lymphocytes 20–40 μm^2, and large cells above 40 μm^2.

The prognostic significance of the number of "large" cell types present in differential counts and the mean nuclear area is shown in Fig. 3. More than 25% "large" cells implied an unfavourable prognosis ($P < 0.01$). A mean nuclear size below or above 40 μm^2 had no significant prognostic implication ($P > 0.20$).

The cell types used in differential counts were not specific with regard to immunological lymphoma type. In the pilot material the differential counts indicated a specific immunological type in

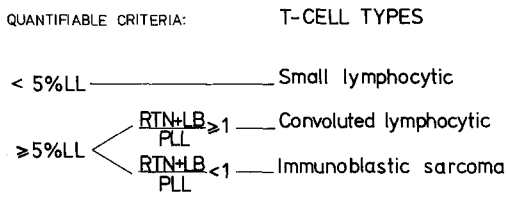

Fig. 4. Quantifiable criteria for T-cell sub-types in the semi-morphometric Lukes and Collins classification. LL = Large cell types; LB = Lymphoblasts; RTN = Round triple-nucleolated cells; PLL = Pleomorphic large cells

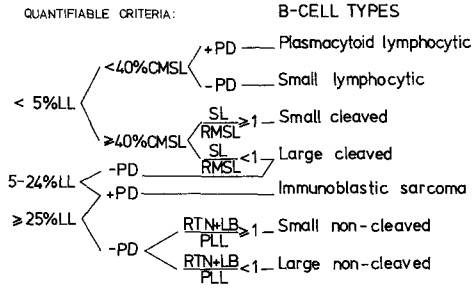

Fig. 5. Quantifiable criteria for B-cell sub-types in the semi-morphometric Lukes and Collins classification. LL = Large cell types; PD = Plasmacytoid differentiation; SL = Small lymphocytes; RMSL = Round medium-sized lymphocytes; CMSL = Cleaved medium-sized lymphocytes; LB = Lymphoblasts; RTN = Round triple-nucleolated cells; PLL = Pleomorphic large cells

only a few situations: 1) more than 2% plasmacytoid cells were found solely in PL and BIB corresponding to a B-cell origin; and 2) more than 40% cleaved medium-sized cells were found solely in SC and LC follicular center cell lymphomas also of B-cell origin.

From the data in the pilot material, quantifiable criteria for a semi-morphometric classification into T-cell and B-cell categories were proposed (Figs. 4 and 5). The following four variables were used in the classification: the percentages of large cell types divided into three categories 0–4%, 5–24% and 25–100%, the percentages of the cleaved medium-sized cell type in two categories 0–39% and 40–100%. More than 40% was found in the majority of SC and LC lymphomas. The lymphomas of the other cytological types contained less than 40% of the cells. The ratios between specific cell types were examined and that between small lymphocyte/round medium-sized lymphocyte was characteristically above 1/1 in SC and below 1/1 in LC. The ratio (round triple-nucleolated cells plus lymphoblasts)/(pleomorphic large cells) was characteristically above 1/1 in SNC and below 1/1 in LNC lymphomas. Finally plasmacytoid differentiation separated PL from SL, and BIB from LNC.

Table 2. 58 T-cell type lymphomas classified according to the Lukes and Collins classification. Correlation between the conventional and the semi-morphometric classification

Conventional classification		Semi-morphometric classification			Total
		TSL	COL	TIB	
Small lymphocytic	TSL	12			12
Convoluted lymphocytic	COL		22		22
Immunoblastic sarcoma	TIB	2	6	16	24
Total		14	28	16	58

The reproducibility of the semi-morphometric classification was 100% for the T-cell and 78% for the B-cell lymphomas when examined twice.

The translational value of the semi-morphometric classification in relation to the conventional classification was tested on 461 lymphomas (Tables 2 and 3). A correct prognostic category – "low grade malignant" versus "high grade malignant" – was found in 92% of the cases (35/35 U-cell, 56/58 of T-cell, and 335/368 of B-cell lymphomas). A correct subclassification into three T-cell and seven B-cell types was obtained in 68% of the cases (50/58 T-cell and 238/368 B-cell lymphomas).

Discussion

A major problem in the classification of non-Hodgkin's lymphomas has been low reproducibility. In a study with experienced haematopathologists, the intra-pathologist reproducibility varied from 55% to 93% (NCI Non-Hodgkin's Classification Project Writing Committee 1985). Morphometric methods have proved useful in the cytological characterization of cellular compositions (Crocker and Curran 1979; Meijer et al. 1980; van der Loo 1980; Abbott et al. 1982; Crocker et al. 1982; van der Valk 1982; Dardick et al. 1983; Tosi et al. 1983; van der Valk 1983; Dardick et al. 1984; Donhuijsen et al. 1984; Lessana-Leibowitch et al. 1984; Tosi et al. 1984; van der Valk et al. 1984; Zardawi et al. 1984; Ball et al. 1985; Dardick et al. 1985). These methods require special laboratory facilities and are rather time consuming. They are thus less suitable in daily routine situations. In the sub-classification of follicular lymphomas actual counting of the relative number of large cells in twenty high power fields per lymphoma has been employed by Berard (Mann and Berard 1983). Using this method, Nathwani et al. (1986) concluded that actual counting of cells was probably superior to subjective evaluation of cellular composition,

Table 3. 368 B-cell type lymphomas classified according to the Lukes & Collins classification. Correlation between the conventional and the semi-morphometric classification

Conventional classification		Semi-morphometric classification							Total
		BSL	PL	SC	LC	SNC	LNC	BIB	
Small lymphocytic	BSL	9		1	1			1	12
Plasmacytoid lymphocytic	PL	1	16	1				5	23
Small cleaved	SC	17	3	59	22				101
Large cleaved	LC	1	2	9	38	2	7	10	69
Small non-cleaved	SNC					8	8	3	19
Large non-cleaved	LNC			1	6	14	30	9	60
Immunoblastic sarcoma	BIB		2			1	3	78	84
Total		28	23	71	67	25	48	106	368

but that more objective and reproducible methods were needed for the separation of patients into favourable and unfavourable groups.

In the present study, we applied two semi-morphometric methods in histological classification designed for daily diagnostic use; the classification of cells by nuclear size, and differential counting. The former method would require a special ocular grid, but the latter only required 100 cells to be counted in a single representative high power field (Schultz 1982).

The Lukes and Collins classification of non-Hodgkin's lymphomas is based on the morphological recognition of the T- and B-cell systems and the phenomenon of lymphocyte transformation. This is a process whereby small, dormant lymphocytes transform to large, dividing cells (Lukes and Collins 1974). According to the immunological scheme, the major categories are termed undefined, T-cell, and B-cell types. In the Kiel classification and Working Formulation, the major categories are termed according to prognostic characteristics.

In the Lukes and Collins classification, the small cell types (TSL, BSL, PL, SC, and LC) represent low grade malignant lymphomas and the large cell types (COL, TIB, SNC, LNC, and BIB) high grade malignant lymphomas (see Table 1). There are several important contradictions in the Lukes and Collins terminology: firstly LC belongs to the low grade malignant, small cell category with MNA below 40 μm^2 (see Figs. 1 and 2); secondly SNC belongs to the high grade malignant, large cell category with MNA above 40 μm^2. COL designates lymphomas of high grade malignancy. The term lympho-cytic is in contrast to the corresponding term lympho-blastic in the other classifications. The cytology and clinical behaviour of this lymphoma type is totally different from the other lymphocytic lymphomas (Nathwani et al. 1976; Come et al. 1980; Ersbøll et al. 1985b). The definition of cell types used in this study and the definition of cytological categories provided in Figs. 4 and 5 should minimize the confusion.

With regard to prognostic significance, differential counting is superior to measurements of nuclear size (Fig. 3). This conclusion is in agreement with two other studies, one which failed to detect any independent value of nuclear volume (Hauser et al. 1986), the other demonstrating prognostic significance of actual counting of "large cells" (Nathwani et al. 1986). The application of quantifiable criteria based on differential counts was valuable in the definition of prognostically significant cytologic types: In the test material more than 90% of lymphomas were classified in the correct prognostical category.

The description of histological types in the Lukes and Collins classification is based on H & E stained sections (Lukes and Collins 1974). According to Lukes, the T- and B-cell types, for the most part, can be effectively identified by an experienced haematopathologists (Lukes et al. 1982; The Non-Hodgkin's Lymphoma Pathologic Classification Project 1982). In the Kiel classification, special emphasis is placed on cytological features in the Giemsa stain (Lennert 1978). We found both stains equally valuable in histological classification, and the cytomorphological criteria easily applicable in the majority of cases. However, several immunohistological studies have not been in concurrence with the assumption that lymphomas may be classified immunologically by cytological criteria alone. This is especially true for the large cell lymphomas (Bloomfield et al. 1979; Jaffe et al. 1982; Schneider et al. 1985; Weiss et al. 1985). We did not attempt to define specific T- and B-cell types for differential counting. Apart from cases with follicular architecture or unequivocal plasma-

cytoid differentiation indicative of a B-cell nature, this distinction should optimally be based on functional marker analysis.

The quantifiable criteria for the differentation between the three T-cell types were simple (Fig. 4), and the reproducibility was high. In the test material a correct diagnosis was obtained in 86%, and in all cases of the clinically important COL lymphomas.

The quantifiable criteria for the seven B-cell types were rather complicated regarding the definition of the follicular center cell lymphomas (see Fig. 5). Two cleaved cell types are distinguished in the Lukes and Collins classification: SC and LC. Only one cleaved cell type was recognized in differential counts. The smallest cleaved cells have pycnotic chromatin and the largest have coarse and light chromatin. In planes of section in which the cleavages are not apparent, these cells will be classified as small and round medium-sized lymphocytes respectively. In the semi-morphometric classification this cellular ratio represent a quantifiable measure of chromatin density, and together with the number of "large" cells distinguish SC from LC.

Two non-cleaved cell types are distinguished in the Lukes and Collins classification: SNC and LNC. In the SNC type, compared to the LNC type, the nuclei are more regular, chromatin more finely dispersed, and nucleoli smaller and more numerous (Lukes 1978). We found no differences in nuclear size between the SNC and LNC lymphomas, but the features mentioned resulted in the high ratio (round triple-nucleolated cells plus lymphoblasts)/(pleomorphic large cells) found in SNC lymphomas. In the terminology of the Working Formulation and the Kiel classification, the presence of a mixture of cell types is emphasized (see Table 1). The results of the present study favour this principle.

In the semi-morphometric classification, the intra-observer reproducibility of the seven B-cell types was 78%, and the correlation between the two classification systems 65%. These figures are high compared to an intra-observer consistency between conventional classification and Berard's counting principle of 43–70% among three types of follicular lymphomas in a collaborative study with experienced haematopathologists (Metter et al. 1985).

Our conclusion is that differential counting of an H & E stained histological section – requiring about 10 minutes – is an easy way to meet the need for a more objective evaluation of the cellular composition in non-Hodgkin's lymphomas. Clinico-pathological studies based on quantifiable morphology is needed in order to further simplify clinically relevant sub-classification and, consequently, terminology.

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