Non-Hodgkin's Lymphomas

Analysis of 109 Japanese Cases With the Use of LSGJ Classification

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Recently the Lymphoma Study Group of Japan (LSGJ) proposed a new classification of non-Hodgkin's lymphomas (NHLs), dividing NHLs into the follicular group consisting of three subsets and the diffuse group, 7. Each subset of the diffuse group is further divided into B or T cell types according to immunologic markers and/or morphologic prediction. In the review of 118 malignant lymphomas, the authors studied the 109 cases of NHLs, attempting to assess the clinicopathologic utility of this classification. Morphologic criteria, enzyme histochemistry, and immunoperoxidase technique were used to ensure the accuracy of the immunologic phenotyping. The results suggest that the LSGJ classification is easily reproducible and yields a more precise clinicopathologic correlation than traditional, morphologic classifications. Consistent with similar studies in Japan, this study demonstrated a low incidence of Hodgkin's disease (7.6% of all lymphomas) and follicular lymphomas (8.3% of all NHLs) and a high incidence of T cell lymphomas (34.9% of all NHLs). The incidence (45.9%) of extranodal presentation was high. These four features seem characteristic of lymphomas in Japan. (Am J Pathol 1982, 106:30–39)

AS A SOLUTION to the current international controversy over the classification of non-Hodgkin's lymphomas, the Lymphoma Study Group of Japan (LSGJ) recently proposed its own interim classification, which has four major features (Table 1).[1] First, the LSGJ separated follicular, lymphoblastic, and Burkitt lymphomas from the rest of non-Hodgkin's lymphomas because these were valid clinicopathologic entities deserving independent categories. Second, a new category of "pleomorphic type" was made in order to accommodate a particular adult T cell lymphoma presumably prevalent in Japan. Third, the remaining diffuse lymphomas were classified according to the size of the lymphoma cells, and debatable terms such as "histiocyte" or "poorly differentiated lymphocyte" were not used. Fourth, it was made obligatory to include the immunologic typing of individual lymphomas with a note whether the type was estimated by morphologic evaluation of conventional slides alone[2,3] or in combination with cell surface marker studies.

The purpose of this study was to apply the LSGJ classification to 109 non-Hodgkin's lymphomas seen at our institutions, to correlate immunologic phenotypes predicted morphologically with those determined by special studies, to compare results of our series with those of others in and outside of Japan, and to evaluate the utility of LSGJ classification in terms of clinicopathologic correlation.

Materials and Methods

Patients

All cases diagnosed as malignant lymphomas between April 1970 and October 1980 from the files of the Saitama Medical School, Nakano Koseikai, and

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Tokyo Saiseikai Chuo Hospitals were reviewed. After elimination of cases with unavailable blocks, poor histology, or inconsistent diagnoses, 122 cases were studied. Further elimination of 9 cases of Hodgkin's disease, 1 mycosis fungoides, and 3 lymphocytic leukemias (which had overt leukemic manifestations already at the time of lymph node biopsy) left 109 cases of non-Hodgkin's lymphomas, which served as the object of this study. Clinical records and laboratory data were reviewed, and follow-up information was obtained on each of these patients.

Histologic Study

The majority of biopsies were routinely fixed in buffered formalin and embedded in paraffin, while specimens from the most recent 15 patients were processed according to our method.[4] In this method, fresh biopsy specimens were fixed in formalin acetone, dehydrated in graded acetone containing 0.02% Triton X-100, and embedded in paraffin. All paraffin blocks were cut at 6 μ and stained with hematoxylin and eosin (H&E), periodic acid-Schiff (PAS), and reticulin.

Criteria for LSGJ Classification

Generally accepted criteria were applied to the diagnosis of follicular, lymphoblastic, and Burkitt lymphomas.[5] The remaining diffuse lymphomas were classified as *small cell type* when the sections showed a monotonous growth of small round lymphocytes, *medium cell type* when the predominant tumor cells had a nuclear size intermediate between that of small lymphocytes and macrophages (the medium cell of LSGJ includes the small cleaved cell of Lukes and Collins), *mixed type* when medium and large tumor cells coexisted and large cells occupied about 30 to 50% of the field, *large cell type* when the predominant tumor cells had nuclei larger than those of macrophages, and *pleomorphic type* when tumor cells varied greatly in size and shape and included a good number of multinucleate forms reminiscent of Reed-Sternberg cells.[1]

Criteria for Morphologic Prediction of Immunologic Phenotypes

As delineated by others,[2,3] B cell lymphomas were suspected because of cleaved nuclear configuration, distinct nucleoli located eccentrically along the nuclear membrane of large cells, plasmacytoid small and transformed large lymphocytes, and the low-power observation of vague nodularity. T cell lymphomas were suspected because of convoluted or cerebriform nuclei, more marked variation in the size and shape of tumor cells, prominence of post-capillary venules, occasional sparing of follicles due to a predilection for the paracortical zone, and a tendency to heterogeneous inflammatory cell infiltration. A non-T, non-B category was not instituted for two reasons. First, morphologic criteria had not been made available for identification of such lymphomas by Lukes and Collins or by subsequent authors.[2,3,5-7] Second, non-T, non-B lymphomas (judged as such because surface marker studies are negative) may not derive from null cells. Perhaps these tumor cells only fail to express their surface markers because of disordered differentiation.[8]

Enzyme Histochemistry

Standard incubation time was applied to sections from the 15 biopsies prepared according to our method[4]: 10 minutes for peroxidase, 21 hours for acid phosphatase (ACP), and 21 hours for alpha naphthyl acetate (ANAE) and alpha naphthyl butyrate esterases. Prolonged incubation time (up to 6 days by our modification[4] of Higuchi's method[9]) was used when ANAE and ACP reactions were applied to sections from the routinely processed blocks of the remaining 94 cases. Sections treated similarly, but with omission of appropriate substrates, served as controls for respective enzyme reactions.

PAP Immunoperoxidase Method

With an immunoperoxidase method using the unlabeled peroxidase-antiperoxidase (PAP) technique described by De Lellis et al,[10] paraffin sections cut at 4 μ were stained for cytoplasmic immunoglobulin and lysozyme. Rabbit antihuman globulins and lysozyme were purchased from the Accurate Chemical and Scientific Co., Hicksville, New York. Anti-human globulins included monovalent sera for IgG, IgM, IgA, and IgD heavy chains and kappa and lambda light chains. Antiserum dilutions were: 1:3000 for heavy chains, 1:6000 for light chains and lysozyme, and 1:50 for PAP complex. Clinical controls consisted of 28 bone marrow biopsy specimens demonstrative of multiple myeloma and 27 spleens demonstrative of hairy cell leukemia (HCL).

Technical controls were sections treated similarly, but with omission of the primary serum (anti-human globulin or lysozyme) or of the secondary serum (swine anti-rabbit immunoglobulin). When evaluating the results, test slides were compared with tech-

nical control slides, region by region, to ensure that cells were free of nonspecific staining in the region of the tissue block under scrutiny.

Reference to Other Series

In order to compare the prevalence of subsets of lymphomas between our series and others in and outside of Japan, we drew incidence figures from Lukes' 299 patients,[7] Frizzera's 60 patients,[2] Lennert's 2175 patients,[11] Rudders' 380 patients,[12] Freeman's 1467 patients,[13] Yamanaka's 44 patients,[14] Tajima's 111 patients,[3] Suchi's 110 patients,[1] and Yamashita's 532 patients.[15]

Results

Enzyme Histochemistry

Paranuclear ACP- or ANAE-positive globules characteristic of T cell nature were demonstrated not only in sections prepared according to our method but also in sections routinely formalin-fixed and paraffin-embedded (Figure 1). However, such positive results could be obtained in only about one-third of lymphomas with morphologic features of T cell-derivation. Enzyme histochemistry was also helpful in our recognizing the histiocytic nature of one diffuse large cell type lymphoma that showed intensive, diffuse ACP and ANAE reactions.

PAP Immunoperoxidase Method

Clinical Controls

All cases of multiple myeloma demonstrated the same monoclonal immunoglobulin as had been determined clinically by serum immunoelectrophoresis. In 26 of 27 spleens affected by HCL, although plasma cells stained in polyclonal fashion, hairy cells did not stain either monoclonally or polyclonally. In the one exception, there were clusters of immunoblasts with monoclonal staining suggestive of focal sarcomatous transformation.

Table 1—LSGJ Classification

I. Follicular lymphomas	II. Diffuse lymphomas
1. Medium-cell type	1. Small-cell type
2. Mixed type	2. Medium-cell type
3. Large-cell type	3. Mixed type
	4. Large-cell type
	5. Pleomorphic type
	6. Lymphoblastic type
	7. Burkitt type

Table 2—Demonstration of Cytoplasmic Monoclonal Immunoglobulin

Classification	No. patients examined	No. patients with monoclonality
B-cell lineage		
Follicular lymphomas		
Medium-cell	4	3
Mixed	4	3
Large-cell	1	1
Diffuse lymphomas		
Small-cell	5	3
Medium-cell	7	6
Mixed	11	8
Large-cell	37	23
Burkitt	1	1
Total	70	48
T-cell lineage		
Medium-cell	3	0
Mixed	14	0
Large-cell	6	0
Pleomorphic	6	0
Lymphoblastic	9	0
Total	38	0

Immunoglobulin Stain (Table 2)

Forty-eight cases demonstrated cytoplasmic monoclonal immunoglobulin characteristic of B cell derivation (Figure 2). We classified an additional 22 cases as B cell type, despite their failure to demonstrate monoclonal immunoglobulin, because they could not be distinguished morphologically from cases with positive monoclonal immunoglobulin, although it could not be excluded that some of them might in fact be of T cell or non-T, non-B type.

It is noteworthy that whereas 6 follicular lymphomas showed monoclonal immunoglobulin-positive cells confined primarily within the lymphoid follicles, as would be expected from the nature of follicular lymphomas, one case demonstrated a heavy concentration of such cells in the perifollicular zone (Figure 3). The same unexpected pattern was described by Taylor.[16]

Lysozyme Stain

The histiocytic origin of one of the diffuse, large-cell lymphomas was supported by demonstration of lysozyme in the cytoplasm of the tumor cells (Figure 4).

Clinicopathologic Findings of Individual Lymphomas (Table 3)

Follicular Lymphomas

There were 9 patients, 6 male and 3 female, whose average age was 64.6 years (range 32–82). Histo-

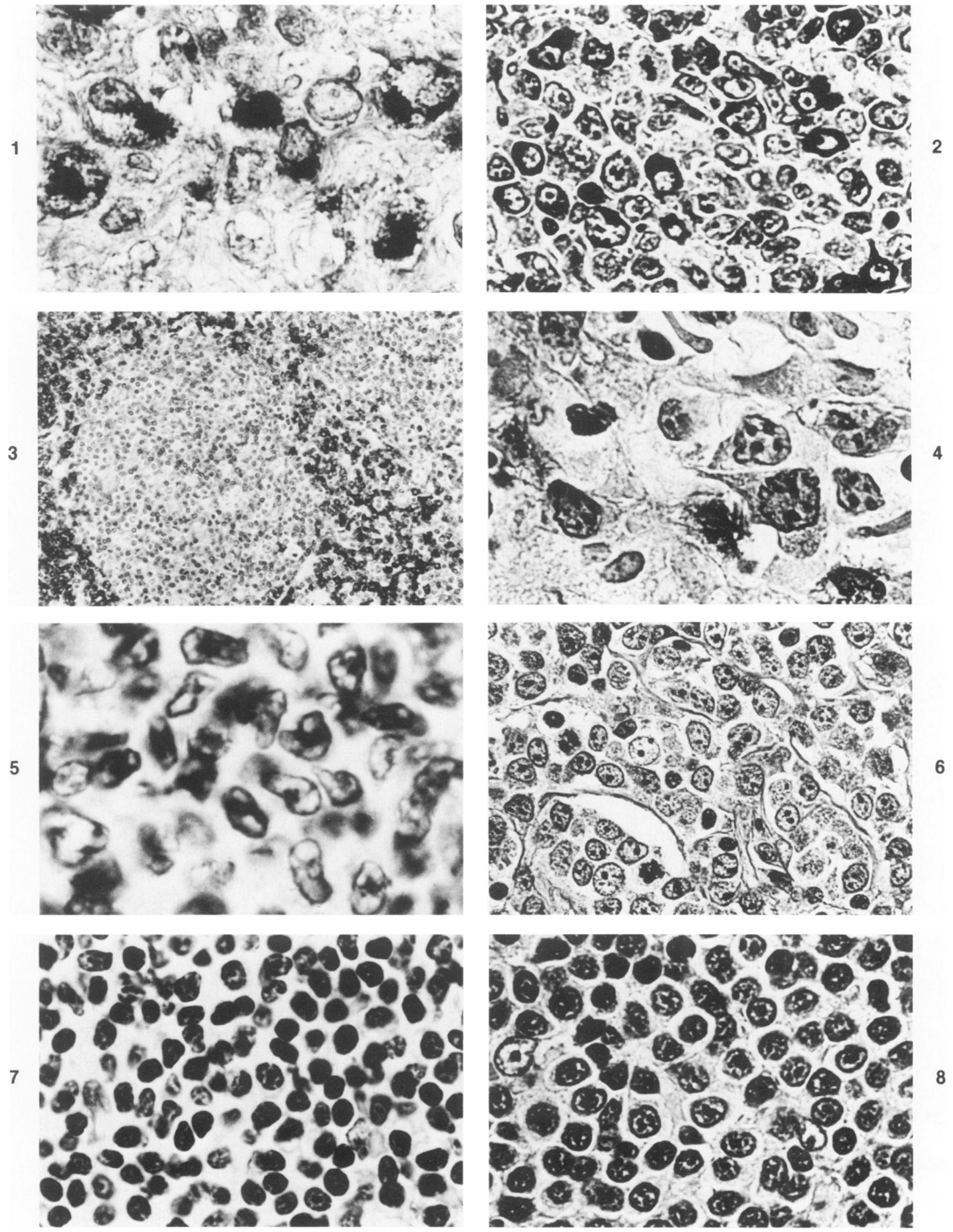

Figure 1—A positive ANAE reaction of a T cell lymphoma obtained after prolonged incubation for 6 days. Both this section and the H&E-stained section of Figure 13 were cut from the same block of tissue, routinely fixed in formalin and embedded in paraffin. (× 1500) **Figure 2**—A diffuse large-cell lymphoma demonstrates cytoplasmic monoclonal immunoglobulin, thus confirming its B cell origin. (PAP immunoperoxidase method, × 620) **Figure 3**—In this follicular lymphoma, monoclonal immunoglobulin-positive cells are concentrated in the interfollicular zone. (PAP immunoperoxidase method, × 80) **Figure 4**—A true histiocytic lymphoma showing positive lysozyme stain of the stretched, relatively abundant cytoplasm of tumor cells. (PAP immunoperoxidase method, × 1200) **Figure 5**—A follicular lymphoma, medium-cell type, showing numerous small cleaved cells. A large cell in the lower left corner shows nucleoli closely associated with the nuclear membrane. (H&E, × 1500) **Figure 6**—A follicular lymphoma, large-cell type, comprising predominantly large noncleaved cells. The fine compartmentalizing fibrosis is characteristic of "sclerosing reticulum cell sarcoma." (H&E, × 580) **Figure 7**—A diffuse lymphoma, small-cell type (B cell), showing a monotonous proliferation of small lymphocytes. Note the plasmacytoid differentiation of the cell in the center. (H&E, × 720) **Figure 8**—A diffuse lymphoma, medium-cell type (B cell), showing monomorphous growth of lymphocytes larger than small lymphocytes and smaller than macrophages. One macrophage is seen in the left center of the field. (H&E, × 780)

Table 3—Clinical Features of Patients With Non-Hodgkin's Lymphomas

Classification	Immunologic phenotype	No. patients (M/F)	Mean age (range)	Presentation					Stages		Constitutional symptoms		Survival (months)*		
				Nodal	Skin	GI	Waldeyer	Other	I, II	III, IV	–	+	Alive	Dead	Lost to follow-up
Follicular lymphomas															
Medium-cell	B	4 (3/1)	67.5 (54-75)	4	0	0	0	0	2	1	1	0	2 (13)	0	2
Mixed	B	4 (3/1)	61.0 (32-82)	3	1	0	0	0	3	1	1	2	2 (48)	1 (7)	1
Large-cell	B	1 (0/1)	65.0	1	0	0	0	0	1	0	1	0	1 (192)	0	0
Diffuse lymphomas															
Small-cell	B	5 (3/2)	60.4 (40-71)	1	0	0	3	1	3	0	3	0	2 (33)	2 (54)	1
	B	7 (3/4)	45.6 (4-64)	4	0	1	0	2	4	0	1	1	4 (67)	3 (13)	0
Medium-cell	T	3 (1/2)	49.0 (7-77)	0	2	0	1	0	3	0	1	0	2 (24)	0	1
	B	11 (6/5)	61.9 (25-86)	5	1	4	1	0	3	6	1	2	1 (6)	4 (21)	6
Mixed	T	14 (9/5)	66.6 (27-82)	8	1	2	2	1	4	9	4	5	3 (26)	7 (14)	4
	B	37 (21/16)	59.0 (10-82)	24	4	3	3	3	15	15	4	7	12 (17)	18 (10)	7
Large-cell	T	6 (6/0)	63.0 (44-88)	1	1	2	0	2	1	5	1	2	2 (13)	3 (1)	1
	H†	1 (0/1)	17.0	0	1	0	0	0	1	0	1	0	1 (48)	0	0
Pleomorphic	T	6 (4/2)	50.0 (30-74)	4	2	0	0	0	1	5	0	5	1 (4)	3 (6)	2
Lymphoblastic	T	9 (5/4)	8.9 (3-24)	4	1	1	0	3	5	4	4	4	2 (15)	6 (13)	1
Burkitt	B	1 (0/1)	4.0	0	0	1	0	0	0	1	0	1	1 (67)	0	0
Total		109 (64/45)	48.4 (3-88)	59	14	14	10	12	46	47‡	23	29‡	36 (32.2)	47 (13.1)	26

* Number in parentheses indicates average.
† H = histocyte-derived.
‡ Total is less than 109 due to lack of information in some cases.

logically the normal architecture of the lymph node was replaced by circular and even-sized tumor nodules containing cleaved and noncleaved cells characteristic of follicular center B cells. Of these 9, 4 were the medium-cell type (Figure 5, consisting predominantly of small cleaved cells), 4 were the mixed type, and 1 the large-cell type. The last patient, large-cell type, was a 65-year-old woman who had tonsillar "reticulum cell sarcoma," successfully treated 8 years prior to development of recurrent, massive cervical lymphadenopathy. The recurrent lymphadenopathy resolved completely with therapy, but she died 8 months later after a cerebrovascular accident. Histologic sections demonstrated a lymphoma with both follicular and diffuse growth patterns, both areas divided by fine bands of fibrosis (Figure 6). Thus, the clinicopathologic picture of this patient was that of the "sclerosing reticulum cell sarcoma" described by Rosas-Uribe and Rappaport.[17]

Diffuse Lymphomas

Small Cell Type

There were 5 patients, 3 male and 2 female, whose average age was 60.4 years (range 40–71). Histologically, there was a diffuse, monotonous proliferation of small lymphocytes without mitoses (Figure 7). All 5 cases were judged to be B cell type because they all failed to demonstrate globular ACP or ANAE stains characteristic of T lymphocytes, and 3 demonstrated cytoplasmic monoclonal immunoglobulin. Plasmacytoid differentiation of occasional small lymphocytes was observed in those cases with positive monoclonal immunoglobulin stain (Figure 7). It is noteworthy that 4 of the 5 patients presented with a tumor in either the nasopharyngeal or Waldeyer's ring region that was highly sensitive to irradiation. Evolution to chronic lymphocytic leukemia or macroglobulinemia was not seen in any of these patients.

Medium Cell Type

There were 10 patients, 4 male and 6 female, whose average age was 46.5 years (range 4–77). Histologically, the B cell type (7 cases) demonstrated a monomorphous growth of intermediate lymphocytes with round nuclear configuration and occasional mitoses (Figure 8). There was no B cell type consisting predominantly of small cleaved cells (ie, the diffuse counterpart of follicular lymphoma, medium cell type, was not seen). The T cell type (3 cases) demonstrated a diffuse proliferation of medium lymphocytes with occasional nuclear convolution (Figure 9). This medium T cell type was distinguished from the mixed T cell type by the lesser variability in the nuclear size and shape as compared to the latter. It could be distinguished from lymphoblastic lymphoma because the tumor cells failed to demonstrate the high degree of nuclear monomorphism and of peppery chromatinic distribution characteristic of lymphoblastic lymphoma. Most patients (B and T types) presented in Stage I or II without systemic symptoms and responded well to treatment. It is interesting that 2 of 3 patients with T cell type presented as primary, cutaneous malignant lymphoma.

Mixed Type

There were 25 patients, 15 male and 10 female, whose average age was 42.5 years (range 25–86). Histologically, the B cell type (11 cases) was quite similar to its follicular counterpart, showing the same dual population of cleaved and noncleaved cells. The T cell type (14 cases) was characterized by a mixed population of medium and large lymphocytes, the latter constituting 30–50% of the population. Nuclear convolution was often evident, and in some cases postcapillary venules (the epithelioid venules of Lennert[11]) were prominent (Figure 10).

Large Cell Type

There were 44 patients, 27 male and 17 female, whose average age was 58.6 years (range 10–88). Histologically, the B cell type (37 cases) showed a spectrum in composition and cytology. At one end of the spectrum was a mixed population of medium and large cleaved and noncleaved cells with the predominant large cells showing nucleoli attached to the nuclear membrane, characteristic of what Lennert has called centroblasts[11] (Figure 11). At the other end of the spectrum was a monomorphic proliferation of immunoblasts with large round nuclei, prominent nucleoli, amphophilic cytoplasm, and frequent mitoses (immunoblastic sarcomas). Some cases showed a certain degree of pleomorphism, with formation of occasional multinucleated giant cells (Figure 12).

The T cell type (6 cases) showed a diffuse proliferation of predominantly large lymphocytes, the nuclei often convoluted or cerebriform in configuration. Mitoses were frequent (Figure 13). As discussed in Materials and Methods, the morphologic recognition of T cell lymphoma depended not only on the nuclear convolution but also on the variability of nuclear size and shape, predilection for the paracortical zone, with occasional sparing of follicles, and the prominence of postcapillary venules. However, when these features (other than nuclear convolution) were missing, it was

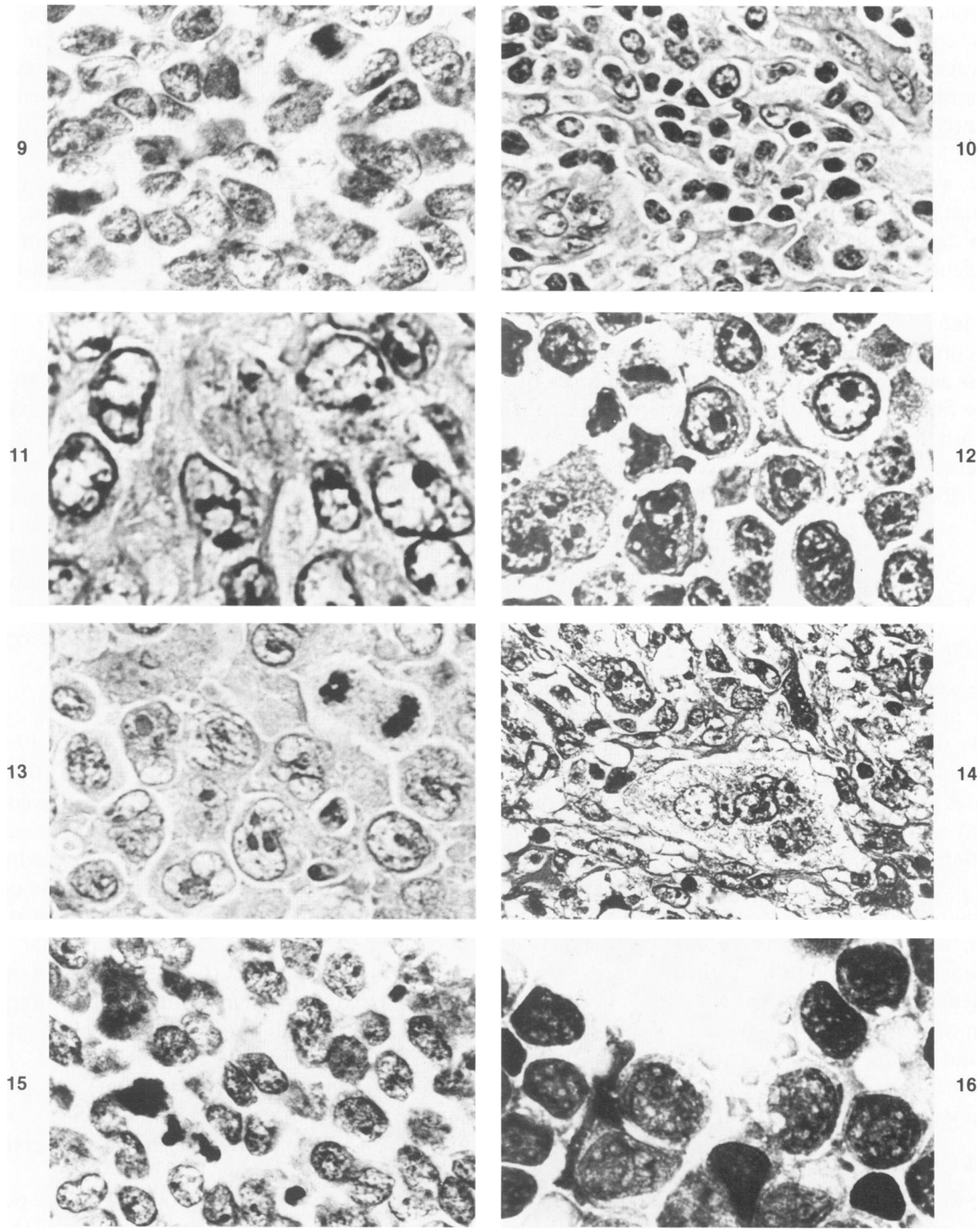

Figure 9—A diffuse lymphoma, medium-cell type (T cell). Differentiation from lymphoblastic type and mixed type (T cell) is discussed in the text. (H&E, × 1000) **Figure 10**—A diffuse lymphoma, mixed type (T cell), demonstrating lymphocytes of varying size and shape. A plasma cell is seen in the lower right corner. Prominent venules are present. (H&E, × 610) **Figure 11**—A diffuse lymphoma, large-cell type (B cell), showing large lymphocytes with prominent nucleoli attached to the nuclear membrane. (H&E, × 1800) **Figure 12**—A diffuse lymphoma, large-cell type (B cell), showing proliferation of immunoblasts, mitoses, and multinucleate giant cells. (H&E, × 1200) **Figure 13**—A diffuse lymphoma, large-cell type (T cell), showing monomorphous proliferation of large lymphocytes with convoluted nuclei and frequent mitoses. (H&E, × 1300) **Figure 14**—A diffuse lymphoma, pleomorphic type (T cell). Tumor cells vary greatly in size and shape, and a large multinucleate giant cell can be seen in the center of the field. (H&E, × 580) **Figure 15**—A diffuse lymphoma, lymphoblastic type, showing a monotonous proliferation of lymphoblasts with mild nuclear convolution. Mitoses are frequent. (H&E, × 850) **Figure 16**—An imprint showing Burkitt lymphoma cells characterized by large, round nuclei, multiple small but prominent nucleoli, and vacuoles in the amphophilic cytoplasm. (Giemsa stain, × 1200)

impossible to identify with certainty the T cell large-cell type because convoluted large T cells and cleaved large B cells were frequently indistinguishable by cytology alone. Hence, additional criteria were necessary. For example, the focal globular ANAE reaction (Figure 1) confirmed the cytologic prediction as T cell type (Figure 13). Figures 1 and 13 were made from the same formalin-fixed paraffin-embedded tissue block.

The remaining case was determined to be a lymphoma of true histiocytic origin. It occurred in a 17-year-old woman who developed skin tumors on one arm, one thigh, and the back in succession during 4 years. Each time, the tumors resolved completely after combined radiotherapy and chemotherapy. Biopsies on all three occasions demonstrated patchy infiltration of the cutis and subcutis by mononuclear cells, which resembled benign histiocytes cytologically. The cytoplasm also stained positively for lysozyme, ACP, and ANAE reactions as described earlier (Figure 4).

Pleomorphic Type

There were 6 patients, 4 male and 2 female, whose average age was 50 years (range 30–74). Microscopically, there was a diffuse proliferation of atypical lymphocytes, often with convoluted nuclei. Cell size and shape varied greatly, and bizarre multinucleate tumor cells were frequent (Figure 14).

Lymphoblastic Type

There were 9 patients, 5 male and 4 female, whose average age was 8.9 years (range 3–24). The disease presented in the lymph nodes (4 patients), the mediastinum (3 patients), and the skin and gut (1 patient each). Microscopic examinations revealed diffuse proliferation of monomorphic lymphoblasts with frequent mitoses (Figure 15). Nuclear convolution was conspicuous in 3 cases and less evident in 6 cases. In all cases the nuclear chromatin was peppered, a distribution characteristic of lymphoblastic lymphoma cells.

Burkitt type

There was 1 patient. A 10-year-old girl presented at age 4 with rectal hemorrhage, which was found by biopsy to be due to multiple polypoid involvement of the colon by Burkitt lymphoma. Chemotherapy induced a complete remission lasting until age 8, when she developed a recurrent tumor in the cerebellum. Sections of both the initial and recurrent tumors demonstrated a starry-sky appearance characterized by sheets of monomorphic tumor cells with scattered tingible-body macrophages. Tumor cells contained large, round nuclei with multiple small but prominent nucleoli and amphophilic cytoplasm with vacuoles. Mitoses were frequent (Figure 16).

Comparison of B and T Lymphomas

There were 70 lymphomas judged to be B cell type, of which 9 were follicular, 5 diffuse small-cell, 7 diffuse medium-cell, 11 diffuse mixed, 37 diffuse large-cell, and 1 Burkitt type. There were 38 diffuse lymphomas judged to be T cell type, of which 3 were medium-cell, 14 mixed, 6 large-cell, 6 pleomorphic, and 9 lymphoblastic type. The unfavorable clinical features of T cell lymphomas were suggested when all patients with various subsets of T cell lymphomas were compared as a group with a second group of patients with various subsets of B cell lymphomas. Namely, late-stage presentation was seen in 43.6% of B lymphomas and 62.2% of T lymphomas, while constitutional symptoms were present at the time of diagnosis in 52.0% of B lymphomas and 61.5% of T lymphomas. The average length of survival (for patients who had died) was 14.9 months for patients with B and 10.9 months for patients with T lymphoma. However, the number of patients was too small for these differences to be statistically significant.

Comparison With Other Series (Table 4)

There were 9 patients with Hodgkin's disease seen during the same period as these 109 non-Hodgkin's lymphomas were diagnosed. Thus, Hodgkin's disease constituted 7.6% of all lymphomas in our series, an incidence distinctly low when compared with series outside of Japan—eg, 43.6% in the Lennert's series.[11] Follicular lymphomas constituted 8.3% of non-Hodgkin's lymphomas in our series and 9.0–18.2% in other Japanese series, whereas high incidences up to 45.0% were reported in the Western countries. T cell

Table 4—Relative Incidence of Lymphomas Compared

	No. cases	Follicular lymphomas (%)	B (%)	T (%)	U* (%)
Lukes[7]	299	41.2	64.9	21.0	16.0
Frizzerra[2]	60	45.0	91.6	6.7	1.7
Lennert[11]	2175†	21.0	77.2‡	7.5‡	15.3‡
Yamanaka[14]	44	9.0	59.1	29.5	11.4
Tajima[3]	111	12.6	44.1	31.5	24.3
Suchi[1]	110	18.2	49.1	38.2	12.7
Our series	109	8.3	64.2	34.9	0.9

* U includes non-T, non-B lymphocyte, macrophage, and unclassifiable cell.

† Original table was adjusted for exclusion of hairy cell leukemia, mycosis fungoides, and Sézary's syndrome.

‡ Two hundred six immunoblastic sarcomas were excluded from calculation.

lymphomas constituted 34.9% of non-Hodgkin's lymphomas in our series and 29.5–38.2% in other Japanese series, whereas only 6.7–21.0% in the Western countries. Extranodal presentation of non-Hodgkin's lymphomas was documented in 45.9% of our 109 patients (Table 3) and in 62% of Yamashita's 532 patients gathered from various parts of Japan.[15] In the West, only 25% of Freeman's 1467 patients, and 10% of Rudders' 380 patients presented in the extranodal sites.[12,13]

Discussion

The LSGJ classification was proposed by the Lymphoma Study Group of Japan as an interim solution to the current controversy over the classification of non-Hodgkin's lymphomas.[1] Fortunately, the more recent formula recommended for clinical usage by the Expert International Panel[18] agrees substantially with the LSGJ classification. Both systems categorize non-Hodgkin's lymphomas into 10 subsets, although each uses different order and nomenclature.

The present study found the LSGJ classification easy to understand and reproduce. The incidence figures for subsets of lymphomas in our series are quite similar to those of other Japanese series.[1,3,14,15,19] A good clinicopathologic correlation is also suggested. The diagnosis of pleomorphic type, for example, seems to convey a highly unfavorable clinical picture characterized by late-stage presentation, positive constitutional symptoms, and rapidly fatal outcome. Furthermore, the present study found the morphologic prediction of immunologic phenotypes to be practicable in most instances.

The feasibility of morphologically recognizing B or T cell derivation of lymphomas was advocated initially by Lukes and Collins[6] and has since been pursued by subsequent investigators.[2,3,20] While these investigators postulated criteria for the morphologic identification of B or T lymphomas, they were unable to offer criteria for the morphologic identification of non-T, non-B lymphomas. The present general practice seems to call a lymphoma non-T, non-B when immunologic studies fail to demonstrate any detectable cell surface markers, even when the lymphoma shows morphologic features of B or T cell derivation. In the present study, our morphologic prediction of B or T cell derivation was confirmed by enzyme histochemical and immunoperoxidase studies in the majority of cases, as tabulated in the Table 2. We chose to designate the minority that did not show these immunologic or histochemical features for B or T lymphomas as B or T cell lymphomas according to the morphologic features. Although we did not conduct cell surface marker studies on live cell suspensions (because of the retrospective nature of the present study), our results agreed with those of other Japanese series in which B or T phenotypes were determined by special immunologic studies.[14] Furthermore, patients within the same LSGJ classification demonstrated differences in clinical features according to our morphologic prediction of B or T cell derivation.

We called one of the 44 diffuse large-cell lymphomas a true histiocytic lymphoma because of the benign histiocyte-like cytologic character of the tumor cells, intercellular reticulin fibrosis, and positive ACP, ANAE, and lysozyme reactions. Clinically, this case presented as recurrent skin tumors highly responsive to treatment. The incidence in the literature of true histiocytic lymphoma varies from 1 out of 299 cases (0.3%) of non-Hodgkin's lymphomas[7] to 1 out of 25 cases (4%)[21] or 4 out of 90 cases (4%)[22] of diffuse large-cell lymphomas. Although the difference between 0.3% and 4% was in part due to the use as denominators of the number of non-Hodgkin's lymphomas versus the number of large-cell lymphomas, it was due also to the different emphasis on the diagnostic significance of the cytologic features of the tumor cells. Whereas Lukes determined the histiocytic derivation of lymphomas on the basis of the benign histiocyte-resembling cytology as well as on the results of enzyme-histochemical and immunoperoxidase studies, others determined it purely on the basis of special studies.[21,22] Hence, their histiocytic lymphomas could not be differentiated morphologically from either B or T cell neoplasms.

LSGJ created the "pleomorphic type" as a special category distinct from all other diffuse lymphomas to accommodate a particular subset of adult T cell lymphomas that the LSGJ considered quite prevalent in Japan. However, its incidence among diffuse lymphomas turned out to be 6% (6 out of 100 cases) in this study. This incidence is similar to the 3.5% (16 out of 457 cases) in a series contributed from various parts of Japan[15] and 2.7% (10 out of 365 cases) in a series from the Kagoshima prefecture, a region well known for the highest incidence of adult T cell lymphomas in Japan.[19] Not only do these figures tend to refute the presumed prevalence of the pleomorphic type in Japan, but the entity may not necessarily be rare outside of Japan.[23,24] Histologically, it was sometimes difficult to differentiate the pleomorphic type from T cell lymphomas of mixed or large-cell type because these T cell lymphomas occasionally showed foci with marked pleomorphism characteristic of the pleomorphic type. Even B cell lymphomas (large-cell type) could occasionally show significant

pleomorphism with bizarre multinucleate tumor cells (Figure 12). Despite its unexpected low incidence and the necessary distinction from pleomorphic B cell lymphomas, it is likely that the "pleomorphic type" will be established as a valid clinicopathologic entity because of its fulminant clinical course.

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